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DEPRESSIVE SYMPTOMS AND SURVIVAL AMONG LUNG CANCER
PATIENTS: BIOMARKERS AND POTENTIAL BENEFITS OF AN IPOD- AND
MINDFULNESS-BASED INTERVENTION

By

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B.A., University of Wisconsin-Madison, 2014
M.S., University of Louisville, 2017

A Dissertation
Submitted to the Faculty of the
College of Arts and Sciences of the University of Louisville
in Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy in Clinical Psychology

Department of Psychological and Brain Sciences
University of Louisville
Louisville, Kentucky

August 2020

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A Dissertation Approved on

June 10, 2019

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Elizabeth Cash, Ph.D.

Benjamin Mast, Ph.D.

Tamara Newton, Ph.D.

DEDICATION

This dissertation is dedicated to the lung cancer patient participants who altruistically donated their time and efforts to providing data for the current investigation and for their contribution to science

and

To all of the scientists and clinicians who have dedicated their life's work to understanding and providing care to those inflicted by cancer.

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I am also extremely grateful for the guidance that I have received from Dr. Elizabeth Cash, as she exemplifies the female, scientist-practitioner that I strive to be. I feel extremely grateful to have received the degree of support and the opportunity to grow under such rich mentorship over the past four years, an experience that would not have been complete without you.

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Overall, I feel extremely fortunate to have been a member of the Mindfulness and Biobehavioral Health Research Lab, not only for the wealth of knowledge I have gained, but also for the people it has connected me with. I am deeply appreciative of all of my fellow labmates, and especially grateful for my friend, Kala Phillips, as your assistance has remained a stable, reliable source of support since day one. I am also very grateful for all of those who have assisted with the current study, including Lauren Zimmaro, and the many research assistants that maintained the momentum of the project.

I would like to thank my family and friends, near and far. To my partner, Brian, and my fur-baby, Kora, each one of these very long days would have been considerably more difficult and much less meaningful without your presence, love, and support. I appreciate all that you do in support of my aspirations and love you both very much. To my greater Louisville family – Catherine, Nonah, Judy, and Kirsten – it is difficult to express how grateful I am to have endured this journey together. I will always cherish the memories we have made. Thank you for helping make Louisville home.

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ABSTRACT

DEPRESSIVE SYMPTOMS AND SURVIVAL AMONG LUNG CANCER PATIENTS; BIOMARKERS AND POTENTIAL BENEFITS OF AN IPOD- AND MINDFULNESS-BASED INTERVENTION

Chelsea J. Siwik, M.S.

June 10, 2019

Lung cancer patients experience high levels of distress, which commonly manifests as depressive symptoms. Importantly, depressive symptoms have demonstrated prognostic significance in cancer contexts, although the biological pathways by which depressive symptoms lead to poorer survival remain unclear and warrant greater attention. In addition to understanding the biological pathways by which depressive symptoms accelerate disease, identification of efficacious and effective psychological treatments for depressive symptoms are needed to improve both quality and quantity of life for cancer patients. Interventions that reduce depressive symptoms and improve downstream clinical outcomes are certainly needed; however, because many cancer patients face considerable burden, interventions that offer feasibility and accessibility are also desirable. Thus, this study has two primary aims: 1) to test the prognostic significance of depressive symptoms and explore the role of two biomarkers – cortisol and leukocyte telomere length (LTL) – as they relate to the depression-survival pathway and 2) to explore the ameliorative role of an iPod and mindfulness-based intervention on depressive symptoms and related outcomes among lung cancer patients.

Non-small cell lung cancer patients (N = 67) who had received a diagnosis within five years were recruited to participate in the current study. Participants reported on depressive symptoms, provided a blood sample for LTL assessment, and collected home-based saliva samples for cortisol assessment at both baseline and at a three-month follow-up. Participants were invited to partake in an optional iPod and mindfulness-based pilot intervention that occurred between baseline and follow-up. The intervention involved listening to pre-recorded audio tracks adapted from the Mindfulness-based Stress Reduction program. A number of statistical tests, including ANCOVAs, hierarchical linear regressions, Cox Proportional Hazards regressions, and Kaplan-Meier analyses using the log rank test, were conducted to assess hypothesized relationships. Spearman's rank-order correlations were used to assess theoretically derived control variables. Variables that were moderately related to outcomes ($r > .3$, $< .5$) were adjusted for.

Regarding Aim 1, results revealed only clinical, not sub-clinical levels of depression at baseline predicted shorter survival; ethnic minorities evidenced greater shortening of LTL; and contrary to expectation, an increase in LTL was associated with shorter survival. Regarding Aim 2, results revealed that the intervention was associated with an increase in depressive symptoms and LTL and shorter survival. Although an increase in depressive symptoms was initially observed to be associated with a decrease in LTL, upon closer examination, there was an interaction effect. *Post-hoc* analyses revealed that as depressive symptoms increased, LTL only shortened among patients who did not participate in the intervention, whereas LTL lengthened among those who participated.

Although results from the current investigation should be interpreted cautiously due to a number of limitations, these findings point to longer LTL as one potential biological explanation for the depression-survival relationship among lung cancer patients. Surprisingly, the less supported biomarker, LTL, as compared to cortisol, emerged as a potential link between depressive symptoms and shorter survival, a relationship that warrants continued attention and greater clarification. These results also cohesively suggest that the intervention was associated with poorer psychological and physical health and poorer clinical outcomes among this small sample of lung patients. Contrary to the intended and expected benefits of the pilot iPod- and mindfulness-based intervention, it yielded concerning negative associations that cannot be ignored. While a number of potential explanations for the current findings are discussed, elucidation of the components of the current intervention that may have worsened outcomes demand further investigation.

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INTRODUCTION

A cancer diagnosis and treatment are exceptionally stressful experiences that pose significant psychological and physical challenges. In addition to the acute stress of receiving a life-threatening diagnosis, patients must cope with treatment side effects and disruption of social and vocational roles (Andersen, Kiecolt-Glaser, & Glaser, 1994). Cancer-related stressors, such as fear of recurrence (Costanzo et al., 2007) and psychosocial symptoms (Harrington, Hansen, Moskowitz, Todd, & Feuerstein, 2010) can persist beyond treatment into survivorship, demonstrating the potentially profound and pervasive impact of on-going cancer-related stress over the course of a cancer journey.

Lung Cancer

In addition to stressors common to all cancers, lung cancer patients experience disease-specific challenges. Compared to other cancers, lung cancer grows rapidly, spreads quickly, and often remains undiagnosed until the disease has progressed to a later stage – an indicator of the extent of tumor growth and metastasis – that is a strong predictor of survival (Yang et al., 2005). Indeed, 65.1% of lung cancers are diagnosed at a late (III or IV) opposed to early (I or II) stage (Siegel, Ma, Zou, & Jemal, 2014). While the 5-year survival rate of lung cancer is estimated at 18%, those diagnosed at a later stage have a survival rate of less than 5%, and more than half of those with lung cancer die within the first year of their diagnosis (Henningfield & Adjei, 2017; Siegel, Miller, & Jemal, 2016). Despite efforts to improve diagnostic and treatment methods, the survival rate has remained relatively unchanged for the past three decades

(Siegel, Miller, & Jemal, 2018), suggesting there may be other prognostic factors that are currently unrecognized. Although immunotherapy, a newer, molecular targeted treatment, has demonstrate improvement to the median survival in a limited group of non-small cell lung cancer (NSCLC) patients, these therapies are, unfortunately, not available to many patients (Massarelli, Papadimitrakopoulou, Welsh, Tang, & Tsao, 2014). In addition to the aggressive nature of lung malignancy, lung cancer patients report experiencing high levels of disease-related stigma (LoConte, Else-Quest, Eickhoff, Hyde, & Schiller, 2008), as lung cancer is often perceived as a self-inflicted disease due to its strong association with smoking (Henningfield & Adjei, 2017). Thus, lung cancer patients are among the most distressed of all cancer patients (Carlson et al., 2004).

Depression and Cancer

Depression is a common psychological manifestation of stress in cancer contexts. Estimated at approximately 12.5% (Linden, Vodermaier, Mackenzie, & Greig, 2012), depression rates across cancer types exceed those among non-medically ill populations by four times (Lutgendorf & Andersen, 2015; Raison & Miller, 2003). Among lung cancer specifically, the prevalence of depression has been estimated between 11- 44% (Hopwood, Stephens, & Party, 2000; Massie, 2004), which is among the highest when compared to other cancers (Linden et al., 2012). Nonetheless, not all cancer patients become depressed and depressive symptoms are not explained by disease severity (Brown, Levy, Rosberger, & Edgar, 2003), indicating cancer-related stress confers risk for depression, but does not predict it (Raison & Miller, 2003). While sadness and other vegetative symptoms are common in cancer contexts, and although it can be difficult to tease apart (Fisch, 2004), patients with comorbid symptoms of depression suffer from

distinct and intensified symptoms that extend beyond typical adjustment and lead to marked impairment of functioning (Chochinov, 2001) that can affect treatment compliance and clinical outcomes.

Depression and cancer survival. Mounting evidence points to depression as a predictor of shorter survival in cancer (Spiegel & Giese-Davis, 2003). Not only do meta-analyses indicate depression is predictive of earlier mortality across a number of cancers (Satin, Linden, & Phillips, 2009), including lung (Pinquart & Duberstein, 2010), but in a different study, depressive symptoms were the most consistent psychological predictor of shortened survival compared to cancer-related distress, anxiety, mood, sense of control, and perception of physical health, even after controlling for demographic (e.g., age, gender) and medical (e.g., cancer site and stage, treatment status) factors (Brown et al., 2003). Thus, depressive symptomology specifically appears to be a strong prognostic indicator of survival in cancer compared to other psychopathologies and distress more broadly (Brown et al., 2003), and some have identified depressive symptoms to be as important as traditional prognostic indicators of survival including stage at diagnosis and disease recurrence (Zimmaro et al., 2018). Furthermore, decreases in depressive symptoms obtained via psychosocial interventions have been linked to longer survival among breast cancer patients (Giese-Davis et al., 2011; Spiegel, Kraemer, Bloom, & Gottheil, 1989). In one randomized control trial (RCT) in metastatic breast cancer, after adjusting for medical factors, women with improved depressive symptoms lived almost twice as long over a 14 year span as women whose depressive symptoms worsened over the course of the year following study entry (Giese-Davis et al., 2011), demonstrating the magnitude of untreated depression in cancer contexts. Taken together, although a handful

of studies have reported a null association between depression and earlier cancer mortality (Spiegel & Giese-Davis, 2003), considerable evidence points to depressive symptoms as a predictor of shorter survival in cancer.

Current gaps. First, despite abundant evidence demonstrating the prognostic nature of depressive symptoms across a number of cancers, the mechanisms by which depressive symptoms lead to shorter survival in cancer contexts remains unknown. Behavioral pathways, such as treatment noncompliance, have been examined as potential explanations for this relationship given that depression-related motivation deficits can inhibit patients from attending appointments. Indeed, depressed patients are more likely to experience breaks in treatment (DiMatteo, Lepper, & Croghan, 2000), which can lead to increased risk for earlier mortality (Fesinmeyer, Mehta, Blough, Tock, & Ramsey, 2010). However, a recent study among head and neck cancer patients identified biological, opposed to behavioral, pathways as a significant mediator of the depression-survival relationship (Zimmaro et al., 2018). In this study, depressive symptoms, measured prior to treatment onset, predicted shorter 2-year overall survival. Additionally, although depressive symptoms were associated with increased treatment disruption, treatment disruption did not mediate the depression-survival relationship, whereas treatment response – a dichotomous clinical biological indicator of treatment success – did. When entered simultaneously into survival models, depression remained a significant predictor, indicating treatment response partially mediated the depression-survival relationship. This recent investigation points to biological, opposed to behavioral mechanisms as an explanation for the depression-survival relationship.

Indeed, many biobehavioral reviews foundational for the field of psycho-oncology have already proposed a number of biological pathways by which psychological distress, including depressive symptoms, may promote poorer cancer outcomes (Andersen et al., 1994; Antoni et al., 2006; Armaiz-Pena, Lutgendorf, Cole, & Sood, 2009; Eismann, Lush, & Sephton, 2010; Lutgendorf & Sood, 2011; Reiche, Nunes, & Morimoto, 2004; Sephton & Spiegel, 2003). Yet, no clear explanation for how depressive symptoms lead to shorter survival in cancer has been reported to date, necessitating continued effort. The majority of these seminal overviews emphasize the role of immune and neuroendocrine biomarkers given that substantial literature has demonstrated dysregulation of these systems in depressive and cancer contexts, both individually and jointly. However, few comprehensive biobehavioral reviews have integrated telomeres, a marker of cellular aging, and the majority of these reviews are largely all encompassing, such that they provide detailed explanations of the biological underpinnings associated with psychological stress and cancer broadly, but do not focus on depressive symptoms specifically. Given that Brown and colleagues (2003) demonstrated distinct forms of distress (e.g., depression) have unique effects on survival outcomes, broad stress models may not be adequately capturing meaningful, nuanced explanations for the depression-survival pathway. Thus, a more specific approach may be required to elucidate how depressive symptoms cause shorter survival in cancer.

Second, despite growing evidence for the prognostic significance of depressive symptoms, the treatment of depressive symptoms remain under prioritized in cancer contexts. Although efforts to acknowledge and treat comorbid mental illnesses among cancer populations have certainly improved (Pirl, 2004), interventions that are both

efficacious and effective warrant continued attention to potentially improve both quality and quantity of life for cancer patients. Psychosocial interventions have demonstrated efficacy in decreasing depressive symptoms in cancer contexts, although less attention has been given to mindfulness-based interventions, especially compared to cognitive-behavioral and supportive group approaches (Li, Fitzgerald, & Rodin, 2012).

Mindfulness-based approaches, which foster attitudes of acceptance, detachment from an anticipated outcome, and emotion regulation by enhancing present moment awareness, warrant greater exploration given the lack of control, considerable uncertainty, and continual adjustment that accompanies cancer (Carlson et al., 2013). Additionally, given the considerable burden many cancer patients face, interventions that promote feasibility, through mobile and flexible formats, for example, are desirable. Thus, interventions that reduce depressive symptoms and prevent/ameliorate related downstream clinical consequences and promote feasibility in cancer populations remain a need.

Therefore, the current study attempts to begin elucidating how depressive symptoms lead to shorter survival and how to efficaciously and effectively treat depressive symptoms and related outcomes among NSCLC patients via two primary aims: 1) test the prognostic significance of depressive symptoms and the role of two biomarkers – cortisol and leukocyte telomere length (LTL) – as they relate to the depression-survival pathway and 2) explore the ameliorative role of an iPod-based MBSR intervention on depressive symptoms and related outcomes.

Aim 1: The Potential Role of Two Biomarkers in the Depression-Survival Pathway

1) Cortisol. Cortisol, a glucocorticoid hormone, has many widespread biological functions, implicated in mood, emotional memory, and cognition (Keller et al., 2006). It

is both the end product of the hypothalamic-pituitary-adrenal (HPA) neuroendocrine stress response and a central communicator between the central nervous system (CNS) and the periphery that synchronizes biological function and initiate behavioral action. Cortisol secretion, therefore, occurs both in response to stressors and operates diurnally on a circadian schedule.

The neuroendocrine stress response. When threat is detected, a downward cascade of biological reactions is initiated via the sympathetic nervous system and the HPA axis, resulting in the production of catecholamines and glucocorticoids (cortisol in humans), respectively (Sapolsky, Romero, & Munck, 2000). Activation of the HPA axis is initiated via secretion of corticotropin release hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus. The pituitary gland is then stimulated and releases adrenocorticotrophic hormone (ACTH), which travels via systemic circulation to the adrenal gland and stimulates the release of cortisol into the blood (Sapolsky et al., 2000). Because cortisol is the product of the neuroendocrine stress response, it is both a biomarker of acute and chronic stress, with particular sensitivity to uncontrollable and social-evaluative stressors (Dickerson & Kemeny, 2004).

Although cortisol secretion is adaptive in response to a stressor, as it prepares an organism to endure threat (Armaiz-Pena et al., 2009), chronic production of cortisol can become maladaptive. Excessive cortisol production can cause desynchronization of the HPA-axis and other cortisol-related biological systems, disrupting a number of biological functions (Pariante & Miller, 2001). Upon chronic exposure to cortisol, glucocorticoid receptors (GRs) become desensitized and negative feedback loops fail to regulate cortisol levels, eventually causing the system to become blunted. Because GRs are widely

distributed across the human body with dense concentrations in certain areas of the brain (Rosenfeld, Van Eekelen, Levine, & de Kloet, 1993), it is apparent cortisol has influence on a number of diverse biological processes (Weiner, 1992), including neural, cardiovascular, immune, and metabolic functions (McEwen, 2008). Consequently, in addition to the considerable “wear and tear” chronic stress can ensue on the HPA axis, it can also cause widespread biological dysregulation with far reaching consequences, including greater risk for disease. For a comprehensive overviews of the extensive inner workings of a neuroendocrine response via the HPA axis, see McEwen (2000, 2008) and Miller et al. (2007).

Circadian rhythms. In addition to production of cortisol in response to a stressor, cortisol secretion occurs rhythmically on a diurnal schedule (Halberg, 1960). In fact, it is becoming more evident that many biological functions in addition to cortisol production, such as sleep/wake cycles, cell proliferation, immune activity (Fu & Lee, 2003), DNA damage repair mechanisms (Innominato et al., 2014), and cell senescence (Fu & Kettner, 2013), are regulated via an internal “clock.” This clock appears to function normally independent of external cues, but aligns closely with the Earth’s 24-hour rotation (Shostak, 2017). These biological circadian rhythms are believed to be evolutionarily advantageous as they allow the host’s physiology to naturally adapt to environmental surroundings. Although cortisol production is responsive to the environment, circadian rhythms allow the CNS to control biological function without taxing limited higher-level resources (i.e., conscious thought). Glucocorticoids are one of the primary mechanisms by which the suprachiasmatic nuclei (SCN; i.e., the central pacemaker or mammalian clock) of the CNS can communicate peripherally to coordinate important biological

functions (Innominato et al., 2014). Thus, cortisol secretion follows an endogenous diurnal rhythm to facilitate synchronization of these functions (Fu & Lee, 2003). For an extensive review on the mammalian central clock and how it coordinates peripheral systems, see Dibner et al. (2010).

Cortisol profiles. Research has identified typical, healthy diurnal cortisol profiles as the following: highest levels in the morning upon waking, known as the cortisol awakening response (CAR), followed by tapering levels throughout the day, and lowest levels prior to sleep between 2100 – 2400 hours (Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010). Therefore, steeper diurnal cortisol slopes are considered normal/healthy, whereas flattened slopes are aberrant, indicative of circadian and/or HPA dysregulation, and have been linked with poorer health outcomes. See *Figure 1* for a depiction of a normal cortisol profile and a steep slope. Although cortisol rhythms tend to follow this daily pattern, cortisol secretion is influenced by a number of factors including exercise, sleep, and consumption of food, medication, and other substances (e.g., alcohol, tobacco, etc.). Daily mean diurnal cortisol is also influenced by these factors, and can be more challenging to interpret, as it is more inter-individually variable. While chronic production of cortisol and elevated mean cortisol levels at bedtime are considered aberrant, higher overall diurnal mean cortisol is more challenging to classify given that cortisol production is influenced by genetics (Ouellet-Morin et al., 2008). In other words, diurnal cortisol slope is a more stable marker of circadian rhythmicity as it reflects daily pattern, whereas overall diurnal mean cortisol is more susceptible to inter-individual variation. Thus, although elevated mean cortisol can be indicative HPA hyperactivity, it should be interpreted cautiously, as higher overall mean cortisol does not *always* reflect

aberration. Lastly, CAR, despite substantial discussion in depression literature, has significant methodological limitations (Clow, Thorn, Evans, & Hucklebridge, 2004) and its significance regarding health outcomes remains complex (Clow et al., 2004). Therefore, empirically supported markers of cortisol profiles – mean diurnal cortisol and diurnal cortisol slopes - will remain the focus of the current study.

Taken together, cortisol has become a widely used, reliable biomarker of acute and chronic psychological stress (Hellhammer, Wust, & Kudielka, 2009), the neuroendocrine stress response (Riad-Fahmy, Read, & Walker, 1980), and systemic circadian coordination (Windle, Wood, Lightman, & Ingram, 1998) when assessed and interpreted correctly. Because the PVN receives neural input from the SCN, which controls the HPA axis and circadian coordination, respectively, the two systems are tightly linked (Clow et al., 2010). Thus, given the diagnostic hallmarks of depression, which include significant changes to metabolic function (e.g., appetite and sleep), it is not surprising abnormal cortisol profiles have been observed among depressed individuals. Additionally, because circadian rhythms are central to many biological processes including cortisol secretion and cell proliferation (Hrushesky, Lannin, & Haus, 1998), it is logical that desynchronization of circadian cortisol rhythms has been observed in patients with cancer, a disease described by rapid and uncontrolled cell division.

Depression and cortisol. Substantial literature has linked aberrant cortisol profiles and depression. Elevated cortisol was originally observed among depressed patients upwards of 50 years ago (Board, Wadeson, & Persky, 1957) and a significant number of experiments and subsequent reviews on the depression-cortisol association have confirmed HPA axis hyperactivity and diminished sensitivity of GR feedback loops

among depressed individuals (Burke, Davis, Otte, & Mohr, 2005; Herbert, 2013; Pariante & Miller, 2001). Approximately half of depressed individuals demonstrate an impaired recovery response to a dexamethasone suppression test (Gold et al., 1986), which is used to assess functioning of GR mediated feedback loops (see Carroll (1984) for a comprehensive description and overview). Despite inconsistent prevalence rates, Miller et al. (2007) reported a striking effect: depressed individuals have demonstrated cortisol levels one standard deviation greater than levels among non-depressed counterparts following a dexamethasone test, suggesting meaningful differences in GR-mediated HPA axis function.

With respect to diurnal cortisol rhythms, a couple of small studies have reported abnormal circadian profiles – one among men suffering from an acute depressive episode ($n = 11$) compared to age-matched controls ($n = 7$; Linkowski et al. (1987), and another among individuals with MDD ($n = 14$) compared to individuals with PTSD ($n = 15$) and healthy men ($n = 15$; Yehuda, Teicher, Trestman, Levengood, and Siever (1996). Both of these studies, however, collected multiple samples of cortisol over one day, which has been shown to be an unreliable estimate (Segerstrom, Boggero, Smith, & Sephton, 2014). In a different study, approximately half of individuals with depression demonstrated elevated evening cortisol levels (Claustrat, Chazot, Brun, Jordan, & Sassolas, 1984), a marker of abnormal diurnal rhythmicity. Taken together, decades of research have identified hyperactivation and subsequent dysregulation of the HPA axis, measured through cortisol, as a hallmark of depression (Herbert, 2013; Jehn et al., 2006), although the evidence of disrupted diurnal rhythmicity is more limited. Consequently, depression has been hypothesized to be a result of chronic activation of the neuroendocrine stress

response (Pariante & Lightman, 2008). Despite consistent observation of aberrant cortisol in depression, the inconsistencies associated with the type of aberration (e.g., only 50% demonstrate elevated evening cortisol levels) are puzzling, but may be explained by methodological discrepancies in cortisol assessment. Alternatively, these inconsistencies may be indicative of subtypes of depression, as Bonanno's longitudinal work has consistently identified distinct depressive trajectories (e.g., emergent post-event, chronic, depressed prior followed by improvement) following a host of stressful events including a spinal cord injury (Bonanno, Kennedy, Galatzer-Levy, Lude, & Elfström, 2012), bereavement (Galatzer-Levy & Bonanno, 2012), and a medical diagnosis (Morin, Galatzer-Levy, Maccallum, & Bonanno), all of which activate the HPA axis. Thus, greater exploration into the role of dysregulated cortisol profiles in different depressive contexts (e.g., cancer) warrants greater attention.

The prognostic significance of cortisol in cancer. Miller et al. (2007) stated, “stressors that threaten physical integrity, involve trauma, and are uncontrollable,” much like cancer, “elicit a high, flat diurnal profile of cortisol secretion” (p. 25). Indeed, aberrant diurnal cortisol profiles marking circadian disruption have been linked to poorer clinical outcomes in cancer, including tumor development, disease progression (Eismann et al., 2010; Fu & Lee, 2003; Hrushesky et al., 1998; Mormont & Levi, 1997), and shorter survival in breast (Sephton, Sapolsky, Kraemer, & Spiegel, 2000), renal cell (Cohen et al., 2012), lung (Sephton et al., 2013), and ovarian (Schrepf et al., 2015) cancer. Although the number of studies examining cortisol and survival in cancer are limited, mounting evidence points to the prognostic significance of circadian-regulated neuroendocrine disruption in cancer. Because the circadian clock regulates diurnal

cortisol and important aspects of the cell cycle, disruption to its function appears to have profound influence on tumor development and the host's survival. Indeed, experimental manipulation of circadian disruption of endocrine function has been shown to cause spontaneous tumor onset (Filipski et al., 2002; Fu & Lee, 2003) and accelerate growth (Sapolsky & Donnelly, 1985) in animal models. Despite the long held belief that the circadian clock suppresses tumors (Eismann et al., 2010; Fu & Kettner, 2013), more recent evidence suggests, in some circumstances, it may also promote tumorigenesis (Shostak, 2017), highlighting the vital, yet debated, role of circadian function on tumor behavior. Nonetheless, glucocorticoids have been shown to stimulate growth (Moran, Gray, Mikosz, & Conzen, 2000), increase the invasive potential (Sood et al., 2006), and inhibit tumor cell death (Volden & Conzen, 2013) in tumor microenvironments. Taken together, circadian clock regulated coordination of diurnal cortisol appears to play a central role to maintenance of healthy biological functioning on a systemic, cellular, and molecular level, and disruptions to this system have been linked to cancer onset, growth, and poorer survival.

Depression and cortisol in cancer. Cortisol appears to be a biological correlate of depression and cancer (Pasquini & Biondi, 2007). Elevated bedtime cortisol has been associated with depressive symptoms (Lutgendorf et al., 2008) and shorter survival (Schrepf et al., 2015) in ovarian cancer patients. Dysregulated diurnal cortisol profiles have also been linked with greater vegetative depression, but not stress or distress, among ovarian cancer patients (Weinrib et al., 2010). Additionally, a decline in vegetative depressive symptoms reported by ovarian cancer patients six months post-surgery was associated with reductions in mean bedtime cortisol levels (Schrepf et al., 2013),

suggesting patients with improved psychological symptoms also experienced improvements in physiological health.

Jehn et al. (2006) extended these findings beyond ovarian cancer by demonstrating greater dysregulation of diurnal cortisol among depressed compared to non-depressed cancer patients; although depression and disease status were not independent, suggesting the depression-cortisol association could be confounded by disease severity. In a different sample, however, depressed compared to non-depressed breast cancer patients had significantly lower mean waking cortisol levels at study entry, which could not be fully explained by disease status, suggesting a unique association between depression and circadian coordinated cortisol function independent of disease (Giese-Davis et al., 2006). In a unique study involving a dexamethasone suppression test, patients with both depression and cancer demonstrated high plasma cortisol levels following the test, indicating disrupted glucocorticoid-mediated feedback loops in the HPA axis (Musselman et al., 2001). Depressive symptoms were also correlated with plasma cortisol levels in this sample, suggesting HPA dysregulation increased with depression severity.

In contrast, Sephton and colleagues (2000) reported a null association between depressive symptoms and cortisol slopes, which are prognostic of survival, among a sample of metastatic breast cancer patients. In a later analysis using a subset of the same metastatic breast cancer sample, however, Sephton and colleagues (2009) reported an association between greater depressive symptoms and *higher* waking cortisol and “*accentuated*” cortisol slopes. While these findings are somewhat contrary to expectation as higher waking cortisol is typically interpreted as physiologically beneficial, this

relationship may be reflective of increases in HPA activity. Taken together, although these findings are somewhat inconsistent, majority of the positive associations between depression and cortisol were observed among ovarian cancer, whereas most null and contradictory findings were among breast cancer patients. Further, the number of studies examining depression and cortisol in cancer, let alone cancer survival, is surprisingly scarce. Even fewer studies report null or contradictory findings, making it difficult to deduce conclusions. Nonetheless, a comprehensive meta-analytic review of 80 studies that examined associations between diurnal cortisol slopes and 12 different indices of mental and physical health indicated flatter diurnal cortisol slopes were associated with 10 of the 12 health outcomes, which included depression and cancer, suggesting dysregulation of circadian markers correspond to poor downstream health outcomes (Adam et al., 2017).

It is not surprising depressed cancer patients experience earlier mortality (Pinquart & Duberstein, 2010; Satin et al., 2009) Theoretically, cancer patients with comorbid depression experience compounded cortisol dysregulation, both depression-driven HPA axis disruptions as well as aberrations in diurnal cortisol rhythmicity that have been linked with tumors. A comprehensive review on the interaction of circadian clock regulated cortisol profiles and HPA axis systems by Nadar and colleagues (2010) provided evidence that the two systems are highly interrelated biologically and that the central circadian clock system dictates activity of the HPA axis. It remains intriguing, however, that the cortisol aberrations observed in depressed individuals appears to be HPA-related, whereas the aberrations associated with cancer seem to reflect dysregulation in diurnal cortisol rhythmicity. Thus, although cortisol is a clear correlate of depression and cancer,

the nuanced biological underpinnings of the aberrations in cortisol profiles observed across conditions are complex and should be interpreted thoughtfully.

Cortisol and the depression-survival relationship. All together, the literature indicates a complex interaction between depressive symptoms, aberrant cortisol profiles, and survival in cancer contexts, although the directionality of the relationship between depression and cortisol remains unknown. Because the temporal onset of HPA dysregulation in depression remains unclear, elucidation of these relationships in the context of illness, especially an illness strongly linked to aberrations in cortisol profiles, is a challenge. While the role of genetics will be central in clarifying these relationships, further examination of these stress factors offer opportunity to begin understanding such relationships.

Dysregulated cortisol profiles have been proposed as a mediator of the depression-survival relationship (Cohen et al., 2012; Eismann et al., 2010; Sephton et al., 2003). Cohen and colleagues (2012) replicated the association between both depressive symptoms and aberrant cortisol profiles with shorter survival among renal cell carcinoma patients. When controlling for diurnal cortisol rhythms, the strength of the association between depressive symptoms and survival time was substantially reduced, suggesting aberrant cortisol profiles may have partially mediated the depression-survival relationship. However, because the authors reported a null association between depressive symptoms and cortisol and did not report if the main effect of cortisol or the interaction between depression and cortisol were statistically significant, the analytic approach was not clear and did not seem to meet updated criteria for mediation (Chmura Kraemer, Kiernan, Essex, & Kupfer, 2008). Further, it is unlikely the authors included

the interaction term in the Cox regression models, which is another criterion of mediation outlined in the MacArthur approach (Chmura Kraemer et al., 2008). This is problematic because it is unclear if depressive symptoms and aberrant cortisol profiles were “working together” to cause earlier mortality or if cortisol truly serves as an explanation for how depressive symptoms lead to shorter survival (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001), warranting prospective analysis following more rigorous statistical criteria.

Nonetheless, Cohen and colleagues (2012) only reported partial, opposed to full mediation, suggesting other biological processes may also be contributing to this pathway. Indeed, substantial literature has already demonstrated a central role of the immune system in the intersection of depression, neuroendocrine function, and cancer (Costanzo, Sood, & Lutgendorf, 2011; Lutgendorf & Andersen, 2015; Reiche et al., 2004), yet no evidence exists to date suggests immune markers explain the depression-survival relationship. A more recent, yet growing body of evidence (discussed below) suggests telomeres, typically extracted from leukocytes, may be an important biomarker of psychological stress, including depressive symptoms, and clinical outcomes in cancer as well. Although empirical exploration continues to unravel the underlying complexities of telomere biology, emerging evidence suggests telomeres are intertwined with tumor onset and growth, and therefore, survival. Thus, the current study aims to expand on current biobehavioral literature by integrating a newer, less amalgamated biomarker – telomere length – that holds promise as a contributor to the depression-survival relationship.

2) Telomere length (TL). Telomeres are DNA-based protein structures capping the ends of chromosomes that serve to maintain cellular integrity and stability

(Blackburn, Epel, & Lin, 2015). Upon each cell division, telomeric DNA is lost, resulting in cumulative shortening of telomeres over time; a process that determines how fast cells age and when they die (Rivera-Tavarez, 2017). Thus, the slow, cumulative shortening of telomeres over the course of the lifespan is consistent with typical, healthy aging; however, the loss of TL can be accelerated by environmental factors such as chronic stress (Epel et al., 2004), an effect that is observable as early as intrauterine life (Entringer et al., 2011), and is inconsistent with typical, healthy aging as it is considered premature. Indeed, stress has been experimentally shown to accelerate telomere attrition in animal models (Haussmann & Heidinger, 2015; Kotrschal, Ilmonen, & Penn, 2007). Therefore, the lifetime decline in TL is influenced by a host of elements including genetics, developmental and environment factors, and physiology (e.g., oxidative stress exposure; Blackburn (2001). Telomeres are also under control of a biological (mitotic) clock, although timing of this clock is related to previous number of cell replications, rather than diurnal circadian rhythmicity (von Zglinicki, 2002). Nonetheless, telomeric processes including cell proliferation (Fu & Lee, 2003), DNA damage repair mechanisms (Innominato et al., 2014), and programmed cell death, or senescence (Fu & Kettner, 2013), are all regulated via an internal biological “clock,” demonstrating biological parallels between cortisol and telomeric function.

When telomeres become “too short,” the cell initiates a DNA damage response – it stops dividing or dies – causing cellular changes that can permanently inhibit tissue replacement and subsequent wide-spread genomic instability (Augustine, Maitra, & Goel, 2017). Cells are only able to divide a finite number of times, known as the Hayflick limit (Hayflick, 1965), and when cells approach the limit, they become senescent (Blackburn,

2000). The underlying biological role of senescence is to prevent growth arrest (McHugh & Gil, 2017), and cells become senescent via two pathways: programmed (naturally occurring) and premature stress-induced (Bielak-Zmijewska, Mosieniak, & Sikora, 2017). Cell senescence is biologically beneficial as it limits excessive cell proliferation (e.g., tumor progression) since cells are unable to replicate under such conditions. In contrast, cell senescence has been identified as a cause of age related disease, such as cancer (McHugh & Gil, 2017), and experimental ablation of senescent cells in mice has been shown to extend health (Baker et al., 2011) and life (Baker et al., 2016) by delaying onset of age-related pathologies.

Consistent with other biological systems, when functioning properly in a state of homeostasis, cell division is seamless, balanced between cell proliferation and senescence. However, stressors commonly disturb homeostasis. The body elicits biological responses in response to stress in an attempt to restore equilibrium, a process known as allostasis – fluctuations in biological processes to meet the demands of external pressures (McEwen & Stellar, 1993). Just as the release of cortisol is adaptive in response to perceived stress, but can become maladaptive when chronically activated, cell senescence adaptively counterbalances cell proliferation, but can also become problematic when the system is strained, telomeres shorten rapidly, and cells become senescent prematurely. Telomere shortening and cell senescence are therefore natural biological processes that seem to become maladaptive when they occur prematurely at an accelerated rate as a result of an unbalanced system, potentially caused by stress. Thus, telomeres appear to be yet another biomarker of how “stress gets under the skin” and can lead to poorer health. Indeed, aged, senescent cells have been linked with tumor

progression and appear to support cancer cell proliferation (Krtolica, Parrinello, Lockett, Desprez, & Campisi, 2001), factors that influence the host's survival.

Fortunately, telomeres are maintained and can be lengthened by the enzyme telomerase, which serves to balance terminal DNA loss during cell proliferation (Blackburn, 2000). Without telomerase, cells would continuously divide and shorten at an accelerated rate, leading to widespread, premature cell senescence and greater risk of age-related diseases including cancer and earlier mortality (Blackburn et al., 2015). Although telomeres are maintained and lengthened via telomerase, which is required for eukaryotic survival, there appears to be a delicate balance between the two and their related processes (Blackburn, 2001). Recent work by Margalef and colleagues (2017) demonstrated telomerase can compromise cell replication and contribute to telomere shortening under certain conditions, highlighting the complex molecular relationship between TL and telomerase that is not yet fully understood. The complexity of this relationship is further complicated by the fact that telomerase is not the only determinant of TL, as growing evidence suggests other biological processes including oxidative stress and inflammation can also accelerate TL shortening (von Zglinicki, 2002; Wolkowitz et al., 2011).

Despite the need for elucidation of the interactions between TL attrition during cell division, TL maintenance via telomerase, and cell senescence both in and out of allostatic contexts, the past two decades of research have identified TL as a robust biomarker of cellular aging. When controlling for chronological age, which accounts for only 10% of TL variation (Blackburn et al., 2015), and other risk factors, shorter TL has been shown to predict all-cause mortality (Needham et al., 2015; Rode, Nordestgaard, &

Bojesen, 2015). Demonstrated by within-pair twin analyses, Bakaysa and colleagues (2007) evidenced twins with shorter telomeres had a three times greater risk of dying compared to co-twins with longer telomeres (Bakaysa et al., 2007), suggesting TL may account for all-cause mortality in older age even when controlling for developmental and genetic influence. Given that TL has been crowned the biomarker of cellular aging, and that both depression and cancer have been conceptualized as age-related diseases (Herrmann, Pusceddu, März, & Herrmann, 2018; Lindqvist et al., 2015), it makes sense TL has been linked to both depression and cancer independently; however, these relationships have rarely been explored simultaneously. In fact, Elizabeth Blackburn, a Nobel Prize recipient, and colleagues (2015), have explicitly encouraged further exploration into the interaction between psychological distress, telomeres, and disease, as they are likely “powerful” and remain relatively “unexplored” (p. 1197). Thus, to adhere to the scope of the current investigation, the relationships between depression, TL, and cancer will be reviewed briefly. For more comprehensive, detailed reviews, see Lindqvist et al. (2015) and Manoliu, Bosch, Brakowski, Brühl, and Seifritz (2018) for a review on depression and TL, and Gunes, Avilla, and Rudolph (2017) and Herrmann et al. (2018) for a review on TL and cancer.

Depression and TL. According to Schutte and Malouff’s (2015) relatively recent meta-analysis, only 25 studies have examined depression and TL, which is considerably less than the existent literature examining the association between depression and cortisol. Nonetheless, a growing body of evidence demonstrates a link between psychological stress, depressive symptoms, and TL. Simon et al. (2006) demonstrated individuals with mood disorders (MDD and bipolar with and without comorbid anxiety)

had significantly shorter leukocyte telomere length (LTL) compared to aged-matched controls. The three mood disorders were grouped together as significant differences in TL were not observed between them, likely due to power restrictions ($n = 15$). Nonetheless, the authors reported a striking effect among the depression-only group: telomere attrition represented approximately 10 years of accelerated aging compared to healthy controls, demonstrating clinical opposed to statistical significance. Further, Vakonaki and colleagues (2018) recently reviewed the current empirical evidence on the relationship between psychological illness (schizophrenia, depression, and anxiety) and TL and concluded that majority of studies report shorter TL among patients with a psychological disorder. Taken together, it seems mental health disparities broadly are linked with shorter telomeres.

Furthermore, Hartmann and colleagues (2010), among others, have provided evidence of an association between depression and shorter TL, independent of other mood disorders. A prospective study showed depression predicted shorter LTL at a two-year follow-up compared to age-matched controls when controlling for potential confounds including sex, smoking status, activity, physical health, and body mass index (Vance et al., 2018). Further, a relatively recent meta-analysis involving over 21,040 individuals and 32 studies reported those with depression had 71% greater odds of having shorter TL (Schutte & Malouff, 2015). Although the reported effect size of this meta-analysis was small ($r = -.12$), the results reflect a difference of approximately 97 chromosomal base pairs. This finding is meaningful because the minimum TL required to maintain stability in human leukocytes is 3.81kb (Lin et al., 2014), demonstrating that a small change in TL can have a significant impact despite small statistical magnitude

(Blackburn et al., 2015). Further, a more recent meta-analysis reported a moderate to large effect size between depression and shorter LTL among 5,369 individuals (Hedge's $g = -.55$; Darrow et al. (2016). Nonetheless, not all studies reported a significant association between depression and TL. In a recent review, Lindqvist et al. (2015) evidenced just under half of the included studies (4 out of 11) reported no significant differences in LTL between depressed and non-depressed individuals. Additionally, of the studies that did reported a significant difference, the effect size ranged from .04 to .98 with a mean of .41, suggesting that as TL continues to become integrated into interdisciplinary research, standardization of assessment procedures need to be established and communicated.

A number of additional inconsistencies regarding the depression-TL relationship have been reported. For instance, Schutte and Malouff's meta-analysis (2015) suggested cross sectional associations between depression and TL were stronger than longitudinal relationships, which is puzzling, but could explain why a recent prospective study did not see a relationship between depression and shorter LTL at an 11-year follow-up among 1,250 middle aged female nurses (Chang et al., 2018). In contrast, a dose-response relationship between depression duration and severity and shorter TL over a four year span was observed by Verhoeven et al. (2014), and Wolkowitz et al. (2011) have reported proportionally shorter LTL among individuals with a lifetime history of MDD, especially when untreated. However, Hartman et al. (2010) and Vance et al. (2018) reported their results indicated duration, symptom severity, and treatment did not differentially influence TL. Taken together, although a majority of studies report an association

between depression and shorter TL (Lindqvist et al., 2015), the strength as well as a number of factors related to the relationship remain unclear.

The prognostic significance of TL in cancer. Given the fundamental role of telomere biology during cell proliferation and that cancer is defined as the uncontrolled division of cells, it is not surprising telomeres have exploded in cancer research over the past two decades (Blackburn, Greider, & Szostak, 2006). Telomeres appear to be shorter in cancer cells than cells from normal tissue (Hastie et al., 1990; Heaphy et al., 2010; Nakamura et al., 2000; Odagiri et al., 1994), and shorter cancer tissue telomeres have been linked with advanced disease, accelerated disease progression, metastasis, and poorer survival (Heaphy et al., 2013; Herrmann et al., 2018). Current hypotheses posit that as telomeres from cancer cells shorten rapidly and near senescence, telomerase facilitates indefinite cell division in an attempt to re-stabilize telomeres, which ultimately leads to a state of “immortalization” (Augustine et al., 2017). As such, overexpression of telomerase has been observed in 90% of cancer cells and experimentally induced inhibition of telomerase limited the number of cancer cell divisions (Kim et al., 1994). It has therefore been hypothesized that depletion of telomerase in tumor microenvironments would eliminate the cell’s ability to excessively proliferate, although experiments have revealed the opposite – eventual loss of telomere function among cells depleted of telomerase led to greater tumor progression (De Lange & Jacks, 1999). This research indicates that the disruption of the delicate balance between cell division (telomere shortening) and telomerase in the tumor microenvironment appears to activate tumorigenesis, although the specific timing and mechanisms of this process remain unclear (Hackett & Greider, 2002). See Gunes et al. (2017) for an extensive review on

telomeric biology and tumors. Taken together, although elucidation of telomeric biology in tumor environments continues to unfold, it is becoming clear that telomeres play a central role in tumor onset and progression, and therefore, survival in cancer.

Peripheral TL has also been identified as a prognostic marker in cancer. Typically measured as a mean from leukocytes, shorter LTL has been linked to increased risk (Ma et al., 2011; Shao et al., 2007; Wentzensen, Mirabello, Pfeiffer, & Savage, 2011; Willeit et al., 2010; Wu et al., 2003), earlier mortality (Wentzensen et al., 2011; Willeit et al., 2010), and shorter survival (Callahan et al., 2017; Renner, Krenn-Pilko, Gruber, Herrmann, & Langsenlehner, 2018; Valls, Piñol, Reñé, Buenestado, & Viñas, 2011; Weischer et al., 2013; Zhang, Chen, et al., 2015) across a number of cancer types, and a few reviews have demonstrated a robust relationship between shorter TL and shorter cancer survival. For instance, in one longitudinal study (N = 47,102), shorter LTL was associated with reduced survival across multiple cancer types at a 20-year follow-up (Weischer et al., 2013). A meta-analytic review by Wentzensen and colleagues (2011) involving 25 studies demonstrated patients with shorter TL had higher risk of incidence and mortality across a number of cancer types, although the strength and consistency of these relationships may have been driven by stronger effects among specific cancers. This analysis only included two studies in lung cancer, evidencing a clear underrepresentation of this disease type. Lastly, a more recent meta-analysis involving 33 studies by Zhang and colleagues (2015) supported the association between shorter TL and poorer cancer survival (n = 11,429). However, their analysis included studies that collected TL from both tumor tissue and blood, which is problematic given the distinct biological underpinnings of peripheral telomeres and telomeres collected from tumor

microenvironments. Nonetheless, similar to the findings reported by Wentzensen and colleagues (2011), upon examination of disease-specific associations between TL and survival, Zhang et al (2015) reported variation in the strength of the relationship across cancer types, pointing to the importance of examining these relationships in disease-specific contexts. Of the 27 studies examining overall survival included in the analysis, only one study was among lung cancer patients, further demonstrating the need for greater inclusion of lung cancer samples in future investigations.

Consistent with these meta-analytic findings, Callahan and et al. (2017) reported shorter LTL predicted shorter disease-specific survival in renal cell carcinoma, but noted strong effects among stage-I patients, indicating prognostic significance of LTL early in the disease. Puzzling and contradictory findings by Svenson and et al. (2008) demonstrated *longer* TL was prognostic of disease-specific survival among breast cancer patients with advanced disease. Others have also reported null and contradictory associations between TL and cancer risk (Hou, Zhang, Gawron, & Liu, 2012; Yuan et al., 2018), although fewer have reported these associations with survival outcomes. Despite these discrepancies, promising evidence points to a relatively robust relationship between shorter systemic TL and shorter survival in cancer, although this relationship has yet to be examined in lung cancer.

Depression and TL in cancer. TL appears to be an important biomarker in both depressed and cancer populations, although only two studies have examined them simultaneously, neither of which were among lung cancer. One of the studies, conducted among a large sample of bladder cancer patients (n = 464), reported current depressive symptoms, both independently and combined with shorter TL, were associated with

shorter survival (Lin et al., 2015). The authors reported shorter TL was a stronger predictor of survival than depressive symptoms, but the differences were negligible. In this sample, patients with depressive symptoms and shorter TL had a 4-times greater risk for mortality and shorter disease-free survival compared to patients without depressive symptoms and longer TL, suggesting TL accounted for some of the variance explaining the depression-survival relationship. However, the authors reported no association between depressive symptoms and TL, thus mediation analysis criteria was not met. The only other study examining depression and TL in cancer was conducted by Sharpley et al. (2018), but survival was not included in the analysis. In this sample of prostate cancer patients, irritability, but not depression (both measured via the PHQ-9 depression questionnaire), was associated with shorter TL. The authors suggested that because depression is typically characterized by irritability opposed to sadness in males these results are not unexpected. Although only two studies have examined depression and TL in cancer, the results are promising for the possibility that TL may partially explain the depression-survival relationship.

Integration of TL into psychobiological cancer models. There is paucity of telomere biology in current biobehavioral cancer models despite mounting evidence demonstrating a robust effect of stress on TL (Shalev et al., 2013; Starkweather et al., 2014), a biomarker that appears to play a central role in tumor onset and progression and has been linked to shorter cancer survival. Nonetheless, there have been some attempts to integrate telomeres into stress-aging models (Epel, 2009; Epel & Prather, 2018; Wolkowitz, Epel, Reus, & Mellon, 2010). Although the causal association between psychological stress/depressive symptoms and telomere attrition remains unknown, Epel

(2009) provided compelling evidence for the downstream effects of chronic stress on cortisol disruption and subsequent telomere attrition. In contrast, Wolkowitz and colleagues' (2010) model postulates stress-related biomarkers (e.g., cortisol and TL) precede psychiatric and medical symptoms. Although longitudinal and experimental studies among humans and animals have demonstrated psychological and experimentally induced stress, respectively, can lead to telomere attrition (Epel et al., 2004; Hau et al., 2015; Herborn et al., 2014; Kotrschal et al., 2007), this does not translate directly to psychological illness, such as depression. While Chen et al. (2007) provided evidence for depression's shortening effect on TL, and the majority of the literature suggests depressive symptoms precede telomere attrition, Gotlib and colleagues (2015) provided evidence suggesting the opposite. The authors demonstrated that at-risk females aged 10 – 14 whose mothers have depression had significantly shorter telomeres compared to peers who did not have a familial risk for depression. These associations were not assessed longitudinally, but demonstrated the possibility that telomere attrition could have a role in the onset of depression rather than just a consequence. Taken together, although it is known psychiatric disorders including depression predict shorter TL, it remains unclear if the telomeric shortening process precedes onset of certain disorders (Epel & Prather, 2018). Therefore, greater exploration of this association is needed.

Biological Interplay Between Cortisol and TL. Manipulation of glucocorticoids in animal models has helped establish the causal effect of cortisol on TL. In one study, experimental exposure to corticosterone, the main glucocorticoid in many species, resulted in significantly shorter telomeres during the “late life” phase in seabirds compared to controls (Herborn et al., 2014). In a different study, following one year of

experimental exposure to stressors during adulthood (intended to mimic experience of chronic stressors typical in humans), stress-exposed birds had shorter TL than non-stressed controls (Hau et al., 2015), although no differences in glucocorticoids were observed. These findings further demonstrate the impact of stress on TL, but also the possibility that chronic stress may burden cellular aging systems prior to and potentially independent of endocrine systems. However, because there are considerable differences in stress appraisal and biological processes between non-mammals and humans, the generalizability of these findings is limited. Reductions in leukocyte telomerase, implying reductions in telomere maintenance, however, have been observed in humans following experimental exposure to cortisol (Choi, Fauce, & Effros, 2008). Taken together, although the results of these studies demonstrate glucocorticoid cause telomere attrition in animal models, the opposite effect is still possible, as the effect of telomere attrition on glucocorticoids has not been reported to date.

Cortisol and TL and the depression-survival relationship. Decades of research have evidenced strong associations between depressive symptoms, cortisol profile aberrations, and shorter survival in cancer patients. Although TL is a relatively new biomarker, supported by far less research and associated with greater uncertainties, evidence for associations between these constructs and shorter TL also exists. Certainty, fewer investigations have examined depressive symptoms, telomeres, and survival in cancer simultaneously, but of the studies that have, lung cancer is markedly underrepresented. The causality of the relationships between depressive symptoms and each of the two biomarkers remains unconfirmed, yet the integration of depression and cancer literature adequately supports the plausibility that aberrant cortisol profiles and

shorter TL could play a role in the pathway linking depressive symptoms and shorter survival in cancer. Thus, it is proposed cortisol profiles, a biomarker of circadian coordinated neuroendocrine function, and TL, a biomarker of cellular aging, help explain how depressive symptoms lead to shorter survival in lung and other cancers.

While the elucidation of biological explanations for the depression-survival relationship in lung and other cancers is needed, cancer patients with untreated depression continue to suffer from poorer quality and quantity of life, pointing to the need for efficacious and effective psychosocial interventions. Despite more recent improvements in efforts to acknowledge and treat comorbid mental illnesses among cancer populations, continued efforts are warranted as they have the potential to mitigate the unpleasant experience of depressive symptoms and related downstream clinical consequences. Mindfulness-based interventions (MBIs) broadly and Mindfulness-based Stress Reduction (MBSR) in particular, have demonstrated promise for reducing psychological and biological aspects of stress in cancer populations, although fewer studies have examined their role in reducing depressive symptoms and related outcomes.

Aim 2: Mindfulness-based Interventions in Cancer Contexts

Since Jon Kabat-Zinn (1982) introduced the first MBI, known as the MBSR program, to chronic pain patients at the University of Massachusetts Medical Center in 1979, the use of MBIs in western health settings has advanced at an accelerated rate (R. A. Baer, 2003). Rooted in Buddhist philosophy, mindfulness has been described as “paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally” (Kabat-Zinn (1994), p. 4). A skill that is typically obtained through meditative practice – “the intentional self-regulation of attention from moment to

moment” (Kabat-Zinn, 1982), p.34) – these philosophies and skills, stemming largely from Kabat-Zinn’s seminal work, have been adapted into a host of health-related interventions. Referred to as the “third wave” of therapy (Hayes, 2004), MBI’s have been adapted to reduce symptoms of distress in traditional psychotherapeutic settings as well as in medical contexts.

Despite differences between them, MBI’s, including MBSR, are largely centered on acceptance without judgment, practice without attachment to an outcome, and an intention to enhance the mind-body connection in order to regain a degree of control over one’s well being. Unlike other stress-reducing strategies, such as problem-focused coping, which involves direct attempts to change a stressor (Lazarus & Folkman, 1984), mindfulness-based strategies are detached from the expectation for things to be different via an attitude of acceptance. These theoretical pillars resonate with many aspects of chronic illness, including cancer, given that illness typically sources a lack of control and considerable uncertainty and requires continual adjustment (Carlson et al., 2013). As such, MBSR has been adapted specifically for cancer patients by Carlson and colleagues (2010), a program referred to as mindfulness-based cancer recovery (MBCR), demonstrating the applicability of mindfulness in cancer contexts.

The traditional, manualized MBSR program developed by Kabat-Zinn is an 8-week group intervention that meets weekly for approximately two and a half hours to provide participants with instruction, practice, and discussion of mindfulness and mindfulness-based skills (e.g., walking, standing, eating, body scan). In addition to meditation practices, to obtain “detached self-observation” (Kabat-Zinn (1982), p. 34) hatha yoga is included to enhance bodily sensations and strengthen the mind-body

connection. Participants are also asked to practice at least 45 minutes per day, six days per week between in-person weekly group meetings, and are encouraged to participate in a day log (~6 hour) retreat toward the end of the program. For an extensive description of the structure and content of the MBSR program, see Kabat-Zinn (1982). Taken together, the format of MBSR and MBCR, which mirrors the format of MBSR closely, requires considerable commitment and in-person attendance.

Effectiveness of MBSR in Cancer. Certainly, the in-person group format of these interventions likely fosters benefit, potentially in the form of a sense of connectedness (Carlson, 2013), social support, and accountability; however, the commitment in-person interventions require limits feasibility for some patients, particularly those with greater burden and fewer resources. A focus group conducted among a small group of lung cancer patients (N = 11) designed to discuss perceptions of MBIs identified the following barriers to participation: transportation and financial issues, limits to physical functioning, lack of interest, feeling overwhelmed with new appointments/obligations, cognitive changes including forgetfulness, and time commitment (Lehto & Wyatt, 2013). Further, as MBSR has recently been described as “a phenomenon of wealthy white western women” (Carlson, 2018), it is plausible group-based MBIs may not be appealing to individuals who do not fall into those sociodemographic categories.

To start addressing these barriers, Zernicke and colleagues (2013) conducted an online MBCR program to promote feasibility. Although this program reported a small (20%) drop out rate, confirming feasibility for this program in mobile format, this intervention preserved the group component by requiring a set virtual meeting time each

week. Participants essentially formed an online classroom environment equipped with an instructor. Thus, this study largely maintained the structure of traditional MBSR despite being accessible remotely via a website. Although the intervention demonstrated significant improvements in mood disturbance and stress symptoms, it did not shed light on whether group participation is an active component or if these changes can be achieved through mobile platforms that forego a group commitment. Of the 1,800 patients invited to participate, only 180 expressed interest with a final enrollment of 62, warranting further exploration into the potential benefits of a mobile MBSR program that delivers core components (e.g., meditation practice), but does not require group involvement.

Lengacher and colleagues (2018) recently piloted the efficacy and feasibility of an iPad-based MBSR(CR) intervention that eliminated the group component among a small sample ($N = 15$) of breast cancer survivors. Results from the study revealed statistically significant improvements in psychological and somatic symptoms of depression with a large effect size ($d = 0.85$), in addition to a host of other symptom improvements. Additionally, patients described the iPad intervention as “convenient and easy to use,” and approximately 87% of the enrolled participants completed the program (p. 527). Although a small pilot, this study provides preliminary evidence for the efficacy and feasibility of mobile MBSR intervention that forgo the group, face-to-face components.

Efficacy of MBSR in Cancer. *Depressive symptoms.* Although the active components and mechanisms by which MBSR enhances one’s ability to cope with disease, the optimal “prescribed” amount and the optimal intervention time point remains unknown (Dobkin & Zhao, 2011; Hunt, Al-Braiki, Dailey, Russell, & Simon, 2018),

MBSR has demonstrated efficacy in reducing psychological distress and depressive symptoms in cancer contexts (Dobkin & Zhao, 2011; Lengacher et al., 2018; Shennan, Payne, & Fenlon, 2011). Two separate meta-analyses that examined the efficacy of MBSR interventions among breast cancer patients demonstrated significant improvements in depressive symptoms (Huang, He, Wang, & Zhou, 2016; Zainal, Booth, & Huppert, 2013); $d = 0.575$). In contrast, a more recent meta-analysis indicated MBSR efficaciously reduced depressive symptoms for all cancers patients except for breast cancer (Zhang, Wen, et al., 2015). These contradictory results are somewhat puzzling, especially given that the majority of MBI studies have been conducted among breast cancer samples.

Further, although the majority of studies report improvements to stress symptoms broadly, some report no improvements to depressive symptoms specifically. For instance, in one RCT among cancer patients with varied types of cancers, MBSR did not demonstrate a significant reduction in depressive symptoms at a 6-month follow-up (Bränström, Kvillemo, & Moskowitz, 2012). In this study, however, the majority of patients (86%) had received their diagnosis over a year from study participation, suggesting MBSR interventions may be most efficacious when conducted closer to diagnosis. Taken together, some of the inconsistent findings regarding MBSR's effects on depressive symptoms may stem from variation in cancer types, assessment time frames, and intervention time points in the cancer trajectory (e.g., at diagnosis versus in survivorship), necessitating further investigation into the effects of MBSR's on depressive symptom among patients who suffer from cancers other than breast, including lung, and at time points more proximal to the intervention.

Cortisol. In addition to reducing psychological aspect of stress, MBIs and MBSR have demonstrated some, although more mixed, evidence for the efficacy of improving aspects of physical health (Ledesma & Kumano, 2009). Although, few interventions to date have examined the efficacy of MBSR on markers of cortisol in cancer contexts, some evidence exists. For example, Lengacher and colleagues (2012) reported a significant reduction in cortisol levels from pre-MBSR following week one and three of the 6-week intervention among a sample of advanced (stage III or IV) cancer patients, which included lung malignancies (20% of the sample). Although there were no significant differences in cortisol levels pre- and post-intervention, only at week one and three during the intervention, the authors reported cortisol levels were much lower (roughly half) from pre to post, differences that may have been undetected due to a small sample size (N = 26). Similarly, Branstrom and colleagues (2013) did not observe effects of the MBSR intervention on cortisol at a 3- and 6-month follow-up among women with different cancers, but the authors observed a moderating intervention effect – patients that participated in the intervention with initially low levels of waking cortisol demonstrated an increase whereas those with initially high levels of waking cortisol demonstrated a decrease at the 3-month follow-up. Although the implications of these findings are somewhat ambiguous, these results suggest MBSR may have the potential to regulate aberrant HPA-axis activity, whether initially hyper- or hypo-active.

Similarly, Carlson and colleagues (2004) reported no changes in diurnal mean cortisol or cortisol slope among early staged (I or II) breast and prostate cancer patients (N = 59) following an MBSR intervention. However, they did observed fewer elevations in evening cortisol post-intervention as well as shifts in abnormal cortisol secretion

patterns from an inverted V shape (highest levels in the afternoon) to a V shape (lowest levels in the afternoon), reflecting a shift toward more regulated diurnal cortisol profiles. Interestingly, upon re-assessment at 6- and 12-months post-intervention (N = 33), a linear decrease in overall diurnal mean cortisol, mostly driven by decreases in evening levels, was observed across time points (Carlson, Speca, Faris, & Patel, 2007), indicative of a healthier diurnal cortisol profile. In a different RCT comparing the effects of an MBSR intervention to a group, emotion-focused intervention (SET) and a one-day stress management control condition among breast cancer survivors, cortisol slopes were maintained in both treatments compared to the control condition, whose slopes became flatter (Carlson et al., 2013). Although these results did not demonstrate unique effects of MBSR on cortisol profiles, it highlights the potential for decline in neuroendocrine function when cancer patients forego psychosocial interventions. Taken together, the evidence for the efficacy of MBSR interventions on regulation of cortisol profiles remains both mixed and convoluted, but seem to suggest MBSR interventions may delay, rather than improve dysregulation of neuroendocrine function that tends to accompany tumor progression. However, the majority of studies examining these effects have been conducted primarily among certain cancers (i.e., breast) among earlier stages of disease, warranting greater attention to other malignancies, especially those typically diagnosed at later stages, such as lung.

TL. Despite the relatively recent surge of both TL and MBIs in stress and cancer research, nearly no studies to date have examined them simultaneously. While somewhat greater attention has been directed toward the effects of MBIs on TL in non-clinical samples (Epel, Daubenmier, Moskowitz, Folkman, & Blackburn, 2009) and has

demonstrated some efficacy for lengthening telomeres (Conklin et al., 2018; Hoge et al., 2013), limited studies have been conducted in and out of cancer populations. One non-mindfulness-based intervention (phone counseling) among cervical cancer survivors reported a moderating effect of decreased distress with increased TL, indicating TL is potentially modifiable via psychosocial interventions following reduction in psychological distress (Biegler, Anderson, Wenzel, Osann, & Nelson, 2012). The only study that has examined the effects of an MBI on TL in cancer contexts to date was conducted by Carlson and colleagues (2015). Building on the parent RCT described above (Carlson et al., 2013), a sample of distressed breast cancer survivors were randomized to the MBCR, SET, or a one-day stress management control condition. Results revealed no significant differences in TL between groups post intervention. Similar to the cortisol findings, however, there was a trend observed between the intervention groups and the control condition – TL in either intervention group (MBCR or SET) was maintained, whereas TL decreased among control condition patients. While the differences were not statistically significant and the long-term effects were not reported, these results point to the *possibility* that MBSR could contribute to TL maintenance (lack of a decrease) over the course of a 3-month intervention period, although further investigation is needed.

The only other intervention study in cancer that examined TL was conducted by Ornish and colleagues (2013). The intervention consisted of a host of comprehensive lifestyle changes in diet, activity, social support, and stress management, which included elements of MBSR (i.e., yoga-based stretching, breathing, meditation, progressive relaxation) among low-risk prostate cancer patients that had opted to undergo

surveillance opposed to typical treatment. Results from a 5-year follow-up demonstrated a significant increase in TL among the intervention group and a decrease in TL among the control group, although it is unclear if the improvements stemmed from the stress management component or were driven by other aspects of the intervention. Taken together, the potential benefits of an MBI on TL among cancer patients remains relatively unexplored despite considerable evidence demonstrating psychological distress has shortening effects on TL, a biological mechanism that has important implications in tumor development and progression. Although the evidence is scarce, MBSR may be one avenue to target depressive symptoms and downstream consequences, including TL.

Survival. Although debated extensively for some time, psychological interventions have demonstrated efficacy for improving survival time among cancer patients (Andersen et al., 2008; Spiegel et al., 1989). Reviewed comprehensively by Spiegel (2011) and Antoni (2013), a number of studies have established compelling evidence to conclude psychosocial interventions can foster benefit by enhancing quality and quality of life for cancer patients. Despite being one of the most distressed cancer type populations (Carlson et al., 2004), the effects of a psychosocial intervention, including an MBI, on survival have yet to be tested among lung cancer patients. The majority of psychosocial interventions have been rooted in cognitive behavioral therapy (CBT) or functioned as an emotional support group and have largely been conducted among breast cancer patients/survivors (Antoni, 2013), necessitating greater attention to the potential benefits of MBIs on both quality and quantity of life among lung cancer patients.

Taken all together, evidence suggests that cancer patients experience high levels of distress and depressive symptoms, which have demonstrated prognostic significance in cancer contexts. Although the biological pathways by which depressive symptoms lead to poorer survival currently remain unclear, evidence points to the dysregulation of circadian coordinated neuroendocrine function and cellular aging processes, which can be assessed by markers of cortisol and TL, respectively. Current literature points to the need for greater exploration into the role of these biological systems in the context of the depression-survival relationship. Nonetheless, knowing that depressive symptoms worsen both quality and quantity of life in cancer contexts, interventions that efficaciously and effectively reduce depressive symptoms that offer feasibility and accessibility are a clinical priority.

Study Aims

The current study attempts to begin elucidating how depressive symptoms lead to shorter survival and how to efficaciously and effectively treat depressive symptoms and related outcomes among NSCLC patients. Thus, the primary aims of the current study are to 1) replicate the prognostic significance of depressive symptoms and explore the role of two biomarkers – cortisol and leukocyte telomere length (LTL) – as they relate to the depression-survival pathway and 2) explore the ameliorative role of an iPod-based MBSR intervention on depressive symptoms and related outcomes among NSCLC patients. Specifically, regarding Aim 1, if depressive symptoms emerge as a significant predictor of shorter survival and are significantly associated with a biomarker (cortisol and LTL), then the association between the significant biomarker(s) and the depression-survival pathway will be explored. Additionally, regarding Aim 2, if the iPod-based

MBSR intervention attenuates depressive symptoms, then the benefits of the intervention will be explored among biological and clinical outcomes. In accordance with the primary aims of this study, the following hypotheses are outlined below and visually presented in Figure 1.

Hypotheses

Aim 1. Hypothesis 1a. More depressive symptoms will predict shorter survival.

Hypothesis 1b. More depressive symptoms will be associated with greater cortisol dysregulation (higher overall mean and bedtime cortisol and flatter diurnal cortisol slopes).

Hypothesis 1c. More depressive symptoms will be associated with shorter LTL.

Hypothesis 1d. If hypothesis 1a and 1b emerge as significant, then greater cortisol dysregulation will be associated with both depressive symptoms and shorter survival.

Hypothesis 1e. If hypothesis 1a and 1c emerge as significant, then shorter LTL will be associated with both depressive symptoms and shorter survival.

Aim 2. Hypothesis 2a. Participation in and use of the intervention will be associated with fewer depressive symptoms from baseline to follow-up.

Hypothesis 2b. Participation in and greater use of the intervention will be associated with improved diurnal cortisol rhythmicity from baseline to follow-up.

Hypothesis 2c. Participation in and greater use of the intervention will be associated with maintenance of LTL (lack of a decrease) from baseline to follow-up.

Hypothesis 2d. Participation in and use of the intervention will be associated with longer survival.

METHODS

Data were collected as part of a larger study investigating the prognostic significance of circadian disruption in lung cancer patients (University of Louisville IRB 13.0508).

Participants

NSCLC patients were recruited from the James Graham Brown Cancer Center with the assistance and support of collaborating medical staff, such as oncologists and nurses. Eligible patients were diagnosed with non-small cell lung cancer within five years of study entry, were ages 18–85, resided within a 120-mile radius of the recruitment center, had no medical diagnosis likely to influence six-month survival, no immune-compromising condition, and no recent history of psychiatric hospitalization or substance abuse. A total of 65 patients met inclusion criteria and consented.

Procedure

Recruitment. Recruitment personnel checked eligibility criteria using a standardized chart review. Following identification of eligible participants, collaborating physicians introduced patients to study personnel during their scheduled appointment. Recruitment personnel provided patients with an overview of the study, answered questions, and obtained informed consent from those willing to participate. All study procedures were conducted in accordance with University of Louisville Human Subjects Protection Program guidelines.

Baseline data collection. Participants received detailed instructions and materials for 10-day at home baseline data collection. Materials included a packet containing a battery of questionnaires to be completed in one sitting, a packet of daily questionnaires to be completed each morning and night over the course of the 10 days, and a salivary cortisol kit containing 20 salivettes. Prior to leaving the clinic, participants completed a blood draw for telomere length assessment conducted by a trained phlebotomist. Study personnel called participants mid-way through data collection (approximately day five) to check-in, provide reminders, and answer questions regarding data collection. Following the baseline data collection, study personnel collected materials from participants, compensated their efforts with a \$100 Visa gift card, and re-introduced the iPod-based MBSR intervention in detail.

iPod- and mindfulness-based pilot intervention. Study personnel introduced mindfulness to participants as a distress-reducing technique, invited participants to attend a bi-weekly drop-in mindfulness-based cancer support group, and provided participants with an iPod containing mindfulness audio tracks. The audio tracks were recorded by clinical psychologist and co-investigator, who is both knowledgeable and skilled in mindfulness practice. The tracks were based on the Mindfulness-based Stress Reduction (MBSR) program (Kabat-Zinn, 1982). Some of the tracks provide instructional narratives about the foundations of mindfulness, whereas others function as guided meditation on eating, breathing, listening, thinking, feeling and the body as a whole. A list of tracks is provided in Table 1. Participants that agreed to participate in the optional pilot intervention were taught how to use the device, and to enhance feasibility and adherence, patients were asked to listen to tracks of their choice for 30 minutes per day, five days per

week. Although the iPods documented which tracks were selected and completed, participants were also provided with a log to document listening behavior. Participants returned their iPods and listening logs at their three month follow-up appointment. Over the course of the three month intervention, study personnel called to check-in, provide reminders, and answer questions about the intervention at approximately one and two months. Study personnel downloaded track data using iTunes software and returned the iPod to participants to compensate their intervention participation efforts.

Follow-up data collection. Regardless of whether patients opted to participate in the intervention, they were asked to attend a three month follow-up appointment at the Cancer Center. Similar to baseline data collection, participants were provided with instructions and materials for at home data collection, but for six instead of 10 days. Materials included a packet containing a battery of questionnaires to be completed in one sitting, a packet of daily questionnaires to be completed each morning and night over the course of the six days, and a salivary cortisol kit containing 12 salivettes. Participants provided another blood sample prior to leaving the clinic. Following follow-up data collection, study personnel met with participants to collect materials, provide them with a second \$100 Visa gift card to compensate them for follow-up data collection efforts, and obtain feedback about the study.

Salivary cortisol. Collection. Participants were asked to collect two saliva samples per day – one immediately upon waking and the other as close to bedtime as possible for 10 and six consecutive days of baseline and follow-up data collection, respectively, to enable calculation of diurnal cortisol profiles. The salivary cortisol kit that participants received for baseline and follow-up contained 20 and 12 “salivettes,”

respectively. The salivettes were pre-labeled and arranged consecutively by day and time with space for participants to record their assigned study ID, the date, and the exact time that the sample was collected in sharpie. Salivettes were also color coordinated by collection time; salivettes to be collected at waking had yellow labels whereas bedtime salivettes had blue labels to maximize likelihood of participants' accuracy.

To collect a sample, participants were instructed to remove the salivette cap, place the cotton swab in their mouth for approximately two minutes, or until the swab was fully saturated. While the cotton swab was in the participants' mouths, they were advised to record their study ID, the date, and time of collection on the tube. Participants were then asked to spit the saturated cottons swab back into the salivette tube, replace the salivette cap, and store the sample in the refrigerator in the provided Ziploc bag. Participants were instructed to keep collected saliva samples in the refrigerator until materials were returned to study personnel. Participants were instructed not to put anything in their mouth – eat, drink, smoke, chew gum, brush their teeth, etc. – 30 minutes prior to collection a sample to minimize contamination of cortisol. The importance of collecting morning samples immediately upon waking, recording the exact time that the sample was collected, and reporting any deviations from the protocol was explained to participants by study personnel. To enhance adherence and accuracy, participants were advised to keep the salivary cortisol kit next to their bedside. The daily questionnaire packet participants were asked to complete each morning and night contained detailed instructions for saliva collection and space to record deviations from the protocol as needed.

Assay. Once study materials were returned, saliva samples remained in the refrigerator until they were prepared to be assayed. The majority of the samples were

prepped within a few days of collection of the last sample, although no samples were prepped beyond one month of the at home collection of the last sample. Saliva samples were centrifuged for 15 minutes at 453 g at 25°C. Samples were then aliquoted into microcentrifuge tubes and stored at -80°C until they were assayed. Cortisol levels were then assayed using an enzyme-linked immunoabsorbent assay (ELISA; Salimetrics, Inc., State College, PA). Assay sensitivity was 0.007 µg/dL. The average inter-assay and intra-assay coefficients of variation (*CV*) were under 10% for both the low and high control.

Leukocyte telomere length (LTL). *Collection.* Blood samples were collected in K2 EDTA purple top tubes during baseline and follow-up appointments at the Cancer Center and were kept on ice until they were transferred to the laboratory by study personnel. At the laboratory samples were centrifuged at 1300 RCF for 10 minutes at 4°C. The layer of plasma on top of each tube was transferred via pipet into 3-5 (volume dependent) 1.5 mL microcentrifuge tubes that were kept on ice. The remaining cell pellet (red blood cell + white blood cell) at the bottom of each tube was also transferred via pipet into 3-5 (volume dependent) 1.5 mL microcentrifuge tubes that were kept on ice. All tubes were then frozen immediately at -80°C. This procedure did not exceed two hours from the blood draw.

Following completion of data collection, a total of 107 (67 baseline and 40 follow-up) frozen blood cell pellet samples were packed and shipped from the University of Louisville to Dr. Elizabeth Blackburn's laboratory at the University of California San Francisco. Shipping procedures adhered to the University of Louisville's Department of Environmental Health and Safety protocol. Grant funds were used to compensate Dr. Jue Lin of Dr. Blackburn's Laboratory, who conducted telomere length assays using an

adapted protocol (Lin et al., 2010) from methodology originally outlined by Cawthon (2002).

Assay. The following methodological description of the assay process was provided by Dr. Lin, “A telomere (T) primer and single copy gene (S) primer pair were prepared. The primers used for the telomere polymerase chain reaction (PCR) were *tel1b* [5'-CGGTTT(GTTTGG)₅GTT-3'], used at a final concentration of 100 nM, and *tel2b* [5'-GGCTTG(CCTTAC)₅CCT-3'], used at a final concentration of 900 nM. The primers used for the single-copy gene (human beta-globin) PCR were *hbg1* [5'-GCTTCTGACACAACCTGTGTTCACTAGC-3'], at a final concentration of 300 nM, and *hbg2* [5'-CACCAACTTCATCCACGTTCAACC-3'], at a final concentration of 700 nM. The final reaction mix contained 20 mM Tris-HCl, pH 8.4; 50 mM KCl; 200 mM each dNTP; 1% DMSO; 0.4x Syber Green I; 22 ng E. coli DNA per reaction; 0.4 Units of Platinum Taq DNA polymerase (Invitrogen Inc.) per 11 µl reaction; ~6ng of genomic DNA. Tubes containing 26, 8.75, 2.9, 0.97, 0.324 and 0.108ng of a reference DNA (a commercial genomic DNA from pooled leukocytes from Roche Diagnostics Corporation, Indianapolis, IN) are included in each PCR run so that the quantity of targeted templates in each research sample can be determined relative to the reference DNA sample by the standard curve method. The same reference DNA was used for all PCR runs.

The telomere thermal cycling profile consisted of cycling for telomeric (**T**) PRC: 96°C for 1 minute; denature at 96°C for 1 second, anneal/extend at 54°C for 60 seconds, with fluorescence data collection for 30 cycles and cycling for single copy gene (**S**) PCR: 96°C for 1 minute; denature at 95°C for 15 seconds, anneal at 58°C for 1 second, extend

at 72°C for 20 seconds, 8 cycles; followed by denature at 96°C for 1 second, anneal at 58°C for 1 second, extend at 72°C for 20 seconds, hold at 83°C for 5 seconds with data collection for 35 cycles.

To control for inter-assay variability, 8 control DNA samples are included in each run. In each batch, the T (telomeric) /S (single copy gene) ratio of each control DNA is divided by the average T/S ratio for the same DNA from 10 runs to get a normalizing factor. This is done for all 8 samples and the average normalizing factor for all 8 samples is used to correct the participant DNA samples to get the final T/S ratio. The T/S ratio for each sample will be measured twice. When the duplicate T/S value and the initial value vary by more than 7%, the sample will be run the third time and the two closest values were reported. The average *CV* for this study was 2.4%.”

Survival data. An electronic chart review was conducted on February 15th, 2019 at the Cancer Center, which revealed a survival rate sufficient for analysis (46.3%; Bland and Altman (2004). The date of death was recorded and entered into SPSS for any participant who had passed away. It is expected, that as of the cut off date (2/15/19), survival data may lag behind actual data by approximately six months.

See Figure 3 for a visual depiction of the phases of the study when variables of interest were collected.

Measures

Demographic and medical variables. Medical and demographic variables were gathered via self-report and confirmed through medical chart review and are summarized in Table 2. Smoking history was quantified as ‘pack years,’ which reflects the product of number of packs of cigarettes per day by years of smoking.

Depressive symptoms. The packet of questionnaires completed by participants during baseline and follow-up data collection included the Center for Epidemiological Studies – Depression (CES-D; Radloff (1977), which was used to measure depressive symptoms. The CES-D is composed of 20 items that assess depressive symptoms over the past week on a four-point scale ranging from “rarely or none of the time (less than one day)” and “most of all of the time (5-7 days).” The total score is comprised of the sum of the 16 depressive symptoms items and the reverse score of the four positive affect items. Scores greater than 16 indicate risk for clinical depression. The CES-D is a commonly used measure of depressive symptoms among medically ill populations, including cancer. Among breast cancer patients, the CES-D has demonstrated high internal consistency (Cronbach $\alpha = 0.85$), adequate test-retest reliability, and construct validity (Hann, Winter, & Jacobsen, 1999). In the present study, internal consistency was acceptable and good at baseline and follow-up (Cronbach $\alpha = .77; .83$), respectively.

Cortisol. Salivary cortisol was collected at two time points over the course of 10 days based on empirically driven recommendations for reliable between-person cortisol estimates for calculation of diurnal cortisol slope (Segerstrom et al., 2014). However, to lessen the burden and increase likelihood of participation, follow-up cortisol data procedures were reduced to six days of at home collection. After samples were assayed, the *CV* was checked.

LTL. The relative T/S ratios obtained from the quantitative PCR is a reflection of overall LTL.

Statistical Analyses

Data preprocessing. Data preparation and analyses were conducted using SPSS v25.0 (SPSS IBM, Armonk, NY, 2017). Data was entered by two research assistants separately in independent datasets and subsequently compared to ensure accuracy.

Data reduction and scoring. *Sample characteristics.* Characteristics of the sample were determined by calculating frequency, percentage, and mean data on demographic and medical factors and are provided in Table 2.

Depressive symptoms. Summary scores were calculated for the CES-D assessed at baseline and follow-up. For less than 50% of data missing from the CES-D, missing data points were replaced using the mean of other responses. If a participant missed more than half of the questionnaire, missing data was not replaced.

Cortisol. Raw cortisol data consisted of an exact collection time from the saliva collection tubes and a laboratory-generated cortisol value ($\mu\text{g/dl}$) from the assay. Sample collection times reported by subjects were checked and corrected using wrist-worn actigraphy data, which was collected for aims of the parent study. Cortisol samples collected more than 15 minutes after waking (as determined by the actigraphy data) were excluded. Raw cortisol values were log-transformed to adjust for positive skew. Diurnal mean cortisol values were calculated for waking, bedtime, and overall mean using log-transformed values for each individual. Cortisol values were also regressed on collection time to calculate a diurnal cortisol slope for each individual (Sephton, 2000; Sephton et al., 2013). The regression of 20 values (waking and bedtime collected over 10 days) and 12 values (waking and bedtime collected over six days) were calculated for baseline and follow-up, respectively. The unstandardized beta (slope of the regression) represents the diurnal salivary cortisol slope (Kraemer et al., 2006). Diurnal slopes are typically

negative with higher values indicative of flattened slopes. Thus, three indicators of diurnal cortisol included in analyses included: 1) log-transformed overall mean, 2) log-transformed bedtime mean, and 3) diurnal slope using log-transformed values. Waking mean will be excluded as a variable in the analysis as it has not previously demonstrated distinct associations with depression or survival in cancer, whereas overall mean (Board et al., 1957), bedtime mean (Schrepf et al., 2015), and slope (Sephton et al., 2013) have.

Intervention. Because the intervention was a pilot, presented as optional, and lacked a randomized control group, participants' participation status was coded as participated (n = 25) or not (n = 42). Using the data logged by the iPod and downloaded by study personnel following the intervention, variables indicating total listening time and total number of tracks listened to were created. Prior to calculation of variables, the listening log that participants completed by hand was used to crosscheck the data recorded by the device.

Survival. A categorical variable (yes/no) indicating whether the patient had died (all cause mortality) as of February 15, 2019 was created. The amount of time (in days) from date of study entry to date of death was calculated for patients who had died. For living patients, this tracking variable reflects the number of days from study entry to the cessation of tracking on February 15th, 2019. Survival or tracking time (in days) was also calculated from each participant's date of diagnosis to either date of death or the date of tracking cessation (e.g., February 15, 2019).

Analytic approach. The overall analytic approach followed the MacArthur approach (Chmura Kraemer et al., 2008) and recommendations outlined by Kraemer and colleagues (2001). Prior to regression analysis, all continuous independent and control

variables (e.g., age at diagnosis) were median centered and binary control variables (e.g., sex) were effects coded (i.e., -1/2, +1/2) to improve interpretation and minimize error (Kraemer & Blasey, 2004).

Theoretically derived control variables were identified for each dependent variable. A data driven approach was then taken to test the contribution of each proposed variable using Spearman's rank-order correlations. According to Kraemer and colleagues (2001) indicators that are only associated with the dependent variable should be entered into the first step of the model as a covariate, whereas indicators that are associated with both the independent and the dependent variable should be entered into the first step of the model as a 'proxy' with the independent variable and the interaction between the two. 'Proxy risk factors' are risk factors, but are correlates of the independent variable, an association that should be accounted for according to Kraemer et al. (2001). This approach was taken for the current analysis. Thus, the association between each theoretically derived covariate and the independent and dependent variable was examined prior to the proposed analysis. Indicators were included in the model if they demonstrated a strong enough relationship with the dependent and/or independent variable (effect size ≥ 0.3) to ensure contribution without increasing risk of multicollinearity (effect size ≤ 0.5). Additionally, because the intervention was not randomized, intervention participation status (yes/no) was also tested as a covariate in all models that included a longitudinal variable.

Preliminary analysis. Data were explored and tested for assumptions of parametric data, including tests for normality, significant outliers, linearity, and homoscedasticity (Field, 2013). All variables were examined for outliers; scores greater

than four standard deviations from the mean were assessed for removal prior to analysis. Scatterplots, boxplots, histograms, and Predicted probability (P-P) plots were examined for each continuous variable. Skewness and kurtosis statistics were calculated for continuous variables by dividing the statistic by the standard error. Those that failed to meet assumptions by visual inspection or by z-skewness values outside of the 95% confidence interval (values > 1.96) were assessed for transformation. Variables were transformed according to the parameters provided by Field (2013). All transformed variables were re-assessed for assumptions prior to analysis.

Additional assumptions were checked prior to conducting ANCOVA tests. To confirm the independence of the covariate and treatment effect, independent-samples t-tests were conducted between the independent variable and the covariant to ensure that the covariate was independent of the treatment effect. As a part of the analysis, the Levine's test was used as a preliminary assessment of the homogeneity of regression slopes analysis.

All other assumptions for survival statistical tests (i.e., Kaplan-Meier using log rank and Cox Proportional Hazards regressions) were confirmed prior to running analyses.

Primary analysis. In addition to examining each hypothesized association including constructs assessed at baseline, to examine change in constructs over time (from baseline to follow-up), a within-subjects regression coefficient analysis was conducted on depressive symptoms, markers of cortisol, and LTL for each participant. In other words, for each participant, the slope of change (from baseline to follow-up) and intercepts were calculated for depressive symptoms, markers of cortisol, and LTL. Each

variable (e.g., depressive symptoms) was regressed on collection time points – baseline and follow-up – to calculate a slope of change (the unstandardized beta) using a linear regression. Thus, the calculated slope represents a change (e.g., in depressive symptoms) over the intervention period for each participant, regardless of participation status. The intercept value was entered as a covariate to control for baseline individual differences.

Regarding loss to follow-up, analyses were first conducted with the available data. Analyses were subsequently conducted handling missing data using the intent-to-treat principles outlined by Lachin (2000). Following these principles, baseline values were used to replace missing values at follow-up, resulting in a slope of zero (i.e., no observed change).

Covariates. Spearman's rank-order correlations were used to assess the contribution of theoretically derived indicators in cancer samples for each independent and dependent variable. Theoretically derived and tested indicators of survival, depression, and markers of cortisol included: disease stage, age, age at diagnosis, sex, prior/current treatment (chemotherapy/radiotherapy), and tobacco history in pack-years. Theoretically derived and tested indicators of LTL included: disease stage, age, age at diagnosis, sex, prior/current treatment (chemotherapy/radiotherapy), tobacco history in pack-years and ethnic minority status. Results from these analyses were used to determine inclusion of covariates in the subsequent analyses (see Tables 3 – 5).

Aim 1. Hypothesis 1a. Baseline. To test the prognostic value of baseline depressive symptoms on survival calculated from the date of study entry and the date of diagnosis two separate two-tailed Cox Proportional Hazards regressions were conducted. Sex was entered into the first step of the model as a covariate on survival calculated from

study entry (Table 3). Each model was run with and without intervention participation status included as a covariate.

Slope of change and intent-to-treat principles. To test the prognostic value of change in depressive symptoms on survival calculated from the date of study entry and the date of diagnosis, two separate two-tailed Cox Proportional Hazards regressions were conducted. Sex was entered into the first step of the model as a covariate on survival calculated from study entry (Table 3). Each model was run with and without use of the intervention included as a covariate. The same analyses were subsequently conducted using intent-to-treat principles outlined by Lachin (2000); i.e., baseline values were used to replace missing values at follow-up, resulting in a slope of zero (i.e., no observed change), resulting in a total of eight regressions.

Hypothesis 1b. Baseline. To test the baseline association between depressive symptoms and markers of diurnal cortisol profiles (overall mean, bedtime mean, and diurnal slope), separate hierarchical linear regressions were conducted. Each marker of cortisol was tested as the outcomes in separate models. Age at study entry and age at diagnosis were entered into the first step of two separate models as a covariate on bedtime mean cortisol (Table 4).

Slope of change and intent-to-treat principles. To test the association between change in depressive symptoms and change in cortisol profiles (overall mean, bedtime mean, and diurnal slope), separate hierarchical linear regressions were conducted. Each marker of cortisol was tested as the outcome in separate models. Each model was run with and without use of the intervention included as a covariate. The same analyses were

subsequently re-conducted using intent-to-treat principles outlined by Lachin (2000), resulting in a total of 12 regressions.

Hypothesis 1c. Baseline. To test the association between depressive symptoms and LTL assessed at baseline, a hierarchical linear regression was conducted. Age at diagnosis was entered into the first step of the model as covariate (Table 5).

Slope of change and intent-to-treat principles. To test the association between change in depressive symptoms and change in LTL, a hierarchical linear regression was conducted. Minority status was entered into the first step of the model as covariate (Table 5). The model was run with and without use of the intervention included as a covariate. The same analyses were subsequently re-conducted using intent-to-treat principles outlined by Lachin (2000), resulting in a total of four regressions.

Hypothesis 1d. Because the proposed conditions were not met (see results of hypothesis 1a and 1b), hypothesis 1d (i.e., if hypothesis 1a and 1b emerge as significant, then greater cortisol dysregulation will be associated with both depressive symptoms and shorter survival) was not examined.

Hypothesis 1e. Because the proposed conditions were only partially supported independent of the intervention (see results of hypothesis 1a), hypothesis 1e (i.e., if hypothesis 1a and 1c emerge as significant, then shorter LTL will be associated with both depressive symptoms and shorter survival) was not examined as proposed. However, as a part of the *post-hoc* analysis to elucidate results that emerged following the analysis of hypothesis 2c, the prognostic significance of LTL was ultimately examined.

Aim 2. Because the intervention was a pilot, not randomized, an exploratory analysis was conducted to elucidate baseline group differences between patients who

participated in the intervention and those who did not. Demographic and medical factors were compared between the two groups using independent samples t-tests, Chi-square tests, and Mann-Whitney U tests to elucidate potential confounding continuous, dichotomous, and categorical variables, respectively. Results from these analyses were used to determine inclusion of covariates in the subsequent analyses (see Table 6).

Hypothesis 2a. Participation. To test if participation in the intervention (yes/no) was associated with a change in depressive symptoms, an ANCOVA was conducted. Both chemotherapy treatment status at baseline (yes/no; Table 6), and the intercept from the within-subjects regression coefficient analysis (to control for individual differences at baseline) were entered as covariates. The same analyses were subsequently re-conducted using intent-to-treat principles outlined by Lachin (2000), resulting in a total of two ANCOVAs. Levene's tests were used to test the assumption of homogeneity of variances.

Use of the intervention. Among those who completed the intervention, to test if greater participation (total listening time and total number of tracks listened to) was associated with a change in depressive symptoms, separate hierarchical linear regressions were conducted. The same analyses were subsequently conducted using intent-to-treat principles outlined by Lachin (2000), resulting in a total of four regressions.

Hypothesis 2b. Participation. To test if participation in the intervention (yes/no) was associated with a change in markers of cortisol (overall mean, mean bedtime, and diurnal cortisol slope), separate ANCOVAs were conducted. Chemotherapy treatment status at baseline (yes/no; Table 6) and the intercept from the within-subjects regression coefficient analysis (to control for individual differences at baseline) were entered as covariates in each model. The same analyses were subsequently conducted using intent-

to-treat principles outlined by Lachin (2000), resulting in a total of six ANCOVAs.

Levene's tests were used to test the assumption of homogeneity of variances.

Use of the intervention. Among those who completed the intervention ($n = 25$), to test if greater participation (total listening time and total number of tracks listened to) was associated with a change in markers of cortisol (overall mean, mean bedtime, and diurnal cortisol slope), separate hierarchical linear regressions were conducted. The same analyses were subsequently conducted using intent-to-treat principles outlined by Lachin (2000), resulting in a total of 12 regressions.

Hypothesis 2c. Participation. To test if participation in the intervention (yes/no) maintained LTL, an ANCOVA was conducted. Chemotherapy treatment status at baseline (yes/no; Table 6) and the intercept from the within-subjects regression coefficient analysis (to control for baseline differences) were entered as covariates. The same analyses were subsequently conducted using intent-to-treat principles outlined by Lachin (2000), resulting in a total of two ANCOVAs. Levene's tests were used to test the assumption of homogeneity of variances.

Use of the intervention. Among those who completed the intervention, to test if greater participation (total listening time and total number of tracks listened to) was associated with change in LTL, two hierarchical linear regression was conducted. The same analyses were subsequently conducted using intent-to-treat principles outlined by Lachin (2000), resulting in a total of four regressions.

Hypothesis 2d. Participation. To test if participation in the intervention (yes/no) was associated with survival time calculated from date of study entry and date of

diagnosis, two separate Kaplan-Meier analyses (Kaplan & Meier, 1958) using the log rank test were conducted.

Use of the intervention. Among those who completed the intervention, to test if greater participation (total listening time and total number of tracks listened to) was associated with survival time calculated from study entry and date of diagnosis, four separate two-tailed Cox Proportional Hazards regressions were conducted. In models with survival calculated from study entry as the outcome, sex was entered into the model as a covariate (Table 3).

Post-hoc analysis. Aim 1. Hypothesis 1a. Baseline. To determine if clinically significant depressive symptoms at baseline predicted overall survival, the sample was split between participants who endorsed clinically significant levels of depression (score ≥ 16 on the CES-D, $n = 29$) and those who did not (score ≤ 16 on the CES-D, $n = 30$). Two separate Kaplan-Meier analyses using log rank tests were conducted to test if survival distributions calculated from study entry and date of diagnosis differed between those who endorsed experiencing clinically significant depressive symptoms and those who did not.

Hypothesis 1b. Baseline. To determine if clinically significant depressive symptoms were associated with markers of cortisol dysregulation (higher overall mean and bedtime cortisol and flatter diurnal cortisol slopes), the sample was split between participants who endorsed clinically significant levels of depression (score ≥ 16 on the CES-D) and those who did not (score ≤ 16 on the CES-D), and separate hierarchical linear regressions were conducted. Each marker of cortisol was tested in a separate model. The covariates that emerged as significantly associated with bedtime mean

cortisol (age at baseline and age at diagnosis; Table 4) were included in the models with bedtime mean cortisol as the outcome.

Hypothesis 1c. Baseline. To determine if clinically significant depressive symptoms were associated with LTL, the sample was split between participants who endorsed clinically significant levels of depression (score ≥ 16 on the CES-D) and those who did not (score ≤ 16 on the CES-D), a hierarchical linear regression was conducted. The covariate that emerged as significantly associated with LTL (age at diagnosis; Table 5) was included in the model.

Hypothesis 1c. Slope of change and intent-to-treat principles. To elucidate findings that emerged as significant following primary analysis of hypothesis 1c, an interaction term between change in depressive symptoms and minority status (yes/no) was calculated. A hierarchical linear regression was conducted to re-assess the association between change in depressive symptoms and change in LTL including the same covariates that were included in the model initially (primary analysis) of hypothesis 1c (minority status (Table 5) and participation in the intervention (yes/no) in addition to the interaction term.

Aim 2. *Hypothesis 2a. Participation.* To elucidate the findings that emerged as significant following the primary analysis of hypothesis 2a, an interaction term between participation in the intervention (yes/no) and chemotherapy treatment status at baseline (yes/no) was calculated. An ANCOVA was conducted to re-assess the association between the intervention and change in depressive symptoms using intent-to-treat principles. The same covariates were included as the primary analysis (the intercept from the within-subjects regression coefficient analyses and chemotherapy treatment status at

baseline) in addition to the interaction term. The Levene's test was assessed to test the assumption of homogeneity of variances.

Use of the intervention. In an attempt elucidate results that emerged contrary to hypotheses following primary analysis of hypothesis 2a, subsequent *post-hoc* analysis were conducted using variables reflective of intervention use (i.e., total listening time and total number of tracks listened to).

Among those who participated in the intervention ($n = 25$), total listening time and total number of tracks listened to were median split to create two groups: low and high use of the intervention. Two separate independent-samples t-tests were conducted to determine if change in depressive symptoms following intent-to-treat principles differed between low versus high use of the intervention.

Among those who participated in the intervention, variables were created to capture use of didactic (i.e., instructional) and practice tracks. For each participant, the average total amount of time that didactic and practice tracks were listened to was calculated. Similarly, for each participant, the total number of tracks that were categorized as didactic and practice were calculated. Unexpectedly, separate linear regressions could not be conducted using didactic track variables (total time and total number of tracks listened to) due to a low sub-sample size ($n = 2$). Thus, separate linear regressions were conducted to test the association between total amount of listening time and number of tracks listened to for practice tracks and change in depressive symptoms following intent-to-treat principles.

Finally, the total listening time and total number of times that the practice track titled, "Awareness of the breath" (11 minutes and 5 seconds in length) was listened to was

examined using separate linear regressions to test the association with change in depressive symptoms following intent-to-treat principles.

Hypothesis 2c. Participation. An independent-samples t-test was conducted to elucidate the findings that emerged following primary analysis of hypothesis 2b, which demonstrated that there was a significant difference in baseline diurnal cortisol slope between the two groups (those who participated in the intervention versus those who declined).

Hypothesis 2c. Participation. To elucidate findings that emerged following primary analysis of hypothesis 2c, an ANCOVA was conducted to examine the association between the intervention (yes/no) and change in LTL with an interaction term between participation intervention status and chemotherapy treatment status at baseline. The model adjusted for baseline differences in LTL (the intercept from the within-subjects analysis) and chemotherapy treatment status at baseline (yes/no; Table 6).

Cox Proportional Hazard regressions were conducted to examine the prognostic value of LTL with and without adjusting for intervention participation status (yes/no). Separate models including survival calculated from date of study entry and date of diagnosis were conducted.

Despite being considerably underpowered, a hierarchical linear regression was subsequently conducted to examine the association between change in depressive symptoms and change in LTL with an interaction between change in depressive symptoms and the intervention after controlling for minority status (yes/no; Table 5).

Hypothesis 2d. Use of the intervention. In an attempt elucidate results that emerged contrary to hypothesis 2d, subsequent *post-hoc* analysis were conducted using

variables capturing intervention use (i.e., total listening time and total number of tracks listened to).

Similar to hypothesis 2a, among those who participated in the intervention, total listening time and total number of tracks listened to were median split to create two groups: low and high use of the intervention. Kaplan-Meier analysis using log rank tests were conducted to test if survival distributions calculated from study entry and date of diagnosis differed between low versus high use of the intervention.

Among those who participated in the intervention, variables were created to capture use of didactic (i.e., instructional) and practice tracks. For each participant, the average total amount of time that didactic and practice tracks were listened to was calculated. Similarly, for each participant, the total number of tracks that were categorized as didactic and practice were calculated. Similar to hypothesis 2a, Cox Proportional Hazard regressions could not be conducted using didactic track variables (total time and total number of tracks listened to) due to a low sub-sample size ($n = 2$). Thus, total of four Cox Proportional Hazard regressions were conducted to test the association between total amount of listening time and number of tracks listened to for practice tracks and survival calculated from study entry and date of diagnosis.

Finally, the total listening time and total number of times that the practice track titled, “Awareness of the breath” (11 minutes and 5 seconds in length) listened to was examined using four Cox Proportional Hazard regressions to test potential associations with survival calculated from study entry and date of diagnosis.

Power analysis

G*Power version 3.1, previous studies, and an online power calculator (HyLown Consulting LLC) were all used to estimate the anticipated power of the proposed study aims based on final samples sizes: $N = 67$; $n = 59, 58, 58, 57$, and 64 for depressive symptoms, overall mean cortisol, mean bedtime cortisol, diurnal cortisol slope, and LTL, respectively. All power estimates were calculated with a 5% Type I error ($\alpha = .05$).

Aim 1. Hypothesis 1a. The estimated power for hypothesis 1a is based on a similar study that reported depression was a significant predictor of 6-month survival among 43 NSCLC patients, 13 of which experienced death, with a medium to large odds ratio of 5.30 (Pirl et al., 2008). These results suggest the current sample of 59 with approximately a 50% rate of death should attain adequate power. Further, based on the expectation of a hazards ratio of 2 in our sample of 57, the online power calculator (HyLown Consulting LLC) provided an estimated of .66.

Hypothesis 1b – 1c. Small to large effect sizes have been reported between depressive symptoms and markers of cortisol. Large effect sizes between depression and higher afternoon cortisol (Cohen's $d = .83$; (Burke et al., 2005) and overall mean cortisol (Cohen's $d = .60$; (Stetler & Miller, 2011) have been reported among non-medically ill samples. Small to moderate effects (Cohen's $f = .17$) have been reported between depressive symptoms and higher evening cortisol in an ovarian cancer sample (Lutgendorf et al., 2008). Among non-medically ill participants, moderate effect sizes have been reported between depressive symptoms and shorter LTL (Hedge's $g = -.55$; Darrow et al. (2016). No effect size estimates are available for depressive symptoms and TL in cancer contexts given that only two studies have examined these constructs among cancer populations, neither of which reported an effect size. Based on the expectation of a

small to large effect size on biological markers in our sample of 57, our power will range between .18 and .99.

Aim 2. Hypothesis 2a. Medium to large effect sizes of an MBSR intervention on depressive symptoms have been reported among cancer patients in mobile (Cohen's $d = 0.85$; $N = 15$) and non-mobile (Cohen's $d = 0.56$) formats, respectively (Lengacher et al., 2018; Zhang, Wen, et al., 2015). Based on the expectation of a medium to large effect size on depressive symptoms in our sample of 59, our power will range between .17 and .99.

Hypothesis 2b – 2c. Small effects of an MBSR intervention on cortisol slope ($\eta^2 = 0.02$) and medium effects on bedtime cortisol ($\eta^2 = 0.05$) have been reported among breast cancer patients (Carlson et al., 2013); overall diurnal mean cortisol was not reported. A small to medium effect ($\eta^2 = 0.043$) of an intervention involving components of MBSR on maintenance of TL has been reported among a breast cancer sample (Carlson et al., 2015). However, there are a limited number of studies that have examined the effects of an MBSR intervention on biological markers. Thus, it should be noted that the current investigation is exploratory opposed to confirmatory in nature. Nonetheless, based on the expectation of a small to medium effect of the intervention on biological outcomes in our sample of 57, our power will range between .06 and .99.

Hypothesis 2d. The effects of MBSR or an MBI on survival have not been tested among cancer populations. A small effect of a psychological intervention involving a combination of stress reduction, problem solving, social support enhancing, and health behavior techniques on 11 year survival ($HR = 0.44$) has been reported, which indicated breast cancer patients who were randomized to the intervention were half as likely to die

from breast cancer (Andersen et al., 2008). Based on the expectation of a hazards ratio of 2 in our sample of 67, the online power calculator (HyLown Consulting LLC) provided a power estimate of .66. Nonetheless, the proposed analyses are exploratory, not confirmatory, in nature.

RESULTS

Preliminary analysis

All of the independent-samples t-tests conducted to assess the independence of the treatment variable and the covariate assumption for the ANCOVA were not statistically significant; thus, the assumption was met for each analysis.

Primary analysis

Covariates. Results of the Spearman's rank-order correlations are summarized in Tables 3 – 5.

Aim 1. Hypothesis 1a. Baseline. Sex (female) emerged as significantly associated with longer survival calculated from study entry. No theoretically derived covariates were significantly associated with survival calculated from date of diagnosis. No theoretically derived covariates were significantly associated with the independent variable, depressive symptoms; therefore, no variables were entered as a 'proxy' (Table 3).

Contrary to hypotheses, after adjusting for participation in the intervention, although both Cox Proportional Hazards regression models emerged as significant (study entry: $p = .018$; date of diagnosis: $p = .022$), depressive symptoms assessed at baseline did not predict survival calculated from study entry or date of diagnosis. Participation in the intervention emerged as a significant predictor of shorter survival in both models calculated from study entry ($P(\text{Wald}) = .017$; hazard ratio, 0.396; 95% confidence interval [CI], .185 - .850) and date of diagnosis ($P(\text{Wald}) = 0.021$; hazard ratio, 0.405; 95% confidence interval [CI], .188 - .870). Results are presented in Table 7.

Slope of change and intent-to-treat principles. No indicators emerged as significantly associated with the independent variable, change in depressive symptoms (including intent-to-treat variables). Therefore, because sex emerged as significantly associated with longer survival calculated from study entry, it was again entered as a covariate in models with survival calculated from study entry at the outcome. No additional covariates were entered into models with survival calculated from date of diagnosis as the outcome. No models included a ‘proxy’ (Table 3).

Contrary to hypotheses, change in depressive symptoms did not emerge as a statistically significant predictor of survival calculated from study entry or date of diagnosis following Cox Proportional Hazards regression analysis with or without use of the intervention included in the model. Results are summarized in Table 7.

Loss to follow-up Cox Proportional Hazards regression analyses using intent-to-treat principles yielded similar statistically non-significant associations between change in depressive symptoms and both measures of survival with and without the intervention included in the model. Although the overall model was again significant for survival calculated from study entry ($p = .040$), only participation in the intervention emerged as a significant predictor ($P(\text{Wald}) = .021$; hazard ratio, 0.400; 95% confidence interval [CI], .184 - .871). The model including survival calculated from date of diagnosis neared significance ($p = .052$), but only use of the intervention emerged as a significant predictor ($P(\text{Wald}) = 0.020$; hazard ratio, 0.391; 95% confidence interval [CI], .178 - .860). Results are summarized in Table 7.

Hypothesis 1b. Baseline. In the anticipated direction, both older age at study entry and older age at diagnosis emerged significantly associated with increased bedtime mean

cortisol. No theoretically derived covariates were significantly associated with any other marker of cortisol. No theoretically derived covariates were significantly associated with the independent variable, depressive symptoms; therefore, no variables were entered as a ‘proxy’ (Table 4).

The regression conducted to assess the association between depressive symptoms and mean bedtime cortisol assessed at baseline while controlling for age emerged as significant, $F(2,52) = 3.720, p = .031$ and accounted for 12.5% variance. Only age was significantly associated with mean bedtime cortisol ($p = .010$) and accounted for 11.5% of the variance. Similarly, the regression used to assess the association between depressive symptoms and mean bedtime cortisol assessed at baseline while controlling for age at diagnosis emerged as nearly significant, $F(2,52) = 3.133, p = .052$ and accounted for 10.8% variance. Again, only age at diagnosis was significantly associated with mean bedtime cortisol ($p = .017$) and accounted for 8.3% of the variance. The association between depressive symptoms and both diurnal cortisol slope and overall mean cortisol assessed at baseline did not emerge as significant in the model. Results are summarized in Table 8.

Slope of change and intent-to-treat principles. No theoretically derived covariates were significantly associated with any change in any of the markers of cortisol (including intent-to-treat variables; Table 4). Therefore, no additional theoretically derived variables were entered as a covariate or a ‘proxy’ in any of the models.

Contrary to hypotheses, the hierarchical linear regressions conducted to assess the associations between change in depressive symptoms and change in markers of cortisol

(overall mean, bedtime mean, and diurnal slope) both with and without adjusting for the intervention did not emerge as significant. Results are summarized in Table 8.

Loss to follow-up analyses using intent-to-treat principles similarly yielded no statistically significant associations between change in depressive symptoms and change in markers of cortisol. Results are summarized in Table 8.

Hypothesis 1c. Baseline. Older age at diagnosis emerged as significantly associated with shorter LTL at baseline. No theoretically derived covariates were significantly associated with the independent variable, depressive symptoms; therefore, no variables were entered as a ‘proxy.’ Spearman’s rank-order correlations are summarized in Table 5.

The regression conducted to assess the association between depressive symptoms and LTL at baseline while controlling for age at diagnosis emerged as significant, $F(2,54) = 3.915, p = .026$, and accounted for 12.7% variance. However, only age at diagnosis was significantly associated with TL ($p = .015$) and accounted for 9.1% of the variance.

Slope of change and intent-to-treat principles. As expected, minority status (non-White participants) emerged as significantly associated with a more negative change (steeper slope) in LTL and was entered into the first step of the model as a covariate. Because minority status was not significantly associated with the independent variable, change in depressive symptoms, no variables were entered as a ‘proxy.’ Spearman’s rank-order correlations are summarized in Table 5.

The regression conducted to assess the association between change in depressive symptoms and change in LTL while controlling for minority status emerged as significant, $F(2,24) = 4.914, p = .016$ and accounted for 29% of variance. Both minority

status ($p = .012$) and change in depressive symptoms ($p = .029$) were significantly associated with LTL. The regression controlling for both minority status and the intervention also emerged as significant, $F(3, 23) = 4.930, p < .01$ and accounted for 39% of variance. Both minority status ($p = .015$) and change in depressive symptoms ($p < .01$) were, again, significantly associated with LTL, but participation in the intervention did not significantly contribute to the model (Table 9). As demonstrated in Figure 4, the slope of change in depressive symptoms and change in LTL was negative. Consistent with hypotheses, as depressive symptoms increased over time (from baseline to follow-up) LTL decreased over time, and the LTL among minority participants was shorter than non-Hispanic White participants.

No indicators, including minority status, were significantly associated with a change in LTL and following intent-to-treat principles; therefore, no covariates or proxies were included in the models. Loss to follow-up analyses using intent-to-treat principles yielded no statistically significant associations (Table 9).

Aim 2. The Chi-square test between intervention status and current chemotherapy status revealed a significant difference between groups, $\chi^2(1, N = 59) = 3.845, p = .050$. No other factors emerged as significant. Results of the exploratory analysis are presented in Table 6.

Hypothesis 2a. Participation. After adjusting for baseline individual differences in depressive symptoms and chemotherapy treatment status at baseline, the intervention did not demonstrate statistically significant associations with change in depressive symptoms (Table 10). There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance ($p = .503$).

Loss to follow-up ANCOVA analysis using intent-to-treat principles yielded a statistically significant intervention effect on change in depressive symptoms after adjusting for chemotherapy treatment status at baseline, $F(1,54) = 5.360$, $p = .024$, partial $\eta^2 = 0.090$. Contrary to hypotheses, the change in depressive symptoms was positive; scores increased over time (by approximately three points on the CES-D) in the intervention group ($M = .035$, $SE = .084$) whereas scores decreased/were maintained (approximately half of a point decrease) among participants who did not complete the intervention ($M = -.005$, $SE = .047$), a mean difference of .042, 95% CI [.006, .079], $p = .024$. However, the assumption of homogeneity of variances was violated as assessed by Levene's test for equality of variances ($p = .003$). Therefore, the dependent variable, change in depressive symptoms following intent-to-treat principles, was re-examined more conservatively. Outliers ($n = 1$) beyond three, opposed to four, standard deviations (values less than .22) were excluded from a subsequent ANCOVA analysis. The model remained significant, $F(1,53) = 4.275$, $p = .044$, partial $\eta^2 = 0.075$ and the change in depressive symptoms remained significantly positive in the intervention group ($M = .024$, $SE = .064$) whereas the change in depressive symptoms remained negative among those who did not complete the intervention ($M = -.005$, $SE = .047$), a mean difference of .032, 95% CI [.001, .062], $p = .044$ (see Figure 6). Although the Levine's test for equality of variances remained significant after excluding the outlier ($p = .022$), Field (2013) suggests the Levene's test is not the most reliable measure of the equal variances assumption. Instead Field (2013) recommends checking the assumption using a variance ratio by squaring each group standard deviation, dividing the largest standard deviation by the smallest, and referencing Figure 5 to determine if the quotient exceeds the critical

value. In this case, the largest squared standard deviation (.004; $n = 23$) divided by the smallest squared standard deviation (.002; $n = 34$) yielded a variance ratio of 2, which did not exceed the critical value of ~ 3 as determined using Figure 5. Thus, according to Field (2013) the homogeneity of variances assumption was not violated. Results are summarized in Table 10.

Use of the intervention. Among those who completed the intervention ($n = 25$) and provided depression assessment at baseline and follow-up ($n = 20$), the regressions conducted to test the associations between intervention use (total listening time and total number of tracks listened to) and change in depressive symptoms did not emerge as significant. Results are summarized in Table 11.

Loss to follow-up regression analysis using intent-to-treat principles yielded similar insignificant associations. Among those who completed the intervention ($n = 25$), the regressions conducted to test the associations between intervention use (total listening time and total number of tracks listened to) and change in depressive symptoms did not emerge as significant (Table 11).

Hypothesis 2b. Participation. After adjusting for baseline individual differences in cortisol profiles and chemotherapy treatment status at baseline, the ANCOVA analysis demonstrated that the intervention did not demonstrate statistically significant association with change in any of the markers of cortisol (overall mean, bedtime mean, diurnal slope). However, the intercept from the within-subjects analysis emerged significant $F(1,24) = 9.844, p = .004$, partial $\eta^2 = 0.291$, suggesting that there were significant baseline differences in diurnal cortisol slope between the two groups. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance for

each ANCOVA ($p = .825$, $p = .572$, $p = .445$, respectively). The results are presented in Table 12.

Similarly, loss to follow-up ANCOVA analysis using intent-to-treat principles and adjusting for chemotherapy treatment status baseline did not yield statistically significant associations between the intervention and change in each marker of cortisol (overall mean, bedtime mean, diurnal slope). There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance for each ANCOVA ($p = .080$, $p = .239$, $p = .171$, respectively). The results are also presented in Table 12.

Use of the intervention. Among those who completed the intervention, none of the regression conducted to assess the association between total listening time and number of tracks listened to and change and markers of cortisol emerged as significant. The results are presented in Table 13.

Similarly, loss to follow-up regression analyses using intent-to-treat principles yielded no statistically significant associations. Results are also presented in Table 13.

Hypothesis 2c. Participation. After adjusting for baseline individual differences in LTL and chemotherapy treatment status at baseline, the ANCOVA revealed a statistically significant intervention effect on change in LTL, $F(1,34) = 5.454$, $p = .026$, partial $\eta^2 = 0.138$. As demonstrated in Figure 7, for visual not statistical purposes, the slope of change in LTL was positive among those in the intervention group ($M = .0000423$, $SE = .000725$) whereas the slope of change was negative among those who did not complete the intervention ($M = -.000327$, $SE = .000437$), a mean difference of 0.000470 , 95% CI [0.000061 , 0.000879], $p = .026$. In other words, LTL seemed to increase among those in the intervention group, whereas LTL appeared to decrease

among those who did not participate. Chemotherapy treatment at baseline also significantly contributed to the model $F(1,34) = 4.914, p = .033$, partial $\eta^2 = 0.126$. Contrary to expectations, patients who were receiving chemotherapy treatment at baseline demonstrated an increase in LTL compared to those who did not (see Figure 8). There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance ($p = .615$). The mean number of days from date of blood collection at baseline to follow-up was 139 (~4.6 months). Results are summarized in Table 14.

Loss to follow-up ANCOVA analysis using intent-to-treat principles that adjusted for baseline differences in LTL and chemotherapy treatment status at baseline yielded statistically insignificant associations between the intervention and change in LTL; however, the statistical significance of chemotherapy at baseline persisted, $F(1,53) = 5.652, p = .021$, partial $\eta^2 = 0.096$. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance ($p = .210$). Results are also summarized in Table 14.

Use of the intervention. Among those who completed the intervention, the regressions conducted to assess the association between both total listening time and total number of tracks listened to and change in TL yielded statistically insignificant results. Results are presented in Table 15.

Similarly, loss to follow-up regression analyses using intent-to-treat principles yielded no statistically significant associations. Results are also presented in Table 15.

Hypothesis 2d. Participation. Consistent with results that emerged following hypothesis 1a analyses, the Kaplan-Meier survival analysis using a log rank test revealed statistically significant differences in survival distributions calculated both from study

entry and date of diagnosis between those who participated in the intervention ($n = 25$) and those who did not ($n = 42$), $\chi^2(1) = 5.536, p = .019$ and $\chi^2(1) = 6.033, p = .014$, respectively. As demonstrated in Figure 9, contrary to hypotheses, participants that participated in the intervention on average had a shorter time to death in days calculated from study entry ($M = 824.200, SD = 532.443$) than those who did not ($M = 944.810, DE = 400.392$). Similarly, on average, patients that participated in the intervention had a shorter time to death in days calculated from date of diagnosis ($M = 1450.920, SD = 638.400$) than those who did not ($M = 1694.260, SD = 751.716$; Figure 10).

Use of the intervention. As stated in hypothesis 1a, sex (female) emerged as significantly associated with longer survival calculated from study entry and was entered as a covariate in the model (see Table 3).

Among those who completed the intervention ($n = 25$), the Cox Proportional Hazards Regression models conducted to test the association between intervention use (total listening time and total number of tracks listened to) and survival calculated from study entry (after controlling for sex) and date of diagnosis did not yield statistically significant results. Results are presented in Table 16.

Post-hoc analysis

Aim 1. Hypothesis 1a. A score of ≥ 16 is indicative of clinical significant on the CES-D (Radloff, 1977). On average, patients reported experiencing nearly clinically significant levels of depressive symptoms at baseline ($M = 15.5$) and clinically significant levels at follow-up ($M = 17.7$). Consistent with previous reports that have suggested lung cancer patients experience some of the highest levels of depression (Linden et al., 2012), the average depression scores were higher in the current sample than the mean of 11 that

was reported by a different sample of breast cancer patients ($N = 117$; Hann et al. (1999), suggesting that the reported levels of depressive symptoms were not abnormally low in the current sample. Change in depressive symptoms ranged from $-.16$ and 3 , however, and the average change was $.025$. In other words, from baseline to follow-up, regardless of intervention participation status, the overall change in depressive symptoms was less than one point on the CES-D.

Baseline. The Kaplan-Meier survival analysis using a log rank test demonstrated statistically significant differences in survival distributions calculated from date of diagnosis between participants who endorsed experiencing clinically significant levels of depression (CES-D score ≥ 16) and those who did not, $\chi^2(1) = 3.832, p = .050$. Consistent with primary analysis of hypothesis 1a, survival calculated from study entry did not emerge as significant, $\chi^2(1) = 3.232, p = .072$. As demonstrated in Figure 11, patients who endorsed experienced clinically significant depressive symptoms experienced earlier mortality ($M = 23.9, SD = 6.375$), than those who did not ($M = 7.4, SD = 4.734$).

Hypothesis 1b. Baseline. After adjusting for age at study entry (Table 4), the overall model containing sub-clinical levels of depression emerged as significantly associated with bedtime mean cortisol, $F(2, 24) = 4.265, p = .026$; however, sub-clinical levels of depressive symptoms did not significantly contribute to the model ($p = .519$). Similarly, after adjusting for age at diagnosis (Table 4), the overall model containing sub-clinical levels of depression emerged as significantly associated with bedtime mean cortisol, $F(2, 24) = 3.698, p = .040$, although sub-clinical levels of depressive symptoms did not significantly contribute to the model ($p = .461$). Contrary to hypothesis, neither model including clinical levels of depression emerged as significantly associated with

bedtime mean cortisol. Regarding diurnal slope, only sub-clinical levels of depression were significantly associated with a flatter slope, $F(1, 26) = 5.073, p = .033$. No regressions with overall mean cortisol emerged as significant. Results are presented in Table 17.

Hypothesis 1c. Baseline. Contrary to hypothesis, after adjusting for age at diagnosis (Table 5), neither model containing sub-clinical nor clinical levels of depression emerged as significantly associated with LTL. Results are presented in Table 18.

Slope of change and intent-to-treat principles. The hierarchical linear regression conducted to assess the association between change in depressive symptoms and change in LTL remained significant when the interaction term between change in depressive symptoms and minority status was added to the model, $F(4, 22) = 3.795, p = .017$ and accounted for 41% of variance; however, the interaction term did not significantly contribute to the model ($p = .436$). Results are presented in Table 19.

Aim 2. Hypothesis 2a. Participation. The ANCOVA used to assess the association between the intervention and change in depressive symptoms using intent-to-treat principles including the interaction term between the intervention and chemotherapy treatment status at baseline yielded nearly significant results, $F(1, 53) = 3.142, p = .051$, partial $\eta^2 = 0.106$, although the interaction term was not significant. However, similar to primary analysis of hypothesis 2a, the assumption of homogeneity of variances was violated, as assessed by Levene's test for equality of variances ($p = .003$). Using the same procedures outlined for primary analysis of hypothesis 2a, a subsequent ANCOVA was conducted after excluding outliers ($n = 1$) beyond three standard deviations (values less

than 0.22). The model and the interaction term remained insignificant, and similar to hypothesis 2a, the assumption remained violated as assessed by Levine's test ($p = .022$). However, using the procedures outlined by Field (2013), the largest squared standard deviation (.004; $n = 23$) divided by the smallest squared standard deviation (.002; $n = 34$) yielded a variance ratio of 2, which did not exceed the critical value of ~ 3 as determined using Figure 5. Thus, according to Field (2013) the homogeneity of variances assumption was not violated. Results are summarized in Table 20.

Use of the intervention. The median total listening time was 806 minutes and the median total number of tracks listened to was 82 yielding two groups: low ($n = 12$) and high ($n = 13$) use of the intervention. Neither of the independent samples t-tests conducted to test the association between median split total listening time and total number of tracks listened to yielded statistically significant differences in change in depressive symptoms following intent-to-treat principles, suggesting that there was not a dose-response relationship between use of the intervention and depressive symptoms. Results are presented in Table 21.

Among the patients that participated in the intervention ($n = 25$), the average total amount of time that didactic and practice tracks were listened to were 1633.28 and 1531.357 minutes, respectively, and average number of tracks listened to that were categorized as didactic and practice were 260 and 129.083, respectively. Of the 44 tracks recorded and provided to participants via the iPod, 33 of them were didactic (a total of 208.30 minutes) and 11 were practice (a total of 180.85 minutes; Table 1). Neither of the linear regressions conducted to test the association of use of practice tracks on change in

depressive symptoms following intent-to-treat principles emerged as significant. Results are presented in Table 22.

Twenty-three of the 25 patients who participated in the intervention listened to the “Awareness of the breath” practice track. The total number of minutes the track was listened to ranged from 11.10 (i.e., once) – 277.50 ($M = 77.70$, $SE = 78.560$), and the number of times the track was played ranged from 1 – 25 ($M = 7.00$, $SE = 7.077$). Neither regression conducted to test the association of use of the practice track “Awareness of the breath” emerged as a significant predictor of change in depressive symptoms following intent-to-treat principles. Results are also presented in Table 22.

Hypothesis 2b. Participation. The independent-samples t-test revealed nearly statistically significant difference in diurnal cortisol slopes at baseline between patients who agreed to participate in the intervention than those who declined the intervention $t(55) = 1.971$, $p = .054$. As shown in Figure 12, patients who participated in the intervention demonstrated steeper diurnal cortisol slopes than those who declined the intervention.

Hypothesis 2c. Participation. The ANCOVA used to assess the association between the intervention and change in LTL including the interaction term between the intervention and chemotherapy treatment status at baseline demonstrated a statistically significant effect of the interaction term, $F(1,33) = 5.831$, $p = .021$, partial $\eta^2 = 0.150$, after adjusting for baseline differences in LTL and chemotherapy treatment status at baseline. As demonstrated for visual not statistical purposes, in Figure 13, it seems patients who received chemotherapy at baseline and participated in the intervention demonstrated an increase in LTL, whereas patients who were not receiving chemotherapy

at baseline and did not participate in the intervention evidenced a decrease in LTL. All other patients did not appear to evidence a change in LTL from baseline to follow-up; LTL appeared to have been maintained. Results are presented in Table 23.

Change in LTL emerged as a significant predictor of survival calculated from date of study entry ($P(\text{Wald}) < .01$) and date of diagnosis ($P(\text{Wald}) = .026$) following the Cox Proportional Hazard regressions. Contrary to expectation, however, an increase in LTL predicted shorter survival in both models. For visual, not statistical purposes, change in LTL was median split to demonstrate significant differences in survival patterns from date of study entry (Figure 14) and date of diagnosis (Figure 15). After adjusting for intervention participation, both models calculated from study entry ($P(\text{Wald}) < .01$) and date of diagnosis ($P(\text{Wald}) = 0.17$) remained significant, although the intervention did not significantly contribute to either model and LTL was not significant in the model including survival calculated from date of diagnosis. Consistent with findings from hypothesis 2a, participation in the intervention was associated with shorter survival. Results are presented in Table 24.

The hierarchical linear regression examining the association between change in depressive symptoms and change in LTL with an interaction term between change in depressive symptoms and the intervention participation status, after adjusting for minority status, emerged as significant, $F(4, 22) = 3.623, p = .021$ and accounted for approximately 40% of variance, although the interaction term did not significantly contribute to the model. Results are presented in Table 25. However, as demonstrated for visual, not statistical purposes in Figure 16, there appear to be differences in the pattern of association between change in depressive symptoms and change in LTL between

intervention groups (participated versus not). The association between change in depressive symptoms and change in LTL was positive (as depressive symptoms increased, LTL also increased/lengthened) among those who participated in the group, whereas the association was negative (as depressive symptoms increased, LTL decreased/shortened) among those who did not.

Hypothesis 2d. Use of the intervention. The Kaplan-Meier survival analysis using a log rank tests after median splitting total listening time and total number of tracks listened to yielded no statistically significant differences in survival distributions calculated both from either study entry (Time: $\chi^2(1) = .566, p = .019$; Tracks: $\chi^2(1) = .329, p = .566$) or date of diagnosis (Time: $\chi^2(1) = .556, p = .456$; Tracks: $\chi^2(1) = .556, p = .456$), suggesting that there was not a dose-response relationship between the intervention and survival.

None of the Cox Proportional Hazard regressions conducted to test the association between use of practice tracks and survival emerged as significant. Results are presented in Table 26.

None of the four Cox Proportional Hazard regressions conducted to test potential associations between use of the practice track “Awareness of the breath” and survival calculated from study entry or date of diagnosis emerged as a significant. Results are also presented in Table 26.

DISCUSSION

In an attempt to integrate a dual emphasis on improving both quality and quantity of life among cancer patients, this dissertation explored the role of depressive symptoms and related biological markers of stress and cellular aging on survival as well as the potential benefits of a pilot MBI among a small sample of NSCLC patients. This dissertation approached elucidating the hypothesized association between depressive symptoms and survival from two angles exploring: 1) potential biological pathways and 2) the potential benefits of an intervention as a means to improve psychological and clinical outcomes among a population facing high mortality. The importance of elucidating the biological underpinnings of the hypothesized depression-survival pathway in this population cannot be disregarded, as it provides one avenue to inform interventions to improve the poor survival rates that lung cancer patients face. As such, identifying feasible interventions that effectively improve psychological and clinical outcomes also remains a priority in lung cancer patients, a subset of the cancer population that remains highly underrepresented in the psycho-oncology literature.

Although all cancer patients face considerable stress from the burden of treatment, shifts in social and vocational roles, and fear of death as well as a host of other challenges, lung cancer patients face unique and considerable burden given the low five-year overall survival rate that was recently estimated at 18% (Henningfield & Adjei, 2017; Siegel et al., 2016). Not only do more than half of those diagnosed with lung

cancer die within the first year of diagnosis (Henningfield & Adjei, 2017; Siegel et al., 2016), a stress-evoking statistic in and of itself, but cancer patients are four times more likely to experience depression than the non-medically ill populations (Lutgendorf & Andersen, 2015; Raison & Miller, 2003). Lung cancer patients in particular experience some of the highest prevalence rates of depression compared to any other type of cancer (Linden et al., 2012), which cannot be explained by disease severity (Brown et al., 2003). Thus, when faced with difficult mortality rates, stress may be inevitable, but depression is not, despite being highly prevalent. Fortunately, there are effective treatments for depression, providing one avenue for intervention that may subsequently result in improvements to both quality and quantity of life, given that depression has demonstrated prognostic value in cancer populations (Pinquart & Duberstein, 2010; Satin et al., 2009).

The current lung cancer sample was recruited within a 120-mile radius of Louisville, KY, and can be described as mostly female, White, aged 50 – 60 with a high school education and an annual household income of less than \$40,000. Consistent with the larger lung cancer population, 65% of which are diagnosed at a later stage (Siegel et al., 2014), the majority of patients from the current sample also received an initial diagnosis of stage III or IV (65.7%) within two years of study enrollment. Patients diagnosed at a later stage have a poorer prognosis, and as such, several study participants in the current study have since passed away – 46.3% of the overall current study sample, 83.9% of which were initially diagnosed with a later stage.

Aim 1 Discussion: The Potential Role of Two Biomarkers in the Depression-Survival Relationship

While the intersection of mind and body has gained increasing attention in medical contexts, the biological underpinning of depression as it relates to shorter survival among cancer populations remains unknown. The majority of efforts to elucidate these pathways have primarily focused on the roles of the immune and the neuroendocrine systems. Although aberrant cortisol profiles have been associated with both depression and shorter survival among a number of cancer types (Cohen et al., 2012; Schrepf et al., 2015; Sephton et al., 2000), including lung (Sephton et al., 2013), much less attention has been given to the role of telomere biology, a system responsible for maintaining cellular integrity and stability, and is fundamental to cell proliferation (Blackburn et al., 2015). Despite mounting evidence demonstrating an association between shorter telomeres and stress (Shalev et al., 2013; Starkweather et al., 2014), depression (Vance et al., 2018), and shorter survival (Heaphy et al., 2013; Herrmann et al., 2018), there is a paucity of telomere biology in current biobehavioral cancer models. Thus, Aim 1 of the current study was to replicate the prognostic significance of depressive symptoms and to explore the role of two biomarkers – cortisol and leukocyte telomere length (LTL) – as they relate to the hypothesized depression-survival pathway.

Hypothesis 1a. Hypothesis 1a proposed that more depressive symptoms would predict shorter survival. **Hypothesis 1a was partially supported.**

The primary analyses did not yield a significant association between depressive symptoms (assessed at multiple time points) and survival (calculated from two time points). However, *post-hoc* analysis revealed that, when the sample was split between those who reported experiencing clinically significant levels of depression (CES-D score ≥ 16) and those who did not (CES-D score < 16), clinically significant levels of

depression predicted shorter survival calculated from date of diagnosis, but not date of study entry. Although the observed inconsistency between survival from date of diagnosis and study entry was unexpected, it may be understood from the medical heterogeneity of the sample given the inclusion criterion of five years within diagnosis. The average time between dates of diagnosis and study entry was 704 days ($SD = 5423$; ~ 1.9 years), and ranged from 38 – 2455, which reflects considerable variation. Despite this variability, these results highlight the need to consider severity, and specifically clinical significance, when examining the association between depression and survival in cancer samples. This is not to say that sub-clinical levels of depression are of unimportance. In contrast, patients with sub-clinical depression warrant equal attention as patients with clinical levels, as there is an opportunity to prevent worsening of symptoms to clinical levels and the subsequent greater risk of earlier mortality.

These findings extend the growing literature in support of the prognostic significance of depression in cancer samples, and are clearly, of extreme clinical importance. These findings further support the need for on-going efforts to routinely screen all cancer patients for distress and mood symptoms and the need for trained clinical psychologists in oncology settings to effectively prevent and treat sub- and clinical levels of depression. Depression is a treatable condition and these findings further motivate efforts to adapt efficacious interventions for cancer patient populations as well as elucidate mechanisms driving the association between depression and shorter survival.

Hypothesis 1b. Hypothesis 1b proposed that more depressive symptoms would be associated with greater cortisol dysregulation (higher overall mean and bedtime cortisol and flatter diurnal cortisol slopes). **Hypothesis 1b was not supported.**

Contrary to hypothesis 1b, depressive symptoms were not significantly associated with any markers of cortisol assessed at any of the different time points/using different methodologies (i.e., slope, intent-to-treat) upon primary analysis. Interestingly, only older age at study entry and at diagnosis was associated with elevated bedtime mean cortisol levels assessed at baseline. The direction of this association is not surprising given that the HPA-axis tends to function less efficiently with older age and higher bedtime mean cortisol is reflective of an unhealthier neuroendocrine system (see Figure 1). However, it is interesting that older age was only associated with bedtime mean, opposed to overall mean or diurnal cortisol slope, which are more robust markers of neuroendocrine-mediated HPA-axis function. Nonetheless, of the two samples that combine to calculate the overall mean cortisol and diurnal slope (waking and bedtime), higher bedtime mean cortisol has previously emerged as a prognostic indicator and has been proposed as a driver of the HPA-dysregulation observed in cancer samples (Schrepf et al., 2015).

Post-hoc analyses examining sub-and clinical levels of depression only yielded a significant association between sub-clinical levels of depression and flatter diurnal cortisol slope. These results are surprising given the dearth of literature linking depression and hyperactivation/subsequent dysregulation of the HPA axis that worsens with increases in depression severity (Stetler & Miller, 2011). These results further support the notion provided under hypothesis 1a that sub-clinical levels of depression are equally worthy of attention by providers, as flattener diurnal cortisol profiles has been linked to shorter survival among lung cancer patients (Sephton et al., 2013). It is possible flattened diurnal cortisol slopes, indicative of a dysregulated HPA-axis, can be detected earlier, when symptoms are of sub-clinical levels among this population, enhancing the

overall clinical utility of diurnal cortisol as a biomarker for the convergence of worsening psychological and disease-related health. It should be noted, however, that power was limited by the small sub-sample sizes as a result of splitting the sample (sub-clinical: $n = 26 - 27$; clinical: $n = 27 - 28$).

Alternatively, these findings may have been further elucidated by the inclusion of distinct depressive specifiers (e.g., acute versus chronic; first episode versus recurrent) and subtypes (e.g., atypical and melancholic depression; Association (2013)). Although depressive specifiers and subtypes were not assessed in the current study and extend the scope of the current dissertation, there is evidence to suggest that distinct depressive subtypes are differentially associated with aberrant cortisol profiles in non-medically ill populations (O’Keane, Frodl, & Dinan, 2012; Stetler & Miller, 2011). For example, melancholic depression, characterized by anhedonia, insomnia, loss of appetite and feelings of excessive guilt and worthlessness, is associated with greater (54% larger effect) elevations in cortisol than depressive presentations without melancholic features. Moreover, a quantitative review conducted by Stetler & Miller (2011) on depression and HPA-axis activation spanning four decades of research concluded that different depressive symptom clusters are associated with different patterns of HPA-axis activity. Taken together, although the CES-D has been shown to be a valid and reliable measure of depressive symptoms in cancer populations (Hann et al., 1998), it is clear that considerable variability is introduced by the term “depression,” and that much remains unknown about the distinct depressive specifiers and subtypes as they relate to nuanced differences in cortisol profiles both in and out of medical-ill populations. It is plausible to

hypothesize that variations in symptom clusters within the current sample could be contributing to insignificant results observed following analysis of hypothesis 1b.

Hypothesis 1c. Hypothesis 1c proposed that more depressive symptoms would be associated with shorter LTL. **Hypothesis 1c was supported.**

Regarding depressive symptoms and LTL assessed at baseline, although older age at diagnosis was significantly associated with shorter LTL, depressive symptoms did not yield statistical significance. Similar to other biomarkers, including cortisol, it is expected that older age would be associated with shorter LTL, as it is typically reflective of poorer biological functioning. Although chronological age is not synonymous with LTL, a marker of cellular aging (Blackburn et al., 2015), shorter LTL is suggestive of poorer cellular integrity and stability (Blackburn, 2001). Thus, all other factors held constant, it is expected that older individuals would have experienced a greater number of cell divisions and therefore, shorter LTL over the course of their life.

Interestingly, contrary to hypotheses, after adjusting for age at diagnosis, neither model containing sub- nor clinical levels of depression were significantly associated with LTL. Similar to the potential explanation provided in hypothesis 1b, null results may be explained by limited power resulting from small sample sizes after splitting the sample (sub-clinical: $n = 29$; clinical: $n = 28$). Alternatively, given that the time point for assessment of depressive symptoms was arbitrary (at baseline, whenever patients were recruited and opted to enroll in the study), it is possible the detrimental effects of depression reported in the literature would not have affected LTL in the current sample, as LTL was also assessed at baseline (i.e., within the same week). Unlike changes in neuroendocrine functioning via the HPA-axis that can be observed relatively proximal to

a stressor (~within 20 - 30 minutes; Kirschbaum, Pirke, and Hellhammer (1993) through cortisol assessment, measurable LTL attrition is not conceptualized in the literature as an equally rapidly occurring process. Although it is believed that the temporal timeline between depression and subsequent telomere attrition has not yet been reported on in the literature, telomere attrition is conceptualized as a global marker of cellular aging. Thus, although the process of cell division, which leads to cumulative telomere attrition, occurs relatively quickly (within a day), measurable changes in telomere length may require greater time.

Regarding change in symptoms, the hypothesized association between change in depressive symptoms and change in LTL was supported. Consistent with hypothesis 1c, as depressive symptoms increased, LTL decreased. As anticipated, despite a low subsample ($n = 11$), minority status (non-White participants) emerged as a significant predictor of shorter LTL, although the interaction between minority status and change in depressive symptoms did not significantly contribute to the model. In other words, although minority status and change in depressive symptoms were both significantly associated with shorter LTL, the effects of having an ethnic minority background on LTL was unrelatedly to depressive symptoms in the current sample.

Overall, these findings support the mounting evidence demonstrating an association between depression and shorter LTL (Lindqvist et al., 2015) and extend the existing literature linking ethnic differences in LTL observed in non-medically ill populations (Geronimus et al., 2010; Geronimus et al., 2015; Weber et al., 2018) to lung cancer patients. Despite mounting evidence demonstrating a robust effect of stress on TL, there is paucity of telomere biology in current biobehavioral cancer models. TL has been

linked to both depression and cancer outcomes independently; however, this dissertation is one of the first investigations into the relationship between depression and TL in a lung cancer sample.

It is believed that this dissertation is also the first to demonstrate that minority status significantly predicted shorter LTL in a cancer sample. The fact that minority status was predictive of a decrease in LTL regardless of depressive symptoms is puzzling. Given that the majority of the literature discussing shorter LTL among ethnic minorities has postulated this disparity is a result of discrimination (Chae et al., 2014) and greater cumulative life stress, referred to as the “weathering hypothesis,” (Forde, Crookes, Suglia, & Demmer, 2019), it is intriguing that the relationship between ethnic minority status and LTL was not observed at baseline. These results suggest there may have been changes in other factor(s), other than depressive symptoms, over the three months between baseline and follow-up to explain the influence of ethnic minority status on decrease in LTL. Although it extends the scope of the current investigation, it is plausible to hypothesize that other stressors that are commonly reported among minority populations may have been exacerbated by cancer-related stressors to mediate or moderate the association between minority status and shorter LTL during this 3-month period. A rich area for exploration, future investigations should investigate the role of ethnic minority status on stress-related outcomes longitudinally across the cancer trajectory to elucidate stressors unique to patients with an ethnic minority background.

Summary. Because hypothesis 1a was only partially supported and hypothesis 1b was not supported, hypothesis 1d and 1e – the role of cortisol markers and telomere length in the depression-survival relationship – were not tested. Thus, the potential

contribution of the circadian coordinated neuroendocrine system and telomere biology to the depression-survival relationship remain unclear and warrant further investigation. More broadly, although the current investigation was methodologically limited and exploratory rather than confirmatory in nature, the underlying biological mechanisms associated with the prognostic significance of depression in cancer remains unanswered and an important area of future inquiry. Nonetheless, the current investigation provided some important clues. First, the clinical significance, or severity, of depression appears to be an important factor in the depression-survival investigation. Despite limited sub-sample sizes, only clinically significant levels of depression (CES-D score ≥ 16) emerged as a significant predictor of survival. Second, despite considerably more evidence supporting the association between depression and markers of cortisol, LTL emerged as the only significant biomarker in the current investigation. Because cortisol is a hallmark of depression and has demonstrated robust associations with shorter survival across different cancers including lung, it should not be ignored in future investigations. However, the current analyses contribute greater support for future investigations into the role of telomere biology. Although telomere attrition has been linked to both depression and clinical outcomes in cancer samples, this dissertation is one of the first to integrate the two. Taken all together, in depth assessment of depression (i.e., severity, history, features, and subtypes), ethnic minority status, and the role of LTL may be important considerations for future investigations.

Aim 2 Discussion: Mindfulness-based Interventions in Cancer Contexts

The need for feasible psychological care in cancer settings continues to become increasingly more apparent and pressing given the accumulating evidence to suggest

cancer patients experience high prevalence rates of distress, which is associated with poorer clinical outcomes. Despite relatively recent advancements in treatments, including immunotherapy, that have yielded promising results, cancer remains a life-threatening disease without a cure. In addition to facing this stark reality, cancer patients are faced with a plethora of other stressors at different points across the cancer trajectory, warranting stress-reduction strategies. As partially supported by hypothesis 1a, interventions that reduce stress and depression will not only improve quality, but also a patient's quantity of life, and the evidence in support of MBSR as an efficacious treatment for reduction of depressive symptoms among cancer patient populations continues to grow (Huang et al., 2016; Zainal et al., 2013; Zhang, Wen, et al., 2015). Although there are some contradictory findings regarding depressive symptom reduction specifically (Bränström et al., 2012), MBSR interventions have evidenced strong support for stress-reduction more broadly among cancer populations (Ledesma & Kumano, 2009), and no study to date has examined the effects of an MBSR intervention on survival among cancer patients. Nonetheless, the feasibility of interventions, including MBSR is a major priority given that attending weekly, in-person group sessions is challenging for many patients, particularly those experiencing greater burden and fewer resources (i.e., transportation and financial issues, limits to physical functioning, feeling overwhelmed with new appointments/obligations, cognitive changes, etc. (Lehto & Wyatt, 2013). As such, there is growing attention to the "e-health" movement in oncology settings and the healthcare system at large, which provides a host of services, including MBSR/(CR) (Lengacher et al., 2018; Zernicke et al., 2013), through a host of mobile, electronic formats. The most recent pilot iPad-based MBSR/(CR) intervention

conducted by Lengacher and colleagues (2018) demonstrated statistically significant improvements to somatic symptoms of depression ($d = 0.85$) among breast cancer survivors. Thus, Aim 2 of the current study was to explore the ameliorative role of an iPod-based MBSR intervention on depressive symptoms and related outcomes among lung cancer patients

Hypothesis 2a. Hypothesis 2a proposed that participation in and use of the intervention would be associated with fewer depressive symptoms from baseline to follow-up. **Hypothesis 2a was partially supported.**

After adjusting for baseline differences in depressive symptoms and chemotherapy treatment status at baseline since the intervention was optional and not randomized, participation in the intervention only emerged as a significant predictor of change in depressive symptoms following intent-to-treat principles outlined by (Lachin, 2000). Following the outlined procedures, baseline values were used to replace missing values at follow-up, resulting in a slope of zero (i.e., no observed change). Contrary to hypotheses, change in depressive symptoms was positive (scores increased by approximately three points) in the intervention group whereas depressive symptoms were essentially maintained (scores decreased by approximately half of a point) among participants who did not complete the intervention (Figure 6). Interestingly, despite being only a three-point increase, the change in mean scores surpassed the clinical threshold (score of ≥ 16 on the CES-D). In other words, among the intervention group, the average score at baseline fell in the sub-clinical range and elevated to a clinically meaningful level following the intervention, which is consistent with findings that emerged following

the analysis of hypothesis 1a. Thus, the hypothesized association emerged as significant, but not in the hypothesized direction.

Post-hoc analyses examining the interaction between chemotherapy treatment status at baseline and the intervention was not significant, suggesting that, although exploratory analyses revealed patients actively receiving chemotherapy treatment at study enrollment were significantly less likely to participate in the intervention, it was not a correlate of the association between the intervention and change in depressive symptoms in the current investigation. In other words, the stressors that typically accompany chemotherapy treatment could not statistically explain the outcomes following the intervention in the current sample. Importantly, however, only six patients actively in treatment at baseline (chemotherapy: $n = 5$; radiation: $n = 1$) participated in the intervention, providing extremely low power to measure and detect such associations.

Further, *post-hoc* analysis among those who participated in the intervention, suggested greater use of the intervention was not associated with an increase in depressive symptoms, suggesting there was not a dose-response relationship between use of the intervention and an increase in depressive symptoms, although power was limited.

While the results of the current analysis should be interpreted cautiously for a number of reasons, namely the limited sample size, the methodological design of the intervention (optional pilot), and the exploratory, rather than confirmatory nature of the analysis, the statistically significant associations that emerged following participation in the intervention only emerged following intent-to-treat principles. Although these replacement procedures are commonly used among populations with high attrition rates, such as medically ill populations, the use of such replacement procedures follows the

rationale that no change was observed, although it remains unknown if a change actually occurred. In other words, these procedures are not inaccurate based on the data collected (i.e., no observed change), but they do not ensure accuracy (i.e., change was not observed, but could have occurred). It is likely that the intent-to-treat principles yielded significance, whereas the analysis using non-replaced data did not, as a result of increased power given that the sample size nearly doubled (non-replaced: $n = 31$; intent-to-treat: $n = 59$).

Nonetheless, the results not only contradict hypothesis 2a, but they are clinically concerning. Despite evidence to suggest that MBSR/(CR) interventions in both in-person (Huang et al., 2016; Zainal et al., 2013; Zhang, Wen, et al., 2015) and mobile (Lengacher et al., 2018) formats reduce stress and depressive symptoms, the majority of this work was conducted among breast cancer patients, and more specifically, breast cancer survivors. While there are a number of shared stressors across all cancer patients, there are disease-specific differences, such as tumor location, treatments, and prognoses, as well as unique disease-specific stressors that differ across cancer types that could be contributing to the contradictory and unexpected findings in the current investigation. For example, breast and lung cancer patients may exist within unique social contexts. Breast cancer contexts tend to foster a sense of cohesion and societal support as evidenced by the widely known “pink ribbon” symbol, whereas lung cancer is typically coupled with smoking-related stigma (Chapple, Ziebland, & McPherson, 2004). This is not to suggest breast cancer patients do not experience significant distress or stigma or that the pink ribbon phenomenon is always beneficial, it is simply to acknowledge that cancer patients

have differing experiences specific to their disease that may have been underappreciated in the current investigation that are discussed further below.

First, as suggested by the name, lung cancer patient's tumor is located inside the lung, the organ responsible for breathing, which is a major focus/component of mindfulness-based practice (Kabat-Zinn, 1982). In meditative practice, and in many of the tracks, participants were encouraged to focus their attention to a focal point, which is not always, but often the breath. *Post-hoc* analyses revealed that the practice track titled, "Awareness of the breath," which was listened to an average of seven times, was not associated with change in depressive symptoms (following intent-to-treat principles), suggesting explicit instruction to focus on the breath was not associated with an increase in depressive symptoms. Nonetheless, it is possible that without the added support of an in-person instructor, components of the intervention that are inherent to meditative practice predisposed risk for distress in this sub-sample of the cancer population.

Second, a major difference in the time point in the cancer trajectory during which the intervention was administered could elucidate contradictory findings. Although survivorship presents a host of unique stressors (i.e., fear of recurrence), it is distinct psychologically from in the current sample, 24 of which were actively receiving treatment at study enrollment (chemotherapy: $n = 24$; radiation: $n = 3$), and were far from survivorship status. Because treatment is acutely stressful and is accompanied with a host of uncomfortable side effects, it is reasonable to assume that is an optimal time point to provide patients with stress reduction strategies. Alternatively, learning a new skill under acute stress can be ineffective (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006) and potentially overwhelming. Interestingly, chemotherapy treatment status at baseline

significantly differentiated the two groups (those who were actively receiving chemotherapy were more likely to decline the intervention), suggesting that stressors associated with active treatment were likely not responsible for increasing depressive symptoms in the current investigation. Nonetheless, because the intervention was not randomized and only six patients were actively receiving treatment at baseline (chemotherapy: $n = 5$; radiation: $n = 1$), it is difficult to discern if opting out of the intervention during active treatment was protective or if those were the individuals that would have benefited most.

Additionally, it is not uncommon for participants to experience discomfort and an initial increase in distress during participation in an MBI given that the foundation of meditative practice is to approach (i.e., focus attention), rather than avoid internal experiences, which can be unpleasant (Dobkin & Zhao, 2011). Thus, while the underlying goal of meditative practice is not to increase distress, if done correctly, meditation increases awareness to existing distress, if distress is present. Like many psychological interventions, MBIs are often challenging in the short-term, but yield long-term benefit. While the overarching goal of mindfulness-based practice is to simply increase awareness to inner experiences, which can also increase awareness of positive inner experiences, the results from the current investigation suggest this particular sample did not attain the intended longer-term stress-reduction benefits of the MBI. There are a number of potentially explanations for this, including possibilities already discussed; however, minimal instruction and consultation may have contributed to the poor outcomes as well. Participants were not instructed to listen to the tracks in any particular order; they were told to listen to tracks of their choice for 30 minutes per day, five days

per week (equating to 450 minutes over the 3-month period), introducing considerable variability in what the intervention experience might have been like for each participant. *Post-hoc* analyses revealed that surprisingly, intervention participants almost exclusively listened to practice, opposed to didactic tracks. Only two of 25 participants listened to a didactic track. Thus, it is plausible that by listening to almost exclusively practice tracks, participants missed key instruction and guidance surrounding typical experiences following increased awareness of inner experiences, such as the anticipation that greater contact with difficult emotions can be unpleasant. Counterintuitive to the finding (i.e., participation in the intervention increased depressive symptoms), in line with this theoretical position, it is also possible participants did not engage in the intervention *enough* to adequately master skills and attain benefit. Participants, on average, did not listen to the prescribed amount. Following the instruction of 30 minutes per day, five days per week over the course of three months, the prescribed listening amount was 1,800 minutes, and on average, participants listened significantly less (mean = 1624, median = 806). Thus, it is possible that upon experience of increased attention to existing discomfort, participants discontinued use of the intervention prematurely, resulting in the observed increase in depressive symptoms, without the long-term benefits observed after weeks (i.e., eight) of practice following a typical MBSR intervention.

Further, this risk may have been moderated by minimal consultative support. Records indicated that only one participant attended the drop-in mindfulness-based cancer support group once over the 3-month intervention period. Therefore, the format of the pilot intervention essentially eliminated all interpersonal elements of MBSR. While the active components of MBSR and MBI's are unknown, patients not only missed

opportunity for the benefits of social support that the group format facilitates (Lengacher et al., 2009), but participants in the current pilot MBI also did not have on-going access to an instructor, and therefore, lacked the opportunity to engage in on-going dialogue about their experiences. Although study personnel contacted participants twice over the course of the three-month intervention to check-in, provide reminders, and answer questions about the intervention, the degree and consistency of discussion regarding participants' experiences was significantly less than what would have been achieved in a more traditional MBSR intervention.

While the goal of feasibility seemed to be achieved by the current intervention, as evidenced by one third of the sample opting to participate and lack of attendance at the in-person support group, a primary difference between the current e-health intervention and previous studies involving mobile MBIs that yielded psychological benefit, in addition to differences in cancer sub-types, was lack of access to a trained instructor (Zernicke et al., 2013). Although a recent study involving an iPad-based MBSR/(CR) intervention that also lacked access to an in-person instructor led to improvements in depressive symptoms, study personnel contacted participants weekly, providing a more frequent avenue for consultation, and the sample was, again, among breast cancer survivors (Lengacher et al., 2018). Although it cannot be confirmed by the data, as there was no in-person MBSR comparison condition in the current investigation, it plausible to hypothesize that having access to a trained instructor, preferable a clinical psychologist, may have ameliorated the observed increase in depressive symptoms among the intervention group.

Taken all together, this finding should be interpreted cautiously given the possibility of selection effect, but considered, especially given the results that emerged following analysis of hypothesis 1a indicating clinical levels of depression predicted shorter survival in this sample. While it remains unknown which, if any, aspects of the intervention contributed to poor outcomes, there are a number of different factors that warrant greater consideration in future investigations. Differences between cancer types and the point in the cancer trajectory during which previous MBIs were administered may have been underappreciated in the current sample. Researchers and clinicians alike should consider the broader biopsychosocial perspective of the patient's cancer experience to temper the generalizability of conclusions across populations. Lastly, these results further motivate efforts to dismantle active components of MBIs.

Hypothesis 2b. Hypothesis 2b proposed that participation in and use of the intervention would be associated with improved diurnal cortisol rhythmicity from baseline to follow-up. **Hypothesis 2b was not supported.**

Contrary to hypothesis 2b, the intervention did not change any of the markers of diurnal cortisol (including analyses following intent-to-treat principles). Additionally, consistent with hypothesis 1b, no theoretically derived indicators were significantly associated with changes in any of the markers of cortisol. Given the exploratory nature of the analysis and the minimal existent evidence to suggest MBSR is efficacious at improving diurnal cortisol rhythmicity among cancer patients, these null findings are not particularly surprising. Despite growing evidence to suggest that MBSR and other MBIs are efficacious at improving the physical health among non-medically ill populations (Grossman, Niemann, Schmidt, & Walach, 2004), the majority of studies examining the

effects of an MBI on cortisol among cancer patients have not yielded significance (Bränström et al., 2013; Lengacher et al., 2012). It is possible cancer patients' neuroendocrine systems are less malleable to intervention as a result of tumor - and treatment-related effects. Alternatively, more extensive mindfulness-based training might be required to observe significant changes. Given Carlson and colleagues' findings that yielded statistically insignificant changes in cortisol profiles immediately following the intervention (2004), but significance at the one-year follow-up (2007), the latter is more likely. Interestingly, although the current investigation did not test mediation, in conjunction with findings from hypothesis 2a and 1b, it seems cortisol profiles were not a correlate or an underlying explanation for worsening depression among intervention participants in the current sample.

Hypothesis 2c. Hypothesis 2c proposed that participation in and use of the intervention would be associated with maintenance of LTL (lack of a decrease) from baseline to follow-up. **Hypothesis 2c was supported.**

After adjusting for chemotherapy treatment status at baseline, the intervention was significantly associated with a change in LTL. As hypothesized, the slope of change in LTL was positive among those in the intervention whereas the slope of change was negative among those who did not complete the intervention. As demonstrated in Figure 7, the LTL increased among those in the intervention group, whereas LTL decrease among those who did not participate. Chemotherapy treatment status was also significantly associated with change in LTL. As shown in Figure 8, contrary to expectations, patients that were receiving chemotherapy treatment at baseline evidenced longer LTL compared to those who were not. Despite being consistent with the

hypothesized direction, the effect of the intervention was stronger than hypothesized (i.e., LTL was lengthened opposed to just maintained among the intervention group). Contradictory to what was expected, however, was that relatively proximal chemotherapy treatment was associated with an increase in LTL. Although these results technically support hypothesis 2c, they are somewhat puzzling given the results that emerged following analysis of hypothesis 2a, demonstrating that the intervention led to an increase in depressive symptoms. This is especially puzzling given that following analysis of 1c, a significant association emerged between change in depressive symptoms and change in the predicted direction LTL – as depressive symptoms increased, LTL decreased with and without adjusting for use of the intervention.

To elucidate the complexity of these findings, *post-hoc* analyses examining the prognostic significance of LTL revealed that change in LTL predicted survival from both date of study entry and date of diagnosis. The results persisted after adjustment for participation in the intervention. However, contrary to expectations, increasing LTL predicted shorter survival from both date of study entry and date of diagnosis, suggesting that longer LTL may have been associated with poorer clinical outcomes in this lung cancer sample. Moreover, consistent with the results that emerged following analysis of hypothesis 2a, in the analysis demonstrating that longer LTL predicted shorter survival, after adjusting for participation in the intervention, results demonstrated that those who participated in the intervention died sooner. In other words, the intervention was associated with longer LTL, which predicted shorter survival, contrary to expectations.

While these results suggest that the intervention was associated with an increase in depression and longer LTL, which unexpectedly predicted shorter survival, these

findings are inconsistent with results from hypothesis 1c (as depressive symptoms increased, LTL decreased/shortened after adjusting for minority status). Interestingly, the association between depression and LTL persisted after controlling for participation in the intervention. To elucidate these findings and clarify the bigger picture, despite restricted power, a regression re-assessing the association between depressive symptoms and change in LTL (hypothesis 1c) with the addition of the interaction term between change in depressive symptoms and the intervention was conducted. The model emerged as significant, although the interaction term did not significantly contribute to the model. Despite lack of statistical significance, as demonstrated for visual not statistical purposes in Figure 16, there appear to be differences in the pattern of association between change in depressive symptoms and change in LTL between intervention groups (participated versus not). The association between change in depressive symptoms and change in LTL was positive (as depressive symptoms increased, LTL also increased/lengthened) among those who participated in the group, whereas the association was negative (as depressive symptoms increased, LTL decreased/shortened) among those who did not. In contrast, as shown in Figure 17, excluding participation in the intervention, the pattern of findings are consistent with hypothesis 1c – the association between change in depressive symptoms and change in LTL is negative (as depressive symptoms increased, LTL decreased/shortened). Therefore, although the interaction was not statistically significant, it seems an increase in depressive symptoms was only associated with longer LTL among patients in the intervention group, providing a more cohesive picture among the current sample, as each predicted shorter survival and each “worsened” following the intervention. It is likely differential effects regarding minority status may have also

emerged after adjusting for intervention status as well with larger power, as only three individuals from ethnic minority backgrounds participated in the intervention.

Importantly, these findings clarify the results that demonstrated patients who were receiving chemotherapy at baseline evidenced an increase in LTL. These findings cohesively support the *post-hoc* analysis that demonstrated a statistically significant interaction between intervention participation status and chemotherapy treatment status at baseline. As demonstrated in Figure 13, patients who received chemotherapy at baseline *and* participated in the intervention demonstrated an increase in LTL, whereas patients who were not receiving chemotherapy at baseline and did not participate in the intervention evidenced a decrease in LTL (all other patients evidenced no noticeable change), supporting the notion that the intervention was associated with worsening biological health among those who had recently undergone chemotherapy treatment.

What remains unclear from the current investigation, however, is why increasing, opposed to shortening LTL, emerged as a marker of shorter survival, and was associated with an increase in depressive symptoms only among those in the intervention group. These findings are particularly perplexing given the substantial evidence to suggest that, in general, telomeres shorten faster under stressful conditions and shorter telomeres are indicative of poorer health. It is plausible, just as there appear to have been disease-specific psychosocial considerations that were overlooked in the current intervention, that there may be underlying disease-specific biological differences occurring in the current NSCLC sample as well, especially given the complexity of cancer biology. As such, there are still a number of unknowns about telomere biology in tumor environments and what impact that has on the patient's systemic biology.

Greater attention has been directed toward telomerase in cancer contexts, more recently, as it is the enzyme responsible for adding new DNA to the end of chromosomes effectively lengthening telomeres (Blackburn, 2011), and may be a missing piece to elucidating the current findings. Somewhat counter-intuitively, extremely short TLs that are near senescence are actually protective against cell division and uncontrollable cell growth, and therefore tumor progression, whereas continuous cell growth and advancing tumors is associated with reactivation of telomerase (Shay & Wright, 2011). Indeed, overexpression of telomerase has been observed in 90% of cancer cells (Kim et al., 1994), and current hypotheses posit that as telomeres from cancer cells shorten rapidly, telomerase facilitates indefinite cell division in an attempt to re-stabilize telomeres, which ultimately leads to a state of “immortalization,” or unrest of cellular proliferation (Augustine et al., 2017). In other words, as the host’s body produces greater telomerase to rectify the excessively short TLs that may have conferred risk for the disease in the first place (Hou et al., 2012), it actually unlocks tumorigenesis. Importantly, telomere length in the current investigation was assessed peripherally via blood samples and telomerase was not assessed, so limited conclusions can be drawn. Nonetheless, it is plausible that the observed increase in LTL could be explained by an increase in telomerase, which may actually confer risk for shorter survival as it likely indicates greater cell proliferation both in and out of tumor environments, and therefore tumor growth.

It should be acknowledged, however, that the alternative – depletion of telomerase in tumor microenvironments – appears to be equally problematic. Experiments have revealed the elimination of telomerase leads to eventual loss of telomere function, which also facilitates tumor progression (De Lange & Jacks, 1999).

Thus, it is likely more accurate to conceptualize the disruption of the delicate balance between cell division (telomere shortening) and telomerase (telomere lengthening) in the tumor microenvironment as harmful as it appears to activate tumorigenesis. However, the specific timing and mechanisms of this process remain unclear (Hackett & Greider, 2002), and no literature on the longitudinal changes to peripheral LTL in cancer samples currently exists. Both gaps warrant greater attention to elucidate current findings, but also, to strengthen LTL's utility as a feasible, easily obtainable clinical biomarker in cancer contexts.

Consistent with the proposed theory, if longer telomeres are actually indicative of faster tumor growth and stress has been shown to tax telomere biology, then despite being counterintuitive to findings in non-medically ill populations, it is logical that worsening depression would be linked to longer telomeres in cancer populations, as demonstrated in the current sample. It is plausible that, consistent with the literature in non-medically ill populations, depressive symptoms shortened telomeres in the current sample, but instead of being biologically adaptive, greater distress potentially amplified the body's production of telomerase indirectly, which ultimately supported tumorigenesis. To clarify, none of the proposed explanations discussed in the current section were tested in the current investigation, and should therefore, be considered on a theoretical level. Considerably more research examining the nuanced relationships between depression, LTL, telomerase, and medical factors known to influence tumor biology, including disease stage and treatments, from a longitudinal perspective is required to elucidate findings that emerged from the current investigation.

Most importantly, however, elucidating the elements of the intervention that contributed to poorer psychological and biological health should be prioritized. Although it is challenging to interpret the LTL findings in context of the broader literature, as there has only been one study that examined the effects of an MBI on TL among cancer patients, the pilot intervention led to statistically significant increases in LTL, which was unexpectedly associated with shorter survival. The only other study that examined the effects of an MBI on TL to date revealed that TL was maintained following an MBCR intervention compared to the control groups, whose TL decreased (Carlson et al., 2013). Importantly, however, as previously mentioned, this sample was among breast cancer survivors, who from a biological and psychosocial perspective, likely differ from NSCLC patients many of which were far from survivorship status. Although a number of potential explanations have been discussed under hypothesis 2a, findings from primary and *post-hoc* analysis of hypothesis 2c, combine to suggest that active component(s) of the iPod-based MBI were detrimental to the small sample of NSCLC patients included in the current investigation, demanding greater consideration from researchers and clinicians alike.

Hypothesis 2d. Hypothesis 2d proposed that participation in and use of the intervention would be associated with longer survival. **Hypothesis 2d was partially supported.**

As hypothesized, the intervention emerged as a significant predictor of survival calculated both from study entry and date of diagnosis; however, inconsistent with the hypothesis, participation in the intervention was associated with shorter survival (Figures

9 and 10). Thus, the hypothesized association emerged as significant, but not in the hypothesized direction, yielding partial support for hypothesis 2d.

Similar to hypothesis 2a and 2c, among those who participated in the intervention, greater use of the intervention did not predict shorter survival, only participation in the intervention emerged as significant, suggesting that there was not a dose-response relationship and findings could be attributable to a selection effect. Additionally, *post-hoc* analyses demonstrated that use of practice tracks did not predict survival, and shorter survival could not be explained by use of the track “Awareness of the breath,” further suggesting that an aspect of the intervention, rather than the specific content of the intervention, contributed to poorer outcomes. As discussed at length under hypothesis 2a and 2c, there are a number of potential explanations hypothesizing why the pilot iPod intervention was unexpectedly related to poorer outcomes, although greater listening behavior, use of practice tracks, and use of the track with explicit focus on the breath, based on the available data, did not emerge as a likely explanation. However, conclusions surrounding listening behavior are restricted by the fact that participants largely did not listen to didactic tracks, which restricted power to make comparisons. Thus, as discussed under hypothesis 2a, it is possible lack of instruction regarding the order of tracks (didactic followed by or intermixed with practice) inadvertently facilitated an increase in awareness of distressing internal experiences, that without guidance, could have been interpreted by intervention participants as both distressing and concerning, leading them to terminate the intervention prior to fully gaining stress-reduction skills. Thus, it is more likely that limited instruction regarding track order, compiled by a virtual instructor void

of interpersonal dialogue contributed to poorer outcomes than the content of the intervention.

As previously mentioned, although results from the current investigation should be interpreted cautiously given the aforementioned limitations to the study, namely that the design of the intervention was not randomized, results from the current hypothesis are clinically concerning and cannot be dismissed, especially in conjunction with the results that emerged following hypothesis 2a and 2c. While the current study should not be replicated at minimum without random assignment for ethical reasons, these findings will hopefully motivate efforts toward dismantling the active components of MBSR and MBIs to subsequently be tested among cancer patients, and sub-samples of the cancer patient population (i.e., lung cancer). Although the analysis from the current investigation was exploratory in nature, given the gravity of the results, the findings from the current dissertation should still be taken seriously in clinical contexts. The majority of *published* research on the effects of MBSR and MBIs among cancer patients has demonstrated benefit, or at least has not reported harm; thus, it is plausible to conclude that there was an underlying component inherent to the current intervention that was detrimental. It is still possible that the component of attention to the breath, which is common to meditation practice, led to an increase in depressive symptoms and related outcomes among this sample despite results that emerged following *post-hoc* analysis to suggest that greater use of the “Awareness of the breath,” track was not associated with greater depressive symptoms or shorter survival. However, the unspecified track order and limited access to a trained instructor are equally viable competing hypotheses. Indeed, it may have been a combination of the three. With greater power and a stronger

methodological design, it would have been helpful to explore the moderating role of a trained instructor on the potential association between increased attention to the breath and inner experiences and an increase in depressive symptoms and shorter survival.

Summary. The evidence that emerged from analysis of Aim 2 hypotheses cumulatively and cohesively suggest that the intervention was associated with worsening psychological and physical health and shorter survival among a small sample of NSCLC patients. Contrary to the hypothesized and intended benefits of the pilot iPod-based MBI, the intervention yielded sobering negative associations. Because the intervention was not randomized, it is possible there were undetected differences between the two groups predisposing the intervention group to poorer outcomes. However, baseline differences were controlled for in each analysis and the initial exploratory analysis comparing the two groups demonstrated that chemotherapy treatment status at baseline was the only demographic/medical factor differentiating the two groups. Importantly, those who were receiving chemotherapy at study entry were actually less likely to participate in the intervention, suggesting results are likely best explained by an unidentified factor related to the intervention opposed to a biased sample.

Although unintentional, these analyses inadvertently contributed to a gap in the mindfulness-based literature: absence of research on the harmful or negative effects of MBIs (Irving, Dobkin, & Park, 2009). These results demonstrate that under specific conditions, MBIs may in fact confer risk and even be harmful. In accordance with Baer and colleagues' (2019) extensive discussion surrounding the potential sources for harm in MBIs, including program/intervention, participant, and instructor/clinician factors, the current dissertation identifies a number of factors from each of these categories that may

have conferred risk for harm among the current sample. Unfortunately, although these factors cannot be compared, and therefore, confirmed as explanations in the current investigation, each one of these factors was discussed as a hypothetical explanation for the current findings (i.e., program/intervention: iPod-based; participant: lung cancer patients; instructor/clinician: optional and underutilized at the drop-in group). It is clear that Baer and colleagues' (2019) discussion surrounding the potential for MBIs to induce harm should be taken seriously by researchers and clinicians alike.

Conclusions

Taken all together, although results from the current investigation should be interpreted cautiously, the current dissertation provides a number of informative data points regarding depressive symptoms, telomere length, survival, and the use of an iPod-based MBI among NSCLC patients (see Figure 2).

1. Only clinical, not sub-clinical, levels of depression at baseline predicted shorter survival from both date of study entry and date of diagnosis (hypothesis 1a).
2. All things held constant, ethnic minorities evidenced greater shortening of LTL (hypothesis 1c).
3. The intervention was associated with an increase in depressive symptoms, an increase in LTL, and shorter survival from both date of study entry and date of diagnosis (hypothesis 2a, 2c, 2d).
4. An increase in LTL was associated with shorter survival from both date of study entry and date of diagnosis (*post-hoc* hypothesis 2c/hypothesis 1e).
5. Although an increase in depressive symptoms was initially associated with a decrease in LTL (hypothesis 1c), upon closer examination, it seems as depressive

symptoms increased, LTL only shortened among patients who did not participate in the intervention, whereas LTL lengthened among those who participated in the intervention (*post-hoc* hypothesis 2c/1c).

Although mediations and moderation analyses extend the scope of the current dissertation, and the design of the study did not meet criteria for these analyses, these results point to longer LTL as a potential biological explanation for the depression-survival relationship among lung cancer patients. Little is known about the longitudinal changes in LTL across the cancer trajectory and how it is dynamically influenced by telomerase, tumorigenesis, and psychological factors, such as worsening depression, but results from this dissertation further support the importance and complexity of telomere biology in cancer populations. Surprisingly, the less supported biomarker, TL, as compared to cortisol, emerged as the potential link between worsening depressive symptoms and shorter survival.

Results from the current dissertation also highlight the importance of taking a humanistic approach to psycho-oncology by comprehensively considering the entire biopsychosocial perspective of the population of interest. In clinical research it is often both appropriate and efficient to generalize across sub-populations; however, it seems that generalizations cannot always be made across cancer sub-types (i.e., breast to lung), as there are unique factors differentiating their experience. Furthermore, it seems generalizations across patients at different points in the cancer trajectory may not have been appropriate as the majority of support for the intervention stemmed from research among breast cancer survivors. Although the specific factors of the population and the components of the intervention that contributed to poorer health on a psychological,

biological, and clinical level remain unclear, results from the current investigation that starkly contradict other findings in the literature demonstrate that active ingredients of the current intervention were under considered. While these results are unsettling and completely contradictory to *a-priori* hypotheses, they affirm the importance of conducting pilots and may caution against feasibility to the point of sacrificing efficacy of the intervention. Once again, although the underlying cause of risk cannot be confirmed, it is reasonable to speculate that patients facing mortality might require interpersonal support from a trained mental health professional, either in-person or virtually, throughout the MBI, as it can prompt greater attention to difficult inner experiences, both psychologically and physically.

LIMITATIONS

Although a number of limitations to the current dissertation have already been acknowledged, given the gravity of the findings, it is necessary to emphasize the limitations to the current investigation. First, the directionality between depression and biomarkers cannot be assumed since they were collected at roughly the same time point (e.g., baseline and follow-up). For this reason, the temporal precedence criteria discussed by Kraemer and colleagues (2008) for mediation and moderation statistical analysis was not met, limiting the conclusions that could be made in the current investigation.

Although an increase in depressive symptoms was associated with change in LTL, and both were predictive of shorter survival, LTL could not be tested as a mechanism in the depression-survival pathway due to methodological limitations.

As previously mentioned, other methodological limitations also exist. Although the overall sample size supported primary hypotheses, small sub-sample sizes (e.g., minority status, number of participants in the intervention, intervention listening behavior, etc.) limited power and the ability to statistically test differences in observed patterns and elucidate findings. Additionally, the pilot nature of the intervention (optional and not randomized) further limited the conclusive nature of its effects. Although there did not appear to be significant differences between those who opted to participate in the intervention versus those who did not, other than chemotherapy treatment status at

baseline, the intervention was not randomized, which further convolutes the striking and unexpected intervention findings.

Lastly, there was considerable variation in the medical characteristics of the sample given that one of the inclusion criteria was a NSCLC diagnosis within five years of study entry. Interpretation of findings related to biomarkers (i.e., LTL) was limited by the medical heterogeneity of the sample. There was considerable variability in where each patient was in the cancer trajectory given that some were actively receiving treatment (chemotherapy: $n = 24$; radiation: $n = 3$) at study entry, whereas others were not, but had also not reached survivorship status.

FUTURE DIRECTIONS

Given the exploratory rather than confirmatory nature of the current dissertation, a number of questions remain unanswered and warrant future investigation. Regarding Aim 1 and the mechanisms of the depression-survival pathway, future investigations should attempt to elucidate the role of factors and subtypes of depression as it relates to shorter survival. As discussed under hypothesis 1a, greater investigation into the severity, symptom clusters, history, and subtypes of depression could identify the patients at greatest risk and inform nuanced interventions to improve clinical outcomes. Moreover, in addition to testing LTL as a mediator of the depression-survival pathway, greater investigation into the longitudinal change in peripheral TL as relates to telomerase, tumorigenesis and distress/depression in current samples would increase the utility of LTL as potentially feasible clinical biomarker in cancer contexts.

Regarding Aim 2 and the clinically concerning results that emerged following the pilot iPod-based MBI, while future investigations should not aim to replicate the current investigation, dismantling studies should attempt to identify the active components of MBSR and MBIs to subsequently be tested among cancer patients and specific cancer types (e.g., lung) at different points in the cancer trajectory (e.g., prior to survivorship). Although other mobile studies without a group component have demonstrated efficacy in reducing depressive symptoms among cancer patients (Lengacher et al., 2018), the potential benefits of the group component should also be examined given the mounting

evidence demonstrating that social support yields many benefits among cancer patient populations (Uchino, 2004). The order and balance between didactics and practice content in e-health interventions should also be clarified and adapted accordingly. Additionally, future investigations should elucidate the role of a trained, easily accessible instructor in e-health interventions to balance feasibility and efficacy.

FINAL CONCLUSIONS

In conclusion, a cancer diagnosis can be devastating, as it is followed by an arduous battle for survivorship that is, unfortunately, not always won. Typically, the primary goal is to extend life given that much of the distress that accompanies cancer stems from the very real, pressing threat of mortality. However, in consideration of this harsh reality, that survivorship may not be achieved, quality of life becomes highly valued. Said best by June Goodfield, and quoted by Siddhartha Mukherjee, in *The Emperor of All Maladies: A Biography of Cancer*, “Cancer begins and ends with people. In the midst of scientific abstraction, it is sometimes possible to forget this one basic fact” (p. 1). The shortcomings of the well intentioned current intervention may be best explained by this quote, as many of the proposed components that may have conferred risk could have potentially been avoided following greater consideration of the larger biopsychosocial perspective opposed to focus on scientific abstraction. Thus, identifying interventions that treat people, by enhancing both quality and quantity of life remain an overarching priority in oncology settings.

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Table 1.

A list of the Mindfulness-Based iPod Intervention Tracks.

Didactic Tracks (minutes: seconds)	Practice Tracks (minutes: seconds)
1. Introduction (11:26)	1. Sitting Meditation Instructions (8:11)
2. Foundation, Importance of Attitudes (3:54)	2. Awareness of the Breath (11:05)
3. Non-judging (4:04)	3. 5 Minute Sitting Meditation (5:18)
4. Patience (3:46)	4. 10 Minute Sitting Meditation (10:16)
5. Beginner's Mind (3:41)	5. 15 Minute Sitting Meditation (15:16)
6. Trust (4:06)	6. 20 Minute Sitting Meditation (20:19)
7. Non-Striving (6:19)	7. Extended Sitting Meditation (41:03)
8. Acceptance (4:46)	8. Loving Kindness Meditation (5:40)
9. Letting Go (6:53)	9. Informal Mindfulness Practice (3:17)
10. The Present Moment (11:56)	10. Mountain Meditation (20:04)
11. Wandering Mind (1) (7:53)	11. Body Scan Meditation (40:22)
12. Wandering Mind (2) (9:17)	
13. Stress and Mindfulness (1) (7:45)	
14. Stress and Mindfulness (2) (7:08)	
15. Working with Difficult Emotions (7:22)	
16. Taking Care of Yourself (5:43)	
17. Social Support (9:05)	
18. Self Compassion (7:00)	
19. Accepting Emotions (8:52)	
20. Living with Cancer (1) (5:47)	
21. Living with Cancer (2) (5:52)	
22. Living with Cancer (3) (5:18)	
23. Cancer Teamwork (6:17)	
24. Caring and Sharing (8:37)	
25. I am not this Cancer (7:56)	
26. Waiting (11:35)	
27. Holding on and Letting Go (7:40)	
28. Acknowledgment (2:07)	
29. Taking Your Place (4:26)	
30. 'Letting Go' (3:29)	
31. 'Wild Geese' (2:18)	
32. 'The Summer Day' (2:25)	

Table 2.

Sample characteristics.

Variable	Frequency (n)	Percent (%)	Mean
<u>Sex</u>			
Male	21	31.3	
Female	41	61.2	
*	5	7.5	
<u>Age</u>			61.5
<u>Race/Ethnicity</u>			
Non-Hispanic White	39	58.2	
Black/African American	10	14.9	
Hispanic or Latino	1	1.5	
Asian/Asian American	1	1.5	
Other	1	1.5	
*	15	22.4	
Minority Status			
Yes	13	19.4	
No	39	58.2	
<u>Annual Household Income</u>			
≥\$15,000 - 39,999	36	53.7	
\$40,000 - 79,999	15	22.4	
\$80,000 – 149,999	7	10.5	
\$150,000 - 249,999	1	1.5	
*	8	11.9	
<u>Age at Diagnosis</u>			59.6
<u>Disease Stage at Diagnosis</u>			
I	15	22.4	
II	8	11.9	
III	28	41.8	
IV	16	23.9	
Early (I, II)	23	34.3	
Late (III, IV)	44	65.7	
<u>Treatment Factors</u>			
Chemotherapy at study entry			
Yes	21	31.3	
No	38	56.7	
*	8	11.9	
Radiation at study entry			
Yes	3	4.5	
No	57	85.1	
*	7	10.4	
Chemotherapy ever			
Yes	48	71.6	
No	12	17.9	

	*	7	10.4	
Radiation ever				
	Yes	38	56.7	
	No	22	32.8	
	*	7	10.4	
Time since diagnosis (months)				23.5
<u>Predictors and Outcomes at Baseline</u>				
Depression		59	88.1	15.5
*		8	11.9	
Above clinical cut-off ^a		29	43.3	23.9
Overall mean cortisol ^b		58	86.6	-2.17
*		9	13.4	
Bedtime mean cortisol ^b		58	86.6	-2.83
*		9	13.4	
Diurnal cortisol slope ^b		57	85.1	-0.05
*		10	14.9	
TL at baseline		64	95.5	0.82
*		3	4.5	

Notes. *Missing data.

^a The clinical cut off on the CES-D is 16.

^b Log transformed variables.

Table 3.

Correlations between Theoretically-Derived Covariates and Independent and Dependent Variables ('a' and 'd' Hypotheses).

	<i>Correlations</i>				
	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>	<i>14</i>
1. Disease stage	-.066	.017	.094	-.252	-.262
2. Age	-.092	-.247	-.176	-.056	-.088
3. Age at diagnosis	-.074	-.205	-.146	-.056	-.194
4. Sex	-.060	.154	.053	.305*	.209
5. Chemotherapy treatment at baseline	.325*	-.057	-.066	-.183	-.200
6. Ever received chemotherapy	-.063	-.027	.018	.149	.109
7. Radiation treatment at baseline	.077	.265	.201	.002	.000
8. Every received radiation	-.044	-.175	.011	-.132	.091
9. Smoking history	.109	.063	.045	-.265	-.069
10. Depressive symptoms at baseline	1	-	-	-	-
11. Change in depressive symptoms	-	1	-	-	-
12. Intent-to-treat	-	-	1	-	-
13. Survival from study entry	-	-	-	1	-
14. Survival from date of diagnosis	-	-	-	-	1

Note. * $r \geq 0.3$ and ≤ 0.5

Table 4.

Correlations Between Theoretically-Derived Covariates and Independent and Dependent Variables ('b' Hypotheses).

	<i>Correlation</i>											
	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>	<i>14</i>	<i>15</i>	<i>16</i>	<i>17</i>	<i>18</i>	<i>19</i>	<i>20</i>	<i>21</i>
1. Disease stage	-.07	.02	.09	.19	-.14	-.05	.21	-.11	-.10	.04	.12	.06
2. Age	-.09	-.25	-.18	.26	-.18	-.08	.33*	-.06	.01	.13	-.05	-.07
3. Age at diagnosis	-.07	-.21	-.15	.25	-.15	-.07	.31*	-.06	.02	.13	-.04	-.06
4. Sex	-.06	.15	.05	-.08	-.12	-.04	-.11	.10	.08	-.06	-.07	-.06
5. Chemo at baseline	.33*	-.06	-.07	.16	.02	-.01	.05	.01	-.02	.01	.27	.21
6. Ever received chemo	-.06	-.03	.02	-.09	.03	.05	-.09	-.23	-.10	-.06	-.24	-.20
7. Radiation at baseline	.08	.27	.20	.03	.08	.08	.07	-.08	-.10	.11	-.27	-.13
8. Ever received radiation	-.04	-.18	.01	-.01	.01	.03	-.01	-.17	-.11	.03	-.13	-.09
9. Smoking history	.11	.06	.05	.02	-.03	-.01	.08	.07	.10	.21	-.05	.06
10. Depressive symptoms at baseline	1	-	-	-	-	-	-	-	-	-	-	-
11. Change in depressive symptoms	-	1	-	-	-	-	-	-	-	-	-	-
12. Intent-to-treat	-	-	1	-	-	-	-	-	-	-	-	-

13. Baseline overall mean cortisol	-	-	-	1	-	-	-	-	-	-	-	-
14. Change in overall mean cortisol	-	-	-	-	1	-	-	-	-	-	-	-
15. Intent-to-treat	-	-	-	-	-	1	-	-	-	-	-	-
16. Baseline bedtime mean cortisol	-	-	-	-	-	-	1	-	-	-	-	-
17. Change in bedtime mean cortisol	-	-	-	-	-	-	-	1	-	-	-	-
18. Intent-to-treat	-	-	-	-	-	-	-	-	1	-	-	-
19. Baseline diurnal cortisol slope	-	-	-	-	-	-	-	-	-	1	-	-
20. Change in diurnal cortisol slope	-	-	-	-	-	-	-	-	-	-	1	-
21. Intent-to-treat	-	-	-	-	-	-	-	-	-	-	-	1

Note. * $r \geq 0.3$ and ≤ 0.5

Table 5.

Correlations Between Theoretically-Derived Covariates and Independent and Dependent Variables ('c' Hypotheses).

	<i>Correlation</i>					
	<i>11</i>	<i>12</i>	<i>13</i>	<i>14</i>	<i>15</i>	<i>16</i>
1. Disease stage	-.066	.017	.094	.117	-.037	.011
2. Age	-.092	-.247	-.176	-.295	-.070	-.024
3. Age at diagnosis	-.074	-.205	-.146	-.312*	-.120	-.053
4. Sex	-.060	.154	.053	.136	.068	.087
5. Chemo at baseline	.325*	-.057	-.066	-.018	.212	.249
6. Ever received chemo	-.063	-.027	.018	.246	.065	.100
7. Radiation at baseline	.077	.265	.201	-.049	-.134	-.146
8. Ever received radiation	-.044	-.175	.011	.062	.294	.193
9. Smoking history	.109	.063	.045	-.258	.126	.057
10. Ethnic minority status	.151	.251	.265	.003	-.332*	.251
11. Depressive symptoms at baseline	1	-	-	-	-	-
12. Change in depressive symptoms	-	1	-	-	-	-
13. Intent-to-treat	-	-	1	-	-	-
14. Baseline LTL	-	-	-	1	-	-
15. Change in LTL	-	-	-	-	1	-
16. Intent-to-treat	-	-	-	-	-	1

Note. * $r \geq 0.3$ and ≤ 0.5

Table 6.

Demographic and Medical Differences Between Intervention Groups (Exploratory Analysis).

	Completed Intervention		Did not Complete Intervention				
	M	SD	M	SD	<i>t</i> -test	χ^2	<i>U</i>
Demographics							
Age	61.0	9.5	61.7	8.4	.729		
Age at Diagnosis	59.2	9.6	59.8	8.6	.775		
Sex	-	-	-	-	-	.798	
Minority Status	-	-	-	-	-	.142	
Education †	-	-	-	-	-		.301
Income †	-	-	-	-	-		.239
Medical							
Disease Stage	-	-	-	-	-		
Treatment	-	-	-	-	-		
Chemotherapy							
At baseline	-	-	-	-	-	.050*	
Ever	-	-	-	-	-	.190	
Radiation							
At baseline	-	-	-	-	-	.764	
Ever	-	-	-	-	-	.085	
Months between diagnosis and study entry	626.7	389.9	749.5	616.0	.375		
Pack Years	46.7	36.2	37.5	24.4	.269		

Notes. * $p \leq .05$

† Continuous variable, tested with Mann-Whitney U test

Table 7.

Associations Between Depressive Symptoms and Survival (Hypothesis 1a).

Depressive Symptoms at Baseline on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>		Hazard Ratio	95% CI
Sex	0.669	1	.090	1.953	0.901	4.231
Depression	0.023	1	.206	1.023	0.987	1.06
Sex	0.654	1	.096	1.924	0.89	4.16
Intervention	-0.926	1	.017*	0.396	0.185	0.85
Depression	0.025	1	.175	1.025	0.989	1.062
Depressive Symptoms at Baseline on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>		Hazard Ratio	95% CI
Depression	0.027	1	.139	1.027	0.991	1.064
Intervention	-0.905	1	.021*	0.405	0.188	0.87
Depression	0.024	1	.180	1.024	0.989	1.061
Change in Depressive Symptoms on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>		Hazard Ratio	95% CI
Sex	0.763	1	.154	2.145	0.752	6.121
Depression	0.453	1	.869	1.573	0.007	338.148
Sex	0.736	1	.185	2.088	0.736	1
Intervention	-1.12	1	.087	0.326	-1.12	1
Depression	-0.728	1	.810	0.483	-0.728	1
Change in Depressive Symptoms on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>		Hazard Ratio	95% CI
Depression	0.625	1	.798	1.869	0.015	226.456
Intervention	-0.781	1	.241	0.458	0.124	1.688

Depression	-0.318	1	.904	0.727	0.004	128.856
Change in Depressive Symptoms (intent-to-treat) on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>		Hazard Ratio	95% CI
Sex	0.686	1	.086	1.985	0.908	4.338
Depression	1.085	1	.663	2.961	0.022	391.42
Sex	0.684	1	0.09	1.982	0.899	4.371
Intervention	-0.915	1	0.021	0.4	0.184	0.871
Depression	-0.233	1	0.926	0.792	0.006	111.355
Change in Depressive Symptoms (intent-to-treat) on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>		Hazard Ratio	95% CI
Depression	1.5	1	.526		4.484	0.044
Intervention	-0.939	1	.020*		0.391	0.178
Depression	-0.026	1	.991		0.975	0.01
<i>Note.</i> * $p < .05$						

Table 8.

Depressive Symptoms Regressed on Markers of Diurnal Cortisol (Hypothesis 1b).

Depressive Symptoms on Overall Mean Cortisol Assessed at Baseline									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.127	0.016	0.016	.356	.866	.356
Depression	0.127	0.93	0.356						
Depressive Symptoms on Bedtime Mean Cortisol Assessed at Baseline									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.058	0.003	0.003	.675	.178	.675
Depression	0.058	0.422	.675						
Model 2				0.354	0.125	0.122	.010	3.720	.031*
Depression	0.100	0.764	.448						
Age	0.352	2.691	.010*						
Model 2				0.328	0.108	0.104	.017*	3.133	.052
Depression	0.09	0.682	0.499						
Age at diagnosis	0.324	2.464	0.017						
Depressive Symptoms on Diurnal Cortisol Slope Assessed at Baseline									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.069	0.005	0.005	.615	.256	.615
Depression	0.069	0.506	.615						

Change in Depressive Symptoms on Change in Overall Mean Cortisol									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.176	0.031	0.031	0.41	.706	.410
Depression	0.176	0.84	0.410						
Model 2				0.328	0.108	0.077	0.193	1.270	.302
Depression	0.283	1.281	.214						
Intervention	-0.297	-1.344	.193						
Change in Depressive Symptoms on Change in Bedtime Mean Cortisol									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.231	0.053	0.053	0.278	1.237	.278
Depression	0.231	1.112	0.278						
Model 2				0.362	0.131	0.078	0.185	.1580	.229
Depression	0.338	1.55	0.136						
Intervention	-0.298	-1.369	0.185						
Change in Depressive Symptoms on Change in Diurnal Cortisol Slope									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.209	0.044	0.044	.339	.957	.339
Depression	0.209	0.978	.339						
Model 2				0.222	0.049	0.006	.730	.520	.602
Depression	0.181	0.783	.443						
Intervention	0.081	0.350	.730						

Change in Depressive Symptoms on Change in Overall Mean Cortisol (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.138	0.019	0.019	.316	1.024	.316
Depression	0.138	1.012	.316						
Model 2				0.238	0.057	0.038	0.155	1.564	.219
Depression	0.194	1.384	.172						
Intervention	-0.202	-1.443	.155						
Change in Depressive Symptoms on Change in Bedtime Mean Cortisol (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.187	0.035	0.035	.172	1.916	.172
Depression	0.187	1.384	.172						
Model 2				0.248	0.061	0.026	.231	1.700	.193
Depression	0.234	1.672	.100						
Intervention	-0.169	-1.211	.231						
Change in Depressive Symptoms on Change in Diurnal Cortisol Slope (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.198	0.039	0.039	.151	2.122	.151
Depression	0.198	1.457	.151						
Model 2				0.205	0.042	0.003	.693	1.123	.333
Depression	0.182	1.278	.207						
Intervention	0.057	0.397	.693						
<i>Note.</i> * $p < .05$									

Table 9.

Depressive Symptoms Regressed on LTL (Hypothesis 1c).

Depressive Symptoms on LTL Assessed at Baseline									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.157	0.025	0.025	.242	1.398	.242
Depression	-0.157	-1.182	.242						
Model 2				0.356	0.127	0.102	.015	3.915	.026*
Depression	-0.191	-1.495	.141						
Age at diagnosis	-0.321	-2.509	.015*						
Depressive Symptoms on Change in LTL									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.058	0.003	0.003	.675	1.988	.171
Depression	-0.271	-1.41	.171						
Model 2				0.354	0.125	0.122	.010*	4.914	.016*
Depression	-0.418	-2.318	.029*						
Minority Status	0.488	2.708	.012*						
Model 3				0.626	0.391	0.101	.063	4.930	.009**
Depression	-0.508	-2.875	.009**						
Minority Status	0.453	2.639	.015*						
Intervention	0.335	1.952	.063						

Change in Depressive Symptoms on Change in LTL (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.102	0.01	0.01	.449	.582	.449
Depression	-0.102	-0.763	.449						
Model 2				0.228	0.052	0.042	.130	1.481	.237
Depression	-0.159	-1.155	.253						
Intervention	0.211	1.538	.130						
<i>Note.</i> * $p < .05$, ** $p < .01$									

Table 10.

Association Between the Intervention and Change in Depressive Symptoms (Hypothesis 2a).

Change in Depressive Symptoms						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial η^2</i>
Baseline differences (intercept)	0.002	1	0.002	0.264	.612	0.010
Chemotherapy	0.001	1	0.001	0.145	.706	0.006
Intervention	0.018	1	0.018	2.314	.140	0.082
Change in Depressive Symptoms (intent-to-treat)						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial η^2</i>
Baseline differences (intercept)	0.001	1	0.001	0.269	.606	0.005
Chemotherapy	0.002	1	0.002	0.367	.547	0.007
Intervention	0.023	1	0.023	5.36	.024*	0.09
Baseline differences (intercept)	0.002	1	0.002	0.641	.427	0.002
Chemotherapy	0.003	1	0.003	1.139	.291	0.003
Intervention	0.013	1	0.013	4.275	.044*	0.013

Note. * $p < .05$, ** $p < .01$

Table 11.

Use of the Intervention Regressed on Change in Depressive Symptoms (Hypothesis 2a).

Total Listening Time on Change in Depressive Symptoms									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.196	0.038	0.038	.407	.719	.407
Intervention	-0.196	-0.848	.407						
Total Number of Tracks on Change in Depressive Symptoms									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.206	0.043	0.043	.383	.800	.383
Intervention	-0.206	-0.894	.383						
Total Listening Time on Change in Depressive Symptoms (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.313	0.098	0.098	.128	2.494	.128
Intervention	0.313	0.098	.098						
Total Number of Tracks on Change in Depressive Symptoms (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.318	0.101	0.101	0.121	2.587	.121
Intervention	0.318	0.101	0.101						

Note. * $p < .05$

Table 12.

Association Between the Intervention and Change in Markers of Diurnal Cortisol (Hypothesis 2b).

Change in Overall Mean Cortisol						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial η^2</i>
Baseline differences (intercept)	4.70E-05	1	4.70E-05	1.505	.231	0.057
Chemotherapy	1.14E-05	1	1.14E-05	0.364	.552	0.014
Intervention	3.46E-05	1	3.46E-05	1.108	.303	0.042
Change in Bedtime Mean Cortisol						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial η^2</i>
Baseline differences (intercept)	1.86E-05	1	1.86E-05	0.32	.576	0.013
Chemotherapy	1.23E-06	1	1.23E-06	0.021	.886	0.001
Intervention	1.37E-05	1	1.37E-05	0.236	.631	0.009
Change in Diurnal Cortisol Slope						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial η^2</i>
Baseline differences (intercept)	4.49E-06	1	4.49E-06	9.844	.004**	0.291
Chemotherapy	1.32E-06	1	1.32E-06	2.903	.101	0.108
Intervention	2.40E-08	1	2.40E-08	0.053	.821	0.002
Change in Overall Mean Cortisol (intent-to-treat)						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial η^2</i>
Baseline differences (intercept)	2.33E-05	1	2.33E-05	1.398	.243	0.027
Chemotherapy	1.22E-05	1	1.22E-05	0.732	.396	0.014
Intervention	3.24E-05	1	3.24E-05	1.946	.169	0.037

Change in Bedtime Mean Cortisol (intent-to-treat)

Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial</i> η^2
Baseline differences (intercept)	2.42E-05	1	2.42E-05	0.786	.379	0.015
Chemotherapy	4.14E-07	1	4.14E-07	0.013	.908	0
Intervention	2.60E-05	1	2.60E-05	0.844	.363	0.016

Change in Diurnal Cortisol Slope (intent-to-treat)

Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial</i> η^2
Baseline differences (intercept)	1.13E-06	1	1.13E-06	3.58	.064	0.067
Chemotherapy	6.81E-07	1	6.81E-07	2.16	.148	0.041
Intervention	1.21E-07	1	1.21E-07	0.384	.539	0.008

Note. * $p < .05$, ** $p < .01$

Table 13.

Use of the Intervention Regressed on Change in Markers of Diurnal Cortisol (Hypothesis 2b).

Total Listening Time on Change in Overall Mean Cortisol									
Variable	β	T	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.01	0	0	.970	.001	.970
Intervention	0.01	0.038	.970						
Total Number of Tracks on Change in Overall Mean Cortisol									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.018	0	0	.945	.005	.945
Intervention	-0.018	-0.07	.945						
Total Listening Time on Change in Bedtime Mean Cortisol									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.026	0.001	0.001	.921	.010	.921
Intervention	0.026	0.101	.921						
Total Number of Tracks on Change in Bedtime Mean Cortisol									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.020	0	0	.940	.006	.940
Intervention	0.02	0.076	.940						
Total Listening Time on Change in Diurnal Cortisol Slope									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.093	0.009	0.009	.731	.123	.731

Intervention	0.093	0.351	.731						
Total Number of Tracks on Change in Diurnal Cortisol Slope									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.104	0.011	0.011	0.702	.152	.702
Intervention	0.104	0.39	.702						
Total Listening Time on Change in Overall Mean Cortisol (intent-to-treat)									
Variable	β	T	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.02	0	0	.929	.008	.929
Intervention	-0.02	-0.09	.929						
Total Number of Tracks on Change in Overall Mean Cortisol (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.05	0.003	0.003	.819	.053	.819
Intervention	-0.05	-0.231	.819						
Total Listening Time on Change in Bedtime Mean Cortisol (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.015	0	0	.946	.005	.946
Intervention	-0.015	-0.069	.946						
Total Number of Tracks on Change in Bedtime Mean Cortisol (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.031	0.001	0.001	.890	.002	.890
Intervention	-0.031	-0.14	.890						

Total Listening Time on Change in Diurnal Cortisol Slope (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.071	0.005	0.005	.747	.107	.747
Intervention	0.071	0.327	.747						
Total Number of Tracks on Change in Diurnal Cortisol Slope (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.081	0.007	0.007	.007	.140	.712
Intervention	0.081	0.374	.712						

Table 14.

Association Between the Intervention and Change in LTL (Hypothesis 2c).

Change in LTL						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial</i> η^2
Baseline differences (intercept)	9.01E-10	1	9.01E-10	0.003	.960	0
Chemotherapy	1.75E-06	1	1.75E-06	4.915	.033*	0.126
Intervention	1.95E-06	1	1.95E-06	5.454	.026*	0.138
Change in LTL (intent-to-treat)						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial</i> η^2
Baseline differences (intercept)	2.94E-08	1	2.94E-08	0.106	.746	0.002
Chemotherapy	1.57E-06	1	1.57E-06	5.652	.021*	0.096
Intervention	7.75E-07	1	7.75E-07	2.791	.101	0.05

Note. * $p < .05$

Table 15.

Use of the Intervention Regressed on Change in LTL (Hypothesis 2c).

Total Listening Time on Change in LTL									
Variable	β	T	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.167	0.028	0.028	.446	.603	.446
Intervention	-0.167	-0.776	.446						
Total Number of Tracks on Change in LTL									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.134	0.018	0.018	.543	.383	.543
Intervention	-0.134	-0.619	.543						
Total Listening Time on Change in LTL (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.156	0.024	0.024	.466	.551	.466
Intervention	-0.156	-0.742	.466						
Total Number of Tracks on Change in LTL (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.13	0.017	0.017	.546	.376	.546
Intervention	-0.13	-0.613	.546						

Table 16.

Association Between Use of the Intervention and Survival from Date of Study Entry and Date of Diagnosis (Hypothesis 2d).

Total Listening Time on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Intervention	0	1	.107	1	1	1
Sex	0.525	1	.179	1.69	0.787	3.632
Total Number of Tracks on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Intervention	0.001	1	.210	1.001	0.999	1.003
Sex	0.57	1	.177	1.768	0.773	4.043
Total Listening Time on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Intervention	0	1	.094	1	1	1
Total Number of Tracks on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Intervention	0.001	1	.179	1.001	0.999	1.003

Table 17.

Sub- and Clinical Levels of Depressive Symptoms Regressed on Markers of Diurnal Cortisol (Post-hoc, Hypothesis 1b).

Depressive Symptoms on Overall Mean Cortisol Assessed at Baseline									
	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1									
Sub-clinical	0.01	0.049	.961	0.01	0	0	.961	.002	.961
Clinical	-0.258	-1.362	.185	0.258	0.067	0.067	.185	1.854	.185
Depressive Symptoms on Bedtime Mean Cortisol Assessed at Baseline									
	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1									
Sub-clinical	0.239	1.229	.23	0.239	0.057	1.512	.230	1.512	.230
Clinical	-0.342	-1.858	.074	0.342	0.117	3.453	.074	3.453	.074
Model 2									
Sub-clinical	0.119	0.655	.519	0.512	0.262	6.676	.016	4.265	.026*
Age	0.469	2.584	.016*						
Clinical	-0.309	-1.627	.116	0.375	0.141	0.69	.414	2.051	.150
Age	0.158	0.831	.414						
Model 1									
Sub-clinical	0.239	1.229	.230	0.239	0.057	0.057	.230	1.512	.230
Clinical	-0.342	-1.858	.074	0.342	0.117	0.117	.074	3.453	.074

Model 2									
Sub-clinical	0.138	0.75	.461	0.485	0.236	0.179	.026*	3.698	.040*
Age at diagnosis	0.435	2.368	.026*						
Clinical	-0.316	-1.663	.109	0.365	0.133	0.016	.503	1.922	.167
Age at diagnosis	0.129	0.68	.503						
Depressive Symptoms on Diurnal Cortisol Slope Assessed at Baseline									
	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1									
Sub-clinical	0.411	2.252	.033*	0.411	0.169	0.169	.033	5.073	.033*
Clinical	-0.366	-2.002	.056	0.366	0.134	0.134	.056	4.009	.056
<i>Note. *$p < .05$</i>									

Table 18.

Sub- and Clinical Levels of Depressive Symptoms Regressed on LTL (Post-hoc, Hypothesis 1c).

Depressive Symptoms on LTL Assessed at Baseline									
	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1									
Sub-clinical	-0.268	-1.443	.161	0.268	0.072	0.072	.161	2.081	.161
Clinical	0.132	0.68	.503	0.132	0.017	0.017	.503	.462	.503
Model 2									
Sub-clinical	-0.193	-1.051	.303	0.413	0.17	0.099	.091	2.666	.088
Age	-0.323	-1.758	.091						
Clinical	0.075	0.382	.706	0.283	0.08	0.062	.205	1.085	.353
Age	-0.256	-1.302	.205						

Table 19.

Change in Depressive Symptoms Regressed on Change in LTL Including an Interaction Between Change in Depressive Symptoms and Minority Status (Post-hoc, Hypothesis 1c).

Depressive Symptoms on LTL Assessed at Baseline									
	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.271	0.074	0.074	.171	1.988	.171
Depression	-0.271	-1.41	.171						
Model 2				0.539	0.291	0.217	.012	4.914	.016*
Depression	-0.418	-2.318	.029						
Minority Status	0.488	2.708	.012						
Model 3				0.626	0.391	0.101	.063	.4930	.009*
Depression	-0.508	-2.875	.009						
Minority Status	0.453	2.639	.015						
Intervention	0.335	1.952	.063						
Model 4				0.639	0.408	0.017	.436	2.795	.017*
Depression	-0.856	-1.81	.084						
Minority Status	0.485	2.73	.012*						
Intervention	0.362	2.053	.052						
Change in Depression x Minority status	0.357	0.794	.436						

Note. * $p < .05$

Table 20.

Association Between the Intervention and Change in Depressive Symptoms Including an Interaction Between the Intervention and Chemotherapy (Post-hoc, Hypothesis 2a).

Change in Depressive Symptoms (intent-to-treat)						
Source	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial</i> η^2
Baseline differences (intercept)	0.001	1	0.001	0.219	.642	0.004
Chemotherapy	0.001	1	0.001	0.149	.701	0.003
Intervention	0.028	2	0.014	3.142	.051	0.106
Intervention x Chemotherapy	0.001	1	0.001	0.213	.646	0.004

Table 21.

Association Between Low Versus High (Median Split) Use of the Intervention and Depressive Symptoms (Post-hoc, Hypothesis 2a).

	Total Track Time					Total Number of Tracks				
	Low		High		<i>t</i> -test	Low		High		<i>t</i> -test
	M	SD	M	SD		M	SD	M	SD	
Depression (intent-to-treat)	0.052	0.100	0.011	0.068	.233	0.052	0.100	0.011	0.068	.291

Table 22.

Use of the Intervention (Practice Tracks and “Awareness of the Breath” Track) Regressed on Change in Depressive Symptoms (Post-hoc, Hypothesis 2a).

Total Practice Track Listening Time on Change in Depressive Symptoms (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Intervention	-0.535	-2.002	.073	0.535	0.286	0.286	.073	4.007	.073
Total Number of Practice Tracks on Change in Depressive Symptoms (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Intervention	-0.551	-2.089	.063	0.551	0.304	0.304	.063	4.364	.063
Total Listening Time of the “Awareness of the Breath” Track on Change in Depressive Symptoms (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Intervention	-0.327	-1.583	.128	0.327	0.107	0.107	.128	2.507	.128
Total Number of Times the “Awareness of the Breath” Track Listened to on Change in Depressive Symptoms (intent-to-treat)									
Variable	β	t	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Intervention	-0.327	-1.583	.128	0.327	0.107	0.107	.128	2.507	.128

Table 23.

Association Between the Intervention and Change in LTL Including an Interaction Between the Intervention and Chemotherapy (Post-hoc, Hypothesis 2c).

Source	Change in LTL					
	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>	<i>Partial η^2</i>
Baseline differences (intercept)	1.68E-07	1	1.68E-07	0.537	.469	0.016
Chemotherapy	1.91E-06	1	1.91E-06	6.104	.019*	0.156
Intervention	1.55E-07	2	7.73E-08	0.248	.782	0.015
Intervention x Chemotherapy	1.82E-06	1	1.82E-06	5.831	.021*	0.150

Note. * $p < .05$

Table 24.

Change in LTL Regressed on Survival (Post-hoc, Hypothesis 2c/Hypothesis 1e).

Survival Analysis from Study Entry: Change in LTL						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.002**			
LTL	959.435	1	.001**	-	1.92E+166	-
Model		2	.002**			
LTL	731.339	1	.017*	.	9.27E+56	.
Intervention	-1.178	1	.075	0.308	0.084	1.128
Survival Analysis from Diagnosis: Change in LTL						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.026*			
LTL	695.08	1	.018*	7.40E+301	1.00E+52	-
Model		2	.017*			
LTL	496.454	1	.103	4.05E+215	0	.
Intervention	-1.085	1	.100	0.338	0.093	1.231

Note. * $p < .05$, ** $p < .01$.

Table 25.

Change in Depressive Symptoms Regressed on Change in LTL Including an Interaction Between Change in Depressive Symptoms and the Intervention (Post-hoc, Hypothesis 2c).

Variable	β	T	p	R	R^2	ΔR^2	$p(\Delta R^2)$	F	p
Model 1				0.271	0.074	0.074	0.171	1.988	.171
Depression	-0.271	-1.41	.171						
Model 2				0.455	0.207	0.133	0.056	3.133	.062*
Depression	-0.387	-2.029	.054						
Intervention	0.383	2.009	.056						
Model 3				0.626	0.391	0.184	0.015	4.93	.009**
Depression	-0.508	-2.875	.009**						
Intervention	0.335	1.952	.063						
Minority Status	0.453	2.639	.015*						
Model 4				0.63	0.397	0.006	0.65	3.623	.021*
Depression	-0.474	-2.438	.023*						
Intervention	0.325	1.847	.078						
Minority Status	0.43	2.374	.027*						
Depression x Intervention	0.084	0.46	.650						

Note. * $p < .05$, ** $p < .01$

Table 26.

*Use of the Intervention (Practice Tracks and “Awareness of the Breath” Track)
Regressed on Survival (Post-hoc, Hypothesis 2d).*

Total Practice Track Listening Time on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.759			
Intervention	0	1	0.757	1	0.999	1.001
Total Number of Practice Tracks Listened to on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.762			
Intervention	0.001	1	0.76	1.001	0.993	1.009
Total Practice Track Listening Time on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.965			
Intervention	0	1	0.965	1	0.999	1.001
Total Number of Practice Tracks Listened to on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.974			
Intervention	0	1	0.974	1	0.992	1.008
Total Time Listening to “Awareness of the Breath” Track on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.787			
Intervention	-0.001	1	0.79	0.999	0.993	1.006
Total Number of Times Listened to “Awareness of the Breath” Track on Survival from Study Entry						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	

Model		1	.787			
Intervention	-0.01	1	0.79	0.99	0.922	1.064
Total Time Listening to “Awareness of the Breath” Track on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.925			
Intervention	0	1	0.926	1	0.993	1.006
Total Number of Times Listened to “Awareness of the Breath” Track on Survival from Diagnosis						
Predictor	<i>B</i>	<i>df</i>	<i>p</i>	Hazard Ratio	95% CI	
Model		1	.925			
Intervention	-0.003	1	0.926	0.997	0.929	1.069

Figure 1. The yellow line depicts a “normal” diurnal cortisol profile. The red line is a visual representation of cortisol slope calculated from waking and bedtime samples. Steeper slopes have been linked to favorable health outcomes, whereas flatter slopes are considered aberrant and have been linked to shorter survival in cancer.

Figure 2. The proposed study model, aims, and hypotheses. The shaded arrows represent the primary associations that will be examined, whereas the unshaded arrows represent the relationships that will be explored contingent on the associations that emerge following the analysis of the shaded arrows

Figure 3. A timeline of the study outlining when variables of interest were assessed.

Figure 4. Change in depressive symptoms regressed on change in LTL by ethnicity minority status (hypothesis 1c).

Figure 5. Critical values used to determine variance ratio cut-offs for assessment of the homogeneity of variances assumption for ANCOVA analysis (Field, 2013).

Figure 6. Change in depressive symptoms by intervention participation status (hypothesis 2a).

Figure 7. Change in LTL by intervention participation status (hypothesis 2c).

Figure 8. Change in LTL by chemotherapy treatment status at baseline (hypothesis 2c).

Figure 9. Kaplan-Meier curves depicting all-cause mortality for each of the intervention groups from date of study entry (hypothesis 2d).

Figure 10. Kaplan-Meier curves depicting all-cause mortality for each of the intervention groups from date of diagnosis (hypothesis 2d).

Figure 11. Kaplan-Meier curves depicting all-cause mortality for sub- and clinical levels of depressive symptoms from date of study entry (*post-hoc*, hypothesis 2a).

Figure 12. Diurnal cortisol slope at baseline by intervention participation status (*post-hoc*, hypothesis 2b).

Figure 13. Change in LTL by intervention participation status and chemotherapy treatment status at baseline (*post-hoc*, hypothesis 2c).

Figure 14. Kaplan-Meier curves depicting all-cause mortality for low versus high (median split) change in LTL from date of study entry (*post-hoc*, hypothesis 2c).

Figure 15. Kaplan-Meier curves depicting all-cause mortality for low versus high (median split) change in LTL from date of diagnosis (*post-hoc*, hypothesis 2c).

Figure 16. Change in depressive symptoms regressed on change in LTL by intervention participation status (*post-hoc*, hypothesis 2c).

Figure 17. Change in depressive symptoms regressed on change in LTL (hypothesis 1c).

CURRICULUM VITAE

Chelsea J. Siwik, M.S.

EDUCATION

2020 (expected)	Ph.D.	Clinical Psychology University of Louisville, Louisville, KY (APA accredited program) Cumulative GPA: 4.0 Faculty Advisor: Sandra E. Sephton, Ph.D.
2019 - 2020		Clinical Internship Behavioral Medicine Track School of Medicine University of Washington (APA accredited program) Training Directors: Ty Lostutter, Ph.D.
2015 – 2017	M.S.	Clinical Psychology University of Louisville, Louisville, KY Cumulative GPA: 4.0 Faculty Advisor: Sandra E. Sephton, Ph.D.
2010 - 2014	B.A.	Psychology University of Wisconsin, Madison, Madison, WI Cumulative GPA: 3.5 Faculty Advisor: Heather Abercrombie, Ph.D.
2010 – 2014	B.A.	Spanish University of Wisconsin, Madison, Madison, WI; Universidad Complutense de Madrid, Madrid, Spain Cumulative GPA: 3.5

CLINICAL TRAINING

May 2017 – Current

Clinical Graduate Teaching Assistant

Noble H. Kelley Psychological Services Center
University of Louisville, Louisville, KY
Supervisor: Bernadette Walter, Ph.D.

Serve as the first contact for clients initiating services. Collaborate with external agencies to provide referrals, outreach, and case management. Provide peer-supervision of manage crisis situations, clinical interviews, therapy, assessment, and clinic procedures. Manage clinic administrative operations. Attend weekly meetings with clinic director to manage client caseloads and clinic concerns.

THERAPY EXPERIENCE

Aug. 2018 – Current

Graduate Practicum Student: Therapist

Department of Psychology
Frazier Rehab Institute, Kentucky One Health
Supervisor: Abbey Roach, Ph.D. & Courtney Smith, Ph.D.

Implement brief rehabilitation-focused evaluations and interventions with pediatric and adult inpatients. Facilitate coping and ameliorate barriers to rehabilitate stroke, brain and spinal cord injuries, amputation, cancer-related ailments, movement disorders, and pulmonary dysfunction. Co-direct support and psychoeducational groups. Participate in physician-led interdisciplinary ground rounds. Receive individual supervision by a licensed clinical psychologist weekly.

Aug. 2018 – Current

Graduate Practicum Student: Therapist

Cognitive Behavioral Therapy (CBT) Rotation
Noble H. Kelley Psychological Services Center
University of Louisville, Louisville, KY

Supervisor: Jennifer Petrie, Ph.D.

Implement cognitive-behavioral approaches to assessment, conceptualization, treatment and data collection with adult clients. Formulated client conceptualizations and tailored treatment plans with reference to relevant empirical literature. Implement disorder-specific manualized treatments. Participate in weekly, conceptualization-centered group supervision.

Jan. 2017 – Dec. 2018

Mindfulness Meditation Group Facilitator

Mindfulness-Based Cancer Support Group
Gilda's Club, Louisville, KY
Supervisor: Paul Salmon, Ph.D.

Co-facilitate a bi-weekly drop-in mindfulness-based support group for individuals affected by cancer. Lead sitting meditations and discussion of mindfulness-based content and resources.

Jan. – Aug. 2018

Behavioral Health Practicum Student: Therapist

Pain Management Center

University of Louisville Hospital, Louisville, KY

Supervisor: Brian Monsma, Ph.D.

Implemented evidence-based, health-focused interventions to treat chronic pain and cope with psychosocial stressors in an outpatient medical setting. Consulted with medical staff regarding patient care. Received individual supervision by a licensed clinical psychologist weekly.

May 2017 – Aug. 2018

Behavioral Health Practicum Student: Therapist

Bone Marrow Transplant / Oncology Service

University of Louisville Hospital, Louisville, KY

Supervisor: Elizabeth Cash, Ph.D.

Implemented brief and long-term interventions aimed at improving health behaviors, medical adherence, and adjustment to hematologic cancer among inpatients and family members. Participated in physician-led interdisciplinary rounds. Integrated psychological service into patient care via program development efforts. Consulted with medical staff to improve patient care. Received weekly group supervision.

Aug. 2017 – Aug. 2018

Graduate Practicum Student: Therapist

Integrated Therapy Clinical Rotation

Noble H. Kelley Psychological Services Center

University of Louisville, Louisville, KY

Supervisor: Richard Lewine, Ph.D.

Implemented an integrated, person-centered approach to therapy using empirically supported methods (CBT, MBIs, Interpersonal Therapy, CPT and DBT). Treated adults with a variety of psychological disorders including severe mental illness and a history of trauma. Participated in weekly, conceptualization-centered group supervision focused on discussion of treatment implementation, client needs, and review of empirical literature. Received individual supervision regularly.

Aug. 2017 – Aug. 2018

Graduate Peer Supervisor

Integrated Therapy Clinical Rotation

Noble H. Kelley Psychological Services Center

University of Louisville, Louisville, KY

Supervisor: Richard Lewine, Ph.D.

Provided peer supervision for two third-year graduate students simultaneously. Received weekly group supervision from licensed clinical psychologist regarding the peer supervision process.

Aug. 2015 – Aug. 2017

Graduate Practicum Student: Therapist

Mindfulness and Acceptance-based Therapy Rotation

Noble H. Kelley Psychological Services Center

University of Louisville, Louisville, KY

Supervisor: Paul Salmon, Ph.D.

Utilized mindfulness-based interventions including ACT to treat mood and stress-related disorders among community based adult clients from diverse backgrounds. Flexibly adapted treatments to meet clients' needs. Participated in group and individual supervision weekly. Collaboratively provided and received feedback from other graduate students.

ASSESSMENT EXPERIENCE

May 2016 – Current

Graduate Practicum Student: Diagnostic Interviewing and Assessment

Noble H. Kelley Psychological Services Center

University of Louisville, Louisville, KY

Supervisors: Bernadette Walter, Ph.D.; Paul Rosen, Ph.D.; David Winsch, Ph.D.

Conduct structured interviews and administer full diagnostic assessments to a diverse population of adults and pediatric clients for evaluation of cognitive functioning, learning disabilities, Autism, severe mental illness, ADHD, Selective Mutism. Administer assessments to determine placement into Gifted and Talented programs. Consult with external agencies and conduct collateral interviews and assessments as needed. Prepare integrative reports and provide feedback to clients under the supervision of licensed psychologists.

DISSERTATION

Title of Project:

Depressive Symptoms and Survival Among Lung Cancer Patients: Biomarkers and Potential Benefits of an iPod- and Mindfulness-based Intervention

Funding:

Kentucky Lung Cancer Research Grant

Dissertation Chair:

Sandra Sephton, Ph.D.

Committee Members:

Elizabeth Cash, Ph.D. Paul Salmon, Ph.D., Benjamin Mast, Ph.D., and Tamara Newton, Ph.D.

Study aims:

To test the prognostic significance of depressive symptoms and the role of two biomarkers – cortisol and leukocyte telomere length – as they relate to the depression-survival pathway; and to explore the ameliorative role of an iPod-

and mindfulness-based intervention on depressive symptoms and related outcomes among lung cancer patients.

RESEARCH EXPERIENCE

July 2015 – Current

Graduate Student Research Assistant

Mindfulness and Biobehavioral Health Research Lab

Department of Psychological and Brain Sciences

University of Louisville, Louisville, KY

Primary Mentor: Sandra E. Sephton, Ph.D.

EXPERIENCE WITH SPECIFIC PROJECTS

Title of Project:

Are you F.O.M.O. prone?

Study aims:

Pilot an online study exploring the relationships between social media use, the F.O.M.O. (fear of missing out) phenomenon, mental health outcomes, and individual risk and protective factors.

Duties:

Designed study, proposed hypotheses, and prepared IRB materials; managed data collection; supervised undergraduate research assistants.

Title of Project:

A Dyadic Mindfulness Intervention for College Students and their Roommates – Mechanisms and Health Effects

Study aims:

Pilot a Koru iPod-based intervention; explore neural, cognitive and circadian pathways between mindfulness practice and health outcomes; explore the dyadic effects of a Koru iPod-based intervention among college roommates.

Duties:

Prepared and analyzed cognitive (memory and attention) e-Prime tasks and data; assisted with recruitment; collaboratively facilitated neural data collection via functional magnetic resonance imaging (fMRI); facilitated follow-up feedback sessions

Title of Project:

Mindfulness-based Stress Reduction for Parkinson's Disease (PD) Patients and Caregivers

Study aims:

Test feasibility and efficacy of an MBSR intervention among PD patients and their caregiving partners on a host of health factors; examine shared dyadic stress and health effects.

Duties:

Assisted with analytic strategy, analysis and interpretation of findings; disseminate findings through presentation and manuscript preparation.

Title of Project:

Understanding the Prognostic Significance of Circadian Disruption in Lung Cancer

Study aims:	Explore biobehavioral pathways of psychosocial and circadian effects on lung cancer progression; pilot an iPod- and mindfulness-based intervention.
Duties:	Collaborated with physicians to recruit patients; collected, organized, and analyzed psychosocial, circadian, and psychoneuroimmune data; managed study database; supervised undergraduate research assistants; prepared presentations and publications to disseminate findings; managed IRB compliance; prepared and shipped biological samples.
Title of Project:	A Meditation-based Intervention to Reduce Stress in Undergraduates
Study aims:	Pilot an iPod-based mindfulness meditation intervention among university undergraduates; explore the effects of mindfulness meditation on psychosocial and biological indicators of stress and health outcomes.
Duties:	Assisted with data analysis and interpretation of findings; disseminated findings.
Title of Project:	The Role of Mindfulness in Predicting Perceived Stress, Health and Positive Adaptation in College Undergraduates
Study aims:	Assess the relationship between stress, cortisol, and health in college undergraduates; evaluate ameliorative role of mindfulness.
Duties:	Interpreted and disseminated findings.
Title of Project:	Distress and Quality of Life in Head and Neck Cancer
Study aims:	Explore behavioral and biological pathways by which depression may influence cancer survival; examine treatment adherence/interruption and the role of tumor response to treatment in the depression-survival relation.
Duties:	Assisted in the interpretation of findings and preparation of publications.
Title of Project:	Stress, Coping, and Sleep in Breast Cancer
Study aims:	Examine the relationships between stress, coping, and circadian disruption among women with breast cancer.
Duties:	Assisted in interpretation and dissemination of findings.
Title of Project:	Effects of Stress in Women with Cancer
Study aims:	Examine role of stress on disease progression among women with ovarian or endometrial cancer.
Duties:	Generated hypotheses; planned and conducted data analysis; interpreted and disseminated findings; prepared publication materials; maintained IRB compliance

Title of Project: Psychosocial Effects in Lung Cancer Outcomes
Study aims: Elucidate effects of psychosocial factors on medical and health outcomes among lung cancer patients; examine prognostic significance of psychosocial factors as mediated by medical adherence, health behaviors, and neuroendocrine function.
Duties: Conducted data analysis; conceptualized findings; disseminated findings

2014 – 2015 **Post baccalaureate Study Coordinator**
Mood and Memory Laboratory
 Department of Psychiatry
 University of Wisconsin, Madison, Madison, WI
 Faculty Mentor: Heather Abercrombie, Ph.D.

2012 – 2014 **Research Assistant**
Mood and Memory Laboratory
 Department of Psychiatry
 University of Wisconsin, Madison, Madison, WI
 Faculty Mentor: Heather Abercrombie, Ph.D.

Title of Project: Depression, Adversity, and Stress Hormones Study
Study aims: Examine neurocognitive effects of cortisol in women with depression and/or early life adversity to inform pharmacologic treatment for depression subtypes.
Duties: Oversaw integrity of NIMH and NARSAD-funded data collection and procedures; organized data analysis operations among collaborating groups (i.e. medical physics, genetics, and neuroscience); collected genetic, hormonal, cognitive and neuroimaging data; conducted clinical phone screen interviews and fMRI-scanning sessions; followed-up on safety and eligibility concerns with MRI technicians and study physicians; determined eligibility of participants; created recruitment materials targeted for depressed and diverse individuals; tracked study-related materials purchased with department funds.

Title of Project: Memory for Emotional Pictures
Study aims: Pilot stimuli to be used in the fMRI scanner for the parent study, Depression Adversity and Stress Hormones study among undergraduate students.
Duties: Assisted with recruitment; scheduled and tracked participants; independently conducted study sessions; collected and managed cognitive data; developed standardized study procedures.

GRANTS

AWARDED

Title of Project: Associations Between Positive and Negative Self-views, Depressive Symptoms, and Telomere Length in Non-small Cell Lung Cancer
Effective Dates: 07/01/2017 – 06/30/2018
Role: Author (PI: Sandra E. Sephton, Ph.D.)
Funding Agency: Jesse H. Wright, M.D., Ph.D. Mood Disorders Research Endowment
Amount: \$5,000
Aims: Explore how negative and positive self-views relate to depressive symptoms and how relationships between negative and positive self-views, as well as depressive symptoms, relate to telomere length among lung cancer patients.

UNFUNDED SUBMISSIONS

Title of Project: Circadian Disruption in Lung Cancer – Mechanisms & Prognostic Significance
Role: Graduate Research Assistant (PI: Sandra E. Sephton, Ph.D.)
Funding Agency: NIH Research Grant Project Program (R01)
Amount: \$2,815,924.00
Aims: Describe psychoneuroimmune pathways by which stress and circadian disruption affect lung cancer-related health outcomes and accelerate lung cancer progression.

PUBLICATIONS

PEER-REVIEWED JOURNAL ARTICLES

1. Hicks, A., **Siwik, C.**, Phillips, K., Zimmaro, L.A., Salmon, P., Burke, N., ... & Sephton, S.E. (2019). Dispositional mindfulness is associated with lower basal sympathetic arousal and less psychological stress. *International Journal of Stress Management*.
2. Zimmaro, L. A., Sephton, S. E., **Siwik, C. J.**, Phillips, K. M., Rebholz, W. N., Kraemer, H. C., ... & Cash, E. D. (2018). Depressive symptoms predict head and neck cancer survival: Examining plausible behavioral and biological pathways. *Cancer*, 124(5), 1053-1060.
3. **Siwik, C.**, Hicks, A., Phillips, K., Rebholz, W. N., Zimmaro, L. A., Weissbecker, I., ... & Sephton, S. E. (2017). Impact of coping strategies on perceived stress, depression, and cortisol profiles among gynecologic cancer patients. *Journal of health psychology*.
4. Rebholz, W.N., Cash, E., Zimmaro, L.A., Bayley-Veloso, R., Phillips, K., **Siwik, C.**, Chagpar, A.B., Dhabhar, F.S., Spiegel, D., Saltsman-Bell, B.N., & Sephton,

- S.E. (2016). Distress and quality of life in an ethnically diverse sample awaiting breast cancer surgery. *Journal of Health Psychology*.
5. Zimmaro, L.A., Salmon, P., Naidu, H., Rowe, J., Phillips, K., Rebholz, W.N., Giese-Davis, J., Cash, E., Dreeben, S.J., Bayley-Veloso, R., Jablonski, M.E., Hicks, A., **Siwik, C.**, & Sephton, S.E. (2016). Association of dispositional mindfulness with stress, cortisol, and well-being among university undergraduate students. *Mindfulness*, 7(4), 874-885.

MANUSCRIPTS UNDER REVIEW

1. Hicks, A., Phillips, K., **Siwik, C.**, Salmon, P., Litvan, I., Jablonski, M.E., Filoteo, J.V., Kayser, K., Sephton, S.E. (under review, 2018). The role of innate mindfulness in stress-health pathway among Parkinson's disease patients and caregiving partners. Submitted to *Quality of Life Research Journal*.
2. **Siwik, C.J.**, Zimmaro, L., Blevins, T., Salmon, P., Kloecker, G., Cash, E., Phillips, K., Bayley-Veloso, R., Barve, S., & Sephton, S.E. (under review, 2019). Factors related to cancer patients' willingness to participate in an iPod- and mindfulness-based intervention. Submitted to *Annals of Behavioral Medicine*.
3. Bayley-Veloso, R., Szabo, Y., Cash, E., Zimmaro, L., **Siwik, C.**, Kloecker, G., Salmon, P., van der Gryp, K., and Sephton, S.E. (under review, 2019). The role of trauma in the health-related quality of life of lung cancer patients. Submitted as a brief report to *Journal of Psychosocial Oncology*.

MANUSCRIPTS IN PROGRESS

1. Phillips, K., **Siwik, C.J.**, Hicks, A., Salmon, P., Litvan, I., Jablonski, M.E., Filoteo, J.V., Kayser, K., Sephton, S.E. Baseline differences between Parkinson's disease patients and their caregiving partners: Examination of non-independence among members of a dyad. Manuscript in preparation. *Submitting to Movement Disorders*.
2. **Siwik, C.J.**, Hicks, A., Phillips, K., Salmon, P., Litvan, I., Jablonski, M.E., Filoteo, J.V., Kayser, K., Sephton, S.E. An MBSR intervention for Parkinson's disease patients and caregiving partners: Effects on distress, social support, cortisol, and inflammation. Manuscript in preparation. *Submitting to Mindfulness*.
3. **Siwik, C.J.**, Phillips, K., Zimmaro, L., Salmon, P., Kathleen van der Gryp & Sephton, S.E. The relationship between shame, guilt, and depressive symptoms and the ameliorative role of self-compassion among lung cancer patients. Manuscript in preparation. *Submitting to Journal of Clinical Oncology*.
4. **Siwik, C.J.**, Fischbach, A., Phillips, K. & Sephton, S.E. Hashtag F.O.M.O.: Understanding the relationship between mental health, social media use, and the fear of missing out phenomenon. Manuscript in Preparation.
5. Rebholz, W., Cash, L., Weissbecker, I., **Siwik, C.J.**, Phillips, K., Bayley-Veloso, R., van der Gryp, K., Sephton, S. Prognostic value of allostatic load in gynecologic cancer survival. Manuscript in preparation.

PUBLISHED ABSTRACTS

1. **Siwik, C.J.**, Phillips, K., Zimmaro, L., Cash, E., Hicks, A. & Sephton, S.E. (2019). The relationship between shame, guilt, and depressive symptoms and the ameliorative role of self-compassion among lung cancer patients. *Psychosomatic Medicine*, 81(3), A-94.
2. Hicks, A., Salmon, P., Rebholz, W., Phillips, K., **Siwik, C.**, Zimmaro, L., Cash, E., van der Gryp, K., & Sephton, S.E. (2018). The role of self-compassion in a stress-health pathway. *Psychosomatic Medicine*, 80(3), A76-A77.
3. Phillips, K., **Siwik, C.**, Hicks, A., Salmon, P., Cash, E., Litvan, I., Filoteo, J.V., van der Gryp, K., & Sephton, S.E. (2018). Exploration of dyadic associations of anxiety and diurnal cortisol among Parkinson's disease patient/caregiver dyads. *Psychosomatic Medicine*, 80(3), A28-A29.
4. Phillips, K., **Siwik, C.**, Segerstrom, S., Zimmaro, L., Rebholz, W., Cash, E., Hicks, A., van der Gryp, K., & Sephton, S.E. (2018). Associations between daily affect, intrusive thoughts, and cortisol levels among lung cancer patients. *Psychosomatic Medicine*, 80(3), A83.
5. Sephton, S.E., Hicks, A., Phillips, K., **Siwik, C.**, Albert, C., Zimmaro, L., van der Gryp, K., & Salmon, P. (2018). A brief i-Pod-based mindfulness intervention for undergraduates: Effects on psychological and physiological outcomes. *Psychosomatic Medicine*, 80(3), A67.
6. **Siwik, C.**, Segerstrom, S., Phillips, K., Cash, E., Rebholz, W., Zimmaro, L., Hicks, A., van der Gryp, K., & Sephton, S.E. (2018). Associations of actigraphically measured daytime sedentariness and nighttime restfulness with waking and bedtime salivary cortisol levels. *Psychosomatic Medicine*, 80(3), A101.
7. **Siwik, C.**, Phillips, K., Salmon, P., Litvan, I., Filoteo, J.V., Rebholz, W., Cash, E., Hicks, A., van der Gryp, K., & Sephton, S.E. (2018). An MBSR intervention for Parkinson's disease patients and caregiving partners: Effects on distress, social support, cortisol, and inflammation. *Psychosomatic Medicine*, 80(3), A128.
8. van der Gryp, K., **Siwik, C.**, Zimmaro, L., Phillips, K., Rebholz, W., Cash, E., Hicks, A., & Sephton, S.E. (2018). Lung cancer-related distress is associated with elevated mean diurnal cortisol levels. *Psychosomatic Medicine*, 80(3), A32.
9. Cash, E., Rebholz, W., Albert, C., Fields, O., Zimmaro, L., **Siwik, C.**, Phillips, K., Kloecker, G., & Sephton, S.E. (2017). Associations between the prognostic indicators rest/activity rhythm and diurnal cortisol profiles in patients with lung cancer. *Brain, Behavior, and Immunity*, 66, e31-e32.
10. Phillips, K., Salmon, P., **Siwik, C.**, Rebholz, W., Cash, E., Litvan, I., Filoteo, J.V., Kayser, K., & Sephton, S.E. (2017). A dyadic MBSR intervention for Parkinson's disease patients/caregivers: Effects on distress, cortisol, and inflammation. *Brain, Behavior, and Immunity*, 66, e19-e20.
11. Rebholz, W.N., Cash, E., **Siwik, C.**, Phillips, K., Albert, C., Zimmaro, L., Dhabhar, F.S., Barve, S., & Sephton, S.E. (2017). Pro-inflammatory, chemotactic, and anti-inflammatory cytokine responses associate with HPA, but not SNS, function in lung cancer patients. *Brain, Behavior, and Immunity*, 66, e24.

12. **Siwik, C.**, Rebholz, W., Phillips, K., Cash, E., Dhabhar, F.S., Barve, S., Zimmaro, L., & Sephton, S.E. (2017). *Sense of coherence in lung cancer patients: Association with coping, immune function, and fatigue*. *Brain, Behavior, and Immunity*, 66, e25.
13. Zimmaro, L.A., Segerstrom, S., Cash, E., **Siwik, C.**, Phillips, K., Rebholz, W., & Sephton, S.E. (2017). Moderating role of mindfulness on daily affect and cortisol in lung cancer patients. *Psychosomatic Medicine*, 79(4), A52-A52.
14. Hicks, A.M., Salmon, P., Phillips, K., Zimmaro, L., **Siwik, C.**, Bayley-Veloso, R., Cash, E., & Sephton, S.E. (2016). The role of mindfulness in stress and depression of undergraduate students. *Psychosomatic Medicine*, 78(3), A101-A102.
15. Phillips, K., Bayley-Veloso, R., Zimmaro, L.A., **Siwik, C.**, Hicks, A.M., Cash, E., Salmon, P., & Sephton, S.E. (2016). Living situation and quality of life among cancer patients. *Psychosomatic Medicine*, 78(3), A73-A73.
16. **Siwik, C.J.**, Phillips, K., Zimmaro, L.A., Bayley-Veloso, R., Hicks, A., Cash, E., Salmon, P., & Sephton, S.E. (2016). Psychological and physiological effects of problem-focused and emotional approach to coping styles in gynecological cancer patients. *Psychosomatic Medicine*, 78(3), A60.

CONFERENCE PRESENTATIONS (*Oral Presentation)

1. **Siwik, C.J.**, Phillips, K., Zimmaro, L., Cash, E., Hicks, A. & Sephton, S.E. (2019, March). *The Relationship Between Shame, Guilt, and Depressive Symptoms and the Ameliorative Role of Self-compassion Among Lung Cancer Patients*. American Psychosomatic Society 77th Annual Scientific Meeting, Vancouver, BC, Canada.
2. *Hicks, A., Salmon, P., Rebholz, W., Phillips, K., **Siwik, C.**, Zimmaro, L.A., Cash, E., van der Gryp, K., & Sephton, S. E. (2018, March). *The Role of Self-Compassion in a Stress-Health Pathway*. Oral Session on Psychological Wellbeing, American Psychosomatic Society 76th Annual Scientific Meeting, Louisville, KY.
3. *Phillips, K., **Siwik, C.**, Salmon, P., Litvan, I., Filoteo, J.V., Rebholz, W., Cash, E., Hicks, A., van der Gryp, K. & Sephton, S.E. (2018, March). *MBSR Intervention for Parkinson's Disease Patients and Caregiving Partners: Effects on Distress, Social Support, Cortisol, and Inflammation*. Oral Session on Inflammation, American Psychosomatic Society 76th Annual Scientific Meeting, Louisville, KY.
4. *Phillips, K., Salmon, P., **Siwik, C.**, Rebholz, W., Cash, E., Litvan, I., Filoteo, J.V., Kayser, K., & Sephton, S.E. (2018, March). *Associations Between Daily Affect, Intrusive Thoughts, and Cortisol Levels Among Lung Cancer Patients*. Oral Session on Cancer, American Psychosomatic Society 76th Annual Scientific Meeting, Louisville, KY.
5. Phillips, K., **Siwik, C.**, Hicks, A., Salmon, P., Cash, E., Litvan, I., Filoteo, J.V., van der Gryp, K., & Sephton S.E. (2018, March). *Exploration of dyadic associations of anxiety and diurnal cortisol among Parkinson's disease*

- patient/caregiver dyads*. American Psychosomatic Society 76th Annual Scientific Meeting, Louisville, KY.
6. Sephton, S.E., Hicks, A., Phillips, K., **Siwik, C.**, Albert, C., Zimmaro, L., van der Gryp, K.A. & Salmon, P. (2018, March). *A brief iPod-based mindfulness intervention for undergraduates: Effects on psychological and physiological outcomes*. American Psychosomatic Society 76th Annual Scientific Meeting, Louisville, KY.
 7. ***Siwik, C. J.**, Segerstrom, S., Phillips, K., Cash, E., Rebholz, W., Zimmaro, L., Hicks, A., van der Gryp, K., & Sephton, S.E. (2018, March). *Associations of Actigraphically Measured Daytime Sedentariness, Nighttime Restfulness, and Rest-Activity Rhythms with Daily Waking and Bedtime Salivary Cortisol Levels*. Oral Session on Sleep, American Psychosomatic Society 76th Annual Scientific Meeting, Louisville, KY.
 8. van der Gryp, K., **Siwik, C.**, Zimmaro, L., Phillips, K., Rebholz, W., Cash, E., Hicks, A., & Sephton, S.E. (2018, March). *Lung Cancer-related Distress is Associated with Elevated Mean Diurnal Cortisol Levels*. American Psychosomatic Society 76th Annual Scientific Meeting, Louisville, KY.
 9. Phillips, K., **Siwik, C.**, Hicks, A., Salmon, P., Cash, E., Litvan, I., Filoteo, J.V., van der Gryp, K., & Sephton S.E. (2017, October). *Exploration of dyadic associations of anxiety and diurnal cortisol among Parkinson's disease patient/caregiver dyads*. American Psychosomatic Society Mid-Year Meeting – “Emotions in Social Relationships: Implications for Health and Disease,” Berkeley, CA.
 10. **Siwik, C.**, Phillips, K., Salmon, P., Litvan, I., Filoteo, V., Rebholz, W., Cash, E., Hicks, A., van der Gryp, K., & Sephton, S.E. (2017, October). *An MBSR intervention for Parkinson's disease patients and caregiving partners: Effects on distress, social support, cortisol and inflammation*. American Psychosomatic Society Mid-Year Meeting – “Emotions in Social Relationships: Implications for Health and Disease,” Berkeley, CA.
 11. Cash, E., Rebholz, W., Albert, C., Fields, O., Zimmaro, L., **Siwik, C.**, Phillips, K., Kloecker, G., & Sephton, S.E. (2017, June). *Associations between the prognostic indicators rest/activity rhythm and diurnal cortisol profiles in patients with lung cancer*. PsychoNeuroImmunology Research Society 24th Annual Scientific Meeting, Galveston, TX.
 12. ***Phillips, K.**, Salmon, P., **Siwik, C.**, Rebholz, W., Cash, E., Litvan, I., Filoteo, J.V., Kayser, K., & Sephton, S.E. (2017, June). *A dyadic MBSR intervention for Parkinson's disease patients/caregivers: Effects on distress, cortisol, and inflammation*. Oral Session on Inflammation and Relationships Through the Lifespan, PsychoNeuroImmunology Research Society 24th Annual Scientific Meeting, Galveston, TX.
 13. Rebholz, W.N., Cash, E., **Siwik, C.**, Phillips, K., Albert, C., Zimmaro, L., Dhabhar, F.S., Barve, S., & Sephton, S.E. (2017, June). *Pro-inflammatory, chemotactic, and anti-inflammatory cytokine responses associate with HPA, but not SNS, function in lung cancer patients*. PsychoNeuroImmunology Research Society 24th Annual Scientific Meeting, Galveston, TX.

14. **Siwik, C.**, Rebholz, W., Phillips, K., Cash, E., Dhabhar, F.S., Barve, S., Zimmaro, L., & Sephton, S.E. (2017, June). *Sense of coherence in lung cancer patients: Association with coping, immune function, and fatigue*. PsychoNeuroImmunology Research Society 24th Annual Scientific Meeting, Galveston, TX.
15. Zimmaro, L.A., Segerstrom, S., Cash, E., **Siwik, C.**, Phillips, K., Rebholz, W., & Sephton, S.E. (2017, March). *Moderating Role of Mindfulness on Daily Affect and Cortisol in Lung Cancer Patients*. American Psychosomatic Society 75th Annual Scientific Meeting, Sevilla, Spain.
16. Hicks, A., Salmon, P., Phillips, K., Zimmaro, L., **Siwik, C.**, Bayley-Veloso, R., Albert, C., Fields, O., Cash, E., & Sephton, S.E. (2016, March). *The role of mindfulness in stress and depressive symptoms of undergraduate students*. American Psychosomatic Society 74th Annual Scientific Meeting, Denver, CO.
17. Phillips, K., Bayley-Veloso, R., Zimmaro, L.A., **Siwik, C.**, Hicks, A.M., Cash, E., Salmon, P., & Sephton, S.E. (2016, March). *Does living situation affect stress and health outcomes among cancer patients?* American Psychosomatic Society 74th Annual Scientific Meeting, Denver, CO.
18. **Siwik, C.**, Phillips, K., Zimmaro, L.A., Bayley-Veloso, R., Hicks, A., Cash, E., Salmon, P., & Sephton, S.E. (2016, March). *Psychological and physiological effects of problem-focused and emotional approach to coping styles in gynecological cancer patients*. American Psychosomatic Society 74th Annual Scientific Meeting, Denver, CO.
19. **Siwik, C.**, Hoks, R.M., Walsh, E., & Abercrombie, H.C. (2014, May). *Memory Formation: Moments Matter*. University of Wisconsin, Madison Undergraduate Honors Symposium, Madison, WI.
20. ***Siwik, C.** (2012, May). *Emotional Memory: Effects of Valence, Modality, and Distraction*. University of Wisconsin, Madison Experimental Psychology Symposium, Madison, WI.

LAB AND DATA ANALYTIC SKILLS

fMRI

Experience in independently conducting study protocol and collecting data using a GE 3T fMRI scanner.

Endocrinology

Experience in collecting, preparing, processing, and preserving human saliva samples.
Proficient in cortisol data cleaning and reduction.

Immunology and Cellular Aging

Experience in processing and preserving serum and plasma human blood samples.
Experience preparing and preserving whole blood samples for stimulated analysis.

Circadian Rhythms

Experience in initializing and downloading MicroMini Motionlogger Actiwatches.

Data Analysis

Experience conducting univariate and multivariate analyses, structural equation modeling, and survival analyses. Experience using the following statistical software: SPSS, AMOS. Experience in REDCap and Qualtrics data capture systems.

HONORS, AWARDS & SCHOLARSHIPS

March 2018	Selected to Present Orally at a Session on Sleep <i>American Psychosomatic Society 76th Annual Scientific Meeting, Louisville, KY</i>
Fall 2017	Graduate Network in Arts and Sciences Research Fund Award <i>University of Louisville, Louisville, KY</i>
Summer 2017	Graduate Student Council Travel Award <i>University of Louisville, Louisville, KY</i>
Spring 2016 Award	Research Presentation Selected for Citation Poster <i>American Psychosomatic Society, Denver, CO</i>
Spring 2016	Graduate Student Council Travel Award <i>University of Louisville, Louisville, KY</i>
Spring 2016	Graduate Network in Arts and Sciences Research Fund Award <i>University of Louisville, Louisville, KY</i>
Spring 2013	Dean's List <i>College of Arts and Sciences</i> University of Wisconsin, Madison, Madison, WI
Fall 2012	UW Alumni Association Study Abroad Scholarship <i>University of Wisconsin, Madison, Madison, WI</i>

MULTICULTURAL AND DIVERSITY TRAINING

Fall 2015, 2018	Safe Zone Training <i>LGBT Center</i> University of Louisville, Louisville, KY
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This two-part workshop was designed to provide university community members the tools and resources needed to understand LGBTQ+ students and colleagues, and how to appropriately create a welcoming, affirming environment for all. Provided valuable information on how to advocate for individuals who identify as LGBTQ+ and

psychoeducation on common misconceptions, defining terms, and outlining risk factors for mental health disparities.

May 2017

Operation Immersion

Wendell H. Ford, Regional Training Center, Greenville, KY

Attended a four-day/night intensive training for healthcare providers to become immersed in military culture and explore issues unique to service members, veterans, and their families. Hosted by the Kentucky Army National Guard, this immersion required overnight stay in barrack-like quarters to simulate day-to-day military culture. Education activities geared toward behavioral health for active military and veterans accounted for a significant portion of the day.

Jan. 2017

White Allies Training

Multicultural Center

University of Louisville, Louisville, KY

Individuals from primarily white backgrounds gathered together to recognize the need for and brainstorm actions to be taken to protect and minimize discrimination against minorities, both on campus and in the greater Louisville community.

Dec. 2016

Tier One Training: The Impact of Deployment on Service Members and Their Families

Center for Deployment Psychology

Star Behavioral Health Providers

Indiana Family and Social Services Administration, New Albany, IN

A one-day training geared toward training of civilian behavioral health providers in military specific culture, the deployment cycle, and treatments that focus on the needs of the military population.

Jan. 2016

Diversity Workshop

College of Arts and Sciences

University of Louisville, Louisville, KY

This workshop provided opportunity for graduate students and faculty members to gather, discuss, and think critically about diversity in the classroom. Topics included power dynamics, handling conflict, and negotiating social identities.

EDUCATIONAL ACTIVITIES

CLINICAL TEACHING EXPERIENCE

Current

Co-Instructor

Intellectual and Cognitive Assessment
University of Louisville, Louisville, KY

Taught clinical psychology graduate students how to conduct intellectual assessments. Supervised graduate students' first administration of WAIS-IV and WISC-V. Provided extensive and corrective feedback on administration, scoring, and report writing.

Summer 2017, 2018

Co-Instructor

Interview Skills

University of Louisville, Louisville, KY

Taught clinical psychology graduate students introductory material to interviewing and clinical and multicultural competence. Provided direct supervision of graduate students' first therapy intake interview.

Spring 2018

Co-Instructor

Intellectual and Cognitive Assessment

University of Louisville, Louisville, KY

Taught clinical psychology graduate students how to conduct intellectual assessments. Supervised graduate students' first administration of WAIS-IV and WISC-V. Provided extensive and corrective feedback on administration, scoring, and report writing.

RESEARCH TEACHING EXPERIENCE

Sept. 2018 - Current

Graduate Student Mentor

Undergraduate Honors Thesis

"Hashtag F.O.M.O.: Understanding the Relationships Between Mental Health, Social Media Use, and the Fear of Mission Out Phenomenon"

Psychological and Brain Sciences

University of Louisville, Louisville, KY

Student: Abigail Fischbach

I am currently mentoring an undergraduate student through the yearlong process of designing, analyzing, drafting, and defending an honors thesis.

Summer 2018

Graduate Student Mentor

NCI R25 Cancer Education Program

"Factors Related to Cancer Patients' Willingness to Participate in an iPod-based MBSR Intervention"

School of Medicine

University of Louisville, Louisville, KY

Student: Tessa Blevins

Mentored an undergraduate student through a National Cancer Institute (NCI)-funded 10-week summer program. Demonstrated the scientific process and assisted with the steps required to design and present a poster at a local conference.

Sept. 2017 – May 2018

Graduate Student Mentor

Undergraduate Honors Thesis

“Mindfulness, Psychological Distress, and Cognitive Functioning Among University Students”

Psychological and Brain Sciences

University of Louisville, Louisville, KY

Student: Samantha Melton

Mentored an undergraduate student through the yearlong process of designing, analyzing, drafting, and defending an honors thesis.

ACADEMIC TEACHING EXPERIENCE

Summer 2018

Lecturer

Topic: Stress, Health, and Resilience: Optimizing Quality and Quantity of Life

Course: Undergraduate Human Development

University of Louisville, Louisville, KY

Spring 2017

Lecturer

Topic: Pain, the Brain, and Culture

Course: Graduate Cultural Neuroscience

University of Louisville, Louisville, KY

Spring 2017

Graduate Teaching Assistant

Course: Physiological Psychology

University of Louisville, Louisville, KY

Oct. 2016

Lecturer

Topic: Sensorimotor Function

Course: Physiological Psychology

University of Louisville, Louisville, KY

September 2016

Lecturer

Topic: Neural Anatomy

Course: Physiological Psychology

University of Louisville, Louisville, KY

Fall 2016

Graduate Teaching Assistant

Courses: Physiological Psychology; Personality

University of Louisville, Louisville, KY

Summer 2016

Graduate Teaching Assistant

Courses: Physiological Psychology; Intro to Neuroscience;
Abnormal Psychology
University of Louisville, Louisville, KY

2015 - 2016

Graduate Teaching Assistant Academy

School of Interdisciplinary and Graduate Studies
University of Louisville, Louisville, KY

Participated in a yearlong teaching academy designed to assist graduate teaching assistants develop knowledge, skills, and excellence in the classroom. Partook in interactive workshops with faculty mentors selected for their expertise in teaching. Learned scholarly and conceptual frameworks for understanding “today’s” students, practical teaching strategies, and scholarship of teaching and learning.

Spring 2016

Graduate Teaching Assistant

Courses: Personality Psychology; Abnormal Psychology
University of Louisville, Louisville, KY

Fall 2015

Graduate Teaching Assistant

Courses: Abnormal Psychology
University of Louisville, Louisville, KY

PROFESSIONAL ACTIVITIES, LEADERSHIP & SERVICE

2018 – Current

Graduate Student Cohort Liaison

Psychological and Brain Sciences
University of Louisville, Louisville, KY

Serve as a representative of the 4th year Clinical Psychology Doctoral Student cohort. Communicate with peers regarding program-wide issues and ensure concerns are effectively communicated to faculty.

Jan. 2019

Abstract Reviewer

National Conference of Undergraduate Research (NCUR)
Kennesaw State University, Kennesaw, GA

May – Aug. 2018

Graduate Student Advocate

Diversity Recruitment and Retention Committee
Psychological and Brain Sciences
University of Louisville, Louisville, KY

Serve as a graduate student advocate for greater inclusion of underrepresented minorities in the doctoral psychology programs at the University of Louisville and in higher education more broadly. Collaborate with faculty and graduate peers to discuss goals,

outline strategies, and formalize plans to increase and improve recruitment and retention of diverse students and faculty within our department.

Aug. 2016 – Aug. 2018 **Graduate Student Ambassador**
School of Interdisciplinary and Graduate Studies
University of Louisville, Louisville, KY

Assisted the graduate school with recruitment and retention efforts. Provided other graduate students with networking and professional development opportunities and skills. Assisted with the organization and implementation of graduate student orientations and graduation ceremonies.

Aug. 2017 – May 2018 **Colloquium Development and Community Liaison**
Clinical Psychology Professional Development Series
Department of Psychological and Brain Sciences
Noble H. Kelley Psychological Services Center
University of Louisville, Louisville, KY

Communicated with behavioral health professionals in the Louisville community to coordinate the colloquium series for the 2017-2018 academic year. Attendance that is required by all clinical psychology doctoral students, the colloquium series is designed to expand on student and faculty knowledge of community resources and facilitate professional development. Collected and organized APA-accredited materials including presentation aims, CVs, and assessment measures in order to provide faculty with continued education credits.

Oct. 2017 **Ad-Hoc Reviewer**
Journal of Health Psychology

April 2017 **Poster Judge**
Kentucky Psychological Association
Spring Academic Conference
Spalding University, Louisville, KY

Nov. 2016 **Abstract Reviewer**
American Psychosomatic Society 75th Annual Scientific Meeting
Sevilla, Spain

Fall 2016 **Co-facilitator**
20 Minutes of Mindfulness
Health Promotions Office
Campus Health Services
University of Louisville, Louisville, KY

Co-facilitated a university-wide initiative aimed at decreasing stress and improving coping and health among undergraduate students through brief mindfulness-based intervention.

April 2016

Poster Judge

Kentucky Psychological Association
Spring Academic Conference
Georgetown College, Georgetown, KY

Sept. 2015

Psychological Services Center Representative

Community Outreach at Health and Wellness Fair
Baptist Church, Louisville, KY

Spring 2012

Volunteer Tutor

Schools of Hope, Madison, WI

Volunteered for the community initiative aimed at reducing the academic achievement gap between students of color and their white peers. Paired one-on-one with students to ensure adequate preparation for successful completion of academic requirements. Created weekly lesson plans and interactive games to improve literacy and math skills of bilingual students ranging from 5 – 11 in age. Portrayed academic role model characteristics.

COMMUNITY & OTHER PRESENTATIONS

1. **Siwik, C. J.** & Mier-Chairez, J. (2018, June). *Stress and Coping*. Summer Health Professions Education Program (SHPEP). University of Louisville, Louisville, KY.
2. **Siwik, C. J.** (2018, April). *Stress, Health, and Resilience: Optimizing Quality and Quantity of Life*. Oral Session, Clinical Psychology Department Faculty Meeting. University of Louisville, Louisville, KY.
3. **Siwik, C. J.**, Segerstrom, S., Phillips, K., Cash, E., Rebholz, W., Zimmaro, L., Hicks, A., van der Gryp, K., & Sephton, S.E. (2018, April). *Associations of Actigraphically Measured Daytime Sedentariness, Nighttime Restfulness, and Rest-Activity Rhythms with Daily Waking and Bedtime Salivary Cortisol Levels*. Oral Session, Graduate Student Brown Bag Series. University of Louisville, Louisville, KY.
4. **Siwik, C.** & Phillips, K. (2018, April). *Implementing Self-compassion Skills Among Veteran Women*. Athena's Sisters – Support group for women veterans, Louisville, KY.
5. **Siwik, C.** & Phillips, K. (2017, September). *Coping with Symptoms of Anxiety and Depression in the Context of Chronic Illness*. Better Breathers Club – Support group for individuals with chronic lung disease, University of Louisville School of Medicine, Louisville, KY.

PROFESSIONAL DEVELOPMENT

Feb. 2017

Writing a Literature Review Workshop

School of Interdisciplinary & Graduate Studies

University of Louisville, Louisville, KY

Spring 2016

Entrepreneurship Academy

School of Interdisciplinary and Graduate Studies

University of Louisville, Louisville, KY

Participated in a semester-long academy aimed to teach entrepreneurial thinking and skills. Session topics included entrepreneurial thinking, the business model canvas, learning to launch, and social entrepreneurship.

May 2016

Mindfulness Counseling Meeting

Earth and Spirits Center, Louisville, KY

Attended a mindfulness-based practice and discussion among other mental health professionals regarding personal and professional meditation practice.

March 2016

Resilient Families Training Program

Hotel Louisville, Louisville, KY

Facilitator: Dr. Barbara Burns, Ph.D.

Attended a workshop on the Resilient Families Project to learn how science on resilience has informed new approaches to supporting the well being of children from families facing trauma, stress, and adversity.

Fall 2015

Mindfulness-based Stress Reduction (MBSR) Program

Earth and Spirits Center, Louisville, KY

Attended a comprehensive 8-week MBSR program to actively learn by doing. The program facilitated integration of meditation practice, observation of group-based meditation to inform clinical application.

Nov. 2015

Understanding the Gut Brain: Stress, Appetite, Digestion and Mood Workshop

Institute for Brain Potential, Lexington, KY

Facilitator: Dr. Merrily Kuhn, RN, Ph.D., ND

Attended a daylong seminar on the enteric nervous system and its pivotal role in regulating inflammation, stress, metabolism, appetite and mood. The workshop elucidated the mind-body connection by discussing the effects of stress on digestive and gastrointestinal disorders.

PROFESSIONAL AFFILIATIONS AND HONOR SOCIETIES

2016 – 2018	American Psychosomatic Society
2014 – 2018	Psi Chi, The International Honor Society in Psychology
2017 – 2018	Kentucky Psychological Association
2017 – 2018	American Psychological Association