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Effects of a Mindfulness Based Intervention on Diurnal Cortisol in Cancer
Survivors

by

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Abstract

Background. There are approximately 15.5 million individuals alive today in the U.S. with a personal history of cancer. For this large and growing population, ill effects associated with cancer diagnosis and treatment include both physical and psychosocial symptoms adversely affecting quality of life. One low-risk alternative to conventional pharmaceutical use in treating these symptoms is mindfulness practice. Research on self-reported measures provides strong evidence that this type of intervention improves quality of life for cancer survivors, but evidence of impact on objective measures is limited. Cortisol, the body's primary stress hormone, is one relatively easy to measure indicator that has been increasingly favored.

Methods. In this randomized controlled trial, 38 cancer survivors from the Greenville Health System in South Carolina were assigned to either a 4-week mindfulness intervention program or a control group. Six salivary cortisol samples were collected daily at baseline, 6 weeks, and 12 weeks, along with questionnaire data assessing a variety of symptoms and lifestyle behaviors.

Both rhythm, as the change in cortisol over the day, and absolute levels of cortisol were modelled using multivariable linear regression. Specifically, for absolute levels, a treatment effect by categorization at baseline of those with high, normal, and low cortisol

levels was modelled using an interaction between treatment and baseline levels of cortisol.

Results. None of the explored self-report or demographic variables assessed were significantly associated with diurnal cortisol decline at baseline in either the crude or adjusted models. Although non-significant, the intervention was associated with a greater cortisol decline over the day (-1.79 {p=0.52} and -2.71 {p=0.23} respectively for 6 and 12-week follow-up) which has been previously associated with better survival outcomes for cancer patients. No significant or consistent directional results were observed when examining effect modification of baseline cortisol categorizations on change in cortisol levels.

Conclusions. Although the effect size was relatively large, our analysis did not show a significant impact of the mindfulness intervention program on change in cortisol decline or in changes in absolute levels of cortisol as a function of baseline categorization. Our results add to the accumulating literature surrounding the use of alternative medicine practices for symptom treatment in cancer survivors and provide recommendations for future work using cortisol to assess impact of mindfulness interventions.

Table of Contents

List of Tables

Chapter 1: Introduction

1.1   Statement of Problem

In the United States, the current lifetime chance of developing cancer is almost 1 in every 2 persons for men and more than 1 in 3 for women[1]. With incidence rates remaining steady for the past decade, and with large improvements in survival due to early detection methods and better treatment, the population of cancer survivors in the U.S. is substantial (American Cancer Society, 2016). Current estimates suggest that there are approximately 15.5 million individuals with a personal history of cancer alive today in the U.S. and that that population is expected to reach 20 million by the year 2026 (K. D. Miller et al., 2016). For this large and growing population, the distress and uncertainty associated with diagnosis and treatment of cancer is related to both physical and psychosocial symptoms adversely affecting quality of life including anxiety, depression, fear of recurrence, stress, pain, insomnia, and fatigue in addition to long-term side effects of surgery and adjuvant therapies (Linda E. Carlson, 2016).

Addressing these issues is not only vital to creating high quality of life for this sizeable portion of the U.S. population, but failing to manage stress symptoms has been linked to harmful lifestyle behaviors such as overeating, alcohol or drug abuse, disrupted sleep, and physical inactivity and associated adverse health outcomes (McEwen, 2008). Pharmacological approaches to mitigate stress, anxiety, and sleep disturbance have

1

potentially disruptive or dangerous side effects, while evidence for the effectiveness of low risk complementary and alternative medicine practices to treat both psychosocial and physical symptoms in cancer survivors has gained traction in recent years. One such intervention that is well established for use in cancer populations is Mindfulness Based Stress Reduction (MBSR); a program developed in the 1990's by Jon Kabat-Zinn to aid individuals in dealing with both physical and emotional distress through the practice of mindfulness; or present moment awareness and acceptance (Kabat-Zinn, 1990).

There is strong, level 1 evidence in the current literature from meta-analyses and reviews of randomized controlled trials that MBSR is effective for improving psychological, functional, and quality of life outcomes in cancer patients, but this evidence relies primarily on self-reported measures of stress, anxiety, mood, and other common symptoms (Linda E. Carlson, 2012, 2016; Cramer, Lauche, Paul, & Dobos, 2012; Piet, Würtzen, & Zachariae, 2012; Zainal, Booth, & Huppert, 2013). A handful of studies have also examined the biomarker cortisol as an indicator of stress and hypothalamic-pituitary-adrenal (HPA) axis function to assess efficacy of mindfulness interventions in cancer survivors. Results and methodology in these studies is not widely consistent, but point towards a small beneficial effect of mindfulness interventions on cortisol levels in cancer survivors.

1.2   Purpose and Objectives

In 2012, the Greenville Health System (GHS) created the Center for Integrative Oncology and Survivorship to support and study complementary approaches to cancer

2

survivor care. As part of this, practitioners developed a mindfulness program based on Kabat-Zinn's original MBSR program called Cultivating Mindfulness in Cancer Survivorship (CMCS). The CMCS program is an abbreviated 4-week class focusing on meditation practices, attention regulation, and emotional control.

The current study is a randomized controlled trial (RCT) in a sample of cancer survivors from GHS who were randomized to attend the CMCS program or a brief breathing exercise class. As an exploratory study of the CMCS program offered by GHS, this research is meant to provide feedback and preliminary results on effects of the intervention on psychometric and physiologic data. Specifically, the purpose in this paper is to assess impact of the CMCS mindfulness program on cortisol levels in GHS cancer survivors.

Specific Aim 1

To assess association of the diurnal cortisol decline (DCD) at baseline with key psychosocial variables indicated in the literature by testing the following hypotheses:

→ More negative DCD at baseline will be associated with increased physical activity.

→ More negative DCD at baseline will be associated with being female.

→ More negative DCD at baseline will be associated with younger age.

→ More negative DCD at baseline will be associated with fewer symptoms of depression.

→ More negative DCD at baseline will be associated with increased sleep quality.

→ More negative DCD at baseline will be associated with lower perceived stress.

3

→ More negative DCD at baseline will be associated with participants in the Fall program cohort.

Specific Aim 2

To assess association of the GHS mindfulness intervention on diurnal cortisol rhythm by testing the following hypothesis:

→ Change in DCD will be more negative in the intervention group, relative to the control group, after the intervention.

Specific Aim 3

To assess association of the GHS mindfulness intervention on diurnal cortisol levels by testing the following hypothesis:

→ The effect of treatment will be modified by patient cortisol level at baseline: those with high initial cortisol will see a greater decrease, and those with low initial cortisol will see a greater increase in the treatment group relative to the control group.

1.3   Significance of Research

This research will provide insight to guide development of larger trials of the CMCS program at GHS. Furthermore, it will contribute to the literature at large on the effectiveness of mindfulness interventions for cancer patients as assessed using the objective biomarker cortisol. Investigation of cortisol in this context is relevant as an alternative to self-report measures of quality of life indicators such as stress and anxiety.

4

Additionally, abnormal cortisol rhythms and elevated evening cortisol levels have been linked with shortened survival time in cancer patients (L. Cohen et al., 2012; Schrepf et al., 2015; Sephton et al., 2013; Sephton, Sapolsky, Kraemer, & Spiegel, 2000). Despite this, there are few RCTs examining the impact of mindfulness meditation on HPA axis function through assessment of diurnal cortisol rhythm in a population of cancer survivors, and those that exist provide mixed results.

1.4   Study Outline

Within this chapter (Chapter 1) I have briefly reviewed the issues of disruptive symptoms in a growing population of cancer survivors, the purpose and primary objectives of this research, and the expected contributions to the literature concerning both mindfulness interventions and cortisol measures in cancer survivors.

Chapter 2 will provide an update on the impact of cancer survivorship on both a population scale and on an individual level in terms of symptomology and quality of life in cancer survivors. I also will briefly cover the concept of mindfulness practice as a tool to manage psychosocial response to medical conditions through present moment awareness. Additionally, I will introduce the biomarker cortisol as a plausible measure of HPA axis function and describe the biological mechanism underlying its release in the body. Following this, I will discuss the use of cortisol as an outcome measure in research and evaluate the appropriateness of various methods of collection and analysis of cortisol to objectively assess HPA axis function and impact of treatment. This background will provide the reader with the relevant understanding to critically evaluate the final

summary in Chapter 2 of the most relevant literature and to stimulate interest in the topic, methodology, analytical process, and results of this study.

The study design, methodological details, and statistical methods are described in Chapter 3 and Chapter 4 will provide results from the data analysis.

I will conclude in Chapter 5 with a discussion of relevant findings and their implications, including suggestions for future research.

Chapter 2: Background

2.1   Cancer Survivorship

A cancer survivor is anyone living with a history of cancer diagnosis regardless of time since diagnosis, and does not exclude individuals receiving active treatment (Centers for Disease Control, 2016; Morgan, 2009). Improvements in cancer screening, diagnosis, treatment, and care over the past 50 years have led to a dramatic increase in 5-year survival for cancer patients: from 49% between 1975 and 1977 to 69% between 2005-2011 (SEER 9 Region NCI) (American Cancer Society, 2016). This increase in survival coupled with steady incidence rates in the past decade (2003-2012) for women and only slightly declining rates for men during that same time period (avg. 1.4% per year) means the population of cancer survivors in the United States is large and growing (American Cancer Society, 2016).

Cancer survivorship comes with a range of stressors and potentially lasting changes in lifestyle, including disrupted family, job, and social roles, and changes in capabilities and appearance in addition to continued side effects of treatments such as pain and dysfunction. Many survivors also report a lingering fear of the possibility of cancer recurrence, progression, or death (Linda E. Carlson, 2016). Refer to Table 2.1 for a categorized listing of potential negative cancer survivorship outcomes from Morgan, 2009 (Morgan, 2009).

7

Table 2.1 Negative Outcomes of Cancer Survivorship (Morgan, 2009)

Physical Changes	Psychological Changes
Altered body/self-image	Changes in family structure
Cardiac damage secondary to anthracycline treatment	Cognitive changes
Impaired sexuality	Fear of genetic inheritance for families
Osteoporosis	Fear of recurrence
Pain	Financial concerns
Peripheral neuropathies	Loss of ability to work
Premature menopause	Pain
Secondary cancers	Social support
Stress incontinence	Workplace or insurance discrimination

Morgan explains three stages of survivorship: acute, extended, and permanent (Morgan, 2009). The stages are not necessarily experienced by all patients, and provide only a general timeframe, but each stage comes with its own set of challenges for survivors. The acute stage encompasses diagnosis, treatment decisions, and primary treatments including surgery, radiation, and/or chemotherapy. The extended stage is the follow-up period to completion of primary treatments during which the cancer may be in remission; or the patients' condition is identified as terminal. Finally, the permanent stage is the long-term period following remission where probability of recurrence is low and survival is expected to be lasting (Morgan, 2009).

One issue encountered at each stage of cancer survival is the need for emotional regulation in response to increased life stressors. One report found that cancer patients identified emotional effects of cancer as being more difficult to deal with than either physical effects or practical effects (Macmillan Cancer Support, Opinion Leader Research, 2006). Through development of a Cancer Survivor Core Set, Geerse and colleagues

reconfirmed that cancer survivors deal with persistent health and emotional problems (Geerse et al., 2017). Geerse and colleagues developed the Cancer Survivor Core Set with a panel of experts and healthcare workers to identify health-related problems of importance for cancer survivors for practical use in directing long-term care efforts. In this Core Set including three components (body function, activities and participation, and environmental factors) and 19 separate categories within the components, the category for emotional function was the only issue that panelists from prostate, breast, and colorectal cancer all rated with 100% content relevance to survivorship care (Geerse et al., 2017).

It is evident that quality of life is an important consideration for cancer survivors and that emotional dysregulation is reported to be a major negative outcome of cancer survivorship. It is likely that for this reason research into complementary and alternative care programs for survivors has been on the rise in recent decades. One such alternative care practice that has been implemented and researched in cancer populations is mindfulness meditation.

2.2   Mindfulness Practice

Mindfulness, or attention to the present moment with an open, accepting attitude, as a purposeful practice through meditation has its origins 2,500 years ago in Eastern theologies and philosophies. Defining mindfulness and understanding how the process of mindfulness operates to improve a broad range of symptoms has been the focus of some discussion. Jon Kabat-Zinn explained mindfulness as: "awareness that

arises through paying attention, on purpose, in the present moment, non-judgmentally"
(Kabat-Zinn, 1990). In an effort to understand the mechanism of mindfulness, Shapiro and
colleagues formulated a model that centers on three axioms: attention, intentionality,
and non-judgment when processing thoughts and situations and coined the term
'reperceiving' to describe a change in perception without detachment that comes
through practicing these axioms of mindfulness (Shapiro, Carlson, Astin, & Freedman,
2006). Shapiro and colleagues linked these axioms with mechanisms of self-regulation,
exposure, value clarification, and flexibility in thought, emotion, and behavior that are
likely facilitators in positive health outcomes of psychological and psychosomatic
symptom relief as well as valuable outcomes in themselves (Shapiro et al., 2006).

The translation of mindfulness into nonreligious practice for use in clinical
populations began near the close of the 1970s with Joh Kabat-Zinn's research into its
effectiveness for managing anxiety and pain (Kabat-Zinn, 1990). With the development of
a formal practice for clinical populations through the MBSR program, research in the field
of mindfulness meditation has grown and offshoots of the MBSR program have
proliferated. MBSR and other Mindfulness Based Intervention (MBI) programs generally
incorporate a variety of mindfulness training techniques including meditation and body
scanning. Body scanning entails focusing on sensation in various parts of the body
beginning from head down to feet, and meditation promotes attention to the breath
while acting nonjudgmentally as an outside observer to any intruding thoughts that
arise(Rush & Sharma, 2016). Formal practice both in groups and alone provides resources

and training to develop mindfulness in daily life and promotes the nonjudgmental observance of thought processes as a habit.

Because of the way mindfulness is practiced, and its influence on thought processes, mindfulness meditation may be particularly beneficial for cancer patients. Linda Carlson describes how many life changes due to cancer diagnosis require emotional-based coping strategies rather than problem-based coping strategies, particularly post active treatment – something many people are less well equipped to deal with (Linda E. Carlson, 2016). Evidence supports that experiencing thoughts mindfully, allowing for acceptance of the subjective, not necessarily true, nature of thoughts and their transitory nature plays some role in alleviating psychological symptoms. In a 2012 narrative review, Linda Carlson assessed use of MBIs in cancer populations, concluding that level 1 evidence from systematic reviews and meta-analyses of RCTs exists for the effectiveness of MBIs for improving psychological, operational, and quality of life outcomes (Linda E. Carlson, 2012; Yaowarat Matchim, Armer, & Stewart, 2011).

With strong self-reported evidence that mindfulness meditation is effective for alleviating some symptoms commonly experienced by cancer patients, but an incomplete understanding of the underlying process, further research is needed using objective outcome measures that also have potential to provide clues to bodily mechanisms. Salivary cortisol is one such measure that has been used increasingly in recent research.

2.3   Diurnal Cortisol and HPA axis regulation

Cortisol is the primary human glucocorticoid and is an essential steroid hormone produced in the body as an end product of the HPA axis. Its production is stimulated beginning in the hypothalamus which releases corticotrophin releasing hormone (CRH) in response to a range of biological and environmental mediators including both physical and psychological stress (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007). CRH functions to stimulate the release of adrenocorticotropic hormone (ACHT) from the pituitary gland, which in turn acts on the adrenal cortex to produce cortisol. Cortisol functions broadly in the body by suppressing non-essential function of the immune, reproductive, and digestive systems and acting to prepare the body for action by increasing blood pressure, releasing stored energy sources for use, and acting as a powerful anti-inflammatory (Levine et al., 2007). Its flux in the body is affected by environmental stimuli, circadian rhythms, and sleep cycles (Levine et al., 2007). Additionally, as part of a negative feedback loop, cortisol acts as an inhibitor to the HPA axis, suppressing the release of CRH and ACHT. Dysregulation of the HPA axis and its components, including irregular cortisol levels and patterns have been associated with a range of adverse outcomes including reduced cancer survival (L. Cohen et al., 2012; Schrepf et al., 2015; Sephton et al., 2013, 2000) depression (Poole et al., 2016), psychiatric illness (de Kloet, Joëls, & Holsboer, 2005), cardiovascular events and mortality (Kumari, Shipley, Stafford, & Kivimaki, 2011) and chronic fatigue (Powell, Liossi, Moss-Morris, & Schlotz, 2013). Over the past two decades, free cortisol levels have notably been used as a biological indicator of stress and as a surrogate for HPA axis function (Kirschbaum &

12

Hellhammer, 1994). This has been facilitated by the ease of collection of salivary cortisol measures as an economic, non-invasive, and reliable measure of free blood serum cortisol that can be performed without the assistance of medical personnel and in a variety of environments (Hellhammer, Wüst, & Kudielka, 2009).

More recently, and primarily with the use of salivary cortisol measures rather than blood or urinary cortisol, methods have been trending towards measures of diurnal cortisol rhythm as opposed to total cortisol over a 12 or 24-hour period. Research suggests that the rhythm of cortisol levels during the day may be relevant to disease status and prognosis (Adam & Kumari, 2009). Typically, the diurnal cortisol rhythm measured immediately upon awakening begins relatively high with a spike (50-60% increase) within the first 30 to 45 minutes after waking followed by a more gradual decline over the rest of the day to a low point around midnight with established differences between men and women (Adam & Kumari, 2009; Pruessner et al., 1997). This typical daily rhythm has been observed as a consistent pattern in healthy individuals and deviations are associated with dysregulation of the HPA axis function through both environmental influence and disease (Stone et al., 2001).

Although the use of salivary cortisol to measure diurnal rhythm has gained popularity, methodology for collecting and analyzing cortisol samples remain inconsistent. A recent review of RCTs by Ryan and colleagues resulted in a series of recommendations for improving methodology and consistency across studies for the use of salivary cortisol as an indicator of HPA axis function (Ryan, Booth, Spathis, Mollart, &

Clow, 2016). Ryan and colleagues suggested collecting two days of cortisol samples for each assessment period due to intra-individual variation between days, a recommendation that was also made by Clow and colleagues to allow for the assessment of participant adherence (Clow, Thorn, Evans, & Hucklebridge, 2004). Ryan and colleagues also recommend collecting enough salivary samples each sample day to develop a full picture of cortisol rhythm (Ryan et al., 2016). Practically, this included collecting a series of at least two samples beginning with awakening time up to 30-45-minute post awakening in order to assess the cortisol awakening response (CAR) which is the typical spike in cortisol post awakening. Additionally, they suggested a least one evening sample to allow for assessment of total daily cortisol secretion, and to determine the diurnal change in cortisol levels from awakening to evening (generally negative in healthy individuals) (Ryan et al., 2016).

Along with methodological inconsistencies in the sampling of cortisol, interpretation of resulting cortisol values varies across studies. In part, this is due to the broad function and cyclical nature of cortisol in the body but also due to differences in cortisol patterns between populations (i.e. men and women or youth and adults) and a limited understanding of clinical significance. Particularly for absolute measures of total diurnal cortisol, but also for the CAR, both depressed and heightened cortisol levels (hypo- and hyper-cortisolism) have been associated with adverse physical and psychological conditions (Chida & Steptoe, 2009; Heim, Ehlert, & Hellhammer, 2000). Fries and colleagues concluded based on animal models that hypocortisolism may be a reaction to hyperactivity of the HPA axis from chronic stress and suggested several

possible biological mechanisms (Fries, Hesse, Hellhammer, & Hellhammer, 2005). This idea matches with explanations of allostatic overload. Essentially, although an acute stress response adaptively prepares the body for 'fight-or-flight', sustained or chronic stress can trigger allostatic overload, an inability of the body to effectively regulate stress response, which can contribute to bodily deterioration (as in the case of chronically high blood pressure) and exhausts the capability of the HPA axis to react appropriately to environmental cues (McEwen, 2008). Heim and colleagues speculated with hypocortisolism, the reduced ability to respond to stressful stimuli could underlie vulnerability to some stress related diseases (Heim et al., 2000). Furthermore, in a 2009 review, Chida and Steptoe examined associations of various psychosocial factors with the CAR and found that a heightened or depressed CAR is associated with different factors (Chida & Steptoe, 2009). Specifically, they found that heightened CAR was significantly associated with job stress and general life stress and that depressed CAR was significantly associated with fatigue, burnout, or exhaustion; suggesting a link between chronic stress and reduced CAR (Chida & Steptoe, 2009). Chida and Steptoe also proposed that their failure to find an association between CAR and depression may have been because depression has been associated with both heightened and reduced CAR; depending on the intensity of the depressive episode (Chida & Steptoe, 2009). Because dysregulation of the HPA axis leading to either elevated or depressed cortisol levels is thought to be detrimental, interpreting the CAR and total daily cortisol is not straightforward. Researchers have used various strategies to model a normalizing effect of mindfulness interventions or cortisol levels. Bränström and colleagues examined how segmenting by

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tertiles of cortisol levels at baseline predicted change in cortisol levels (Bränström, Kvillemo, & \AAkerstedt, 2013), and Carlson and colleagues divided the baseline sample into 'high' and 'low' cortisol groups, and found that those with low cortisol tended to show increased levels post intervention and those with 'high' cortisol tended to show decreased levels post intervention (Linda E Carlson, Speca, Patel, & Goodey, 2004). There has been a discussion in the literature of identification of standard normative cortisol values (Clow et al., 2004; Heim et al., 2000), and a recent publication using cortisol from a sample of over 18,000 healthy participants has supplied operational reference ranges for salivary cortisol across the day by age categories for both men and women (see Table 2.2 for an excerpt) (R. Miller et al., 2016). These normative ranges have potential to be used in identifying both hypocortisolism and hypercortisolism in diseased populations where supplied reference age groups and sample times are relevant to the comparison population and sampling procedure.

Table 2.2 Reference values from 50th percentiles of salivary cortisol concentrations at various hours after 07:00 (excerpted from R. Miller et al., 2016)

Age	Sex	1 h	3.5 h	6 h	8.5 h	11 h	13.5 h	16 h
31-40	F	6.5	3.6	2.1	1.4	1.0	0.7	0.6
31-40	M	6.6	3.6	2.1	1.4	1.0	0.7	0.6
41-50	F	6.3	3.4	2.0	1.3	0.9	0.7	0.6
41-50	M	6.3	3.4	2.0	1.3	0.9	0.7	0.6
51-60	F	6.4	3.5	2.0	1.3	0.9	0.7	0.6
51-60	M	7.1	3.9	2.3	1.5	1.0	0.8	0.7
61-70	F	6.8	3.7	2.2	1.4	1.0	0.8	0.6
61-70	M	7.3	4.0	2.3	1.5	1.1	0.8	0.7
71-80	F	7.2	3.9	2.3	1.5	1.1	0.8	0.7
71-80	M	7.9	4.3	2.5	1.6	1.2	0.9	0.7

Note. All concentrations are scaled in nmol/L. Abbreviations in the sex column: F = female (grey shaded cells), M = male.

In comparison to assessing CAR and total diurnal cortisol secretion, interpretation of the change in cortisol from awakening (or peak level) to evening (often assessed using diurnal cortisol slope) is relatively direct. Research has shown that little or no decrease over the day in cortisol levels as compared to a steeper decline in cortisol levels is an indicator of HPA axis dysregulation (Adam & Kumari, 2009).

2.4   Current Literature

There has been a proliferation of papers assessing mindfulness based interventions in cancer care in the past decade, and particularly since 2010. The majority have focused on self-reported symptomology such as psychological wellbeing, stress, and fatigue. Current evidence from systematic reviews of RCTs provides strong evidences that use of mindfulness interventions in cancer patients is effective for improving psychological and quality of life outcomes such as mood, distress, and other psychosocial outcomes (Linda E. Carlson, 2012). The evidence of impact of mindfulness interventions in cancer survivors on HPA axis function through assessment of cortisol level is less concrete. Four relatively recent original pre-post or non-randomized controlled clinical trials have been conducted which measured salivary cortisol as an outcome variable (Lengacher et al., 2012; Y. Matchim, Armer, & Stewart, 2011; Matousek, Pruessner, & Dobkin, 2011; Witek-Janusek et al., 2008). Matchim and colleagues (2011) conducted a quasi-experimental design study by comparing a group of 19 breast cancer survivors in one city who participated in an 8-week MBSR class to a group of 17 survivors in a nearby city who did not receive the MBSR intervention (Y. Matchim et al., 2011). For financial reasons, cortisol was not measured in all participants; 10-12 randomly selected

17

individuals from each group provided two cortisol samples over a one-day period, one at awakening and another at 4:00pm. The same individuals provided cortisol samples immediately after conclusion of the 8-week MBSR program and 1-month post conclusion. Matchim and colleagues compared the morning and evening samples separately within and between groups and found a significant decrease of 0.22 μg/dl in the morning cortisol measurement from baseline to directly after the MBSR intervention for the intervention group, but not the control (Y. Matchim et al., 2011). No other significant changes were noted in cortisol. The study also found statistically significant reduction in diastolic blood pressure and increased mindfulness in the intervention arm at 1 month follow-up compared to baseline levels (Y. Matchim et al., 2011). Compared to the control group, heart rate, respiratory rate, and systolic blood pressure were significantly lower and mindfulness was significantly higher in the intervention arm at 1 month follow-up (Y. Matchim et al., 2011). Matousek and colleagues similarly assessed cortisol in a population of 33 all-female breast cancer survivors (Matousek et al., 2011). Their outcome of interest was the CAR, thus only morning salivary cortisol was collected. Salivary samples were self-administered at awakening, and at 30- and 45-minute post awakening for three consecutive days both before and after the 8-week MBSR intervention (Matousek et al., 2011). In their analysis, Matousek and colleagues found the CAR to be stable across the three days sampled at baseline and post intervention, and that CAR increased significantly post intervention compared to baseline, mostly due to sustained awakening response at the 45 minute sampling point (Matousek et al., 2011). Their results contrasted with another study assessing impact of MBSR on CAR in substance abuse patients by Marcus

18

and colleagues (2003) which found CAR was significantly reduced post intervention rather than increased (Marcus et al., 2003). They attributed this reversal of effect to the initial depressed CAR response in their cancer population compared to normative values advanced by Wust and colleagues (2000), a conclusion in line with the idea that chronic stress can lead to lowered reactivity of the HPA axis (Wust et al., 2000). Witek-Janusek and colleagues compared 75 women with early stage breast cancer, scheduled to receive radiation, but not chemotherapy treatment between self-selected control and intervention groups to a healthy cancer-free group of age matched women (Witek-Janusek et al., 2008). The intervention consisted of an 8-week MBSR program modelled after the original Kabat-Zinn 1990 program (Witek-Janusek et al., 2008). Evening blood plasma cortisol was collected from a portion of the cancer-control and intervention groups (only for women who were available to have their blood drawn from 4-6pm) at baseline, mid-intervention, directly post intervention, and 1 month after the conclusion of the intervention (Witek-Janusek et al., 2008). In comparison to the cancer-free group, both the cancer-control and intervention groups had significantly higher cortisol at all time points (Witek-Janusek et al., 2008). The intervention group had significantly lower evening plasma cortisol levels at completion of the MBSR program compared to the cancer-control group (Witek-Janusek et al., 2008). Lengacher and colleagues included both advanced stage cancer patients and their caregivers in a 2012 study; but for the sake of relevancy, only the cortisol response in patients will be discussed here (Lengacher et al., 2012). Breast, colon, lung, and prostate cancer patients were recruited who had completed surgery and were receiving radiation and/or chemotherapy (Lengacher et al.,

19

2012). The intervention was a modified MBSR program for cancer patients, that was reduced to 6-weeks (compared to the standard 8-weeks) and 3 of the 6 sessions were self-directed with the assistance of audiotapes (Lengacher et al., 2012). Patients provided a saliva sample directly before and after the first (n=10), third (n=8), and sixth (n=7) MBSR class (which were in-person and held from 10:00am to 12:00pm). Lengacher and colleagues found significantly reduced cortisol for patients post MBSR class compared to pre MBSR class at the first and third class, but not at the sixth (Lengacher et al., 2012). Cortisol levels were significantly reduced between baseline at the first class and baseline at the sixth class. They did not specifically address confounding by time in cortisol sampling. It would be expected in a healthy diurnal cortisol rhythm for cortisol levels to decline between the hours of 10:00am and 12:00pm in the absence of any situational stress response regardless of participation in a mindfulness program. The authors did concede that lack of a control group disallowed contribution of cortisol reduction exclusively to the MBSR for cancer patients intervention (Lengacher et al., 2012).

Some consistencies and inconsistencies can be seen from this brief review of the most recent original pre-post and non-randomized controlled clinical trials of mindfulness meditation including cortisol as an outcome measure in cancer patients and survivors. Participants were mostly female breast cancer patients, and salivary cortisol was primarily used as the outcome measure (with the exception of the Witek-Janusek study, which used free plasma cortisol) (Witek-Janusek et al., 2008). Sampling procedures for cortisol vary widely between these four studies, from a single evening time point at each follow up by Witek-Janusek and colleagues (Witek-Janusek et al., 2008), to three repeated days

including three morning samples each day to assesses CAR at each follow-up time by Matousek and colleagues (Matousek et al., 2011). None assessed total diurnal cortisol, more than one summary measure for cortisol, or diurnal cortisol decline, although Matchim and colleagues (2011) had the potential to assess diurnal cortisol decline from collections of both awakening and evening samples (Y. Matchim et al., 2011). These studies primarily used a full 8-week MBSR course as the intervention, with the exception of the Lengacher study (2012) which used a shortened program of 6 weeks that included a self-directed portion (Lengacher et al., 2012). Witek-Janusek and colleagues (2008) and Lengacher and colleagues, (2012) included patients actively receiving treatment for cancer rather than post treatment patients (Lengacher et al., 2012; Witek-Janusek et al., 2008). Results from the four studies, although based on various cortisol measurements, were consistently interpreted as suggesting a beneficial effect of mindfulness interventions on cortisol levels. The Matchim study reported decreased awakening cortisol levels post intervention (Y. Matchim et al., 2011), Matousek reported increased CAR post intervention (Matousek et al., 2011), Lengacher reported decreased cortisol after the first and third mindfulness classes (compared to the pre-class measure) and decreased cortisol from the first class to the sixth class (Lengacher et al., 2012), and Witek-Janusek reported decreased evening cortisol levels post intervention compared to a non-randomized control group (Witek-Janusek et al., 2008). Although varied, all significant changes in cortisol post intervention were construed to be positive indicators of improved HPA axis functioning.

Only three RCTs of a mindfulness intervention in cancer patients using cortisol as a measure of HPA axis function have been conducted to date: Bränström and colleagues, (2013); Carlson and colleagues, (2013); and Lipschitz and colleagues, (2013) (Bränström et al., 2013; L. E. Carlson et al., 2013; Lipschitz, Kuhn, Kinney, Donaldson, & Nakamura, 2013). Bränström and colleagues randomized 71 total cancer patients (70 females, 1 male) of various diagnoses, but not currently undergoing treatment to an 8-week MBSR program or a waitlist control (Bränström et al., 2013). A single self-administered awakening cortisol sample was collected from each participant at baseline, 3 months from baseline, and 6 months from baseline. Participants were 93% compliant with cortisol reporting. Results for self-reported measures were described in a separate publication (Bränström, Kvillemo, Brandberg, & Moskowitz, 2010), but briefly, they found significant differences between the intervention and control arms in perceived stress, positive states of mind, and post-traumatic avoidance symptoms at the 3 month follow-up, but not at the 6 month follow-up. In their 2013 publication of cortisol outcomes, Bränström and colleagues failed to find overall effects of the intervention on cortisol levels at the 3-month or 6-month follow-up, but did find significant effect modification by baseline cortisol levels in the intervention group at the 3-month follow-up (Bränström et al., 2013). Participants in the intervention group with initially low cortisol levels (defined as the lower tertile for the study population) at baseline saw an increase in cortisol on average, and participants with initially high cortisol levels (defined as the upper tertile for the study population) saw a decrease in cortisol on average compared to the control group. The effect modification observed by baseline levels was not sustained at 6-month follow-up.

22

They suggest that this normalization of baseline cortisol levels observed at the 3 month follow-up may not have been sustained at the 6-month follow-up due to a lack of continued mindfulness meditation practice by most participants, and acknowledge the use of a single awakening cortisol measurement and small sample size as limitations to their study (Bränström et al., 2013). The largest RCT to date was conducted by Carlson and colleagues (2013) (L. E. Carlson et al., 2013) comparing impact of a Mindfulness Based Cancer Recovery (MBCR) intervention and a Supportive-Expressive Group Therapy (SET) program to a single-day stress management control program. MBCR is adapted from traditional MBSR to be used specifically in a cancer population and closely follows the original MBSR program. MBCR and SET are similar in functional characteristics such as total contact hours, group format, and structure, however SET highlights emotional expression and group support while MBCR is focused on mindfulness meditation and daily mindful awareness. Two hundred and seventy-one female breast cancer survivors who qualified as distressed by scoring above a predetermined cutoff on an indicator of distress were randomly assigned in a 2:2:1 ratio to the MBCR, SET, or a minimal treatment control group. Salivary cortisol was measured 4 times per day over 3 consecutive days at 30-minute post awakening, 12:00pm, 5:00pm, and bedtime at baseline and intervention completion at 8 weeks (L. E. Carlson et al., 2013). Diurnal cortisol slope for each individual was calculated using all 12 samples from the 3-day period at baseline and post-intervention (L. E. Carlson et al., 2013). They found that the steepness of the diurnal cortisol slope was maintained in both the MBCR and SET groups baseline to post-intervention, while the slope for the control group became flatter, indicating that both

23

interventions may have a protective effect against progressive HPA axis dysregulation (L. E. Carlson et al., 2013). Although this is the largest RCT assessing effect of a mindfulness intervention on cortisol levels in a cancer population, the study had a high attrition rate (roughly 30% for each group), no long-term follow-up, and included only female breast cancer survivors (L. E. Carlson et al., 2013). In their 2013 paper, Lipschitz and colleagues (2013) focused primarily on sleep regulation, but measured salivary cortisol as an outcome variable assessing a mindfulness intervention (Lipschitz et al., 2013). Fifty-seven male and female cancer survivors in remission for greater than 3 months and reporting sleep disturbance were randomized to either a Sleep Hygiene Education (SHE) standard care group (n=18), a Mind-Body Bridging (MBB) intervention program (n=19) or a Mindfulness Meditation (MM) intervention program (n=20) (Lipschitz et al., 2013). The SHE program was an information session about dealing with sleep disturbances, the MBB program was centered on teaching awareness of dysfunctional thought processes and identifying sources of sleep problems, and the MM program was a 3-week modification of a traditional MBSR program that focused on mindfulness meditation skills. Cortisol was sampled at baseline prior to the intervention and within one-week post intervention (Lipschitz et al., 2013). At each follow-up, cortisol was sampled on two consecutive days: the first day at 30-minute post awakening, noon, afternoon (5:00pm), and bedtime; the second day at awakening. Having the first sample on the first day be collected 30-minute post awakening was employed to increase compliance, but prevented examination of the CAR as a response measure. In their analysis, they included awakening sample alone as an outcome variable but also examined total diurnal cortisol using an area under the

24

curve summary measure and mean diurnal profile using the 4 samples collected on the same day as outcome variables. No significant effects on salivary cortisol were found for the mindfulness intervention in comparison to either the MBB intervention or SHE control (Lipschitz et al., 2013). They found no significant differences in awakening cortisol post MM or MBB intervention compared to the SHE control group, although the SHE group did show a decline post intervention (p=0.052) (Lipschitz et al., 2013). Models of total diurnal cortisol and mean diurnal profile showed no significant difference between the three groups post intervention when controlling for baseline levels (Lipschitz et al., 2013). There was a significant decrease in self-reported sleep problems for the MM and MBB interventions compared to the SHE control group (Lipschitz et al., 2013).

Similar to the non-randomized clinical trials of mindfulness interventions in cancer survivors, the three RCT studies have varied methodological approaches and different sampling procedures for cortisol and thus examined different outcome variables. Only Lipschitz and colleagues (2013) (Lipschitz et al., 2013) included a relevant sample of both male and female survivors although there was 1 male participant in the Bränström study (Bränström et al., 2013). Bränström and colleagues (Bränström et al., 2013) also was the only study to include a longer-term follow-up on cortisol post-intervention whereas Carlson (2013) and Lipschitz (2013) only assessed cortisol directly post intervention (L. E. Carlson et al., 2013; Lipschitz et al., 2013) although Carlson and colleagues did conduct a longer-term follow-up on self-report measures from the same study (Linda E. Carlson et al., 2016). The Lipschitz study was the only study to evaluate an abbreviated mindfulness program: 3-weeks compared to standard 8-week (Lipschitz et al., 2013). None of the three

studies collected cortisol measures that would allow for the calculation of CAR as an outcome variable, although one did use diurnal cortisol slope (without an awakening anchor sample) as an outcome measure (L. E. Carlson et al., 2013). Two specifically enrolled only distressed cancer survivors – identified from a distress scale or from self-reported sleep dysregulation, and these two also compared the mindfulness intervention to another active intervention group and a minimal-treatment control group (L. E. Carlson et al., 2013; Lipschitz et al., 2013). The Carlson (2013) study was the largest trial to date, with 271 participants, the others including only up to 71 participants (L. E. Carlson et al., 2013). Importantly, outcomes were also varied. Lipschitz and colleagues found no significant effects of the intervention on cortisol levels (Lipschitz et al., 2013) although this could potentially be explained by their use of cortisol averages rather than investigating effect modification by levels of baseline cortisol, and because they did not examine diurnal rhythm parameters. Relevant to this rationale, Bränström and colleagues found no overall effect of the mindfulness intervention on cortisol at the 3- and 6-month follow-up but did observe normalization of awakening cortisol levels at the 3-month follow-up in the treatment group (Bränström et al., 2013). Those with high baseline cortisol values tended to show decreases and those with low baseline cortisol values tended to show increases (Bränström et al., 2013). Finally, Carlson and colleagues (2013) found that diurnal cortisol slope was maintained in the mindfulness intervention group, but became flatter in the control group and that bedtime cortisol levels decreased in the mindfulness group relative to the control (L. E. Carlson et al., 2013).

With this broad range of study methodologies, measurement protocols for cortisol, and cortisol outcome variables examined, it is not surprising that there is a lack of a firm consensus in the literature concerning effectiveness of mindfulness interventions as evaluated by RCTs on the objective marker of HPA axis functioning, cortisol. Our study has potential to add to this growing literature stream through various methodological and analytical strengths. First, we are assessing an abbreviated mindfulness intervention similar to that employed by Lipschitz (ours is 4-weeks versus their 3-week intervention) and examine in our population both significant outcomes from the Carlson and Bränström studies that were not examined in the Lipschits study: modification by baseline cortisol level and diurnal cortisol decline (Bränström et al., 2013; L. E. Carlson et al., 2013; Lipschitz et al., 2013). Evaluation of abbreviated mindfulness programs was encouraged in a 2015 review by Rouleau and colleagues to improve program accessibility if lower 'doses' of mindfulness training are shown to be equally effective (Linda E. Carlson, 2012) and a 2016 review by Ryan and colleagues recommended examining three cortisol outcome measures: total diurnal cortisol (typically calculated as area under the curve), CAR, and diurnal cortisol decline (typically assessed as diurnal slope) (Ryan et al., 2016). Additionally, using a model that allows examination of a normalizing effect of the intervention is based on results from two studies showing regulation of both high and low baseline cortisol after mindfulness interventions (Bränström et al., 2013; Linda E Carlson et al., 2004) and biological indications concerning HPA axis regulation of acute and chronic stress. Furthermore, this study also includes both male and female cancer patients, high subject retention, and a

longer-term follow-up at 3 months (i.e. 2-month post-intervention); elements that are

lacking in the current literature.

Chapter 3: Method

3.1   Study Design

Study Population

Two cohorts selected from Greenville Health Systems (GHS) of cancer patients living in and around Greenville SC, aged greater than 18 years old were identified from clinical records or GHS providers and contacted to determine interest. Trial for the first cohort was conducted beginning in November of 2015 and included 20 total participants randomly assigned to the intervention (n=10) or the control arm (n=10). The second cohort was conducted beginning in January of 2016 and included 18 total participants randomly assigned to the intervention (n=10) or the control arm (n=8). A total of 36 participants were followed to completion of the study. Two participants were lost to follow-up. Participants were incentivized with a 50-dollar gift card at follow-up.

Inclusion and Exclusion Criteria

Recruited participants were cancer survivors 18 years or older, capable of participating in the intervention classes and providing their own transportation to class, and able to read, write, and speak in English. Participants were excluded if they had previous experience or training in MBSR or were taking corticosteroid therapy equal to or greater than prednisone 25mg/day.

Intervention Arm Mindfulness Program

Four weekly meetings of 2.5 hours each for a CMCS class adapted from the original 8-week MBSR program designed by Jon Kabat-Zinn (Kabat-Zinn, 1990). All mindfulness sessions were facilitated by a Licensed Independent Social Worker – Clinical Practice (LISW-CP) with Oncology Social Work Certification (OSW-C) and included introductory meditation practices focusing on attention regulation, body and thought awareness, and emotional control. The twenty participants randomized to the intervention arm had a 95% attendance rate to the 4 CMCS classes.

Control Arm Breathing Course

The control program consisted of a single 30-minute breathing exercise presented to only the control group at week 1 after baseline assessment. Topics included the relaxed breath exercise (4-7-8 count breathing) and breath counting.

3.2   Measurements

Cortisol

Salivary cortisol samples were collected on one day at baseline and at each follow-up day (6 weeks and 3 months). Collection was self-administered using Salivette® (Sarstedt AG & Co, Germany) saliva collection kits which provide chewable roll-shaped synthetic saliva collectors that once chewed until saturation are replaced in the sample tube. The date and time of collection were written on the tube. Participants provided samples and recorded timing of cortisol measurements six times on each sample day; at

awakening, 15-minute, 30-minute, and 45-minute post awakening, and before their evening meal, and before sleeping. Samples were returned to the laboratory in a pre-paid envelope and transit time was recorded. From the samples, salivary cortisol was assessed and reported in nmol/L. Over the three time periods for all participants, compliance with supplying cortisol samples was 97%.

Questionnaires

Self-administered questionnaires were filled out by participants at each time point. Participant compliance with returning questionnaires was 100%. The questionnaires surveyed participants about the following information:

Demographic Information

Self-reported age, gender, race, marital status, education level, height and weight, employment status, and tobacco and alcohol use and frequency.

Mindful Attention Awareness Scale (MAAS)

The MAAS is a survey designed to assess individual differences in attention and regularity of mindfulness. It consists of 15 statements concerning some episode indicating lack of present awareness (e.g. "I do jobs or tasks automatically, without being aware of what I'm doing" or "I forget a person's name almost as soon as I've been told it for the first time"). Participants indicate the frequency of the item over the past 1 month on a scale of 1-6 ("almost always" through "almost never"), a higher average score indicates higher mindfulness (Brown & Ryan, 2003). The MAAS scale was developed and validated

in a nonclinical population in 2003 and has since been assessed for construct validity in a cancer population (Linda E. Carlson & Brown, 2005).

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a 19 item questionnaire relating to sleep quality and disturbances over the past 1-month interval (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Participants respond to statements (e.g. "Cannot get to sleep within 30 minutes", "Feel too hot") by indicating frequency on a scale of 1-4 ("Not within the past month" up to "Three or more times a week"). Seven component scores of 0-3 are developed from raw scores to separately assess sleep quality, latency, duration, efficiency, disturbances, medication, and daytime function. A global sleep quality score is generated by summing the 7 component scores for an overall range of 0-21. In non-clinical populations, a global sleep quality score above 5 is used to identify poor sleep patterns, however Beck and colleagues suggested that in clinical populations, such as cancer patients, a cutoff of 8 may be more appropriate to categorize poor sleepers (Beck, Schwartz, Towsley, Dudley, & Barsevick, 2004). This questionnaire has been validated and assessed for reliability as well as determined to have construct validity in a cancer population (Beck et al., 2004).

Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D is a validated 20 item self-report questionnaire to assess depressive symptomatology in the general population (Radloff, 1977). Participants indicate frequency within the last week in response to statements including "I felt that everything I did was an effort" or "I enjoyed life". Each item is scored from 0-3 with higher scores

indicating higher frequency of depressive symptoms or lower frequency of positive feelings. A final score is calculated as the sum of all indicators (range 0-60) with 16 or greater indicating depression.

Perceived Stress Scale (PSS-10)

The PSS is a 10-item questionnaire asking participants to indicate frequency within the last month of common thoughts and feelings related to stress (e.g. "In the last month how often have you been angered because of things that were outside of your control?"). Participants rate each item on a scale of 0-4 ("Never" through "Very Often") and items are summed for a possible overall score between 0 and 40; with higher scores indicating higher perceived stress (S. Cohen, Kamarck, & Mermelstein, 1983). The PSS-10 has been validated in an older adult population, and higher scores are associated with higher levels of anxiety, depression, and negative affect (Ezzati et al., 2014).

Daily Stress Inventory (DSI)

The DSI is a self-report questionnaire asking participants to rate their stress response to 58 life situations (e.g. "Waited longer than you wanted" and "Heard some bad news") if they occurred within the last 24 hours on a scale of 1-7 ("Occurred but was not stressful" to "Caused me to panic"). Three summary measures are typically calculated: number of events, sum of impact, and average impact per event. The DSI has been validated, and has shown value as a predictor of occurrence of some symptoms of chronic illness (Brantley & Jeffries, n.d.).

Rapid Assessment of Physical Activity (RAPA)

The RAPA is a 9-item questionnaire that serves as an easy-to-administer measure of physical activity for use in clinical settings. The first 7 questions assess aerobic physical activity and combine to categorize individuals as 'sedentary' 'under-active' 'under-active regular light' 'under-active regular' and 'active'. The final two questions combine to provide a strength and flexibility score ranging from 0 to 3, with 3 suggesting higher participation in activities that promote strength and flexibility. The English version of RAPA has been validated for use among older adults (Topolski et al., 2006).

Additional Measures

Additional information not used in this study also was collected; including nutritional information, caffeine intake, fruit and vegetable consumption, as well as blood samples and actigraph data.

3.3   Model Variables

Outcome Variables

Diurnal cortisol decline (DCD): DCD is calculated as the awakening cortisol measurement subtracted from the average of the evening and bedtime cortisol measurement values for each patient. From the following equation, $DCD_{p,d}$ is change in cortisol from measurement point $m1$ to the average of measurement points $m5$ and $m6$ for each patient p on follow-up day d.

$$DCD_{p,d} = \left(\frac{cortisol_{pd5} + cortisol_{pd6}}{2}\right) - cortisol_{pd1}$$

Cortisol values representing the CAR (i.e. those collected at 15-, 30-, and 45-minute post awakening) are not included in the regression line to calculate diurnal cortisol decline for two primary reasons. First, the CAR is thought to be regulated by a mechanism distinct from other cortisol rhythms (Clow et al., 2004). Clow and colleagues proposed that the CAR is regulated by the hypothalamic suprachiasmatic nucleus and indicated that it is affected by light upon awakening – low light leading to higher CAR response (Clow et al., 2004). For this reason, including immediate post-awakening measurements could bias estimates of diurnal cortisol decline. Additionally, in trials where clinical outcomes were indicated with flatter diurnal cortisol slopes (smaller diurnal decline), only the awakening and evening cortisol measurements were included in analysis (Poole et al., 2016; Sephton et al., 2013, 2000).

Change in DCD (ΔDCD_p^1 and ΔDCD_p^2): *Difference between DCD at baseline (0) and follow-up one (1) and baseline and follow-up two (2) respectively for each patient p.*

$$\Delta DCD_p^1 = (DCD_{p1} - DCD_{p0})$$

$$\Delta DCD_p^2 = (DCD_{p2} - DCD_{p0})$$

Change in cortisol level ($\Delta C_{p,m}^1$ and $\Delta C_{p,m}^2$): *Difference in cortisol level between baseline (0) and follow-up one (1) and baseline and follow-up two (2) respectively for each patient p, and cortisol measurement point m.*

$$\Delta C_{p,m}^1 = cortisol_{p1m} - cortisol_{p0m}$$

$$\Delta C_{p,m}^2 = cortisol_{p2m} - cortisol_{p0m}$$

Exposure Variable

Randomization to the intervention mindfulness program or to the control breathing course was the primary exposure of interest.

Confounders

Potential confounders that were assessed for impact on the ability of the model to predict changes in diurnal cortisol patterns: sex, age, race, perceived stress, physical activity level, depression, sleep quality, and cohort (Adam & Kumari, 2009; R. Miller et al., 2016).

Effect Modifiers

Baseline levels of cortisol were examined as a potential effect modifier (Bränström et al., 2013).

3.4 Statistical Analysis

We performed three distinct analyses. First, a baseline analysis to assess association between DCD and variables of interest in the sample population. Second, we investigated the effect of the treatment on change in DCD and third, we investigated the effect of the treatment on cortisol level changes for each cortisol measurement.

36

Baseline Analysis

Baseline DCD can be calculated using the method explained in Subsection 3.3 using baseline day ($d = 0$). We examine the crude and multivariable association between DCD at baseline and measured variables of interest including depression, sex, perceived stress, age, sleep quality, physical activity, and cohort when indicated by a crude association. Refer to Subsection 1.2 specific aim 1 for hypothesized associations.

$$\text{DCD}_{p,d=0} = \beta_0 + \beta_1 depression + \beta_2 sex + \beta_3 stress + \beta_4 age + \beta_5 sleep + \beta_6 PA$$
$$+ \beta_7 cohort + \varepsilon_{p0}$$

Analysis on ΔDCD

ΔDCD for each patient is calculated as explained in Subsection 3.3. We use the following regression model in order to understand the effect of treatment (tr) when controlling for sex, age, and other potential confounders (listed in Subsection 3.3):

$$\Delta\text{DCD}_P = \beta_0 + \beta_1 tr + \beta_2 sex + \beta_3 age + \ldots + \varepsilon_p$$

We expect β_1 to be significantly less than 0 in accordance with specific aim 2 in Subsection 1.2.

Analysis on change in cortisol level ($\Delta C_{p,m}^1$ and $\Delta C_{p,m}^2$)

We used change in each cortisol measurement for each patient, $\Delta C_{p,m}^1$ and $\Delta C_{p,m}^2$ (as explained in Subsection 3.3) as the dependent variable in our linear regression models. This results in 12 total models of change in cortisol (6 for each cortisol measure by 2 for

each follow-up day comparison). Since research indicates that both hypercortisolism and hypocortisolism are related to HPA axis dysregulation and that cancer survivors may have dysregulated HPA axis function (Abercrombie et al., 2004; Heim et al., 2000; Porter et al., 2003), we expect patients with high baseline cortisol measurements to show a negative change after the intervention and patients with low baseline cortisol measurement to show a positive change after the intervention. See specific aim 3 in Subsection 1.2.

For this reason, we divided the sample population into tertiles of cortisol levels by age (< 60 and ≥ 60) and sex at baseline to create an estimate of high, low, and average cortisol levels for each individual by age and sex. Because there are only 10 men in the sample, and all but 1 are in the greater than 60 age category, men were not further divided into age categories before creating tertiles by cortisol level. Using these tertiles of the sample population at baseline we create dummy variables lc (low cortisol) and hc (high cortisol) to classify patients as within the central range ($lc = 0$ and $hc = 0$), in the lower tertile ($lc = 1$ and $hc = 0$), or in the upper tertile ($lc = 0$ and $hc = 1$) by sex and age (for females). We include this new baseline classification variable in the following linear regression models to examine interaction with treatment (tr):

$$\Delta C^1_{p,m} = \beta^1_{0m} + \beta^1_{1m}tr + \beta^1_{2m}hc + \beta^1_{3m}lc + \beta^1_{4m}(tr{\times}hc) + \beta^1_{5m}(tr{\times}lc) + \varepsilon_p$$

$$\Delta C^2_{p,m} = \beta^2_{0m} + \beta^2_{1m}tr + \beta^2_{2m}hc + \beta^2_{3m}lc + \beta^2_{4m}(tr{\times}hc) + \beta^2_{5m}(tr{\times}lc) + \varepsilon_p$$

We expect $\beta^1_{1m} + \beta^1_{4m}$ and $\beta^2_{1m} + \beta^2_{4m}$ to be significantly less than zero (treatment effect for high cortisol level patients) and we expect $\beta^1_{1m} + \beta^1_{5m}$ and $\beta^2_{1m} + \beta^2_{5m}$ to be significantly greater than zero (treatment for low cortisol level patients). All

38

sample calculations are conducted using SAS® 9.4 software, Cary, NC: SAS Institute Inc.

and the GLM or QUANTREG procedure were used for all regression analyses.

Chapter 4: Results

4.1   Sample characteristics

Thirty-eight cancer survivors from GHS were recruited for participation in this study. The mean age was 64 years old with a range from 37 to 79. The sample consisted of 28 females (74%) and 10 males (26%) and was 84% (32) white and 16% (6) black, with one person identifying as ethnically Hispanic. Twenty-nine (76%) participants were married, and 9 (24%) were either single, divorced, separated, common law, or widowed. Fifty-eight percent of participants had a bachelor's or higher degree. Select baseline demographic and clinical characteristics by group are outlined in Table 4.1 and Table 4.2. No significant differences were observed between randomized groups on any measured variables except for perceived stress scores; the control group had significantly higher perceived stress at baseline than the intervention group (p=0.03). The outcome variables assessed are presented in Table 4.3. Average diurnal cortisol decline for the sample group was -7.61 nmol/L at baseline, -7.12 at follow-up day 1 and -6.48 at follow-up day 2. From average DCD we can see that DCD is increasing through the study period and so we also see that change in DCD (ΔDCD_p^d) is positive, 0.41 and 0.88, for follow-up days 1 and 2 respectively. Change in cortisol measurements throughout the day from baseline to follow-up 1 and 2, though small, are consistently negative. On average, for the entire

sample group, both absolute cortisol levels and cortisol decline over the day are decreasing.

Table 4.1. Baseline demographic characteristics of participants across groups

	Intervention Group (n=20)		Control Group (n=18)		
	Mean[a] Frequency[b]	(SD) (Percent)	Mean Frequency	(SD) (Percent)	p-value
Age	63.65	9.80	63.39	12.52	0.47[c]
Gender					0.72[d]
Male	6	30%	4	22%	
Female	14	7%	14	78%	
Race					1.00[d]
Black	3	15%	3	17%	
White	17	85%	15	83%	
Cohort					0.73[e]
Fall	10	50%	10	56%	
Winter	10	50%	8	44%	
BMI	25.89	5.02	28.21	6.90	0.27[c]

Abbreviations: BMI, Body Mass Index; SD, Standard Deviation
[a]Mean and Standard Deviation reported for continuous variables
[b]Frequency and Frequency % reported for categorical variables
[c]p-values from independent t-test
[d]p-values from fisher's exact test
[e]p-values from chi-square test

Table 4.2 Baseline clinical characteristics for participants across groups along with value interpretations

	Intervention (n=20)		Control (n=18)			
	Mean[a] Frequency[b]	(SD) (Percent)	Mean Frequency	(SD) (Percent)	p-value[c]	Standard Cut points
Physical Activity					0.41[d]	Scoring based of the Rapid Assessment of Physical Activity tool. More active categories indicate greater frequency and intensity of exercise(Topolski et al., 2006)
Under-active	2	10%	1	6%		
Under-active, Regular-light	4	20%	1	6%		
Under-active, Regular	5	25%	3	17%		
Active	9	45%	13	72%		

41

Depression						Higher scores reflect greater symptoms on a scale of 0-60. Scores above 16 indicate clinical depression (Radloff, 1977)
CESD Score	5.89	4.20	7.71	4.52	0.32	
Stress						Higher scores reflect greater perceived stress on a scale of 0-40(S. Cohen et al., 1983)
PSS Score	12.61	6.99	18.41	8.16	0.03	
Sleep						A score of 5 or greater is indicative of poor sleep quality (In clinical populations a cutoff of 8 may be more appropriate)(Beck et al., 2004)
PSQI Score	8.28	4.46	6.19	3.33	0.14	
Cortisol						No standardized cut points for identifying high or low daily cortisol levels. Units nmol/L
Average Cortisol	9.64	6.86	9.26	5.15	0.81[e]	

Abbreviations: CESD, Center for Epidemiologic Studies Depression; PSS, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index; SD, Standard Deviation

[a]Mean and Standard Deviation reported for continuous variables

[b]Frequency and Frequency % reported for categorical variables

[c]p-values from independent t-test unless otherwise indicated

[d]p-value from fisher's exact test

[e]p-values from Wilcoxon Rank Sum Test

Table 4.3 Summary statistics for outcome variables

Outcome Variable	Mean	Standard Deviation	Minimum	Maximum	Sample Size (n)
$DCD_{p,1}$	-7.61	6.64	-33.61	6.50	37
$DCD_{p,2}$	-7.12	5.22	-29.48	2.29	34
$DCD_{p,3}$	-6.48	3.74	-16.33	2.45	33
ΔDCD_p^1	0.41	7.59	-17.12	21.62	34
ΔDCD_p^2	0.88	7.22	-22.84	23.31	33
$\Delta C_{p,1}^1$	-0.60	6.77	-21.60	18.01	35
$\Delta C_{p,2}^1$	-1.67	6.35	-23.56	9.15	35
$\Delta C_{p,3}^1$	-1.88	5.73	-15.85	9.56	32

$\Delta C_{p,4}^1$	-0.50	7.36	-26.75	14.24	34
$\Delta C_{p,5}^1$	-0.44	6.86	-34.89	12.29	32
$\Delta C_{p,6}^1$	-0.09	2.48	-6.55	7.74	29
$\Delta C_{p,1}^2$	-0.80	5.84	-21.75	5.87	33
$\Delta C_{p,2}^2$	-1.48	7.27	-20.47	10.16	32
$\Delta C_{p,3}^2$	-0.14	6.91	-13.69	11.78	31
$\Delta C_{p,4}^2$	-0.02	7.31	-24.75	9.19	31
$\Delta C_{p,5}^2$	0.26	7.28	-33.75	16.43	31
$\Delta C_{p,6}^2$	-0.12	2.36	-7.33	4.62	31

Notes: superscripts on outcome variables indicate follow-up day (1 or 2), subscripts indicate p, patient and daily cortisol measurement (1-6)

Abbreviations: DCD, Diurnal Cortisol Decline; C, Cortisol

4.2   Baseline Associations with Diurnal Cortisol Decline

Crude associations with Diurnal Cortisol Decline at baseline are presented in Table 4.4 and multivariable models are presented in Table 4.5. Only the crude association between sleep quality measured using the PSQI sleep index was significant at the alpha=0.1 level in the model at baseline but this does not persist when additional variables are included in models 2 and 3. For the crude PSQI association, for each 1 unit increase in PSQI score (sleep quality on a scale of 0-21 with higher scores representing worse sleep quality), baseline DCD increased by 0.63 nmol/L. Additionally, the coefficients for crude associations of DCD and gender and activity level are not in the direction hypothesized in Subsection 1.2. For activity level, this direction persists in model 3 with all covariates included – one explanation could be the reference category 'Under-active' only includes three participants. The other two 'Under-active' categories (regular, and regular-light) are positive relative to the 'Active' category as hypothesized. The coefficient for gender switches direction when included in the model with other covariates suggesting another measure is strongly associated with gender. Also counterintuitive is that increased PSS score and age have a negative association with DCD when included with the other variables of interest in model 3, though not nearing significance.

43

Table 4.4 Crude association of variables of interest and baseline diurnal cortisol decline

	Coefficient	(SE)	p-value	Sample size (n)
Physical Activity[a]				37
Under-active, Regular-light	1.15	(5.79)	0.84	
Under-active, Regular	1.67	(5.47)	0.76	
Active	0.71	(5.12)	0.89	
Race[b]				37
Black	1.45	(2.99)	0.63	
Cohort[c]				37
Winter	2.39	(2.18)	0.28	
Gender[d]				37
Female	0.20	(2.49)	0.94	
Age	0.03	(0.10)	0.76	37
CESD Score	0.39	(0.24)	0.11	35
PSS Score	0.01	(0.14)	0.95	34
PSQI Score	0.63	(0.32)	0.06	34

Abbreviations: CESD, Center for Epidemiologic Studies Depression; PSS, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index
[a]Reference: Under-active
[b]Reference: White
[c]Reference: Fall
[d]Reference: Male

Table 4.5 Three multivariable regression models on variables of interest with baseline Diurnal Cortisol Decline

	Model 1		Model 2		Model 3	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value
PSQI Score	0.36 (0.43)	0.41	0.39 (0.44)	0.37	0.93 (0.68)	0.19
CESD Score	0.21 (0.32)	0.52	0.25 (0.34)	0.47	0.30 (0.52)	0.57
Cohort[a]						
Winter			2.42 (2.46)	0.33	4.80 (3.67)	0.21
Race[b]						
Black			2.54 (3.25)	0.44	3.12 (3.90)	0.43
Physical Activity[c]						
Under-active, Regular-light					9.66 (7.91)	0.24
Under-active, Regular					11.21 (7.61)	0.16
Active					9.32 (7.56)	0.23
Age					-0.06 (0.16)	0.69
Gender[d]						
Female					-3.84 (4.03)	0.35
PSS Score					-0.22 (0.23)	0.35
Sample size (n)	32		31		30	
R-square	0.08		0.14		0.28	

Abbreviations: CESD, Center for Epidemiologic Studies Depression; PSS, Perceived Stress Scale;

PSQI, Pittsburgh Sleep Quality Index
[a]Reference: Fall
[b]Reference: White
[c]Reference: Under-active
[d]Reference: Male

4.3 Effect of treatment on change in Diurnal Cortisol Decline

Table 4.6 presents results of the multivariable regression using the GLM procedure with outcome variables as change in DCD from baseline to follow-up day 1 and day 2 respectively. We used a forward selection method for both models as recommended by the small sample size. Potential confounders are listed in Subsection 3.3 and were assessed in the model independently with intervention. Cohort and PSS score were included as covariates in both final models. Cohort was significant at the $\alpha=0.1$ level in both models (p=0.03 and p=0.10 for follow-up one and two respectively), improved model fit, and had a greater than 10% impact on the coefficient for intervention. Perceived Stress, as the only significantly different measured variable at baseline between the intervention and control group, was also included in the model. PSS was not significant in the model (p=0.71 and p=0.19 for follow-up 1 and 2 respectively with cohort included) and did not change inference on intervention from baseline to follow-up 1, but did meaningfully attenuate the association between the intervention and change in DCD from baseline to follow-up 2. Other potential confounders, though comparable across the intervention and control groups at baseline, were assessed individually with the intervention for inclusion in the model. PSQI sleep score was significant in the model for follow-up day 1 only, but did not change inference on intervention meaningfully (<10% change in the covariate for intervention) or improve model fit. Other potential confounders did not approach significance at the $\alpha=0.1$ level or have a meaningful impact on the intervention coefficient, thus only cohort and PSS score were included. Treatment showed a non-significant -1.79 nmol/L and -2.71 nmol/L effect on diurnal

cortisol decline from baseline to follow-up 1 and 2 respectively when controlling for cohort and PSS score.

Table 4.6 Change in Diurnal Cortisol Decline from baseline to follow-up day indicated (1 or 2)

Follow-up day (d)	1[a]		2[a]	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value
Treatment[b]	-1.79 (2.72)	0.52	-2.71 (2.22)	0.23
Cohort[c]	4.84 (2.65)	0.08	1.79 (2.19)	0.42
PSS Score	-0.07 (0.18)	0.71	0.20 (0.15)	0.19
R-Squared	0.12		0.18	
Sample Size (n)	32		30	

Abbreviations: SE, Standard Error; PSS, Perceived Stress Scale.
[a]Adjusted for cohort and perceived stress scale
[b]Reference: control group
[c]Reference: Fall cohort

4.4 Treatment effect by baseline categorization

The twelve models assessing change in each of the 6 cortisol measurements from baseline to follow-up time 1 and 2 are presented in Table 4.7. Cohort was indicated in the majority of models and so was included for all. PSS score was not included as it was not significant and did not improve model fit. Results are irregular for the estimates of interest (the combined effect of the treatment coefficient and the treatment and baseline categorization level interaction term). For the treatment effect for those in the high cortisol category at baseline we observed 7 positive estimates and 5 negative estimates, the only significant estimate was positive, opposite the direction hypothesized. For the treatment effect for those in the low cortisol category at baseline we observed again 7 positive and 5 negative estimates.

Apart from the effect of interest, from the high cortisol and low cortisol coefficients we see that participants categorized at baseline in the high cortisol tertile tended to show decreases in cortisol level and those categorized at baseline in the low cortisol tertile tended to show

increases in cortisol throughout the study period compared to those in the central tertile when

adjusting for treatment, cohort, and the treatment and baseline categorization interaction.

Table 4.7 Standard Multiple Linear Regression or Quantile Regression of change in cortisol from baseline to the follow-up day indicated (1 or 2) for each of the 6 cortisol measurements

Measure (*m*)[a]	1 (Awakening)		2 (15-min)		3 (30-min)		4 (45-min)		5 (Dinner time)		6 (Bed time)	
Follow-up day (*d*)	1 [b]	2	1	2	1	2 [b]	1	2 [b]	1 [b]	2 [b]	1	2 [b]
Sample Size (n)	35	33	35	32	32	31	34	31	32	31	29	31
	Coefficients (SE)		Coefficients (SE)		Coefficients (SE)		Coefficients (SE)		Coefficients (SE)		Coefficients (SE)	
Treatment [c]	-3.98	0.47	2.67	5.57	3.53	4.16	5.44	-0.96	-0.05	-0.04	1.92	0.44
	(3.18)	(2.31)	(3.49)	(3.51)	(3.49)	(6.33)	(3.31)	(4.55)	(1.09)	(1.68)	(1.34)	(1.15)
Tertile at Baseline [d]												
High Cortisol	-7.19**	-9.70**	-6.86**	-6.05*	-1.99	-4.62	-11.84**	-7.79	-0.62	-1.57	-2.09	-0.13
	(3.46)	(2.57)	(3.32)	(3.57)	(3.60)	(8.23)	(3.69)	(8.84)	(1.44)	(4.19)	(1.56)	(3.18)
Low Cortisol	0.21	-0.24	0.81	9.13**	3.33	7.01	2.84	2.78	0.26	1.17	0.33	-0.24
	(4.26)	(3.18)	(3.85)	(3.57)	(3.77)	(7.24)	(3.92)	(7.07)	(1.51)	(1.65)	(1.82)	(1.17)
Interaction												
Tr × High Cortisol	0.71	3.39	-1.78	-3.72	-3.45	-4.32	4.22	0.67	0.14	0.27	-2.05	-1.68
	(5.31)	(3.65)	(4.94)	(5.02)	(5.08)	(9.60)	(4.95)	(10.31)	(2.12)	(5.82)	(2.11)	(3.35)
Tr × Low Cortisol	4.90	0.82	-1.86	-9.06*	-3.19	-3.02	-7.06	-3.63	0.37	-0.59	-2.09	0.05
	(4.69)	(3.89)	(5.54)	(5.02)	(5.24)	(8.95)	(5.18)	(8.06)	(1.61)	(2.07)	(2.28)	(1.43)
Treatment effect by tertile at baseline												
Tr + (*Tr* × High Cortisol)	-3.27	3.85	0.88	1.85	0.08	-0.15	9.67**	-0.28	0.09	0.23	-0.14	-1.24
	(4.17)	(2.85)	(3.39)	(3.50)	(3.52)	(6.97)	(3.64)	(9.72)	(1.54)	(5.01)	(1.61)	(2.09)
Tr + (*Tr* × Low Cortisol)	0.92	1.29	0.80	-3.48	0.35	1.14	-1.62	-4.59	0.32	-0.63	-0.17	0.49
	(3.37)	(3.06)	(3.77)	(3.20)	(3.85)	(6.46)	(3.99)	(6.47)	(1.16)	(1.56)	(1.85)	(0.99)
R-Squared	--	0.57	0.36	0.59	0.19	--	0.50	--	--	--	0.34	--

Abbreviations; *Tr*, treatment

*Indicates significance at the 0.1 level

**Indicates significance at the 0.05 level

[a] All models controlled for cohort

[b] Assumptions of linear regression not met; coefficients represent median estimates from quantile regression

[c] Reference: control group

Chapter 5: Discussion

Results of this study did not show a significant impact of CMCS mindfulness program on cortisol levels or rhythm. We found that the treatment was associated with an increased decline in daily cortisol at both the first and second follow-up compared to the control group, but this effect was not significant. When examining effect modification of baseline cortisol categorizations on change in cortisol levels over the study period in the intervention group compared to the control group, no consistent directional results were observed.

Although not statistically significant, the magnitude of the decrease in cortisol decline observed as a treatment effect in our multivariable model examining change in daily cortisol decline from baseline to follow-up 1 and 2 was relatively large (-1.79 nmol/L and -2.71 nmol/L respectively) compared to the average decline over a day for our sample at baseline (-7.61 nmol/L). This is a 23.5% and 35.6% decrease in DCD respectively at follow-up 1 and 2 in the intervention group versus the control group when controlling for cohort and PSS score. As previously mentioned, several studies have identified a significant association between smaller declines in cortisol over the day and decreased survival (L. Cohen et al., 2012; Schrepf et al., 2015; Sephton et al., 2013, 2000). Unfortunately, these studies consistently use a transformation of raw cortisol values

49

making a comparable estimate of what average absolute or percent change in slope is indicative of improved survival outcomes impossible at this time.

The method we present for examining the effect of an interaction between treatment categories of cortisol at baseline was based off of research indicating both elevated and depressed cortisol levels are suggestive of HPA axis dysregulation and is similar to the approach taken by Bränström and colleagues (Bränström et al., 2013). However, we failed to replicate their findings showing significant effect modification of treatment by baseline categorization on the awakening timepoint sample (which they examined) or to find any similar effect modification on the other 5 diurnal cortisol measurements at either follow-up day. It should be noted that their study was approximately twice as large as the current study (n-71) and a full 8-week mindfulness intervention program was used.

In the literature, of the seven current studies assessing the effect of a mindfulness program on cortisol in a population of cancer survivors, six reported at least one significant change in cortisol levels post intervention (Bränström et al., 2013; L. E. Carlson et al., 2013; Lengacher et al., 2012, 2012; Lipschitz et al., 2013; Y. Matchim et al., 2011; Matousek et al., 2011). The only study that did not report significant changes in cortisol levels was also one of two studies that assessed an abbreviated mindfulness program (shortened from the original 8-week course) (Lipschitz et al., 2013). As the intervention program for our current study was also abbreviated at only 4 weeks and our results were not significant, further research is needed to determine what the minimum 'dose' of a mindfulness program is necessary to create meaningful change. Furthermore, in the

50

current literature, most changes in cortisol post mindfulness intervention were shown for a single measure of cortisol rather than for cortisol rhythm (such as the diurnal decline or awakening response), even when multiple cortisol samples were collected (Bränström et al., 2013; Lengacher et al., 2012; Y. Matchim et al., 2011; Witek-Janusek et al., 2008). This gap in the current literature was one that our current study aimed to address, but may have had too small a sample size or too short an intervention to show change in cortisol rhythm that could be confidently attributed to the mindfulness practice. In the single study that did assess the effect of a mindfulness intervention on diurnal cortisol decline in cancer survivors (and the largest study to date), Carlson and colleagues found that participation in the mindfulness intervention significantly attenuated loss of decline from baseline to post intervention compared to the control group (L. E. Carlson et al., 2013).

As briefly touched on through comparison with the current literature, our study has a few apparent limitations to consider. The sample size is relatively small; cortisol was measured over only one day at each follow-up time, and although survey response was complete and cortisol sampling compliance was high, some missing cortisol measurements and missing questionnaire sections further reduced our sample size. Additionally, the mindfulness intervention was abbreviated from the established 8-week course to 4-weeks for this study. Although there is value in understanding what minimum dose of the intervention can be effective, this truncation may have contributed to our inconclusive findings. Finally, survivors were not screened for distress as a requirement for enrollment; if cortisol levels for our patients were not disrupted at the onset of the program there was no way for the CMCS program to lead to improvement.

Some strengths of this study are also evident. As an RCT, the potential for confounding from both measured and unmeasured variables is low and we have a high potential to provide results that suggest causality. Also, loss-to follow-up was low; only two of 38 participants dropped from the program, and follow-up time was moderately long (3 months). Additionally, cortisol collection method included enough daily samples to assess both absolute levels of cortisol throughout the day and rhythm or decline throughout the day. Finally, this study included both men and women with various cancer diagnoses – many studies of mindfulness in cancer survivors primarily include only women with breast cancer.

Our results contribute to the accumulation of research surrounding mindfulness practice in cancer survivors, but even within this study there is much left to explore; potentially a more streamlined approach to examine cortisol levels. Beyond this specific work, the field of literature examining associations between mindfulness meditation in cancer survivors and health and quality of life outcomes is open to research that uses objective measures of these outcomes, and cortisol has strong potential to be used in this capacity.

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54

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