DISSERTATION

REALLOCATING TIME TO PHYSICAL ACTIVITY AND SLEEP: ASSOCIATIONS WITH QUALITY OF LIFE AND BODY MASS INDEX IN CANCER SURVIVORS

Submitted by

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ABSTRACT

REALLOCATING TIME TO PHYSICAL ACTIVITY AND SLEEP: ASSOCIATIONS WITH QUALITY OF LIFE AND BODY MASS INDEX IN CANCER SURVIVORS

Introduction: Quality of Life (QOL) and Body Mass Index (BMI) are important outcomes for cancer survivors due to their association with cancer-related morbidity and mortality. Lifestyle behaviors including physical activity (PA), sedentary time, and sleep are all potential intervention targets to improve QOL and BMI. The effect of these activities on QOL and BMI is most often studied in isolation despite the interdependent nature of these behaviors; time cannot be increased in one activity without decreasing time in another. Since these behaviors are often studied in isolation, it is difficult to assess if an improvement in QOL or BMI is attributed to increasing positive behaviors (i.e., PA or sleep), or decreasing negative behaviors (i.e., sedentary time). The growing interest around 24-hour activity patterns has increased researcher interest in objective measurement of PA and sleep using accelerometers. However, this currently requires researchers to utilize one device to measure sleep (i.e., Actiwatch) and one to measure waking behaviors (i.e., activPAL). This has led to high research costs and burden since the Actiwatch cannot measures waking behaviors and, until recently, the activPAL could not detect time in bed (TIB), limiting researcher's ability to objectively collect 24-hour activity data. In order to move the world of 24-hour activity forward and delineate the role time reallocations throughout the day affect pertinent cancer-related outcomes, additional research must be conducted to explore solutions to the high research costs and burden associated with 24-hour activity measurement. Therefore, the purpose of this dissertation is to (1) evaluate if the new activPAL algorithm designed to measure TIB can estimate TIB similarly to the valid and reliable Actiwatch and 2) evaluate, using an Isotemporal substitution model, the effects of

reallocating time from one activity to another on QOL and BMI using accelerometry (Actiwatch and activPAL pending results of aim 1) to measure 24-hour activities.

Methods: The activPAL algorithm's ability to measure TIB was evaluated using a cross-sectional analysis of participants (n=85) undergoing a time-restricted feeding study. Participants (for all studies) wore the activPAL accelerometer to measure waking behaviors and the Actiwatch to measure sleeping behaviors for 7 days, 24-hours per day. Repeated measures mixed effects models and Bland-Altman plots were used to compare the activPAL TIB estimates to the Actiwatch TIB estimate with type of device and day of wear as fixed effects and participant as a random effect. TIB results were then utilized in a cross-sectional analyses of cancer survivors (n=73) within 60 months of surgery, chemotherapy, and/or radiation. In addition to wearing the activPAL and Actiwatch, participants completed the Functional Assessment of Cancer Therapy-General (FACT-G) to measure QOL. Participants self-reported height and weight to calculate BMI. Demographics were calculated using mean ± standard deviation or frequencies (%). Isotemporal substitution models were used to evaluate the effects of reallocating 30 minutes of each activity to another. Statistical significance for all studies was set at $p<.05$.

Results: The activPAL accelerometer does not estimate TIB similarly to the Actiwatch. Additionally, no significant interaction was observed for type of accelerometer and day of wear. There were no statistically significant reallocations for total QOL score or the included subscales. However for BMI, reallocating 30 minutes of sleep to sedentary time or moving 30 minutes of sedentary time to light PA did result in statistically significant changes in BMI. There were no statistically significant reallocations by moving moderate-vigorous PA to other activities of interest. Despite no statistical significance for QOL, reallocating time from sedentary time or light PA to MVPA resulted in clinically meaningful increases in QOL (>4 points).

Conclusion: Estimates of TIB from the activPAL and Actiwatch accelerometers were not similar, suggesting that researchers who are interested in the 24-hour activity cycle will continue to require the use of both accelerometers to measure both sleep and active/waking behaviors. Results of reallocating time on QOL and BMI indicate that in addition to MVPA, sleep, and light PA are essential behaviors for cancer survivors. The work presented in this dissertation can provide a starting point for the development of 24-hour activity guidelines for improving BMI and QOL in cancer survivors; however, additional time reallocation studies using a larger sample size in order to include bouted and non-bouted activity time as well as more detailed measures of body composition (i.e., dual x-ray absorptiometry) are needed to further understand the role the 24-hour activity cycle has on BMI and QOL in cancer survivors.

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Chapter I: Introduction

INTRODUCTION

“It is as if we have invented sophisticated techniques to save people from drowning, but once they have been pulled from the water, we leave them on the dock to cough and splutter on their own in the belief that we have done all that we can.”

-Fitzhugh Mullen, MD, Cancer Survivor (Mullan, 1985)

RATIONALE

In 2016, there were an estimated 15.5 million cancer survivors in the United States, and as of January 1, 2019, this number increased to 16.9 million (8.1 males, 8.8 females) (Miller et al., 2019). This increase in cancer survivors is partly due to improvements in detection and treatment over the last decades as well as an aging population (de Moor et al., 2013). With cancer diagnoses often occurring at an older age (65 and older), and the population living longer than ever before, an increased prevalence of cancer survivors in the United States is expected to continue to grow with an estimation of 20.3 million cancer survivors by 2026 ("Cancer Statistics," 2018).

With a growing number of cancer survivors comes a large healthcare burden associated with the many side effects associated with the cancer diagnosis itself, and/or treatments such as surgery, chemotherapy, and radiation therapy utilized for the survivor. Side effects often begin during the treatment process and can last long after treatment has ended. Of these common side effects, poor quality of life (QOL) and body composition have been linked to increased morbidity and mortality in cancer survivors (Cleeland et al., 2013). Additionally, QOL and body composition are common risk factors for secondary conditions including cardiovascular disease, metabolic disease, and secondary cancers, disease states cancer survivors are at increased risk for developing (Fogelholm, 2010; Martinelli et al., 2008; Odom, Fang, Zack, Moore, &

Loustalot, 2016). Therefore, QOL and body composition have been identified as important, modifiable treatment-related side effects that can be targeted as part of survivorship care.

QOL is multi-dimensional, and typically focuses on four facets of well-being: physical well-being, social/family well-being, emotional well-being, and functional well-being. In addition, different cancer types have tumor specific burdens associated with treatment type (e.g. reconstructive surgeries, ostomy bags, tracheostomy, etc…) that can negatively affect QOL. QOL is an important patient reported outcome linked to many aspects of cancer survivorship including treatment efficacy, rehabilitation needs, cancer recurrence and mortality (Ferrell & Hassey Dow, 1997; Montazeri, 2009). In addition to improving overall survival, QOL during survivorship indicates the well-being of cancer survivors, an important factor when evaluating healthcare needs and costs associated with these needs. Thus, improving QOL is a desirable target for improving cancer survivorship (Jacobsen & Jim, 2011).

Body composition, is the proportion of fat and non-fat mass in your body. A healthy body composition is one that consists of a lower percentage of body fat and a higher percentage of non-fat mass, including lean muscle mass. Body composition has been found to be associated with health-related outcomes in cancer survivors with higher muscle mass and lower body fat resulting in better outcomes (Brown, Cespedes Feliciano, & Caan, 2018). During active, or adjuvant treatment (e.g., surgery, chemo and radiation therapy), patients often experience weight loss or gain, and nausea/vomiting, leading to negative changes in body composition such as decreased muscle mass and increased fat mass (Davis & Panikkar, 2019; Pin, Couch, & Bonetto, 2018). Numerous systematic reviews and meta-analyses in varying cancer types have documented the negative association between low muscle mass, and high fat mass on survival rates in cancer survivors (Chang et al., 2018; Playdon et al., 2015; Ubachs et al., 2019; Wiegert et al., 2019). Therefore, it is imperative to understand ways to improve body composition during and after cancer treatment to improve cancer-related outcomes. Two

effective, non-pharmacological strategies to improve QOL and body composition in cancer survivors are physical activity (PA) and sleep. (Y. Chen et al., 2018; Collins et al., 2017; Dolezal, Neufeld, Boland, Martin, & Cooper, 2017; Ferrer, Huedo-Medina, Johnson, Ryan, & Pescatello, 2011).

Physical activity is defined as any bodily movement that results in an increase in energy expenditure above resting energy expenditure (American College of Sports Medicine, Riebe, Ehrman, Liguori, & Magal, 2018). To improve QOL, it is recommended that cancer survivors engage in a minimum of two days per week of aerobic activity at 60-80% Heart Rate max (HRmax) for 30 minutes, and two days per week of resistance training at 60-80% 1-repetition (1-RM) max for 2 sets of 8-15 repetitions (K. L. Campbell et al., 2019). Currently, there are no specific recommendations to increase muscle mass or reduce body fat for cancer survivors, but literature suggests achieving the guidelines of healthy adults of 150 minutes of moderate or 75 minutes of vigorous aerobic exercise, with more time the better, and 2-3 days of resistance training, focusing on all major muscle groups (American College of Sports Medicine et al., 2018; Rutledge & Demark-Wahnefried, 2016). Additionally, cancer survivors have higher rates of sedentary time compared to age-matched controls, with an average of 10.6 hours per day of sitting (George et al., 2014). Increased sedentary time has been linked to early death, cardiovascular disease, type II diabetes, and increased cancer risk; therefore, recent guidelines suggest cancer survivors “move more, sit less” (K. L. Campbell et al., 2019; Rosenberger et al., 2019). Thus, there exists clear guidelines and recommendations with regard to frequency, intensity, type, and time for MVPA and guidelines for reducing sedentary time for improving QOL and body composition; however, other daily activities such as standing or light PA have received less attention despite their known contributions to health outcomes in cancer survivors (Fong et al., 2012; George et al., 2014; Komarzynski et al., 2019; Swain et al., 2020). For example, standing time aids in breaking up bouts of sedentary time, which is known to decrease

mortality risk, improve QOL, and improve metabolic and cardiovascular risk factors (P. T. Campbell, Patel, Newton, Jacobs, & Gapstur, 2013; Dunstan et al., 2012; Lynch, Cerin, Owen, Hawkes, & Aitken, 2011), and light PA has been found to attenuate functional decline in cancer survivors (Blair et al., 2014). These benefits support the need to expand knowledge regarding prolonged vs. non-prolonged sedentary time and light PA in cancer survivors.

Sleep disturbance includes difficulty initiating or maintaining sleep, excessive fatigue, dysfunction related to sleep-wake cycles, and/or dysfunction related to sleep and sleep stages (RE, 1990). Sleep disturbances in cancer survivors can directly impact QOL with those experiencing more significant sleep disturbances having greater deficits in QOL (Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002; Otte et al., 2015). Sleep disturbances are also associated with decreased lean mass and increased fat mass (Jurado-Fasoli et al., 2018), body composition components which are known to affect cancer mortality and recurrence (Coronha, Camilo, & Ravasco, 2011). Despite growing understanding of the relationship between sleep disturbance and cancer-related outcomes, limited guidelines exist regarding improving sleep in survivors experiencing sleep disturbances (Y. Chen et al., 2018; Collins et al., 2017). For example, the National Comprehensive Cancer Network (NCCN) provides few recommendations regarding sleep, focusing primarily on the relationship between sleep and cancer-related fatigue, neglecting other cancer-related side effects (Denlinger et al., 2018).

Current literature points to the potential impact that MVPA (i.e., exercise), light PA sedentary behavior, and sleep, can have on QOL and body composition in cancer survivors. However, the majority of the existing evidence treats these behaviors as isolated activities (Boyle, Vallance, Buman, & Lynch, 2017; Vallance, Buman, Lynch, & Boyle, 2017), without accounting for the multidimensional, intertwined activity patterns experienced throughout the 24-hour day. With the 24-hour day being held constant, when one of these behaviors is changed (i.e., sleep or MVPA time is increased by 30, or 60 minutes), the time to engage in this behavior

must come from replacing another activity (i.e., sedentary time). Thus, to know the true impact of sedentary time, light PA, MVPA, and sleep on QOL and body composition requires evaluating these activities together, within the context of the 24-hour day, rather than in isolation. By understanding activity in the context of the 24-hour day, clinicians will be able to provide more specific, individualized recommendations to cancer survivors for utilizing non-pharmacological approaches to improve cancer-related side effects. By including previously neglected behaviors such as standing time, light PA, and sleep, recommendations can be given to those that may struggle to meet MVPA guidelines or experience other barriers to achieving exercise guidelines. An understanding of the multidimensional, 24-hour activity cycle and how these behaviors interact to produce positive or negative outcomes in survivors will allow for personalized approaches based on survivor's capabilities.

Only recently have researchers begun to examine the effects of reallocating time from various daily activities on health-related outcomes among cancer survivors. A 2017 study of non-Hodgkin lymphoma survivors found that reallocating time from sleep, light PA, and sedentary time to moderate to vigorous PA was associated with lower fatigue (Vallance et al., 2017). Similarly, a 2017 study among breast cancer survivors found that reallocating time from sleep, prolonged sedentary time, or light PA to moderate to vigorous PA was associated with lower waist circumference and BMI (Boyle et al., 2017). However, due to lack of objective measures (i.e., accelerometer-based activity/sleep measurement, body composition) and limited research on various cancer types, the most beneficial ratio of time spent in sleep, light PA, MVPA, and sedentary time to improve QOL and body composition in varying cancer types is unknown (van Roekel et al., 2016a). By utilizing objective activity and sleep measurements and gold-standard body composition measurement, reliable, more detailed conclusion can be drawn regarding the effects of varying daily activities on important cancer-related outcomes, including QOL and body composition.

Over the last decade, measurement of PA and sleep have gone through much improvement with the introduction of activity trackers. Two activity trackers, the activPAL and the Actiwatch-2, are currently validated to measure PA and sleep in a variety of populations (P. H. Lee & Suen, 2017; Lyden, Keadle, Staudenmayer, & Freedson, 2017). The activPAL is known for its validity to measure sedentary time, standing time, light PA, and moderate-vigorous PA (MVPA) (Lyden et al., 2017), and the Actiwatch-2 is known for its validity to measure sleep duration, sleep quality, and sleep efficiency (P. H. Lee & Suen, 2017). However, these devices also have the functionality to measure both PA and sleep, but currently, the reliability of the activPAL to measure sleep and the Actiwatch-2 to measure PA is unknown; therefore, both devices are used when objective measurement of daytime and sleep activities are required, increasing the burden on research teams and participants.

Despite a growing body of literature demonstrating the positive impact of sleep and PA for cancer survivors, there is still much to learn with regard to the effects of reallocating time between sleep and daily activities on QOL and body composition. Currently, no previous studies in cancer survivors have examined the effects of time reallocation between sedentary time, PA and sleep using objective measures of both activity and sleep behaviors. Thus, to gain a better understanding of how time spent within the 24-hour activity cycle impacts QOL and body composition in cancer survivors, researchers must be equipped with the proper measurement tools to ensure accuracy of 24-hour activity measurements (i.e., sleep, sedentary, light PA, and MVPA) and outcome measurement (i.e., QOL and body composition).

Based on the literature summary presented above, the studies herein aim to (1) compare the time in bed estimates of a free-living activity monitor used to assess PA, sedentary behaviors, and sleep behaviors (activPAL) against a validated, free-living sleep monitor (Actiwatch-2) to advance measurement science in order to decrease participant and research burden, and (2) utilize objective measures of sleep, sedentary time and PA to examine the

effects of reallocating time between sleep, sedentary time and PA on QOL and body composition in cancer survivors.

PROBLEM STATEMENT AND RESEARCH QUESTIONS

Problem Statement

The current guidelines provided by the American College of Sports Medicine (ACSM) and National Comprehensive Cancer Network (NCCN) provide guidelines for MVPA, and recommend reducing sedentary time to improve cancer-related outcomes in cancer survivors. However, these guideline do not take into account the other activities completed within the 24-hour day, including standing, light PA, and sleep (K. L. Campbell et al., 2019; Denlinger et al., 2016). The positive effects of MVPA, light PA, and sleep, and the negative effects of sedentary time on QOL and body composition have been evaluated in isolation, but the interaction of these behaviors across the 24-hour day and the effect on QOL and body composition is unknown. This leaves a gap for providing guidance on the remaining 23-23.5 hours of the day not spent doing MVPA. In order to fill this literature gap, accurate measurements of both sleep and PA need be utilized across the 24-hour day. However, the current standard for objective measurement of the 24-hour cycle requires use of two measurement devices. These devices are costly and burdensome on both researchers (i.e., increased data burden) and participants (i.e., required to wear two devices). Therefore, it is advantageous to determine if one device is capable of reliably measuring all 24-hour activity. Recently, the activPAL accelerometer underwent an update to include sleep measurements; however, this new algorithm has not been tested against a validated sleep measurement device such as the Actiwatch-2. Therefore, the primary research questions are as follows:

Research Questions

1. Can the activPAL estimate time in bed similarly to the Actiwatch-2 in cancer survivors?

2. What is the appropriate amount of time to spend sleeping, sedentary (i.e., sitting or lying down), in light PA, and in MVPA to achieve clinically relevant improvements in subscales and overall QOL in cancer survivors?

3. What is the appropriate amount of time to spend sleeping, sedentary (i.e., sitting of lying down), in light PA, and in MVPA to improve body composition, measured by BMI, in cancer survivors?

Specific Research Objectives and Hypotheses

Study 1: Comparison of the activPAL accelerometer against the Actiwatch-2 accelerometer to measure time in bed.

Purpose: The purpose of this study is to compare the reliability of the activPAL accelerometer to measure time in bed similarly the Actiwatch-2 device. The Actiwatch-2 has been validated against PSG to objectively measure sleep, making it the gold standard for sleep measurement in free-living conditions (P. H. Lee & Suen, 2017). As of 2019, the activPAL accelerometer developed and released new algorithms to measure time in bed; however, it has not been compared to a validated sleep measurement device such as the Actiwatch-2.

Aims: Compare the time in bed estimate of the activPAL accelerometer to the time in bed measurement from the Actiwatch-2 device

Hypotheses:

Hypothesis 1a: The activPAL monitor will estimate time in bed similarly to the Actiwatch.

Study 2: Reallocating Time to Physical Activity and Sleep: Associations with Quality of Life in a Mixed Sample of Cancer Survivors

Purpose: The purpose of this study is to understand the appropriate allocation of time in a 24-hour period to improve separate dimensions and overall QOL. QOL will be assessed using the

Functional Assessment of Cancer Therapy-General (FACT-G). This questionnaire consists of 37-items assessing the four dimensions of physical, social, emotional, and functional well-being (D. F. Cella et al., 1993). The activPAL will be used to measure light PA, MVPA, sedentary time, and standing time. The Actiwatch-2 will be used to measure sleep time, quality, and efficiency. An Isotemporal substitution statistical model will be utilized to reallocate time between sleep, sedentary behavior, light physical activity, and moderate to vigorous physical activity to understand the differential effects of behaviors on QOL.

Aim: Examine the effects of reallocating time between sleep, sedentary, light PA, and MVPA on QOL in cancer survivors

Hypotheses:

Hypothesis 2a: Reallocating 30 of sedentary time, light physical activity, or sleep to MVPA will be associated with higher overall QOL and subscales of QOL.

Hypothesis 2b: Reallocating 30 of sedentary time or light physical activity to sleep will be associated with higher overall QOL and subscales of QOL.

Hypothesis 2c: Reallocating 30 minutes of MVPA to sedentary time, light physical activity, or sleep will not be associated with higher overall QOL and subscales of QOL.

Study 3: Reallocating Time to Physical Activity and Sleep: Associations with Body Mass Index in a Mixed Sample of Cancer Survivors

Purpose: The purpose of this study is to understand the appropriate allocation of time in a 24-hour period to improve body composition. BMI will be the measurement tool used to measure body composition. The activPAL will be used to measure light PA, MVPA, sedentary time, and standing time. The Actiwatch-2 will be used to measure time in bed (TIB). An Isotemporal Substitution statistical model will be utilized to reallocate time between sleep, sedentary

behavior, light physical activity, and moderate to vigorous physical activity to understand the differential effects of behaviors on BMI.

Aims: Examine the effects of reallocating time between sleep, sedentary, light PA, and MVPA on body mass index in cancer survivors

Hypotheses:

Hypothesis 3a: Reallocating 30 minutes of sedentary time, light physical activity, or sleep to MVPA will be associated with lower BMI.

Hypothesis 2b: Reallocating 30 minutes of sedentary time or light physical activity to sleep will be associated with lower BMI.

Hypothesis 3c: Reallocating 30 minutes of MVPA to prolonged sedentary time, light physical activity, or sleep will not be associated with lower BMI.

Chapter II: Review of Literature

INTRODUCTION

This literature review intends to provide an overview of the current knowledge related to how lifestyle behaviors, specifically PA, sedentary behaviors, and sleep, contribute to the improvement or decline of common treatment-related side effects in cancer survivors. The components to be reviewed in this literature review are 1) cancer survivorship: definitions, history, prevalence of cancer survivors, and acute and late effects of treatment, 2) Importance/relevance of body composition and QOL for cancer survivors, 3) the role of lifestyle behaviors, including light PA, MVPA, sedentary behavior, and sleep, on body composition and QOL, 4) importance of analyzing lifestyle behaviors in the context of the 24-hour day rather than in isolation 5) measurement of lifestyle behaviors including PA, sedentary behavior, and sleep, 6) overview of the isotemporal statistical model to evaluate 24-hour activity patterns and the relationship to cancer-related outcomes. Each of these components are essential aspects of the research questions explored in this dissertation and will shed light on the necessity of completing the proposed studies.

To date, little research has been conducted to better understand the effects of lifestyle behaviors, taken together rather than in isolation, on common treatment related side effects including QOL and body composition in cancer survivors; however, relevant research exists, providing justification and guidance for the completion of this research project. This review will highlight the importance of conducting the studies herein and provide the background knowledge needed to understand the methods utilized to complete this dissertation. The definition of cancer survivor and relevant stages of the cancer care continuum will be reviewed in the cancer survivorship section of this review followed by a review of two common treatment-related side effects, impaired QOL and body composition changes. The effects of these side effects on cancer survivorship will be discussed and non-pharmacologic treatment strategies will

be reviewed in the PA, sedentary behavior, and sleep sections of this review. Finally, a proposed statistical model to evaluate the effects of these lifestyle behaviors on QOL and body composition, known as Isotemporal substitution, will be explained and evaluated for utilization in answering the proposed research questions.

CANCER SURVIVORSHIP

A cancer survivor is defined as individuals from the time of a cancer diagnosis until the end of life (Miller et al., 2019; Morgan, 2009). Although this definition is inclusive to all those with a current or past cancer diagnosis, it can be problematic for some survivors as some do not consider themselves “survivors” until successful completion of treatment (Berry, Davis, Godfrey Flynn, Landercasper, & Deming, 2019). When working with those with a cancer diagnosis, the emotions associated with the term survivor must be considered. For the purposes of this dissertation, survivor will be defined in congruence with the Center for Disease Control and Prevention definition.

In 2016, there were an estimated 15.5 million cancer survivors in the United States, and as of 2019, there were an estimated 16.9 million (8.1 males, 8.8 females) cancer survivors in the United States (Miller et al., 2019). The increase in cancer survivors is partly due to improvements in detection and treatment over the last decades as well as an aging population (de Moor et al., 2013). With cancer diagnoses often occurring at an older age (65 and older), and the population living longer than ever before, an increased prevalence of cancer survivors in the United States is expected to continue to grow with an estimation of 20.3 million cancer survivors by 2026 ("Cancer Statistics," 2018).

With this growing number of cancer survivors, attention must be given to the many side effects a cancer diagnosis and treatment produce for the survivor. Cancer survivorship is categorized into three phases: acute, extended, and permanent (Morgan, 2009). The acute

stage encompasses the time around cancer diagnosis, staging, and treatment planning (Morgan, 2009). The extended stage includes the treatment process through the conclusion of cancer treatment (Morgan, 2009). The permanent stage refers to the time from treatment completion until end of life. This stage includes those that have been cured of their cancer and are no longer receiving anti-cancer therapies as well as those that are still receiving long-term treatment but are deemed a long-term survivor. The risk of recurrence has been reduced and individuals are considered to be in a “permanent” stage (Morgan, 2009; Mullan, 1985). Cancer survivors tend to progress through each of these stages; however, not all will transition through each. Additionally, the degree of disability within each stage varies greatly between survivors of different types, stages, and treatment regimens.

Throughout the cancer care continuum, survivors undergo both physiological and psychosocial adaptations as a result of their diagnosis and/or treatment type. These side effects include diminished quality of life (QOL), fatigue, chemotherapy-induced peripheral neuropathy (CIPN), bone health and musculoskeletal issues, fatigue, and sleep dysfunction (Cleeland et al., 2013; Gegechkori, Haines, & Lin, 2017; Miller et al., 2019). As treatment progresses, side effect management can become increasingly difficult and oftentimes not fully effective. Side effect management throughout the treatment process is often targeted at current side effect profile without much regard for the potential long-term sequelae of the these side effects and additional side effects that may appear after treatment completion (Nurgali, Jagoe, & Abalo, 2018). In addition, research shows that cancer patients often do not receive the appropriate amount of contact with providers to ensure proper cancer management with some patients receiving excess contact and others receiving too little contact (Elston Lafata et al., 2005; Nekhlyudov & Galioto, 2020).

Due to the known detrimental effects of cancer treatment and the necessity to better understand survivorship needs, the Office of Cancer Survivorship at the National Institute of

Health was created in 1996 (Morgan, 2009). The National Cancer Institute Office of Cancer Survivorship (OCS) seeks to minimize and manage treatment-related side effects during survivorship to enhance quality and length of survival from cancer ((NCI), 2020). This includes investing in research related to common treatment-related side effects including diminished QOL and body composition and potential mechanisms to reduce these side effects including lifestyle modifications.

QUALITY OF LIFE

Quality of Life for Cancer Survivors

Over the past decade, the presence of QOL as a primary research outcome in cancer treatment and survivorship literature has steadily increased. Diminished QOL has been associated with higher rates of recurrence, morbidity, and mortality in cancer survivors and may be of prognostic value to clinicians (Montazeri, 2009; Nayak et al., 2017). Gotay et al. suggests four potential mechanisms for the relationship between QOL and survival in cancer survivors: (i) QOL includes a multitude of parameters and therefore may provide more specific information than other common measurements including performance status and toxicity; (ii) baseline QOL, or data collected prior to any treatment or disease progression, may provide additional insight earlier in the treatment process than other established clinical prognostic factors; (iii) QOL data may be indicators of patients' behavior in relation to diagnosis, treatment and long-term outcomes; and (iv) QOL data provides insight on individual characteristics including personality style and coping ability, which may affect cancer progression and treatment tolerability (Gotay, Kawamoto, Bottomley, & Efficace, 2008). Additionally, QOL has been found to affect treatment completion rates, as many survivors make treatment-related decisions based on their own health perspective (de Mol et al., 2019; Heydarnejad, Hassanpour, & Solati, 2011); therefore, patients and physicians have begun to utilize QOL as a means to make better decisions regarding treatment strategy and patient management (Montazeri, 2009). By collecting and

evaluating observational QOL data, information can be derived regarding the effects and extent of these effects associated with cancer type/stage, treatment type, and time since diagnosis and/or treatment, allowing for informing patients of expected consequences of treatment as well as better understand rehabilitation needs following treatment completion (Jacobsen & Jim, 2011).

As cancer treatment progresses, different subscales of QOL may be affected. For example, psychosocial and physical issues tend to develop and persist long-term in cancer survivors whereas social and emotional subscales tend to decline during the acute and extended phases of treatment but may improve after completion of treatment (Heydarnejad et al., 2011; Morgan, 2009). In a review of QOL outcomes in breast cancer survivors, it was found that QOL typically suffers at diagnosis, potentially due to the shock and uncertainty at the beginning of the treatment process. After treatment is established and underway, QOL may begin to improve, pending symptoms associated with treatment type. As treatment comes to an end, QOL may begin to suffer once again in a paradoxical manner as more decisions need to be made with regard to long-term care increasing anxiety, fear, and uncertainty (Paraskevi, 2012). In a study by Zhang et al. (2018) evaluating changes in QOL after completion of radiation therapy in breast cancer survivors, social functioning, pain symptoms, and future health concerns improved across time following treatment completion; however, other QOL factors tended to fluctuate across time (J. J. Zhang et al., 2018). In a study by Yucel et al. (2014) found that in a mixed sample of cancer survivors, QOL parameters tend to gradually decline during radiation therapy, varying based on dose and location of radiation therapy with higher doses affecting physical functioning, role functioning, emotional functioning, fatigue, pain, insomnia, and constipation to a higher extent than lower doses. However, QOL does recover rapidly after completion, with significant improvements seen at 6 months after radiation completion (Yucel et al., 2014).

This evidence has established QOL as an important target for cancer survivors. Therefore, it is of interest to understand how different lifestyle behaviors can improve QOL for cancer survivors, providing a non-pharmacological approach to increase rates of survival and decrease rates of cancer recurrence. Substantial evidence exists to support increasing MVPA and decreasing sedentary time as a mechanism to improve QOL in cancer survivors (Ferrer et al., 2011; George et al., 2014; Gerritsen & Vincent, 2016). However, the effects of other activities, including light PA and sleep, and the role these behaviors play in conjunction with each other, have received less attention with regard to QOL outcomes in cancer survivors. Therefore, this dissertation intends to better understand the role all activities, within a 24-hour day, may have on QOL outcomes in cancer survivors.

As the number of cancer survivors continues to grow, research initiatives are expanding to include the post-treatment survivorship period. This area of research is necessary as the economic burden associated with cancer survivorship is high and continuing to grow, not only during treatment but for many years following treatment (Guy et al., 2013). By better understand the side effects associated with high healthcare costs, specifically body composition changes and QOL, and developing cost-effective, accessible strategies to combat these symptoms, the mission of OCS will be attained.

Overview of QOL

Quality of life (QOL) is a multidimensional, patient-reported outcome measure designed to understand an individual's general well-being including physical, social/family, emotional, and functional well-being. In addition, for cancer survivors QOL can also include cancer-specific well-being, (i.e., sequelae specific to a type of cancer) ("Functional Assessment of Cancer Therapy-General (FACT-G)," 2010; E. H. Lee, Chun, Kang, & Lee, 2004). The World Health Organization defines QOL as an individual's perception of his or her life, values, objectives, standards, and interests in the context of the environment surrounding him/her (Heydarnejad et

al., 2011). When assessing QOL, questions pertaining to the following areas are common: physical symptoms (i.e., nausea, vomiting), functional ability, sexual intimacy/desire, body perception, emotional symptoms (i.e., anxiety, depression), social function, work life, family, future plans, spiritual satisfaction, general life satisfaction (Gunnars, Nygren, Glimelius, & Care, 2001).

In order to determine the prominent factors that contribute to QOL, theoretical models have been proposed. The three most frequently referenced models to determine the various biopsychosocial factors contributing to QOL are the Centre for Health Promotion Model (CHPM), the Contextual Model of Health-related QOL (CM-HRQoL), and the Conceptual Model of Patient-reported Outcomes (CMPRO) (Sosnowski et al., 2017).

The CHPM was developed based on the World Health Organization's definition of QOL. Simply, it defines QOL as how an individual utilizes the opportunities life brings, focusing in on being, belonging, and becoming, which are considered to be the top three areas in human life (Raphael D, 1996; Renwick R, 2002). "Being" consist of physical, psychological, and spiritual being whereas "belonging" encompasses physical, social, and community belonging. "Becoming" encompasses practical, leisure, and growth becoming. Additional details regarding each component of the CHPM model can be seen in the figure below (Figure 2.1) (Sosnowski et al., 2017).

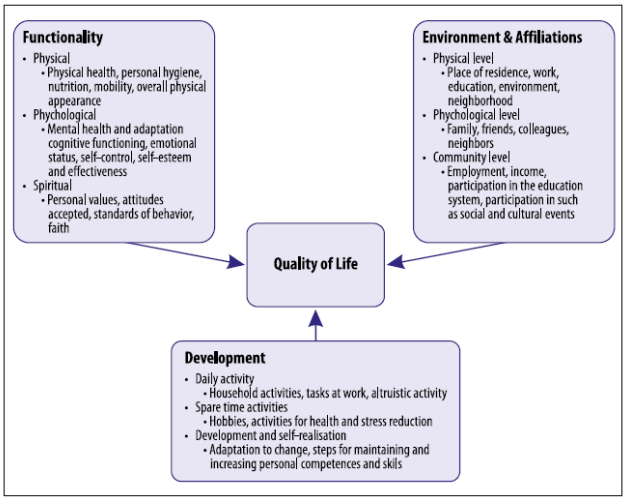


Figure 2.1

The CM-HRQoL model is specifically designed to understand QOL in the cancer population. This model takes into consideration both macro, or factors outside of the individual, and micro, factors within the individuals control, to evaluate overall QOL (Ashing-Giwa, 2005). Components related to the macro and micro levels in this model can be seen in the figures below (Figure 2.2) (Sosnowski et al., 2017).

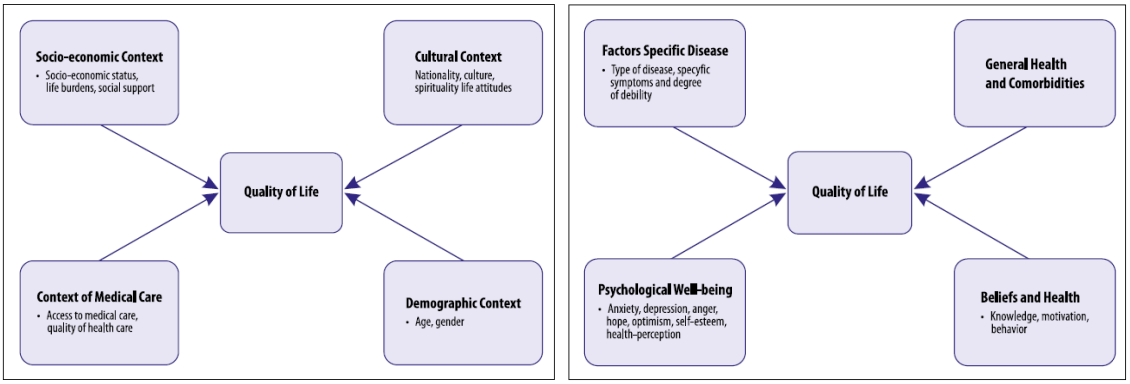


Figure 2.2

The final model, CMPRO, is based on subjective feelings of happiness and satisfaction determined by individual factors and/or environmental characteristics. According to this model, individual factors and environmental factors have an effect on biological functions which can

further impede or improve one's perception of happiness and life satisfaction (Wilson & Cleary, 1995). The below figure provides visual representation of the course biological functions can have on additional determinents of happiness and satisfaction, according to the CMPRO (Figure 2.3) (Sosnowski et al., 2017).

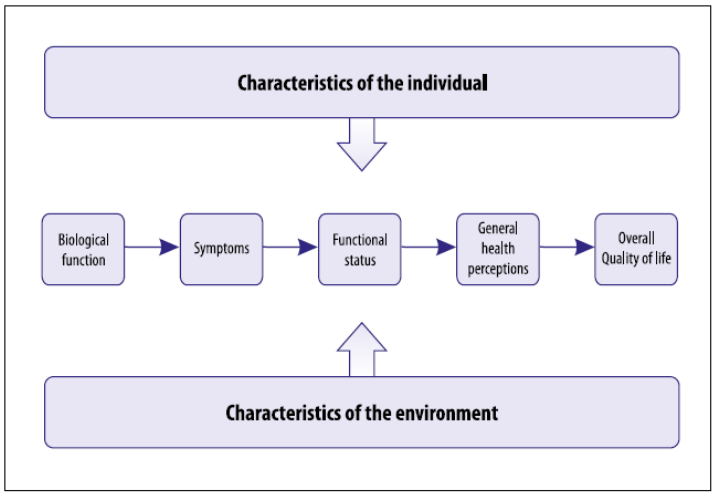


Figure 2.3

These models have been used to develop questionnaires to assess QOL in healthy and clinical populations due to the known implication of poor QOL on health-related outcomes including diminished treatment outcomes and increased mortality (Carr & Higginson, 2001; Gillison, Skevington, Sato, Standage, & Evangelidou, 2009). Therefore, it has become common practice to assess QOL in varying populations to aid in health care decisions.

When developing and validating a QOL questionnaire, such as the FACT-G which will be utilized in this dissertation, these models are utilized in the scale development process. The scale development process includes conducting semi-structured interviews with healthcare professionals and patients to better understand how disease and treatment affect physical status, emotional well-being, functional well-being, family/social issues, sexualtiy/intimacy, work

status, and future orientation, all of which are drawn from previous QOL theoretical models as described above (Webster, Cella, & Yost, 2003).

Measurement of QOL

Numerous measurement devices exist to measure QOL in the cancer survivor population. Objective measurement of QOL would be considered an “assessor” assessment of QOL, meaning an outside individual would evaluate QOL on behalf of the patient. Subjective measurement consists of validated questionnaires, based on participant characteristics, completed by the individual being assessed. Subjective measurement, via the use of validated questionnaires, is the most frequently utilized tool to assess QOL in cancer survivors.

Questionnaires used to subjectively assess QOL are validated across cancer types, stages, and place on the cancer care continuum, allowing researchers to compare changes in QOL across time and disease-specific parameters. In the cancer survivor population, upwards of 14 questionnaires exist to evaluate QOL; however, two questionnaires tend to be utilized most frequently, the Functional Assessment of Cancer Therapy (FACT) system and European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ C-30) Questionnaire with the FACT system most frequently used in North American and Europe and EORTC QLQ C-30 used in European countries (Gunnars et al., 2001). Both questionnaires include disease and treatment-specific questions for patients with varying types and stages of cancer and utilize a Likert scale (Efficace et al., 2019; E. H. Lee et al., 2004). For this dissertation, the FACT questionnaire will be utilized to measure QOL in a mixed sample of cancer survivors.

The FACT system of QOL questionnaires includes subscales addressing physical, social/family, emotional, and functional well-being. In addition, tumor specific FACT questionnaires include subscales specific to that disease site (i.e., FACT-Breast, FACT-

Colorectal). When evaluating mixed samples of cancer survivors, the FACT-General (FACT-G) is utilized. The FACT-G is a validated, self-report measure of QOL (D. F. Cella et al., 1993). This questionnaire consists of 27-items, including subscales to differentiate changes in physical, social/family, emotional, and functional well-being. The FACT-G scores range from 0-108, with a higher score representing a higher QOL for both total and individual subscales. Questions are assessed on a 0-4 Likert scale with 0 representing “not at all” and 4 representing “very much”. Participants are instructed to indicate a response for each question based on how s/he has felt over the past 7-days. The FACT-G is used to assess QOL for cross-sectional analysis as well as to detect changes in QOL after an intervention period, with a change of 5-points indicating a clinically meaningful difference in cancer survivors (Brucker, Yost, Cashy, Webster, & Cella, 2005).

Issues with measuring QOL include adaptability over time of symptoms, meaning cancer patients may be experiencing the same level of symptom burden, but they begin to report lower severity (Gunnars et al., 2001). In addition, the subscales are standardized, limiting the measurement of individual-level factors that may affect QOL. Without individualization of questions assessing QOL, an argument can be made that QOL questionnaires, as they are currently utilized, are actually measured general health rather than QOL (Carr & Higginson, 2001).

BODY COMPOSITION

Body Composition for Cancer Survivors

Excess fat mass has been linked to increased prevalence and risk of recurrence in cancer survivors with some studies suggesting it is a major contributor of cancer-specific morbidity and mortality (Coronha et al., 2011). Many potential mechanism exists for how increased fat mass may contribute to cancer cell development and proliferation, including

systemic and paracrine mechanisms (Donohoe, Doyle, & Reynolds, 2011). These mechanisms are thought to produce a pro-tumorigenic environment which includes hypoxic environments suitable for inflammatory cytokines and adipokines, leading to cancer cell development and growth. This environment allows cancer cells to communicate through intracellular signaling to increase growth and apoptosis (Donohoe et al., 2011). Additionally, adipose tissue plays a role in immune response, a role which may benefit cancer cell communication and progression (Trayhurn & Beattie, 2001). White adipose tissue specifically is known to secrete factors such as tumor necrosis factor-alpha and interleukin-6, which are known hormones to aid in cancer cell development and progression (Trayhurn & Beattie, 2001).

Muscle mass depletion is also of great concern in the cancer survivor population as it has been linked to decreased physical function, increased treatment toxicity, more frequent and longer hospital stays, and increased risk of infection (Coronha et al., 2011). Due to the aging population of cancer survivors, a population already at high risk for reduced muscle mass, it is vital for cancer survivors to maintain or improve muscle mass in order to tolerate treatment and reduce risk of recurrence or secondary malignancy. In cancer survivors, two common, negative body composition alterations are cachexia and sarcopenic obesity.

Cachexia is involuntary weight loss greater than 5% and is associated with survival rates in cancer survivors. When analyzing cachexic individuals, it is important to take into account the body composition of these individuals as considerable variability exists between those gaining/losing muscle and fat mass (Martin et al., 2013). For those increasing fat mass while simultaneously decreasing muscle mass, this is an independent prognostic factor of lower survival in those with cancer, and is known as sarcopenic obesity (Martin et al., 2013).

Sarcopenic obesity, the combination of decreased muscle mass and excess fat mass, is of great interest in the cancer community as it is linked to recurrence rate, morbidity, and mortality. For those with sarcopenic obesity, they are more susceptible to ailments related to

both increased fat mass as well as muscle depletion, making these individuals a very high-risk group (Coronha et al., 2011). Sarcopenic obesity is often caused from the imbalance of nutrient intake to output. In cancer survivors specifically, this is often due to decreased activity levels as well as fluctuating appetites due to treatment. In those experiencing sarcopenic obesity, weight may remain stable or fluctuate, making it hard to diagnose using techniques other than CT or DEXA imaging.

Although body composition changes are partly due to shifts in lifestyle behaviors (i.e., eating patterns, activity patterns), associations between cancer drugs and weight fluctuations have also been established. For example, breast cancer survivors taking Tamoxifen have significantly greater levels of visceral adiposity compared to controls (Ali, al-Ghorabie, Evans, el-Sharkawi, & Hancock, 1998). Additionally, those receiving Tamoxifen had increased intra-abdominal fat and fatty liver (Nguyen, Stewart, Banerji, Gordon, & Kral, 2001). In general, it is not uncommon for those with cancer to gain visceral fat mass, independent of weight increase or decrease (Sheean, Hoskins, & Stolley, 2012). Therefore, in order to better manage cancer survivors during survivorship, it is imperative to implement strategies to prevent and/or manage common body composition changes that can lead to adverse health outcomes, namely sarcopenic obesity. Lifestyle behaviors, including physical activity, sitting time, and sleep are effective treatment options for managing body composition changes for cancer survivors (Beccuti & Pannain, 2011; Chastin, Palarea-Albaladejo, Dontje, & Skelton, 2015), providing support for lifestyle interventions to be integrated into cancer care.

Overview of Body Composition

Body composition provides insight into the nutritional status and functional capacity of the body and has been linked to many health outcomes in both healthy and diseased populations (Kuriyan, 2018). Adipose tissue, or fat mass, is a long-term indicator of energy storage. It consists of adipocytes and embedded collagen as well as elastin fibers to support the

tissue (Storchle et al., 2018). Adipose tissue can be broken down into two types: white adipose tissue (WAT), which is responsible for energy storage, and brown adipose tissue (BAT), which is responsible for generating heat in the body (Schoettl, Fischer, & Ussar, 2018).

BAT is considered a thermogenic tissue responsible for maintaining core temperature even at low temperatures. It consists of many single large lipid droplets as well as copious amounts of mitochondria, increasing the expression of uncoupling protein 1 (UPC1). Due to these properties, BAT is able to turn chemical energy directly into heat for the body, solidifying its crucial role in the health. Despite the necessity of BAT for survival, BAT is often found in limited quantity in adults. As individuals transition from childhood to adulthood, the amount of BAT decreases; however, WAT tends to increase.

WAT is the type of adipose tissue most commonly associated with fuel storage, body insulation, glucose tolerance, and inflammatory response, making it an important player in human health (Trayhurn & Beattie, 2001). Although WAT's historical role was to maintain a fuel reserve in times of decreased energy input (i.e. starvation), providing fatty acids to provide fuel for oxidation in other organs, as well as a role for thermal insulation to maintain core temperature, WAT has developed a more controversial role in human health due to growing rates of obesity (Trayhurn & Beattie, 2001). WAT is the predominant fat tissue in adults, with lower amounts of BAT interlaced typically in response to a cold stimulus (Schoettl et al., 2018). Therefore, WAT is the type of adipose tissue typically being addressed when evaluating fat versus lean mass in clinical research. However, adipose tissue is further categorized into additional types based on location in the body: visceral adipose tissue and subcutaneous adipose tissue.

Visceral adiposity refers to fat mass located centrally in the body and is associated with higher risk of developing chronic diseases including but not limited to cardiovascular disease, metabolic disease, stroke, and cancer (Abraham, Pedley, Massaro, Hoffmann, & Fox, 2015;

Donohoe et al., 2011; Muuronen et al., 2015). Visceral adipose tissue is thought to be more metabolically active, secreting adipokines and cytokines, increasing inflammation and coagulation leading to insulin resistance and metabolic syndromes (Donohoe et al., 2011). Additionally, the secretions related to visceral adipose tissue are strongly associated with cancer development and proliferation, making studying and measuring visceral adiposity a growing interest of cancer researchers (Donohoe et al., 2011). A phenomenon often noted with regard to visceral adiposity is metabolic obesity, a characteristic when someone of normal weight and stature demonstrates metabolic characteristics of those that are overweight or obese. In these “metabolic obese” individuals, visceral adiposity is elevated, providing evidence for the negative effects of increased visceral fat on health (Schoettl et al., 2018).

Men tend to have more visceral adipose tissue than women, carrying on average 20-30% of their fat mass centrally, independent of obesity status (Bjorntorp, 2000). Women tend to carry more fat mass subcutaneously; however, visceral adipose tissue increases as women reach a moderate level of obesity, increasing their risk for negative health outcomes (Bjorntorp, 1992).

Subcutaneous adiposity refers to fat mass located on the periphery, typically the arms and legs, and has less effect on chronic disease development (Donohoe et al., 2011). In fact, subcutaneous adiposity may be protective for cancer survivors. For example, high levels of subcutaneous adiposity in castration resistance prostate cancer was predictive of higher progression-free and survival rates. A proposed explanation for this protective mechanism is the ability of survivors with higher subcutaneous adiposity to tolerate more and/or higher doses of cancer treatment (J. S. Lee et al., 2018). In general, the negative affects with carrying higher levels of fat mass outweigh some of the protective effects, especially considering lifestyle behaviors (i.e. diet and exercise) are unable to target reductions in specific types of fat (visceral

vs. subcutaneous). Therefore, it is recommended to decrease adiposity if body fat percentage is above what is considered healthy percentages.

For men, a healthy amount of fat mass is 10-22% and for women, 20-32% fat mass (American College of Sports Medicine et al., 2018). This higher level in women is due to increased metabolic demand by women's natural physiological processes (i.e. reproductive system). For those already in the overweight/obese category, a reduction in body fat of 10% is recommended, with a reduction of 3-5% associated with many health benefits (Donnelly et al., 2009).

Lean mass, specifically muscle mass, is also an indicator of metabolic health, independent of fat mass (Donohoe et al., 2011; Kuriyan, 2018). Low muscle mass is a predictor of mortality and is associated with surgical complications, decreased physical function, decreased quality of life, and survival in a variety of clinical populations (Caan, Cespedes Feliciano, & Kroenke, 2018; Prado et al., 2018). Muscle mass can be broken down into three categories: cardiac, smooth, and skeletal muscle. Cardiac muscle is responsible for contracting the heart to pump blood to the rest of the body. Smooth muscle is the muscle that forms our organs and allows for flexibility to perform necessary bodily functions. Skeletal muscle is responsible for mobilizing the body, moving the bones and other structures within the musculoskeletal system. In this dissertation, skeletal muscle will be the muscle mass of interest and will be referred to as lean mass for the duration of this dissertation.

Lean mass, consisting of myofibrils, mitochondria, and the sarcoplasmic reticulum, is responsible in part for endurance, posture, ballistic movements, and thermogenesis and accounts for 40% of overall human mass (Lindstedt, 2016). With higher levels of lean mass, an individual's basal metabolic rate is elevated, or the amount of energy expended at rest. This aids in maintaining proper energy balance to ensure a healthy body composition to maintain and/or improve health. For clinical populations, skeletal muscle is important to aid in the proper

metabolism of drugs. When dosing drugs, the dose is typically based off the total weight of an individual; however, in obese adults, drug clearance is often greater and correlates with lean mass (Barras & Legg, 2017). For those underweight or of normal weight, this could lead to potential drug toxicity, due to lower ratios of muscle mass to total weight. For example, the drug doxorubicin, a common chemotherapy agent used to treat many different types of cancer, often accumulates in skeletal muscle, playing an important systematic role in availability and metabolism of the drug (Fabris & MacLean, 2015). If an individual has more muscle mass, s/he may be more likely to tolerate higher doses of the drug with decreased side effects and increased chance of survival. Therefore, it has been proposed that drug dosing should be adjusted, especially in overweight/obese individuals, to determine appropriate drug availability as chronic dosing based solely on total body weight could lead to drug toxicity (Barras & Legg, 2017).

From a lifestyle perspective, muscle mass plays an important role in how individual's function within their everyday lives. As individual's age and/or develop chronic disease, muscle mass decreases, leading to decreases in mobility, strength, and balance. With these changes in function, these individual's will likely experience a diminished ability to complete activities of daily living (ADLs) and increase risk of falls, solidifying the necessity of maintaining and/or increasing muscle mass throughout the lifespan (Prado et al., 2018). Additionally, with lower levels of lean mass and higher levels of fat mass, individuals are at increased risk of decreased bone mineral density, leading to higher chance of bone fractures (Irwin et al., 2009).

With the growing prevalence of obesity, it is important to understand body composition, as fat mass and lean mass have different metabolic consequences in both healthy and diseased populations. By measuring body composition, we can begin to understand the nature of dysfunction of metabolic processes based on the ratio of fat to lean mass in the body. Additionally, a higher level of understanding related to the full body composition profile, rather

than solely total body weight, can lead to changes in clinical care of those with chronic disease, including those undergoing cancer treatments.

Measurement of Body Composition

The true gold-standard of body composition measurement can only be completed post-mortem by analyzing the body during autopsy; however, non-invasive techniques have been developed and validated to assess body composition in both healthy and clinical populations (Kuriyan, 2018).

Hydrodensitometry, air displacement plethysmography, and isotope dilution methods are common laboratory measurements of body composition. These measures require specialized equipment and training to complete and are typically more cost-prohibitive. All of these measures are conducted in a laboratory setting and measure body density (Db). In hydrodensitometry and air displacement plethysmography, the amount of air or water displaced by the body provides an estimate of body volume from which Db can be estimated (Kuriyan, 2018). These measurements require a correction factor for lung volume. In isotope dilution methods, total body water, concentration, and amount of tracer are used to estimate fat free mass (FFM), as total body water typically occupies 40-60% of body weight and is present in the highest concentrations in FFM (Kuriyan, 2018). These measurements are often time-consuming and cause discomfort to the individuals, making them less desirable approaches to measure body composition.

Dual x-ray absorptiometry (DXA), computerized tomography (CT), and magnetic resonance imaging (MRI) are imaging techniques that provide more insight on the type, location, and extent of fat mass and lean mass and therefore are the most desirable methods for assessing body composition, if available. These scans, specifically CT and MRI, are often completed as part of routine care for cancer survivors during the course of treatment, making it

more accessible in this population; however, CT scans use X-rays for imaging, exposing the survivor to additional radiation while the MRI uses magnet fields and radio waves to analyze the body's tissues, making it unavailable to those that have any metal in their body (i.e., cancer treatment ports). For survivors that have completed treatment, CT and MRI are not completed as often, resulting in the need for additional imaging to measure body composition. Additionally, CT and MRI scans require review of a radiologist, making these imaging techniques more cost-prohibitive.

The DXA is a useful tool when interested in body composition imaging and is more cost-effective and interpretable than CT or MRI and therefore is often used in the post-treatment cancer survivor phase. The DXA is a validated measurement tool to measure body fat, muscle mass, and total body bone density (Haarbo, Gotfredsen, Hassager, & Christiansen, 1991). The DXA uses high and low photon energies to distinguish the properties of the underlying tissue. Pending tissue type, the photon energies navigate differently, allowing for distinguishing between types of tissues in the body. The DXA report provides an image to visually assess location of fat mass and muscle mass as well as detailed, regional reports to differentiate between centrally or peripherally located fat mass. The DXA is a quick (typically 3-6 minute) scan requiring little technician training, making it an advantageous method for measuring body composition in clinical populations (Kuriyan, 2018).

The risks associated with the DXA are very low. The maximum radiation dose from one scan is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). There are no discomforts associated with the procedure; however, women who are or could be pregnant should receive no unnecessary radiation and therefore are recommended not to undergo DXA measurements. Due to the possible use of radiation as treatment for cancer survivors, imaging techniques including MRI, CT, and/or DXA may not be desirable for the cancer survivor population due to already large doses of lifetime

radiation treatment. Additionally, these measurements require in-person laboratory visits and can be very costly.

The simplest, most cost-effective body composition measurement techniques are anthropometric measures including waist circumference, BMI, waist-to-hip ratio, skinfold measurements, and bioelectrical impedance. Using validated equations, these measurements, using easily collectable measurements including height, weight, waist and hip measurements, are able to provide information regarding fat mass; however, they vary in their abilities to distinguish between total fat mass, subcutaneous fat mass, and visceral fat mass. For example, waist circumference is used to estimate intra-abdominal, or visceral, fat mass while skinfold measurements are used to estimate subcutaneous fat mass. These methods are best used when assessing nutritional status, changes after a nutritional or activity intervention, or as a health-risk factor assessment, which are common assessments needed in cancer survivors (Kuriyan, 2018). They are easy, accessible measurements often utilized in clinical environments to provide quick feedback on body composition and have known utility in the cancer survivor population.

Body Mass Index

Despite the lack of specificity related to lean mass and fat mass distribution, BMI has been linked to treatment related outcomes and cancer-related mortality among cancer survivors. For example, one study in a sample of endometrial cancer survivors found that survivors with obesity, defined as a BMI ≥ 30 kg/m^2, reported more physical function limitations. Specifically, for every 5 kg/m^2 increase in BMI, survivors saw a decrease of 0.15 in physical function (p=0.045) (X. Zhang, Brown, & Schmitz, 2016). In addition to reductions in physical function, a higher BMI increases the likelihood of developing a secondary cancer in breast cancer survivors. Feigelson et al. (2021) examined the association between BMI and developing a secondary cancer in 6481 breast cancer survivors, finding that a 5 kg/m^2 increase in BMI

increases the risk of developing any type of secondary cancer by 7%. For a secondary breast cancer diagnosis, a 5 kg/m^2 increase in BMI increases risk by 11% and 15% for an estrogen-receptor positive secondary breast cancer. A 5 kg/m^2 increase in BMI increases also increases risk for cancer types specifically linked to obesity (13%) (Feigelson et al., 2021). Finally, BMI has been linked to increased cancer-related mortality with a 5 kg/m^2 increase in BMI resulting in a 10% increase in cancer-related mortality (Basen-Engquist & Chang, 2011).

BMI is not without its limitations. In the cancer survivor population, specifically those currently undergoing treatment, a phenomenon known as the “obesity paradox” exists. This paradox eludes to a potential protective factor for survivors in the overweight or slightly obese BMI categories (Shachar & Williams, 2017). A few explanations exist for this paradox. First, increased fat reserves and lean mass may provide an advantage for survivors experiencing acute illness due to higher nutritional stores. Second, the lower BMI categories (i.e., underweight and normal weight) may disproportionately include sicker survivors with higher frailty. The associated weight loss in this population of survivors could also be linked to more aggressive cancer types and other comorbid factors, potentially increasing the risk of mortality (Shachar & Williams, 2017).

Despite the limitation associated with BMI, it is still an important factor to consider for cancer survivors. Survivors with a higher BMI are known to suffer with decreased physical function, lower QOL, and are less likely to meet PA guidelines (Blanchard, Stein, & Courneya, 2010; Peuckmann et al., 2007; X. Zhang et al., 2016), Due to unforeseen circumstances (switch to virtual data collection during the COVID-19 pandemic) and cost-effectiveness, BMI is was used as an estimate of body composition.

In the following section, I will discuss the lifestyle behaviors being measured in this dissertation and the current evidence on how each effects QOL and body composition in cancer survivors.

THE EFFECTS OF LIFESTYLE BEHAVIORS ON QOL AND BODY COMPOSITION IN CANCER SURVIVORS

Interventions to increase positive lifestyle behaviors, including physical activity, sleep habits, diet, and weight management, have grown in popularity among cancer survivors as these interventions provide non-pharmacological approaches to improving treatment-related side effects. Increases in positive lifestyle behaviors such as physical activity are linked to improved survival, overall functioning, and quality of life in cancer survivors (Basen-Engquist et al., 2017; Garland, Mahon, & Irwin, 2019). Additionally, physical activity is an essential component for increasing muscle mass and decreases fat mass as the overload on muscles and increased energy expenditure will result in positive body composition changes, improving cancer-related outcomes (Brown et al., 2017; Hanson, Wagoner, Anderson, & Battaglini, 2016). Therefore, interventions aimed at improving lifestyle behaviors are important for improving QOL and body composition among cancer survivors.

Physical Activity and Sedentary Behavior

Over the course of the waking day, individuals participate in physical activity (PA) and sedentary behavior (SB). PA, defined as any bodily movement that requires an expenditure of energy above those of resting levels, can be broken down into differing intensities of activity including light PA, and moderate to vigorous PA (MVPA) (American College of Sports Medicine et al., 2018). Light PA is defined as activity 30-39% of heart rate reserve (HRR) while MVPA is defined as activity between 40-89% of HRR (American College of Sports Medicine et al., 2018). Intensities exceeding 89% of HRR would be considered near-maximal or maximal capacity activity while those below 30% would be considered very light activity (American College of Sports Medicine et al., 2018). PA has been found to reduce the risk of developing many chronic diseases and is also beneficial for managing chronic diseases including cardiovascular disease, pulmonary disease, hypertension, diabetes, stroke, and cancer (McKinney et al., 2016). Light

PA, specifically, has been found to lower risk of early death compared to time spent in sedentary behaviors, and strong to moderate evidence exists to support that MVPA is effective in improving cardiorespiratory fitness, cognition, QOL, and sleep while reducing depression, anxiety, and falls in healthy populations (Rosenberger et al., 2019). PA is an essential part of maintaining health and the evidence is strong to support encouraging PA in many clinical populations, including cancer survivors (K. L. Campbell et al., 2019).

Sedentary behavior (SB) is defined as any waking behavior that requires an energy expenditure ≤1.5 Metabolic equivalents (METS) while in a sitting, lying, or reclined position (van der Ploeg & Hillsdon, 2017). The negative effects of SB have been well-established over the past decade revealing that as sitting time increases, all-cause mortality increases, independent of activity levels (Katzmarzyk, Church, Craig, & Bouchard, 2009). SB has become increasingly prevalent with the shift in working patterns. In today's society, jobs and hobbies have become more sedentary with the introduction of computers, televisions, and alternate forms of transportation (i.e., cars, trains, buses). As resources to complete tasks at the touch of a button become more and more accessible, SB continues to rise, while leisure-time PA continues to decrease, leading to increased risk of developing chronic diseases (Owen, Sparling, Healy, Dunstan, & Matthews, 2010).

Implications of PA and sedentary behavior on body comp and QOL among Cancer Survivors

Over the last decade, copious amounts of evidence has been released to support the physical and psychosocial benefits of PA, both light PA and MVPA, and the detrimental effects of SB for cancer survivors, specifically with regard to QOL and body composition. From a psychosocial perspective, PA may establish a positive feedback loop as patient's see positive changes as they progress through an exercise program, leading to improvements in QOL (Ricci, Flores, Kuroyama, Asher, & Tarleton, 2018). From a physiological perspective, PA reduces stress and chronic inflammation, aiding in the prevention and management of chronic diseases

(Ricci et al., 2018). PA also increases daily energy expenditure and engages muscles, helping to enhance body composition.

Numerous systematic reviews and meta-analyses have been published to support the benefits of PA in improving QOL and body composition (Ferrer et al., 2011; Fong et al., 2012; Gerritsen & Vincent, 2016; Irwin, 2009) during and following treatment. In a systematic review of PA in colorectal cancer survivors, light PA and MVPA were associated with higher QOL (Eyl, Xie, Koch-Gallenkamp, Brenner, & Arndt, 2018). Similarly in a review of breast cancer survivors, light PA and sedentary behavior were identified as potential treatment targets as reductions in SB and increases in light PA, independent of MVPA, are known to improve QOL (Lynch et al., 2011; Lynch, Dunstan, Vallance, & Owen, 2013). For body composition, a known dose-response relationship exists between PA levels, sedentary time, and adiposity in cancer survivors (Brown et al., 2017; Lynch et al., 2010; Wijndaele et al., 2009). These known associations between different PA levels and SB have increased awareness regarding the need for PA and SB guidelines for cancer survivors.

Due to the known benefits of PA, in 2010, the American College of Sports Medicine (ACSM) released exercise guidelines for cancer survivors (Schmitz et al., 2010). In 2019, an update was released providing guidelines related to specific treatment-related side effects often experienced by cancer survivors (K. L. Campbell et al., 2019). These new guidelines provide more specific exercise prescriptions for the improvement on common cancer-related side effects including diminished QOL.

Measurement of Physical Activity and Sedentary Behavior

Oftentimes due to low participant burden and cost-effectiveness, subjective measurement of activity patterns have been utilized to better understand the role of lifestyle behaviors on cancer-related outcomes; however, this comes with limitations. Self-report

methods have been found to under- (less active individuals) and over- (more active individuals) estimate PA and SB in individuals due to difficulty recalling past activities, cultural differences in interpretation, social desirability bias, or confusion from question wording (Del Pozo-Cruz et al., 2018; Evenson, Buchner, & Morland, 2012). Therefore, the introduction of actigraphy/accelerometry to measure PA, and SB has provided an objective method to better understand how these lifestyle behaviors affect outcomes in cancer survivors.

Subjective Measurements of PA and SB

Subjective measurements (i.e., self-report), collected through validated questionnaires, most commonly inquire about activity and sedentary time over the past 7-days. Numerous questionnaires exist, typically designed to understand PA and SB in different contexts, including for leisure (i.e., exercise) or for other purposes (i.e., occupational). In cancer survivors two commonly used self-report measures of PA and SB are: the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GLTPAQ) (Amireault, Godin, Lacombe, & Sabiston, 2015) and The International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). In this dissertation, the IPAQ was chosen as the self-reported measure for PA and SB since the GLTPAQ does not collect information regarding sitting time. Additionally, the IPAQ is utilized frequently in the cancer survivor population since it asks questions regarding vigorous PA, moderate PA, walking time, and SB. The IPAQ is a reliable, self-report, 7-item measure of time spent in PA and SB (Lewis, Hernon, Clark, & Saxton, 2018). In this questionnaire, participants are asked if s/he participates in the vigorous PA, moderate PA, walking, and sitting, and if so, how many days per week, hours per day, and minutes per day on average does s/he spend each day in each of these activities. This allows for calculation of average time spent in light PA, MVPA, and SB.

Objective Measurement of PA and SB

PA and SB can be quantified objectively using pedometers and accelerometers. Pedometers are considered the traditional step counter, typically waist-worn and spring-levered. These devices count steps by using a horizontal, spring-suspended lever-arm, set into motion by vertical accelerations of the body during walking or running, that moves up and down with each step. The lever arm signals an electrical counting device to register steps (Bassett, Toth, LaMunion, & Crouter, 2017). Accelerometers are devices that consists of small sensors (typically three, considered tri-axial) and can be worn at various locations on the body including hip, wrist, and thigh. The sensors are able to identify direction and magnitude of accelerations, allowing for PA behaviors to be categorized into different intensities including sedentary, light PA, and MVPA (Arvidsson, Fridolfsson, & Borjesson, 2019).

Accelerometry can provide insight on the effects of lifestyle behaviors (both short- and long-term) to improve outcomes including quality of life, fatigue, physical fitness, and physical function in cancer survivors. With the relatively low-burden of wearing a device, researchers are able and beginning to measure activity patterns longitudinally to better understand how activity changes across the lifespan and its effects on health outcomes.(Je, Jeon, Giovannucci, & Meyerhardt, 2013)

With improvements in accelerometer technology, SB and LPA can now be objectively measured with acceptable validity, allowing for further investigation on how these behaviors affect short- and long-term cancer outcomes (Grant, Ryan, Tigbe, & Granat, 2006). Additionally, the effects of accumulating MVPA in bouts versus non-bouts is not well understood and requires additional research to determine the best way to meet MVPA guidelines to improve cancer-related outcomes.(Piercy et al., 2018) With the help of accelerometers, analyses can be conducted to determine the effect of bout vs. non-bouted PA, helping to improve current PA guidelines. A number of accelerometers exists to measure SB, light PA, and MVPA in cancer

survivors; however, this dissertation will utilize the activPAL accelerometer; therefore, the activPAL will be the accelerometer evaluated moving forward.

The activPAL has been validated to quantify free-living sedentary and ambulatory activities, and has been previously used in cancer survivors (George et al., 2014). The activPAL software quantifies light PA, MVPA, and sitting and lying time based on static and dynamic accelerations (Lyden et al., 2017). In addition to its unique ability to distinguish between different body positions, allowing for identification of cycling, the activPAL accelerometer provides an estimate of energy expenditure using metabolic equivalents (METs). The majority of accelerometers utilized in research settings today are wrist or waist-worn accelerometers. The activPAL accelerometer is a thigh-based sensor, allowing for identification of postures and transitions from different postures. With this functionality, the activPAL is able to identify "events" (i.e., sitting, lying, standing, walking) (Lyden et al., 2017). Additionally, the activPAL accelerometer software has recently undergone an upgrade, allowing the activPAL to more accurately measure sleep behaviors. This new functionality is essential for the purposes of this dissertation and will be evaluated for acceptability of measurement in cancer survivors.

SLEEP

Sleep is a complex, intricate physiologic process that contributes to the maintenance of metabolic homeostasis. Continuous sleep disruption has both short and long-term effects. For otherwise healthy individuals, some of the short-term effects of disrupted sleep include increase stress responsivity, decreased quality of life, increased emotional burden and mood fluctuations, cognitive, memory, and decreased performance of everyday tasks. Long-term consequences for otherwise healthy individuals include hypertension, cardiovascular disease, dyslipidemia, weight issues, metabolic syndrome, and increased cancer risk (Medic, Wille, & Hemels, 2017; Otte et al., 2015). Due to the physiological intricacies of sleep, it is clearly a key player in overall

health, making it a necessary process to evaluate and understand when working with clinical populations.

Numerous potential mechanisms to explain the role sleep has on metabolic homeostasis exist including impaired glucose metabolism, dysregulation of hunger and satiety hormones including leptin and ghrelin, increased sympathetic nervous system activity, endothelial dysfunction, heightened inflammatory response and stress responses (Rangaraj & Knutson, 2016). Sleep measurement is divided into many parameters including sleep duration and sleep quality which can both be further broken down to analyze these potential mechanism and the effects different sleep habits have on health.

Sleep duration includes the amount of time an individual is engaged in sleep behavior, or a state of altered consciousness where responsiveness to external stimuli is reduced. This includes the two distinct states of sleep: rapid eye movement (REM) and non-REM sleep with these stages followed by wakefulness (Dolezal et al., 2017). Non-REM sleep is further divided into 3 stages: N1, N2, and N3, with N1 representing time between wake and sleep and N3 representing slow wave or deep sleep. As individuals transition between sleep stages, additional sleep behaviors may be expressed including periods of wakefulness (Cappuccio, Miller, Lockley, & Rajaratnam, 2018).

Sleep duration can provide important insight on health of individuals based on the current knowledge of the effects of too little or too much sleep on metabolic dysfunction, cognitive function, and mortality (Kline, 2013a). However, total duration of sleep provides only a portion of the story. Over the past decade, the importance of additional parameters including sleep quality have gained traction due to their known effects on health (Lao et al., 2018). In fact, sleep quality may have more of an impact on overall health than duration of sleep ("Good, Fair, or Poor: How well do you sleep? ," 2019). Objective measurements, using actigraphy and/or PSG, allow researchers to study the effects of sleep quality parameters including sleep

efficiency, which has been shown to have an effect on mortality (Dew et al., 2003). In a study by Palesh et al. (2017), sleep efficiency, rather than sleep duration, was found to be associated with increased mortality in advanced breast cancer survivors (Palesh et al., 2017). In order to improve sleep efficiency, interventions must aim to improve total sleep time, WASO, SOL, and/or WASF; however, interventions may differ based on the target behavior change. For example, to target WASO as a change, we would need to know what was causing wakefulness (pain, urination).

Through electroencephalogram (EEG), detailed sleep quality can be measured by time in REM and non-REM sleep stages, with more SWS representing good quality sleep. This provides additional knowledge on the impacts of sleep behavior on health (Ancoli-Israel et al., 2003; Kline, 2013b). Sleep quality, as characterized by slow wave sleep (N3), tends to decrease with age and has been shown to affect metabolic and hormonal processes in addition to appetite regulation (Van Cauter, Spiegel, Tasali, & Leproult, 2008). With impairments in these processes, individuals are at higher risk for developing cardiovascular disease, certain types of cancer, obesity, and diabetes (Beccuti & Pannain, 2011; Y. Chen et al., 2018; Lao et al., 2018). In the case of cancer patients, subjective and objective sleep ratings are often not related, leaving a gap in understanding the sleep features related to patient's perspective (Komarzynski et al., 2019). Without a clear understanding of how different components of sleep affect cancer-related outcomes, both physiologic and psychosocial, and the effect on mortality, treatment options cannot be effectively developed.

Sleep quality does not have a clear definition. For those experiencing sleep difficulties, sleep quality might be defined as self-reported time to fall asleep, wakeful episodes during the night, daytime sleepiness, or awakening feeling rested (Kline, 2013b). From an objective-measurement standpoint, sleep quality is often measured by the following components: sleep onset latency (SOL), wake after sleep onset (WASO), wakefulness after sleep offset (WASF),

and sleep efficiency. Although these behaviors are normal, too much/too long of disruptive periods, causing a decrease in sleep efficiency, can lead to negative health consequences including metabolic dysfunction and increased mortality risk (Kline, 2013b).

Wake after sleep onset, or WASO, describes the period(s) of time that individuals awaken during the night after sleep onset (excludes SOL) (Shrivastava, Jung, Saadat, Sirohi, & Crewson, 2014). WASO is considered a normal sleep behavior with 30-60 minutes over a 7-hour sleep period considered normal; however, too much WASO can negatively impact sleep efficiency (Gibbs, 2018). Sleep efficiency is described as the total percentage of time in bed spent asleep with a normal sleep efficiency considered 85% or higher (Foundation, 2019). Sleep efficiency is calculated by adding the total amount of time in stages N1, N2, N3, and REM sleep, divided by the total amount of time in bed, multiplied by 100 (Shrivastava et al., 2014). By increasing bouts or length of WASO, sleep efficiency will be decreased, indicating poorer sleep quality (Shrivastava et al., 2014).

Implications of sleep for body composition and QOL among Cancer Survivors

Cancer survivors are often burdened by sleep disturbance including difficulty falling asleep, problems maintaining sleep, poor sleep efficiency, early awakening, and excessive daytime sleepiness (Roscoe et al., 2007). 30-75% of cancer survivors report some level of sleep disturbance at some point during their cancer journey with persistent rates of insomnia up to 64% (Bernard et al., 2019; Fiorentino & Ancoli-Israel, 2007). Due in part to the aging process, cancer treatment is also known to produce sleep disturbance, making it an important treatment-related side effect to address as inadequate sleep has been linked to mortality in cancer survivors (Landry, Best, & Liu-Ambrose, 2015). The known effects of sleep disturbance on healthy individuals compounded with the negative effects of cancer treatments likely puts cancer survivors at increased risk of developing secondary conditions and/or cancer recurrence. Specifically, short duration and long duration sleep were both associated with cancer-related

and all-cause mortality in cancer survivors (Stone et al. 2019). However, there is still a substantial lack of information regarding the effects of sleep disturbance on cancer survivorship (Y. Chen et al., 2018). It is thought that sleep disturbance is often not reported to oncologist, limiting the amount of evidence related to sleep disturbance and cancer outcomes (Fiorentino & Ancoli-Israel, 2007).

Sleep disturbance is known to correlate with QOL and body composition, making it a desirable target for intervention (Alfano et al., 2011; Cappuccio et al., 2018; Medysky, Temesi, Culos-Reed, & Millet, 2017). Cancer survivors suffering from sleep disturbance were found to be more likely to have undergone chemotherapy and/or gained weight after diagnosis, demonstrating a relationship between cancer treatment, body composition, and sleep in cancer survivors (Alfano et al., 2011). Interventions have been designed to modify sleep disturbances in cancer survivors with positive results regarding improvements in QOL (Espie et al., 2008). In terms of body composition, cancer treatment often affects numerous metabolic pathways leading to decreases in muscle mass and increases in adiposity, pathways which are also negatively affected by sleep disturbances (Beccuti & Pannain, 2011; Piovezan et al., 2015). Due to the relationships amongst QOL, body composition, and sleep in cancer survivors, it is imperative to consider sleep disturbances when evaluating intervention strategies to improve QOL and body composition during survivorship.

Measurement of Sleep

Subjective Sleep Measurement

Subjective measurements exists to evaluate sleep duration and quality including questionnaires and participant diaries. Validated questionnaires, specifically the Pittsburg Sleep Quality Questionnaire (PSQI), have been deemed appropriate for measuring sleep duration and quality in healthy populations as well as a variety of clinical populations (Grandner, Kripke,

Yoon, & Youngstedt, 2006; Otte, Rand, Carpenter, Russell, & Champion, 2013). The PSQI includes questions to evaluate sleep over the past month, whereas the Post sleep questionnaire (PSQ), is a one-night recall of sleep duration and quality (Canafax, Bhanegaonkar, Bharmal, & Calloway, 2011). Questionnaires also exist to measure sleep dysfunction including sleep apnea and insomnia (Ahmadi, Chung, Gibbs, & Shapiro, 2008; Morin, Belleville, Belanger, & Ivers, 2011). These questionnaires are utilized to detect sleep dysfunction as well as measure change in dysfunction after treatment (Morin, LeBlanc, Daley, Gregoire, & Merette, 2006). The PSQI is a reliable, self-report, 10-item measure of sleep duration and quality (Otte et al., 2013).

Sleep diaries have also been utilized to analyze sleep patterns in clinical populations. The most popular, the Consensus Sleep Diary, is a self-report log completed by the individual every day and has been deemed the “gold standard” of subjective sleep measurement (Carney et al., 2012). The log, in addition to recording time in and out of bed each day, asks additional questions regarding time in bed, time to sleep, awakenings during the night, time awake, time out of bed, and a rating of overall sleep quality (Carney et al., 2012). The diary is designed to fit on a single sheet of paper and record up to 7 days of sleep information.

Objective Sleep Measurement

The gold standard for measurement of sleep duration and sleep quality is polysomnography (PSG) which detects sleep behaviors through physiological signals such as brain, muscle, and eye movement (Kline, 2013a). However, this method of sleep measurement is costly and inconvenient, especially if measuring sleep duration and quality over an extended period of time. To conduct PSG assessments, participants must sleep in the laboratory, which is difficult for cancer survivors already experience cancer treatment related side effects including insomnia and pain (Fiorentino & Ancoli-Israel, 2007). Therefore, there has been limited use of this measure in the cancer survivor population. In order to obtain objectively measured sleep measurements in cancer survivors, the use of actigraphy has been implemented. Actigraphy, a

validated measurement tool against PSG is often utilized to measure the different components of sleep in both healthy and clinical populations. This device is worn on the non-dominant wrist and utilizes bodily movements to detect changes in sleep/wake patterns (Ancoli-Israel et al., 2003; Kline, 2013a). Due to the accessibility, battery life, and light-weight design of these devices, actigraphy, specifically the Actiwatch-2, is a desirable measure when analyzing sleep disturbances in cancer survivors. These devices are cost-effective and are able to be worn for multiple days, if not weeks, pending epoch collection length. These devices allow for analyzing sleep habits over a period of time, in the comfort of one's own home, rather than in a laboratory for a shorter duration.

THE 24-HOUR ACTIVITY CYCLE

For all individuals, regardless of location, health status, and background, the day consists of a 24-hour period. During this period, we transition between periods of sleep and periods of wakefulness. Within the wakefulness period, individuals engage in light PA, MVPA, and SB. All of these activities, light PA, MVPA, SB, and sleep, have an effect on our overall health. Too much or too little of any one activity may induce negative health consequences, and therefore, it is important to monitor and allocate time appropriately throughout the 24-hour cycle to enhance health. In the current research, the effects of each of these lifestyle behaviors are often studied in isolation, neglecting the potential interrelationship between these activities. Evidence is starting to grow that time spent in one activity may modify the health-related effects associated with another activity (Rosenberger et al., 2019). For example, increasing MVPA by substituting SB time may improve health-outcomes to a higher extent than increasing MVPA from sleep time (Grgic et al., 2018).

By measuring activities within the 24-hour day, researchers are better able to create guidelines, identify health risks, discover synergies, and refine interventions to provide the most benefit to participants. Rosenberger et al. (2019) created a visual to understand the interplay

between the measurement of 24-hour activity and the possible research benefits associated with these measurements (Figure 2.4) (Rosenberger et al., 2019).

Figure 2.4

In a review of 24-hour hour activity studies in various populations, Grgic et al. (2018) determined that measuring activity within the context of the 24-hour day rather than in isolation was associated with numerous health outcomes including general health, mental health, adiposity, fitness, cardiometabolic biomarkers, and mortality (Grgic et al., 2018).

This is an important concept to apply to cancer survivors as treatment can negatively affect activity levels, and in turn, physiological and psychosocial outcomes.(Garcia & Thomson, 2014) By using accelerometry across the cancer care continuum (pre-treatment, during treatment, post-treatment), we can better understand how cancer care affects activity levels and develop novel interventions and programs to fit the specific needs of cancer survivors.

Accelerometers use bodily movements to measure time spent in different behaviors throughout a 24-hour period including light PA, MVPA, SB, and sleep (pending device and wear time protocols). It is well-established that increasing time in MVPA will positively affect cancer-related outcomes both during and after cancer treatment; however, time spent in MVPA makes up only a small fraction of total time (K. L. Campbell et al., 2019; Garcia & Thomson, 2014). This leads to the question, how does the remainder of time, outside of MVPA, affect health outcomes in cancer survivors? For those who are unable and/or unwilling to participant in MVPA, how can other daily activities be modified to improve health outcomes? With the development and refinement of measurement techniques of accelerometers, researchers are able to measure activity continuously across a 24-hour day over multiple days, capturing not only time spent in MVPA, but also time spent in LPA, SB, and sleep. With the ability to measure across multiple days (weekdays and weekends), researchers are able to observe and analyze day-to-day variation in activity levels. With this additional information, researchers now have the capacity to observe how an individual's current lifestyle/habitual activity patterns, across a 24-hour day and over and extended period of time, may relate to cancer-related outcomes as well as how a change in that lifestyle (addition of an exercise program, changes in sleep) may positively or negatively impact his or her health. This information will aid in the development of guidelines for optimal activity patterns across the 24-hour day to improve health (Rosenberger et al., 2019). Accelerometry provides knowledge not only on the amount of activity accumulated throughout a day, but also how that activity is accumulated during the day, and for some devices, where that activity is accumulated (GPS monitoring). Recent evidence suggests that how activity is accumulated, specifically SB, may affect cancer-related outcomes.(George et al., 2014; Hartman et al., 2017) As cancer survivors are typically very inactive, targeting reductions in SB may be a promising starting point to improving cancer-related outcomes (Sweegers et al., 2019; Thraen-Borowski, Gennuso, & Cadmus-Bertram, 2017; Troeschel, Leach, Shuval, Stein, & Patel, 2018). With the addition of GPS, researchers can begin to determine where individuals

accumulate their activity behaviors. With this information, interventions can be designed to change behavior, targeting the correct environment for change. For cancer survivors, this could be understanding, across the cancer care continuum, how activity levels shift. For example, if accelerometry supports that on-treatment cancer survivors are accumulating more SB due to increased office visits and wait times (oncology, scans, laboratory, etc…), this could provide support for testing the effects of active waiting rooms in oncology clinics on cancer-related outcomes (increase access, reduce SB by increasing PA, PA improves cancer-related outcomes).

Wear Time Protocols

The current evidence suggests at least a 7-day wear protocol (Edwardson et al., 2017). This duration of monitoring allows for measurement of intra-class correlations > 80% and provides insight into PA behaviors both during the week and on weekends, as these can often differ.(Matthews, Hagstromer, Pober, & Bowles, 2012) However, additional research is needed to determine if this duration of monitoring is able to sufficiently capture inter-individual variation.(Matthews et al., 2012)

Wear protocols have varied between studies with the utilization of 24-hour, 10-hour, or general waking hours recommended. A 10-hour wear protocol is typically used in studies aimed at understanding working day PA and SB behaviors; therefore, this would not be a recommended wear-time protocol considering the outcome of this study.(Matthews et al., 2012) The behaviors this study seeks to understand are those completed during the waking day; therefore, a waking hours protocol could be sufficient.

If interested in any sleep parameters as a secondary outcome or interested in the effects of sleep on changes in physical fitness, the 24-hour wear protocol would be necessary, pending choice of activity monitor and its ability to measure sleep. Additionally, the 24-hour wear

protocol reduces the likelihood of participants forgetting to put on the device each morning and removing it each night. Also, if participants are instructed not to remove the device, the likelihood of misplacing devices is also reduced.(C. Tudor-Locke et al., 2015) A 24-hour wear protocol will require additional instructions, depending on the device, regarding water-based activities (i.e. showering, swimming).

Limitations do exist to analyzing health outcomes using 24-hour activity patterns. It is important to remember that other behaviors take place during the 24-hour period that may affect health outcomes and are not measurable in the same way as light PA, MVPA, SB, and sleep. Examples of these behaviors are smoking, dietary intake, and medication usage (Rosenberger et al., 2019). When analyzing the effects of 24-hour activity patterns on specified health outcomes, it is imperative to include these behaviors as confounders to better draw reasonable conclusions considering the known effects of these other lifestyle behaviors on cancer outcomes including QOL and body composition.

ISOTEMPORAL SUBSTITUTION

Over the course of a 24-hour day, individuals participate in many activities including light PA, MVPA, SB, and sleep. In the past, the effects of these activities on health outcomes have been studied in isolation; however, it is now thought that these activities need to be studied together. Simply put, if you increase time in one activity, you must decrease time in another since the 24-hour day remains constant. Health researchers have begun to explore the effects of time substitution on health outcomes in an attempt to understand the effects of time reallocation between activities. In order to analyze the effects of a substitution of time between activities, the Isotemporal substitution analytical method was developed by Mekary et al. in 2009 (Mekary, Willett, Hu, & Ding, 2009).

Isotemporal substitution models include three linear regression models: a single effects model, a partition model, and the final Isotemporal substitution model. The single effects model allows for interpretation of the effect of each activity with the outcome of interest, while the partition model makes adjustments for inclusion of all activities. Finally, the Isotemporal substitution model represents the outcome when the same unit of time in one activity is substituted with another by including total time and all measured activities minus the activity of interest. From this, the regression coefficient can be interpreted as the mean effect on the outcome when substitution time from the omitted activity to each of the included activities, holding total activity constant (Boyle et al., 2017; Mekary et al., 2009; Vallance et al., 2017). For interpretation of these results, it is critical to acknowledge that the predicted change in outcome should be interpreted as a population level change rather than an individual level change. Causal associations are not to be concluded from these data as these are cross-sectional associations (Boyle et al., 2017; Stovitz & Shrier, 2019).

This method has been utilized in multiple populations to analyze the effects of time reallocation on health including metabolic health, mortality risk, cardiovascular disease risk, and general health (Buman et al., 2014; Grgic et al., 2018; Hamer, Stamatakis, & Steptoe, 2014; Stamatakis et al., 2015). Among cancer survivors, three previous studies have examined the effects of reallocating time from various activities on health-related outcomes in cancer survivors. In a study of non-Hodgkin lymphoma survivors, reallocating 30 minutes from sleep, light PA, or sedentary time to MVPA was associated with improved fatigue (Vallance et al., 2017). Similarly, reallocating 30 minutes to MVPA was associated with lower waist circumference and BMI in a sample of breast cancer survivors (Boyle et al., 2017). In a study of colorectal cancer survivors, substituting sedentary time with standing or PA was associated with improved QOL (van Roekel et al., 2016b).

In the current literature, a major limitation of the Isotemporal substitution model is the lack of objective sleep measurements utilized in analyses. In the majority of studies, objective measures of PA and SB were utilized, but objective measures of sleep were not available for inclusion in the model, limiting the ability to include sleep time as an objective time reallocation component (Grgic et al., 2018).

An opposing model to the Isotemporal substitution model does exist known as the compositional data analysis model created by Chastin et al in 2015 (Chastin et al., 2015). This model utilizes relative values (i.e. percentages) rather than absolute values, making it an undesirable modality of measuring PA as PA is often measured in minutes or bouts of minutes per day (i.e., 30 minutes of aerobic exercise). Relative time allocation with regard to PA would be incredibly variable between individuals, making it difficult to interpret and establish and compare activity guidelines as the current activity guidelines are reported in absolute values. The compositional data analysis method would be an advantageous method if measuring nutritional components as this is how nutritional guidelines are often reported (Mekary & Ding, 2019).

In better understanding activity across the 24-hour day, the Isotemporal substitution model provides the necessary statistical measures to reallocate time to observe changes in specified health outcomes.

GAPS IN THE LITERATURE

The literature regarding cancer-treatment related side effects, PA, SB, and sleep, has grown substantially over the last decade. However, many questions have still been left unanswered. Regarding the utility of modifying lifestyle behaviors to combat common treatment-related side effects, little has been done to understand how activity across the 24-hour day improves or diminishes these symptoms. The majority of studies analyzing the effects of light

PA, MVPA, SB, and sleep on QOL and body composition look at behaviors in isolation, rather than as a collective lifestyle. With each activity only consuming a small-medium portion of the day, it is necessary to look at these behaviors together, considering how alterations in time spent in one activity, change the amount of time spent in another activity. Of the studies that have examined activities within the 24-hour cycle, the majority have focused on replacing SB with either LPA or MVPA, neglecting the effects of substituting sleep with these behaviors (Grgic et al., 2018). In the studies that do include sleep, sleep was measured subjectively using a questionnaire, a method with limited reliability for sleep duration (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008). For cancer survivors, the time reallocation literature is limited, and the studies that do evaluate time reallocation are limited to breast, non-Hodgkin's lymphoma, and colorectal cancer (Boyle et al., 2017; Vallance et al., 2017; van Roekel et al., 2016b).

In order to include reliable measures of all waking behaviors and sleep, we must objectively measure all activities within the 24-hour day including SB, LPA, MVPA, and sleep. Currently, two validated, research-grade devices exist to measure these activities in free-living environments. The first is designed to measure active or waking behaviors, including light PA, MVPA, and SB (activPAL). The second is designed to measure sleep, including duration and quality (Actiwatch-2). However, these devices are expensive individually and both are currently recommended when analyzing the 24-hour day, despite the functionality of both of these devices to measure activities across the 24-hour day. The advancement of the literature examining 24-hour activity, there is a need for studies that evaluate the activPAL ™ accelerometer to measure sleep. This will reduce researcher burden of analyzing information from two separate devices as well as participant burden of wearing multiple devices. This comparison study will open the door to exploring the effects of each of these activities on the outcomes of interest, examining how these activities put together affect outcomes, rather than in isolation [Figure 2.5].

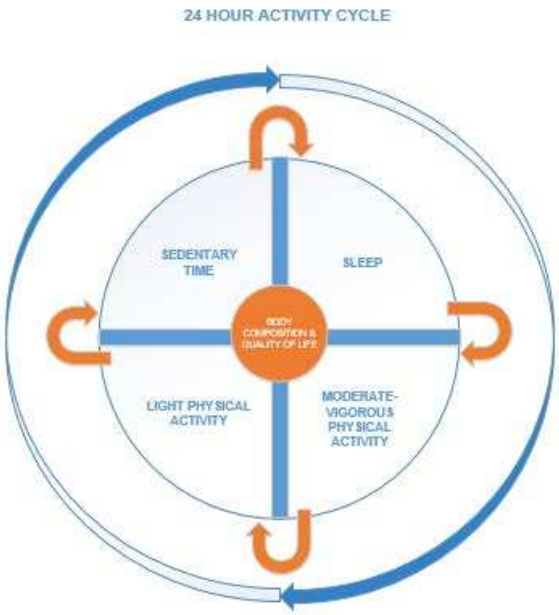


Figure 2.5

This can be accomplished using a novel statistical method known as the Isotemporal substitution model, established by Mekary et al. in 2009 (Mekary et al., 2009).

SUMMARY

This literature review outlines the importance of QOL and body composition in cancer survivorship and the role PA, SB, and sleep have in managing QOL and body composition. Behavior in the context of the 24-hour day has been established as an important research area for understanding health implications of waking and sleep behaviors. Currently, few studies have applied the 24-hour activity cycle to cancer survivorship. The 24-hour activity cycle, evaluated using time reallocation, may induce positive or negative effects on the health of cancer survivors and therefore must be considered when studying the effects of PA, SB, and sleep on cancer-related outcomes. In order to understand time reallocation, the Isotemporal substitution model was introduced and established as an appropriate mechanism to analyze the effect of 24-hour behavioral patterns on cancer-related outcomes, specifically QOL and body composition.

MANUSCRIPT I: COMPARISON OF THE ACTIVPAL AND ACTIWATCH ACCELEROMETERS TO MEASURE TIME IN BED IN FREE-LIVING ADULTS.

Introduction

Cardiovascular disease (CVD), obesity, and diabetes contribute to an estimated $3.5 trillion in annual health care costs (Prevention, 2019). Physical activity (PA) and reduced sedentary time are important for prevention of these chronic diseases, and improving mortality outcomes among those living with CVD, obesity and diabetes (Donnelly et al., 2009; Fogelholm, 2010; Thorp, Owen, Neuhaus, & Dunstan, 2011; USDHHS, 2018). Additional evidence also exists for the benefits of adequate sleep duration and quality for reducing risk for obesity, diabetes, hypertension, CVD, and weight gain (Cooper, Neufeld, Dolezal, & Martin, 2018; Grandner et al., 2016; Lao et al., 2018; Nagai, Hoshide, & Kario, 2010), which has prompted many PA researchers to expand their investigation of waking behaviors (i.e., light PA, moderate-vigorous PA (MVPA), standing, sitting, etc.) to include estimates of time in bed (TIB) (Rosenberger et al., 2019; Ross et al., 2020). However, a challenge in examining the 24-hour activity cycle is the availability of a single accelerometer that is valid and reliable for measuring *both* waking behaviors and TIB.

One of the current gold-standard devices to measure free-living waking activity is the activPAL™, which has been validated against direct observation for light PA, MVPA, standing, and sitting (Lyden et al., 2017; Lyden, Kozey Keadle, Staudenmayer, & Freedson, 2012). However, whether the activPAL accelerometer provides an accurate estimate of TIB in not clear. In contrast, the Actiwatch is currently utilized to estimate TIB to estimate sleep parameters in a free-living environment using light, actigraphy sensors, and an event marker button (P. H. Lee & Suen, 2017). However, the Actiwatch does not have established reliability/validity to measure PA, sitting, or standing (Lambiase, Gabriel, Chang, Kuller, &

Matthews, 2014). Thus, researchers interested in activity patterns and TIB across the 24-hour cycle are required to use two accelerometers, which increases costs, as well as participant and study burden. Therefore, an accelerometer with the ability to accurately measure both PA and TIB is highly desirable.

Recently, a new proprietary algorithm was released by PAL Technologies Ltd (Ltd, 2018), which allows the activPAL to provide a measure of TIB by estimating the time participants went to bed (TIB_{START}) and time participants got out of bed (TIB_{END}) (Ltd., 2019). However, this algorithm has not yet been compared to the frequently utilized Actiwatch. Therefore, this study sought to compare estimates of TIB between activPAL and Actiwatch accelerometers.

Methods

Adults aged 18-50 years with a BMI of 27-45 kg/m^2 and weight stable (≤ 5% change over the previous 6 months) were recruited for a behavioral weight loss trial comparing the effects of time restricted eating plus caloric restriction to caloric restriction alone [NCT03571048]. Participants were excluded for history of CVD, diabetes, uncontrolled hypertension, untreated thyroid, renal, hepatic diseases, dyslipidemia, and any other medical condition affecting weight or lipid metabolism, night shift work over the previous 6 months, night eating syndrome, or binge eating behaviors. Women who were pregnant, breastfeeding or planning to become pregnant were also excluded. The Colorado Multiple Institutional Review Board approved the study protocol and all participants provided written informed consent prior to participation. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Participants completed baseline assessments including height (without shoes to the nearest cm using a stadiometer), fasted morning weight (in light clothing, measured to the nearest 0.1 kg using a digital scale), assessment of body composition via dual x-ray

absorptiometry (Hologic Discovery W, Bedford, MA), and study questionnaires, including demographic information. The activPAL and Actiwatch accelerometers were fitted at the conclusion of the baseline visit and worn for 7 continuous days. Data presented here are from the baseline assessment period prior to any intervention. Both accelerometers are water resistant, allowing for the accelerometers to be worn during showering. Participants were instructed to remove the accelerometers for activities that involved completely submerging the accelerometers in water. Participants were provided instructions on proper wear technique as well as written instructions for proper removal and re-attachment of accelerometers. TIB was the difference, in minutes, from TIB_{START} to TIB_{END}, as detected by the specific algorithm for each individual accelerometer described below.

activPAL accelerometer

The activPAL accelerometer is a thigh-worn, tri-axial accelerometer validated against direct observation to measure free-living LPA, MVPA, and sedentary behavior (Edwardson et al., 2017; Lyden et al., 2017). The activPAL was wrapped in a nitrile sleeve and Tegaderm to waterproof the accelerometer for continuous wear. The activPAL was attached at the midline of the non-dominant thigh, one-third of the way between the hip and the knee, with a Tegaderm patch. The activPAL was worn for 7-days, 24-hours per day, and collected data at 30-second epochs. Wear-time was considered valid if worn for at least 4-days, 24-hours per day.

To measure TIB, TIB_{START}, and TIB_{END}, raw activPAL.datx files were processed using the CREA algorithm in the PALBatch software (PAL, 2010), removing days with 25-75% alignment and/or Dominant Sitting Dice Face >1, which measures the dominant orientation of the accelerometer relative to an upright position. Files were also auto-corrected for inverted wear. Briefly, the processing steps used by the CREA algorithm are as follows: identification of non-upright events and categorization into either primary lying time (i.e., sleep) or a secondary lying time (i.e., sedentary). The primary lying container is the longest time duration without a

change to an upright position and typically contains rolling behaviors. If rolling behaviors are present in other non-upright portions of the day, this behavior is classified as a secondary rolling container. The minimum amount of time needed for the activPAL to detect either primary or secondary lying is 60 minutes. If an upright position or sitting bout of greater than 15 minutes exists, the container period is ended. However, if a subsequent rolling event occurs, the upright time counter will be reset. Additionally, if rolling is present in the container, the first and last non-upright events in the container must include rolling. Simply, when the primary lying period contains rolling of the thigh, any additional sections of non-upright with rolling are marked as secondary lying (i.e., daytime napping or couch lying). In this instance, secondary lying is counted in sitting totals, not sleep (Ltd, 2018). TIB_{START} is determined when non-upright events last > 1 hour. To allow for common sleep interruptions (i.e., bathroom breaks, wake after sleep onset), events are expanded to adjacent non-upright events >1 hour. The time period with the longest non-upright event is marked as “Primary Lying Time”, beginning the estimates of TIB_{START} and TIB_{END} (Ltd., 2019).

Actiwatch accelerometer

The Actiwatch Spectrum Plus accelerometer was worn on the non-dominant wrist. The Actiwatch was programmed to collect activity and light data at 30-second epochs and was worn for 7-days, 24 hours per day. Wear-time was considered valid if worn for at least 4-days, 24-hours per day.

To measure TIB, TIB_{START}, and TIB_{END}, raw AW5 files were processed using the auto scoring settings on the Actiwatch software (Actiware v6.1.1). The processing steps used by the Actiwatch algorithm are as follows: detection of accelerations and light to measure sleep/wake. The sensor is oriented to detect vertical accelerations, has a bandwidth of 0.5-7Hz, and allows for integration of raw counts over an epoch (K. Y. Chen & Bassett, 2005).

Statistical Analyses

Descriptive characteristics such as age, sex, and body fat percentage are presented as mean ± standard deviation or n (%) for categorical variables. Extreme values were present in the data (e.g. minimum: 69.0 minutes of TIB, maximum: 1310.4 minutes of TIB), therefore, the data were trimmed to include observations within 3 standard deviations of the mean (minimum: 151.8 minutes of TIB, maximum: 844.8 minutes of TIB). Additionally, day 1 was removed from all analyses since the accelerometers did not start recording until midnight on the day of placement. Estimates from the activPAL and Actiwatch were compared using two statistical procedures. First, to account for lack of independence of measures within subjects a repeated measures mixed effects model was used to estimate the difference between activPAL and Actiwatch for the response variable TIB. Fixed effects were: accelerometer (activPAL or Actiwatch), day (categorical from 2 to 7), and accelerometer x day interaction. A random effect for participant was included to account for repeated measurements (up to 7 days) over time. Second, mean difference and level of agreement were calculated using repeated measures Bland-Altman plots (D.G. Altman, 1983; Myles & Cui, 2007). For all comparisons, the Actiwatch estimates served as the referent scores given extensive validation against polysomnography. Analyses were conducted using R (v.R-4.0.3). A significance level of 0.05 was used for all tests of hypotheses.

Results

Eighty-five participants completed waking behavior and sleep monitoring using the activPAL and Actiwatch accelerometers for a total of 596 days of data collection. Participants were 39.7 ± 7.6 years of age, white (81%), and mostly female (85.88%; Table 3.1).

Table 3.1: Demographics

	Mean ± SD or % N=85
Age (years)	39.7 ± 7.7

Body Mass Index (BMI) kg/m^2.	34.1 ± 5.7
Body Fat (%)	43.0 ± 6.0
Actiwatch TIB (minutes)	536.7 ± 143.3
activPAL TIB (minutes)	445.1 ± 93.0

There was a significant difference in estimated TIB between the activPAL and Actiwatch accelerometers (p<0.001). There was not a significant interaction between accelerometers and day of wear. The difference in TIB between accelerometers ranged from -72.9 ± 15.7 minutes (day 7) to -98.6 ± 14.5 minutes (day 3). In general, the Actiwatch average TIB was longer in duration as compared to activPAL, regardless of day (Table 3.2; Figure 3.1).

Table 3.2: Difference in TIB between the activPAL and Actiwatch

Day	TIB difference (minutes)	p-value
2	-97.7 ± 14.6	<0.001
3	-98.6 ± 14.5	<0.001
4	-80.9 ± 14.8	<0.001
5	-90.5 ± 14.9	<0.001
6	-93.7 ± 14.9	<0.001
7	-72.9 ± 15.7	<0.001

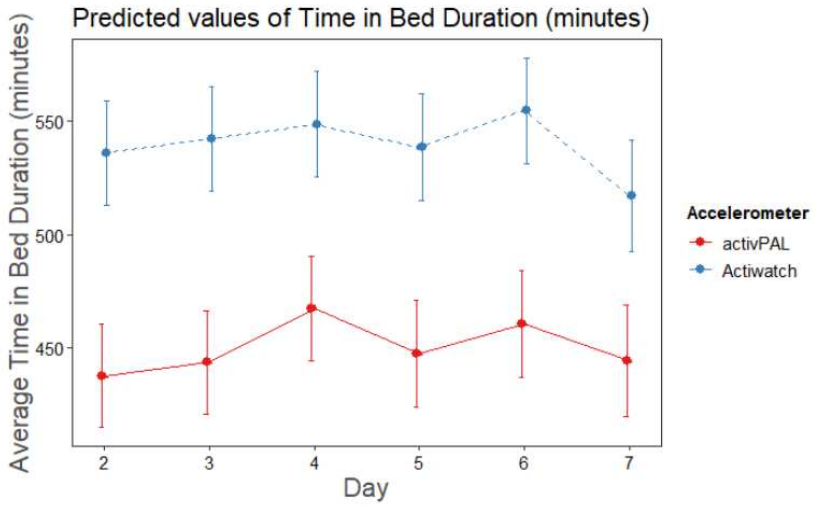


Figure 3.1: Predicted values of TIB for activPAL and Actiwatch

The Bland-Altman plot [Figure 3.2] also indicated differences between the activPAL and Actiwatch TIB estimates with an average difference of -89.8 minutes (95% CI [-81.1, -98.6]), an Lower Limit of Agreement of -281.3 minutes (95% CI [-266.3, -296.3]) and Upper Limit of Agreement of 101.6 minutes (95% CI [116.7, 86.6]) across all days.

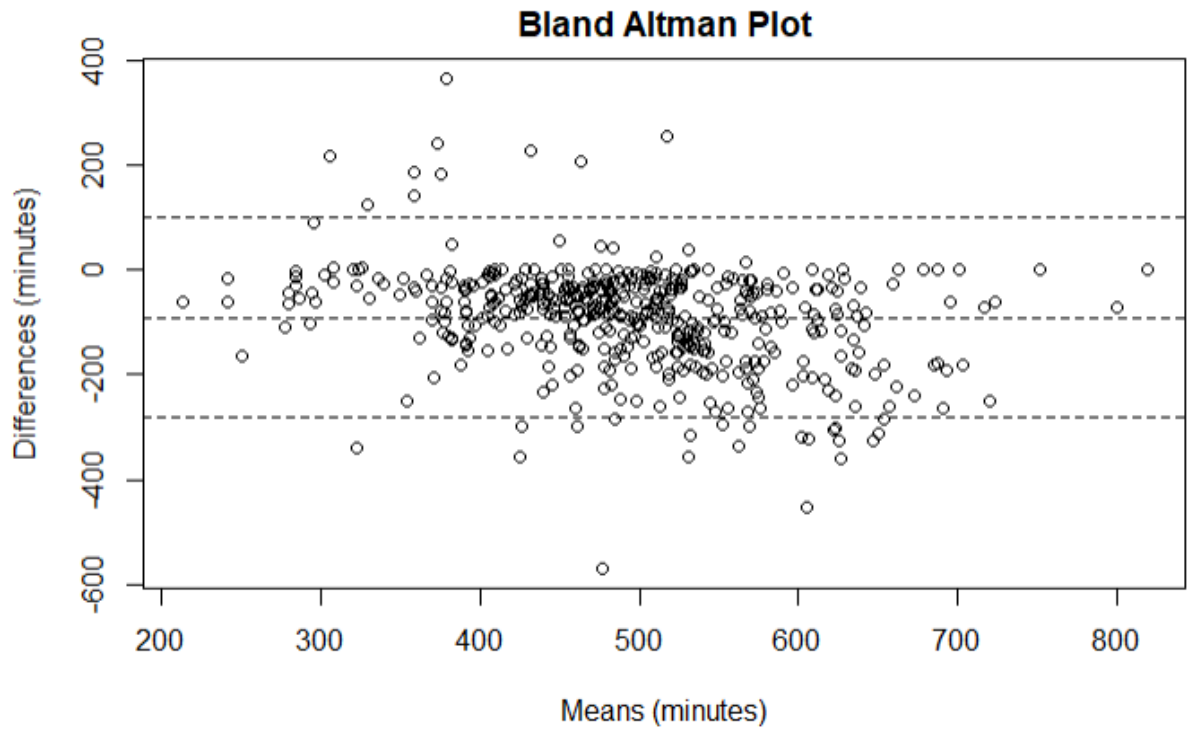


Figure 3.2: Bland-Altman Plot of TIB

Each data point represents the difference in TIB between the Actiwatch and activPAL in minutes. The means (minutes) represents the mean TIB duration for each accelerometer.

Discussion

This study sought to determine if estimates for TIB, using TIB_{START} and TIB_{END}, are comparable between the activPAL and Actiwatch accelerometers. Our findings suggest that the

activPAL and Actiwatch do not derive similar estimates of TIB with the Actiwatch estimating TIB significantly longer than the activPAL.

For both accelerometers, the algorithms used to derive estimates of TIB are proprietary, making it difficult to know the exact sources of disagreement between the two accelerometers. However, there are two fundamental differences between the activPAL and Actiwatch methods that likely contribute to the discrepancy observed in the current study. First, the activPAL uses actigraphy alone to estimate TIB whereas the Actiwatch in the current study uses actigraphy as well as measures of light exposure. Actigraphy-based estimates of TIB rely on lack of movement and body position (e.g., rolling) to infer TIB. This can make distinguishing periods of couch lying (e.g., watching TV) from TIB difficult. Although we are not aware of studies that have specifically investigated the benefit of adding information on light exposure to actigraphy-based estimates of TIB, this additional contextual information could help improve estimates of TIB under challenging conditions like couch lying. Second, the activPAL is worn on the thigh while the Actiwatch is worn on the wrist, thus the acceleration signals collected at the thigh will be different than those collected at the wrist, depending on the behavior. Further, thigh placement of the activPAL can provide important information about rolling, which is not possible with wrist-worn accelerometers.

Moreover, individuals with overweight and obesity, like the participants in this study, are at increased risk for sleep disorders and often present with decreased TIB, and experience poor sleep quality (Cooper et al., 2018). Accurately estimating TIB for participants with disrupted sleep may be particularly challenging for methods that rely on actigraphy alone, such as the activPAL. Of note, this study utilized the automatic algorithm for Actiwatch scoring, though decision trees for manual input or correction of TIB_{START} and TIB_{END} exist. The various decision trees available utilize written sleep logs, event markers, light exposure, and activity marker to determine TIB_{START} and TIB_{END}, all of which improve free-living estimates of TIB. Therefore,

these decision trees should be evaluated to determine if manual input of TIB_{START} and TIB_{END} are necessary to see equivalent measures of TIB from the activPAL (Fekedulegn et al., 2020).

Strengths of this study include the large sample size and multiple days of measurement for each participant. Limitations include lack of gold-standard measurement, such as polysomnography (PSG) or direct observation, to determine the validity and reliability of the activPAL for TIB estimates in a population with overweight/obesity. Additionally, the majority of participants were female, limiting generalizability to males due to known sex differences in sleep health (Mallampalli & Carter, 2014).

Future research should evaluate other physical activity accelerometers for estimations of TIB. To improve the activPAL specifically, utilization of self-reported TIB_{START} and TIB_{END} in conjunction with activPAL estimates have been shown to increase accuracy of 24-hour activity estimates; therefore, additional research should be conducted to determine an appropriate decision tree process when utilizing activPAL to measure TIB (Courtney et al., 2020). This additional research could also allow for development of adjustment algorithms, similar to those typically utilized with the Actiwatch for varying populations including healthy and sleep disturbed populations.

In conclusion, the activPAL and Actiwatch provide different estimates of TIB. Therefore, the Actiwatch should continue to be utilized when objectively measured TIB estimates are needed.

MANUSCRIPT II: REALLOCATING TIME TO PHYSICAL ACTIVITY AND SLEEP: ASSOCIATIONS WITH QUALITY OF LIFE IN CANCER SURVIVORS

Introduction

It is estimated that nearly 1.9 million new cases of cancer will be diagnosed, resulting in an estimated 608,570 cancer-related deaths in 2021 (ACS, 2021). However, with advances in earlier detection and cancer treatments, the 5-year survival rate for most cancer types has increased from 34% in the mid-1970s to 67% in 2016 (ACS, 2021; Siegel, Miller, & Jemal, 2018). With an increasing number of cancer survivors, it is imperative to direct resources and care to the post-treatment cancer survivorship phase.

Cancer survivors are often plagued with lingering side effects from systemic therapy, radiation therapy, and surgery. Side effects include depression, anxiety, fatigue, and diminished physical function, which can result in poor QOL (Eyl et al., 2018). QOL includes physical, functional, emotional, and social well-being and has become a pertinent clinical measure in oncology care due to its known association with morbidity and mortality (Jacobsen & Jim, 2011; Montazeri, 2009).

One of the most salient interventions to improve QOL among cancer survivors are those which target lifestyle behaviors, including physical activity (PA) and sleep. Findings from numerous systematic reviews and meta-analyses support the important role PA plays in improving QOL in cancer survivors. These reviews conclude that QOL improved in cancer survivors who completed PA interventions, as compared to usual care controls, and baseline measurements (Eyl et al., 2018; Ferrer et al., 2011; Gerritsen & Vincent, 2016). In addition to PA, insufficient sleep, a common consequence of cancer treatment, is known to negatively impact QOL in cancer survivors (Fortner et al., 2002; Gooneratne et al., 2007).

Current literature examining the effects of PA, sedentary time, and sleep on health outcomes in cancer survivors largely examines these behaviors in isolation (e.g., sleep on QOL, sedentary time on QOL, light PA on QOL, or MVPA on QOL), disregarding the supposition that increasing time in one activity requires decreasing time in another (Rosenberger et al., 2019). For this reason, many scholars have suggested that sleep, PA and sedentary time should be studied in the context the 24-hour day (Rosenberger et al., 2019). Despite growing interest and knowledge regarding 24-hour activity patterns, only two studies have examined how reallocating time spent in lifestyle behavior improves QOL in cancer survivors (Vallance et al., 2017; van Roekel et al., 2016b). These studies found clinically meaningful improvements in QOL when 30 minutes of MVPA was reallocated from sleep, sedentary time, or light PA (Vallance et al., 2017). However, limitations exist with both these studies. For example, Vallance et al. (2017) utilized a subjective measure of sleep (i.e., self-reported sleep duration), a measure that is known to have only a moderate correlation to objectively measured sleep and systematic bias (Lauderdale et al., 2008; Vallance et al., 2017). In the van Roekel study (2016b), no measures of sleep were utilized, limiting interpretation of time reallocation in the context of the full 24-hour day (van Roekel et al., 2016a).

Therefore, the aims of this study were to evaluate the effects of reallocating sedentary time, light PA, sleep and moderate-vigorous PA (MVPA) on QOL using objective measures of PA and sleep.

Methods

A cross-sectional analysis consisting of a single visit conducted either in-person or virtually (due to COVID-19 safety protocols). The in-person study visit consisted of electronic consent and demographic and QOL questionnaire completion via REDCap, DEXA scan, submaximal exercise test, sit to stand and arm curl assessments. At the conclusion of the visit, participants were fitted with the activPAL and Actiwatch-2 accelerometers at the laboratory.

Virtual study visits consisted of a phone call to complete electronic consent followed by demographic and QOL questionnaire completion, both done through REDCap. The accelerometers were delivered and picked up by study staff to the participant's home or the devices were shipped with a return envelope and label for the participant to return after completing the 7-day wear protocol. Participants were provided written instructions for placing the devices, and if necessary, a virtual visit was conducted to properly place the devices.

Participants

Participants were recruited through local and regional cancer centers, flyers and presentations at community locations and events (e.g., senior center, American Cancer Society Relay for Life), email and website posting via the University faculty and staff listserv, and the Colorado State University Center for Healthy Aging from 01/20 to 06/21. Participants were eligible if they were >18 years at time of diagnosis, and within 60 months of treatment completion (i.e., surgery, chemotherapy, immunotherapy, and/or radiation therapy). Informed consent was obtained from all participants and all procedures performed in this study were in accordance with the ethical standards of Colorado State University's institutional review board (IRB#19-8914H).

Sleep

Sleep duration was measured using an Actiwatch-2, a validated device that utilizes light exposure and accelerations to determine sleep-wake intervals (Lambiase et al., 2014; P. H. Lee & Suen, 2017). Sleep duration was measured as minutes spent in bed. Participants wore the device for 7 days, 24 hours per day. To be included in analyses, participants must have had a minimum of 4 valid days, including 1 weekend day.

Physical Activity and Sedentary Time

PA was measured using the activPAL accelerometer (PAL Technologies, Glasgow, Scotland). The activPAL has been validated to quantify free-living sedentary and ambulatory

activities and has been previously used in cancer survivors (George et al., 2014). The activPAL software quantifies light PA, MVPA, and sitting, and lying time based on static and dynamic accelerations (Lyden et al., 2017; PAL, 2010). Participants wore the activPAL for 7 consecutive days, 24 hours per day. To be included in analyses, participants had to have had a minimum of 4 valid days, including 1 weekend day. Light PA was measured by subtracting “non-wear time” and “primary lying time” from 24 hours to create a “waking wear time” variable. MVPA was measured using “stepping time, in minutes, with a cadence ≥ 75 and duration > 1 minute” and “cycling time”. Sedentary time was measured by the time in minutes that participants were sitting or lying down. Light PA was measured by subtracting “non-wear time” and “primary lying time” from 24 hours to create a “waking wear time” variable. This variable was then used to calculate light PA by subtracting MVPA and sedentary time from waking wear time. All time measurements are in minutes per day.

Quality of Life

QOL was assessed using the Functional Assessment of Cancer Therapy-General (FACT-G). The FACT-G is a validated, self-report measure of QOL (D. F. Cella et al., 1993). This questionnaire consists of 27-items, including subscales to differentiate changes in physical, social, emotional, and functional well-being. The FACT-G scores range from 0-108, with a higher score representing a higher QOL for both total and individual subscales. For the FACT-G, a change of 4 points indicates a clinically meaningful change in QOL (D. Cella, Eton, Lai, Peterman, & Merkel, 2002).

Statistical Analysis

Demographics were summarized using mean ± standard deviation or frequencies. To examine the effects of time reallocation between PA and sleep behaviors on BMI, an Isotemporal substitution model was used. Isotemporal substitution models are done in three parts: single effects, partition effects, and the Isotemporal model. The single effects model will

estimate the association between BMI and each activity individually. The partition model includes BMI as well as all of the activities of interest (sleep, sedentary time, light PA, MVPA). The variance inflation factors for each of the exposure variables in the partition model for BMI were less than 4, suggesting absence of problematic multicollinearity (considered problematic at 5). Isotemporal substitution allows for replacing time in one activity with time in a different activity, analyzed in minutes per day (Mekary et al., 2009). The Isotemporal substitution model represents the outcome when the same unit of time in one activity is substituted with another by including total time and all measured activities minus the activity of interest. From this, the regression coefficient can be interpreted as the mean effect on the outcome when substitution time from the omitted activity to each of the included activities, holding total activity constant (Mekary et al., 2009). In order to understand the substitution units, all variables must be in the same metric; therefore, time spent in each activity were converted to units of 30 minutes (e.g., 30 minutes=1, 60 minutes=2). Covariates included in the models were age, cancer type, and time since diagnosis.

Results

Demographic information and participant characteristics are presented in Table 4.1.

Table 4.1: Demographics

N=73	Mean ± standard deviation or frequency (%)
Age	53 ± 13.0
Sex (% female)	75.7
Race (% white)	93.2
Education (% ≥ undergraduate degree)	74.3
Income (% ≥ $50,000/year)	74.3
Body Mass Index (kg/m^2)	27.0 ± 5.7
QOL-Total	87.0 ± 15.3
QOL-Physical	24.6 ± 3.8
QOL-Functional	20.9 ± 5.6
QOL-Emotional	19.8 ± 3.3
QOL-Social	22.5 ± 5.4
Diagnosis	

Breast	29.7
Colorectal	33.8
Leukemia/Lymphoma	9.7
Other	27.0
Stage	
0	5.4
1	25.7
2	31.1
3	20.3
4	9.5
Do not know	8.1
Time since diagnosis (months)	33.9 ± 26.4
Time since surgery (months) (n=66)	31.2 ± 28.3
Time since chemotherapy (months) (n=54)	24.8 ± 22.8
Time since radiation therapy (months) (n=38)	30.5 ± 17.4
Time since other therapies (months) (n=12)	16.3 ± 13.9

Briefly, participants were 53 ± 13 years, mostly female (75.7%), and the majority were diagnosed with either breast (29.7%) or colorectal cancer (33.8%). The average total QOL score was 87.0 ± 15.3. Table 4.2 outlines average time spent in sleep, sedentary time, light PA, and MVPA.

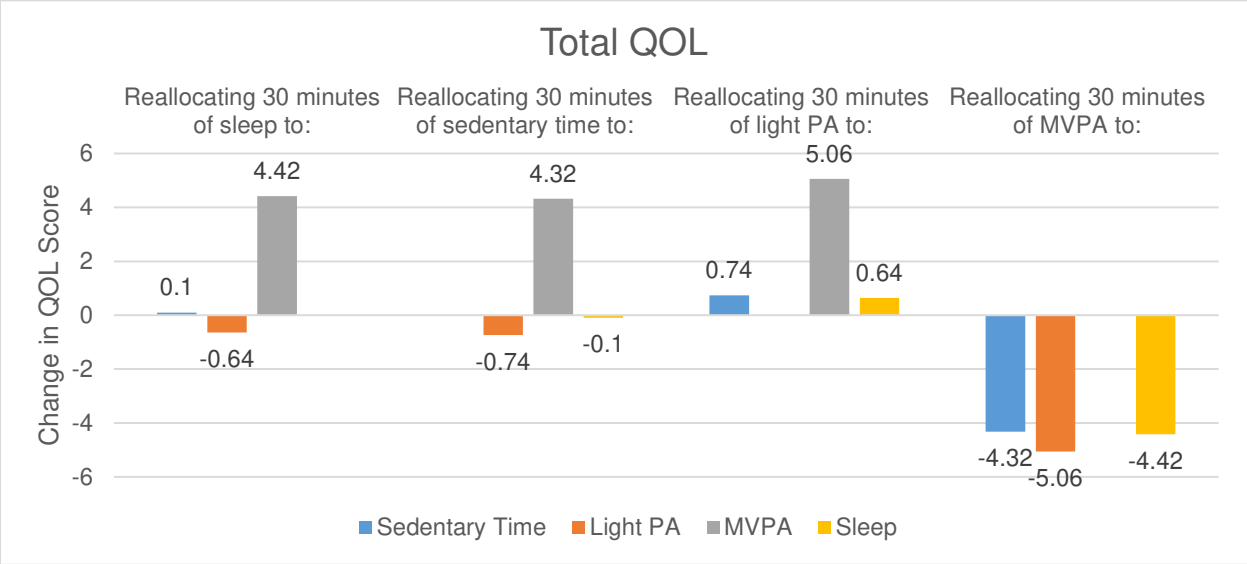
Table 4.2: Physical Activity, Sedentary Time, and Sleep profiles

	Mean ± standard deviation or %
MVPA (minutes/day)	24.0 ± 18.9
Light PA (minutes/day)	291.7 ± 100.4
Sedentary time (minutes/day)	593.1 ± 108.3
Sleep duration (minutes/day)	486.6 ± 57.6
>30 minutes/day of MVPA	80.8%
>7 hours/night of sleep	90.4%

The partition models revealed sedentary time was significantly correlated with light PA (Pearson's r=-0.75) and MVPA (r=-0.48). All other correlations between the different activities were low (.09-.22) and not statistically significant. In the single effects model, there were no significant associations with QOL. When removing sedentary time due to its correlation with light PA and MVPA, no significant associations with QOL were present.

Reallocating 30 minutes from sleep

Reallocating 30 minutes of sleep to light PA resulted in no significant associations with QOL (-0.64, 95% CI [-2.69, 1.42]). Reallocating 30 minutes of sleep to sedentary time resulted in no significant associations with QOL (0.10, 95% CI [-1.93, 2.13]). Reallocating 30 minutes of sleep to MVPA resulted in no significant associations with QOL (0.42, 95% CI [-1.94, 10.79]) (Figure 4.1).

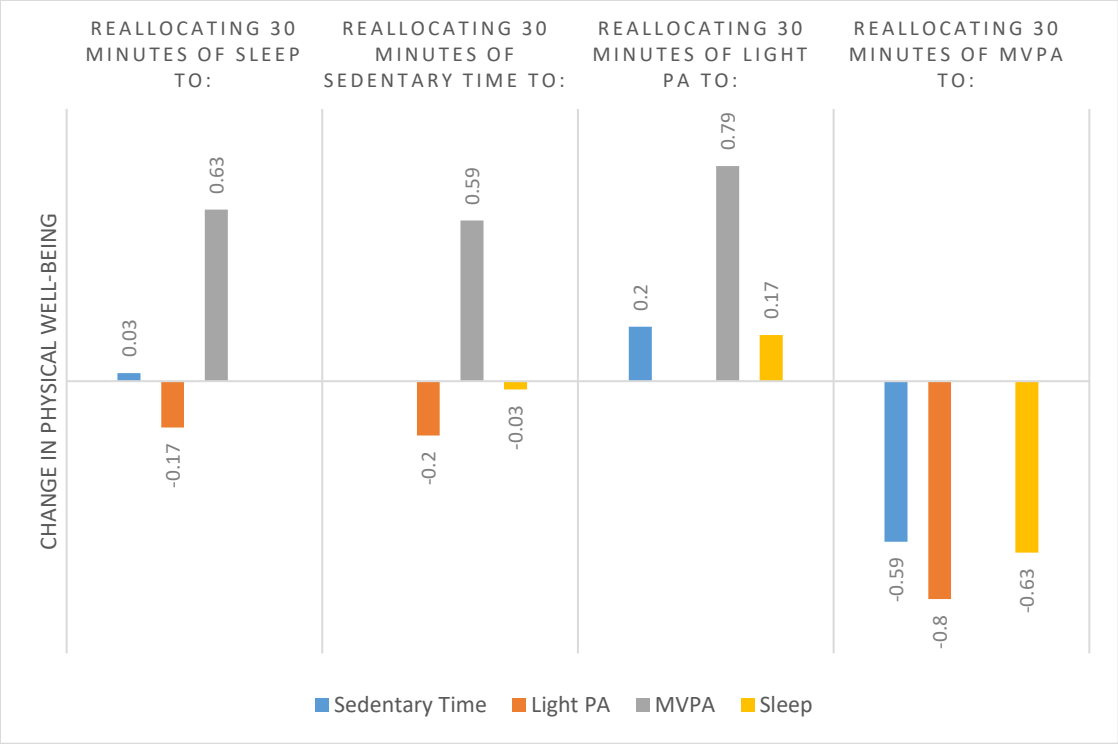


*indicates statistical significance, QOL=Quality of Life, PA=Physical Activity, MVPA=Moderate-Vigorous Physical Activity

Figure 4.1 Time Reallocation for QOL

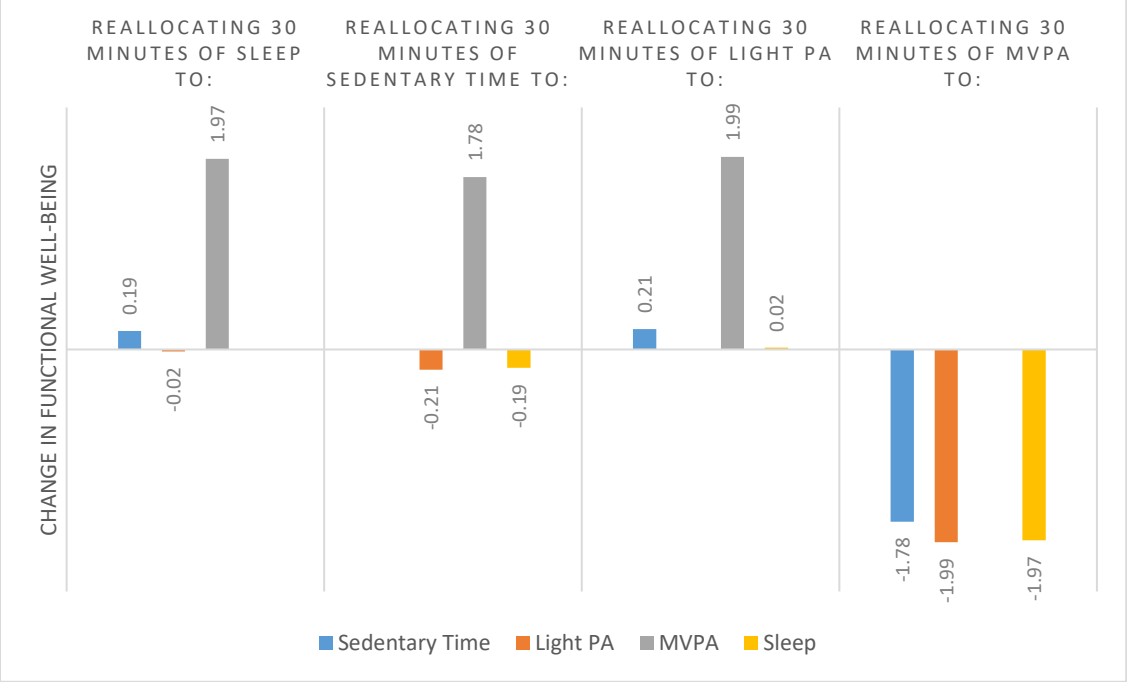
Associations between sleep, sedentary time, light PA, and MVPA on QOL when reallocating 30 minutes of one activity of interest to another activity of interest in a mixed sample of cancer survivors.

Additionally, no significant changes were observed for any of the QOL subscales (Figure 4.2, Figure 4.3, Figure 4.4, Figure 4.5).



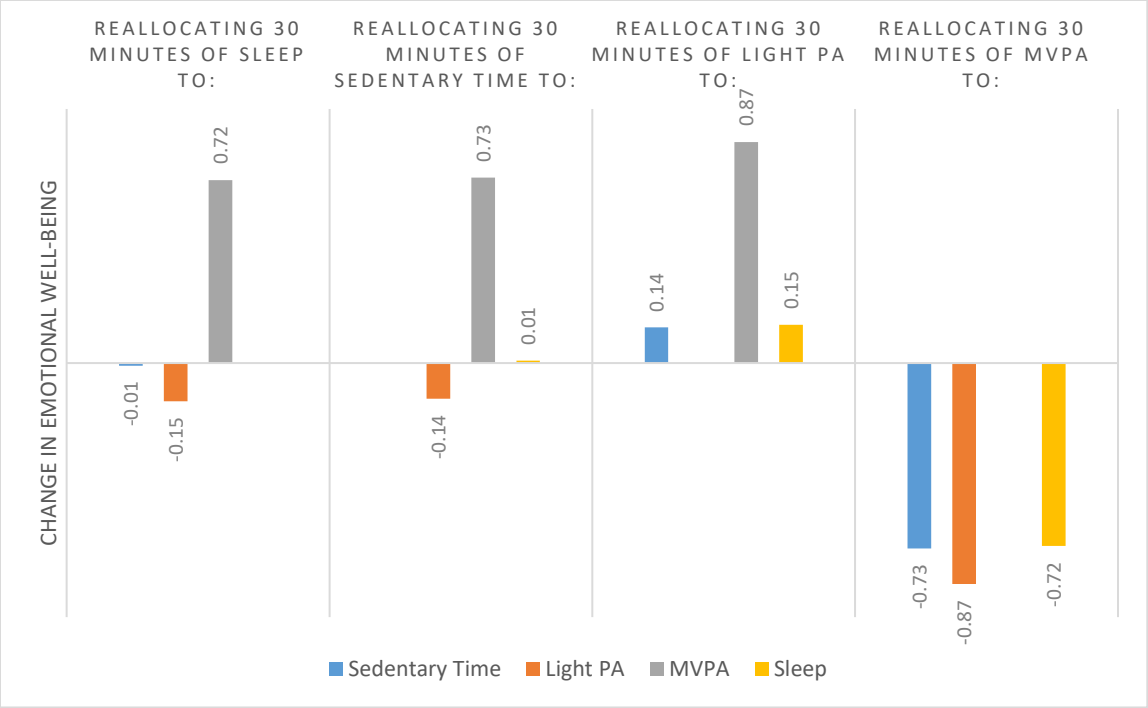
QOL=Quality of Life, PA=Physical Activity, MVPA=Moderate-Vigorous Physical Activity

Figure 4.2 Physical Well-Being



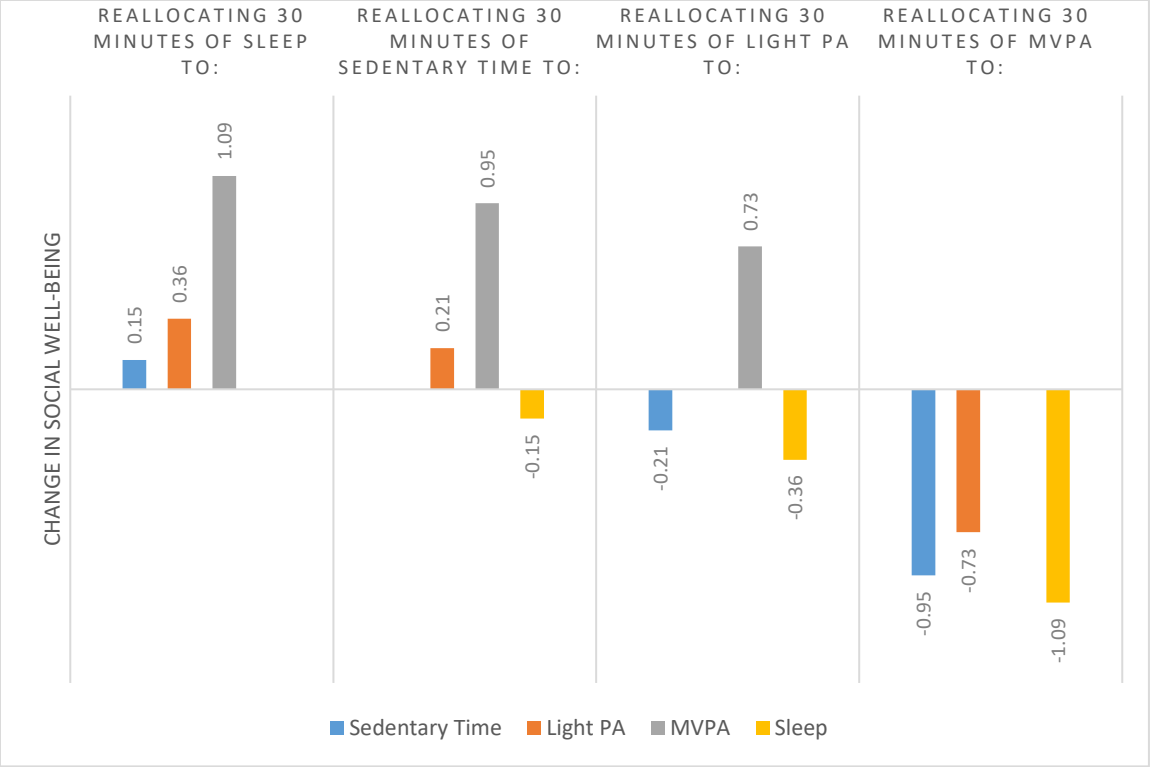
QOL=Quality of Life, PA=Physical Activity, MVPA=Moderate-Vigorous Physical Activity

Figure 4.3 Functional Well-Being



QOL=Quality of Life, PA=Physical Activity, MVPA=Moderate-Vigorous Physical Activity

Figure 4.4 Emotional Well-Being



QOL=Quality of Life, PA=Physical Activity, MVPA=Moderate-Vigorous Physical Activity

Figure 4.5 Social Well-Being

Reallocating 30 minutes from sedentary time

Reallocating 30 minutes of sedentary time to sleep resulted in no significant associations with QOL (-0.10, 95% CI [-2.13, 1.93]). Reallocating 30 minutes of sedentary time to light PA resulted in no significant associations with QOL (-0.74, 95% CI [-1.90, 0.43]). Reallocating 30 minutes of sedentary time to MVPA resulted in no significant associations with QOL (4.32, 95% CI [-1.61, 10.25]) (Figure 4.1). Additionally, no significant changes were observed for any of the QOL subscales (Figure 4.2, Figure 4.3, Figure 4.4, Figure 4.5). However, a clinically meaningful increase was observed for reallocating 30 minutes of sedentary time to MVPA.

Reallocating 30 minutes from light PA

Reallocating 30 minutes of light PA to sleep resulted in no significant associations with QOL (0.64, 95% CI [-1.42, 2.69]). Replacing 30 minutes of light PA to sedentary time resulted in

no significant associations with QOL (0.74, 95% CI [-0.43, 1.90]). Reallocation 30 minutes of light PA to MVPA resulted in no significant associations with QOL (5.06, 95% CI [-1.29, 11.40]) (Figure 4.1). Additionally, no significant associations were observed for any of the QOL subscales (Figure 4.2, Figure 4.3, Figure 4.4, Figure 4.5).

Reallocating 30 minutes from MVPA

Reallocating 30 minutes of MVPA to sleep resulted in no significant association with QOL (-4.42, 95% CI [-10.79, 1.94]). Reallocating 30 minutes of MVPA to sedentary time resulted in no significant association with QOL (-4.32, 95% CI [-10.25, 1.61]). Reallocating 30 minutes of MVPA to light PA resulted in no significant association with QOL (-5.06, 95% CI [-11.40, 1.29]) (Figure 4.1). Additionally, no significant associations were observed for any of the QOL subscales (Figure 4.2, Figure 4.3, Figure 4.4, Figure 4.5). However, a clinically meaningful decrease (>4 points) was observed for all activities when reallocating time from MVPA.

Discussion

This study sought to better understand how reallocating time between daily activities (i.e., MVPA, light PA, sedentary time, and sleep) effects QOL in cancer survivors. This study included majority active cancer survivors obtaining adequate durations of sleep with 80.8% meeting MVPA guidelines and 90.4% meeting sleep guidelines. This study did not result in any statistically significant associations between daily time reallocations and QOL. However, this study found that reallocating 30 minutes from sedentary time or light PA to MVPA resulted in clinically meaningful increases in QOL (>4 points), suggesting increasing MVPA may be advantageous for noticeable changes in QOL for cancer survivors (D. Cella et al., 2002). This finding is in alignment with previous randomized controlled trials evaluating the effects of MVPA on QOL (Duncan et al., 2017).

One previous study in non-Hodgkin's lymphoma survivors that evaluated the effect of reallocating 30 minutes of time spent in MVPA, light PA, sedentary time, and sleep on QOL also found no significant associations, but did observe clinically meaningful improvements (Vallance et al., 2017). In this study, similar to the current study, the majority of survivors were meeting MVPA guidelines and sleep guidelines (7-9 hours/night), which suggests a potential ceiling effect for sleep and MVPA on improvements in QOL (Itani, Jike, Watanabe, & Kaneita, 2017). Another previous study by van Roekel et al. (2016b) found that reallocating sedentary time to PA resulted in statistically significant improvements in QOL in colorectal cancer survivors (van Roekel et al., 2016b). This study included an inactive sample of survivors (10.2 hours/day of sedentary time), revealing the importance of MVPA in both active and inactive survivors for improving QOL (van Roekel et al., 2016b).

Strengths of the current study include objectively measured sleep, sedentary time, light PA, and MVPA. To date, no reallocation studies in cancer survivors have utilized objective measures for all 24-hour activities. Previous time reallocation studies have relied on subjective measures of PA and sleep, a measurement technique known to have poor reliability and validity, potential for recall bias, and floor effects due to questionnaires failing to capture spontaneous or light activities of daily living (i.e., chores, caregiving) (Ainsworth, Cahalin, Buman, & Ross, 2015; C. E. Tudor-Locke & Myers, 2001). This study allowed for evaluating activities simultaneously rather than independently, providing more context for the effects on QOL of increasing or decreasing time in specific activities throughout the 24-hour day (i.e., in order to increase time in one activity, time in another was decreased).

Limitations of this study include small sample size, limiting ability to examine additional activity characteristics (i.e., bouted MVPA and sedentary time, standing time) or to do subgroup analyses (e.g., by cancer type or those meeting vs. not meeting activity or sleep guidelines). Additionally, the cancer survivors in this study were majority female, white, and high income,

limiting generalizability. Future studies should aim to include a larger sample size of cancer survivors in order to increase generalizability and allow for bouted vs. non-bouted time in sedentary time and PA.

In summary, this study suggests reallocating time from other 24-hour activities (i.e., sleep, sedentary time, light PA) to MVPA may be clinically beneficial to improve total QOL and the individual subscales included in QOL measurement. Specifically, replacing 30 minutes of sedentary time, or light PA with MVPA, may help survivors achieve clinically meaningful improvements in QOL. This is in line with the current PA guidelines for cancer survivors to improve QOL, recommending 30 minutes, 2-3 days/week of MVPA (K. L. Campbell et al., 2019). Future studies should continue to utilize objectively measured activity in Isotemporal substitution models to elucidate the interdependent nature of 24-hour activity patterns on psychosocial outcomes for cancer survivors including fatigue, quality of life, and depression/anxiety.

MANUSCRIPT III: REALLOCATING TIME TO PHYSICAL ACTIVITY AND SLEEP: ASSOCIATIONS WITH BODY MASS INDEX IN CANCER SURVIVORS

Introduction

In the United states, 36% of individuals (40.9% of males, 32.2% of female) living with cancer (i.e., cancer survivors) are overweight or obese, often defined as a body mass index (BMI) ≥ 25 kg/m^2 (NCI, 2021). Overweight and obesity is associated with worse cancer-related outcomes including cancer recurrence, progression, and survival (Mehra, Berkowitz, & Sanft, 2017; Petrelli et al., 2021). Therefore, strategies to achieve a healthy body weight or BMI is of utmost importance during cancer survivorship.

Lifestyle behaviors such as physical activity (PA), reducing sedentary time, and getting adequate sleep can help cancer survivors achieve a healthy BMI. (Otte et al., 2015; Segal et al., 2017; Swain et al., 2020). The overall consensus includes increases in moderate-vigorous PA (MVPA), reducing the amount of time spent sedentary, and meeting sleep guidelines result in favorable weight changes (i.e., reduced body fat and increased lean mass) (Brown et al., 2017; Lynch et al., 2010; Wijndaele et al., 2009).

However, the majority of studies that have examined the relationship between PA, sedentary time, sleep and BMI have not accounted for the interdependent nature of these activities (i.e., increasing time in one activity requires decreasing time in another). For this reason, many scholars have suggested that PA, sedentary time and sleep should be studied in the context the 24-hour day (Rosenberger et al., 2019). To date, only one study has examined how reallocating time between PA, sedentary behavior and sleep affects BMI in cancer survivors. This study, by Boyle et al. (2017), found that replacing 30 minutes of sleep, sedentary time, or light PA to moderate-vigorous PA (MVPA) resulted in lower BMI (decrease of 0.52-0.93 kg/m^2). However, this study was limited to breast cancer survivors and relied on subjective

measures of sleep, which are known to only moderately correlate with objective sleep measurement and systematically result in over-reporting (Lauderdale et al., 2008).

Therefore, the aims of this study were to evaluate the effect of reallocating sedentary time, light PA, sleep and MVPA on BMI in a mixed sample of cancer survivors, using objective measures of sleep and active behaviors.

Methods

A cross-sectional analysis consisting of a single visit, conducted either in-person or virtually (due to COVID-19 safety protocols). The in-person study visit consisted of electronic consent and demographic and QOL questionnaire completion via REDCap, DEXA scan, submaximal exercise test, sit to stand and arm curl assessments. At the conclusion of the visit, participants were fitted with the activPAL and Actiwatch-2 accelerometers at the laboratory. Virtual study visits consisted of a phone call to complete electronic consent followed by demographic and QOL questionnaire completion, both done through REDCap. The accelerometers were delivered and picked up by study staff to the participant's home or the devices were shipped with a return envelope and label for the participant to return after completing the 7-day wear protocol. Participants were provided written instructions for placing the devices, and if necessary, a virtual visit was conducted to properly place the devices.

Participants

Participants were recruited through local and regional cancer centers, flyers and presentations at community locations and events (e.g., senior center, American Cancer Society Relay for Life), email and website posting via the University faculty and staff listserv, and the Colorado State University Center for Healthy Aging from 01/20 to 06/21. Participants were eligible if they were >18 years at time of diagnosis, and within 60 months of treatment completion (i.e., surgery, chemotherapy, immunotherapy, and/or radiation therapy). Informed

consent was obtained from all participants and all procedures performed in this study were in accordance with the ethical standards of Colorado State University's institutional review board (IRB#19-8914H).

Sleep

Sleep duration was measured using an Actiwatch-2, a validated device that utilizes light exposure and accelerations to determine sleep-wake intervals (Lambiase et al., 2014; P. H. Lee & Suen, 2017). Sleep duration was measured as minutes spent in bed. Participants wore the device for 7 days, 24 hours per day. To be included in analyses, participants must have had a minimum of 4 valid days, including 1 weekend day.

Physical Activity and Sedentary Time

PA was measured using the activPAL accelerometer (PAL Technologies, Glasgow, Scotland). The activPAL has been validated to quantify free-living sedentary and ambulatory activities and has been previously used in cancer survivors (George et al., 2014). The activPAL software quantifies light PA, MVPA, and sitting, and lying time based on static and dynamic accelerations (Lyden et al., 2017; PAL, 2010). Participants wore the activPAL for 7 consecutive days, 24 hours per day. Participants must have had a minimum of 4 valid days, including 1 weekend day, for data to be included in analyses. Light PA was measured by subtracting "non-wear time" and "primary lying time" from 24 hours to create a "waking wear time" variable. MVPA was measured using "stepping time, in minutes, with a cadence ≥ 75 and duration > 1 minute" and "cycling time". Sedentary time was measured by the time in minutes, participants were sitting or lying down. Light PA was measured by subtracting "non-wear time" and "primary lying time" from 24 hours to create a "waking wear time" variable. This variable was then used to calculate light PA by subtracting MVPA and sedentary time from waking wear time. All time measurements are in minutes per day.

Body Mass Index

Body Mass Index (BMI, kg/m^2) was used to evaluate weight status. Participants either had height and weight measured in the laboratory (primary choice of measurement) or self-reported height and weight via an online questionnaire, pending comfort of reporting to the laboratory due to the COVID-19 pandemic.

Statistical Analysis

Demographics were summarized using mean ± standard deviation or frequencies. To examine the effects of time reallocation between PA and sleep behaviors on BMI, an Isotemporal substitution model was used. Isotemporal substitution models are done in three parts: single effects, partition effects, and the Isotemporal model. The single effects model will estimate the association between BMI and each activity individually. The partition model includes BMI as well as all of the activities of interest (sleep, sedentary time, light PA, MVPA). The variance inflation factors for each of the exposure variables in the partition model for BMI were less than 4, suggesting absence of problematic multicollinearity (considered problematic at 5). Isotemporal substitution allows for replacing time in one activity with time in a different activity, analyzed in minutes per day (Mekary et al., 2009). The Isotemporal substitution model represents the outcome when the same unit of time in one activity is substituted with another by including total time and all measured activities minus the activity of interest. From this, the regression coefficient can be interpreted as the mean effect on the outcome when substitution time from the omitted activity to each of the included activities, holding total activity constant (Mekary et al., 2009). In order to understand the substitution units, all variables must be in the same metric; therefore, time spent in each activity were converted to units of 30 minutes (e.g., 30 minutes=1, 60 minutes=2). Covariates included in the models were age, cancer type, and time since diagnosis.

Results

Demographic information and participant characteristics are presented in Table 5.1.

Table 5.1: Demographics

N=73	Mean ± standard deviation or frequency (%)
Age	53 ± 13
Sex (% female)	75.7
Race (% white)	93.2
Education (% ≥ undergraduate degree)	74.3
Income (% ≥ $50,000/year)	74.3
Body Mass Index (kg/m^2)	27.0 ± 5.7
Normal (18-24.9 kg/m^2)	38.4
Overweight (25-29.9 kg/m^2)	37.0
Obese (≥ 30 kg/m^2)	24.7
Diagnosis	
Breast	29.7
Colorectal	33.8
Leukemia/Lymphoma	9.5
Other	27.0
Stage	
0-2	62.2
3-4	29.7
Do not know	8.1
Time since diagnosis (months)	33.9 ± 26.4
Time since surgery (months) (n=66)	31.2 ± 28.3
Time since chemotherapy (months) (n=54)	24.8 ± 22.8
Time since radiation therapy (months) (n=38)	30.5 ± 17.4
Time since other therapies (months) (n=12)	16.3 ± 13.9

Briefly, participants were 53±12 years old, mostly female (75.7%), the majority were diagnosed with breast (n= 29.7%) or colorectal cancer (n= 33.8%), and the average BMI was 26.7 ± 5.7 kg/m^2. On average, participants accumulated 24.0 ± 18.9 minutes/day of MVPA, 291.8 ± 100.4 minutes/day of light PA, 593.1 ± 108.3 minutes/day of sedentary time, and 486.6 ± 57.6 minutes/night of sleep (Table 5.2).

Table 5.2: Physical Activity, Sedentary Time, and Sleep profiles

	Mean ± standard deviation or %
MVPA (minutes/day)	24.0 ± 18.9
Light PA (minutes/day)	291.7 ± 100.4
Sedentary time (minutes/day)	593.1 ± 108.3
Sleep duration (minutes/day)	486.6 ± 57.6
>30 minutes/day of MVPA	80.8%
>7 hours/night of sleep	90.4%

The partition model revealed significant associations between sedentary time and light PA (Pearson's r=-0.75) and MVPA (r=-0.48). All other correlations between the different activities were low (.09-.22) and not statistically significant. In the single effects model, there were no significant associations with BMI. When removing sedentary time due to its correlation with light PA and MVPA, significant associations with BMI were present for light PA (p=.00) and sleep (p=.00).

Reallocating 30 minutes from sleep (Figure 5.1)

Reallocating 30 minutes of sleep to light PA resulted in no significant association with BMI (+0.27 kg/m^2, 95% CI [-0.41, 0.95]). Replacing 30 minutes of sleep with sedentary time resulted in a statistically significant association with BMI (+0.80 kg/m^2, 95% CI [0.12, 1.50], *p*=0.02). Replacing 30 minutes of sleep with MVPA resulted in no significant association with BMI (-0.05 kg/m^2, 95% CI [-2.16, 2.06]).

Reallocating 30 minutes from sedentary time (Figure 5.1)

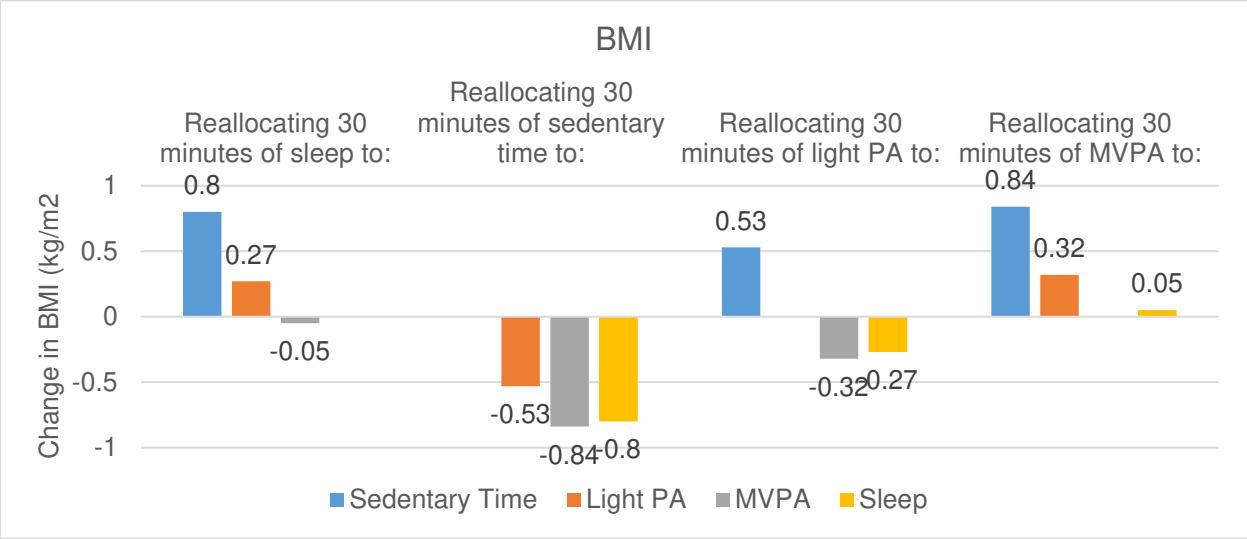
Reallocating 30 minutes of sedentary time to sleep resulted in a statistically significant association with BMI (-0.80 kg/m^2, 95% CI [-1.50, -0.12], *p*=0.02). Reallocating 30 minutes of sedentary time to light PA resulted in a statistically significant association with BMI (-0.53 kg/m^2, 95% CI [-0.91, -0.14], *p*=0.008). Reallocating 30 minutes of sedentary time to MVPA resulted in no significant association with BMI (-0.84 kg/m^2, 95% CI [-2.81, 1.12]).

Reallocating 30 minutes from light PA (Figure 5.1)

Reallocating 30 minutes of light PA to sleep resulted in no significant association with BMI (-0.27 kg/m^2, 95% CI [-0.95, 0.41]). Reallocating 30 minutes from light PA to sedentary time resulted in a statistically significant association with BMI (+0.53 kg/m^2, 95% CI [0.14, 0.91], *p*=0.008). Reallocating 30 minutes from light PA to MVPA resulted in no significant association with BMI (-0.32 kg/m^2, 95% CI [-2.42, 1.80]).

Reallocating 30 minutes from MVPA (Figure 5.1)

Reallocating 30 minutes of MVPA to sleep resulted in no significant association with BMI (0.05 kg/m^2, 95% CI [-2.06, 2.16]). Reallocating 30 minutes of MVPA to sedentary time resulted in no significant association with BMI (+0.84 kg/m^2, 95% CI [-1.12, 2.81]). Reallocating 30 minutes of MVPA to light PA resulted in no significant association with BMI (0.32 kg/m^2, 95% CI [-1.80, 2.42]).



*indicates statistical significance, BMI=Body Mass Index, PA=Physical Activity, MVPA=Moderate-Vigorous Physical Activity

Figure 5.1: Time Reallocations for BMI

Associations between sleep, sedentary time, light PA, and MVPA on BMI when reallocating 30 minutes of one activity of interest to another activity of interest in a mixed sample of cancer survivors.

Discussion

This study sought to better understand how reallocating time between daily activities (i.e., MVPA, light PA, sedentary time, and sleep) effects BMI in cancer survivors. This study found that reallocating (a) 30 minutes of sedentary time to sleep or light PA, (b) 30 minutes of light PA to sedentary time, and (c) 30 minutes of sleep to sedentary time was associated with

lower BMI, indicating that sleep and sedentary time are distinct behaviors and time spent sedentary prior to sleep (i.e., watching tv in bed, reading) may significantly contribute to BMI.

To our knowledge, only one previous study has examined the effects of reallocating activity and sleep on BMI in cancer survivors (Boyle et al. (2017)), and found that reallocating 30 minutes from sleep, sedentary time, and LPA to MVPA was associated with significantly lower BMI. These results differ from the current study which revealed no statistically significant associations between sedentary time, sleep, or light PA when reallocating time to MVPA. However, the study by Boyle et al. (2017) utilized a waist-worn accelerometer to measure waking behaviors, potentially introducing measurement error when distinguishing between sedentary time and standing behaviors or misclassifying MVPA with light PA for ambulatory activities (Freedson, Melanson, & Sirard, 1998). It is also important to note that although the benefits of MVPA are well-established, there is a limit to how much MVPA an individual can realistically do in a 24-hour period (Buman et al., 2014). Additionally, sedentary time has been found to significantly contribute to higher BMI, even when controlling for MVPA, which may explain why moving sedentary time resulted in significant associations with BMI while moving MVPA time did not (Gonze BB, 2021). Therefore, this study indicates that for survivors already meeting MVPA guidelines, reallocating time toward sleep or light PA and away from sedentary time may be an advantageous strategy to further improve BMI.

The findings from the current study add to the literature due to the utilization of objectively measured PA, sedentary time and sleep, adds novel information about the effect of reallocating time to/from sleep on BMI. This finding is highly relevant for cancer survivors due to the high prevalence of sleep disturbance in this population (e.g., 30-75% of cancer survivors report some level of sleep disturbance during treatment, and 64% report insomnia following treatment completion), and the implications of weight status and BMI on cancer-related mortality (Otte et al., 2015; Pin et al., 2018). (Bernard et al., 2019; Fiorentino & Ancoli-Israel, 2007).

These findings support the importance of differentiating between sedentary time and sleep, and the effect that these behaviors may have on important cancer-related outcomes (Gibbs, 2018). Therefore, future studies should explore the role of sedentary time, specifically time spent prior to bedtime (i.e., watching TV, reading in bed), on BMI.

The current study also provides evidence for the positive effect of reallocating sedentary time to light PA on BMI. Previous literature supports the role of light PA in cancer survivor for physical function and decreasing cancer mortality (Blair et al., 2014; Qiu et al., 2020). Light PA prevents functional decline in older cancer survivors at higher risk for age or treatment-related declines, regardless of MVPA (Blair et al., 2014). Therefore, replacing sedentary time with light PA is important, especially for survivors unable to safely complete adequate amounts of MVPA.

Strengths of this study include objectively measured sleep, sedentary time, light PA, and MVPA. To date, no reallocation studies in cancer survivors have utilized objective measures for all 24-hour activities. Previous time reallocation studies have relied on subjective measures of PA and sleep, a measurement technique known to have poor reliability and validity, potential for recall bias, and floor effects due to questionnaires failing to capture spontaneous or light activities of daily living (i.e., chores, caregiving) (Ainsworth et al., 2015; C. E. Tudor-Locke & Myers, 2001). This study allowed for evaluating activities simultaneously rather than independently, providing more context for the effects on BMI of increasing or decreasing time in specific activities throughout the 24-hour day (i.e., in order to increase time in one activity, time in another was decreased).

Limitations of this study include small sample size, limiting ability to examine additional activity characteristics (i.e., bouted MVPA and sedentary time, standing time) or to do subgroup analyses (i.e., different QOL thresholds). Additionally, the cancer survivors in this study were mostly female, white and high income, limiting generalizability. Future studies should aim to

include a larger sample size of inactive cancer survivors in order to increase generalizability and allow for bouted vs. non-bouted time in sedentary time and PA.

Future studies should aim to include a larger sample size in order to increase generalizability and allow for post-hoc analyses to examine those meeting MVPA and sleep guidelines versus those not currently meeting guidelines as well as those with a BMI>25 kg/m^2 versus BMI <25 kg/m^2. In addition, future studies should include more detailed measures of weight status including waist circumference, lean mass, body fat percentage, and bone mass, as these all have important implications in cancer survivors (Boyle et al., 2017; Pin et al., 2018).

In conclusion, this study found that replacing 30 minutes of sedentary time with light PA or sleep was associated with lower BMI, reinforcing the importance of reducing sedentary time and ensuring adequate sleep for cancer survivors (Otte et al., 2015; Paxton, Anderson, Sarkar, & Taylor, 2016). To date, the majority of findings related to the importance of reducing sedentary time and increasing light PA for reducing BMI have come from prospective cohort studies (Gilchrist et al., 2020; Qiu et al., 2020). These findings suggest that reducing sedentary time by replacing it with sleep or light PA may be avenues for intervention to help cancer survivors already accumulating >30 minutes/day of MVPA to achieve a healthy BMI (Blair et al., 2021).

Chapter VI. Conclusions

SUMMARY

QOL and BMI are linked to cancer-related morbidity and mortality, making these important targets for survivorship (Coronha et al., 2011; Nayak et al., 2017; Petrelli et al., 2021). Many treatments for cancer have a negative impact on QOL and BMI, thus, lifestyle interventions which target behaviors known to improve these outcomes are necessary (Mishra et al., 2012; Playdon et al., 2015). However, there are multiple behaviors in the 24-hour day, and we need more information on which ones to target when building interventions for cancer survivors. Although a lot of observational and interventional research has been conducted on each of these behaviors, the majority of these studies often target only MVPA, which makes up a small fraction of the 24-hour day, despite the known contributions of sleep, sedentary time, and light PA to cancer-related outcomes. Additionally, waking behaviors (i.e., sedentary time, light PA, and MVPA) and sleep are often studied in isolation despite the interdependent nature of these activities. Simply, to increase time in one activity, time must be decreased in another. Without taking into account the multidimensional, interdependent nature of activities within the 24-hour day, it is difficult to understand if effects on health outcomes are the result of more time spent in positive behaviors (i.e., MVPA) OR less time spent in negative behavior (i.e., sedentary time). Therefore, this dissertation sought to better understand how sleep, sedentary time, light PA, and MVPA time could be reallocated throughout the 24-hour period to improve QOL and decrease BMI in a mixed sample of cancer survivors.

Currently, only 3 studies analyzing 24-hour time reallocations are available in cancer survivors (Boyle et al., 2017; Vallance et al., 2017; van Roekel et al., 2016a). Although these studies included objective measures of PA and sedentary time, sleep was measured using self-report. By using self-report for sleep, participant self-report error is introduced including recall

bias, and gaps in time across the 24-hour period are often lost. One reason for using self-report measure of sleep may have been that collecting objectively measured 24-hour activity using accelerometers is costly and burdensome, because two devices (one for PA, one for sleep) are required (Lambiase et al., 2014). Therefore, another purpose of this dissertation was to advance the science of measuring the 24-hour day by determining if the activPAL accelerometer, which has demonstrated reliability/validity to measure PA and SB, demonstrated similar estimates of TIB as the Actiwatch, a validated and reliable measurement of free-living TIB.

Findings from this work revealed that activPAL did not estimate TIB similarly to the Actiwatch, thus requiring utilization of the Actiwatch to objectively measure TIB in future studies. Since objective measures of sleep and PA are needed in the cancer survivor population, it is advisable to continue to utilize both a validated PA device as well as a validated sleep device to obtain valid and reliable estimates of 24-hour activity patterns.

Following the results of study one, the activPAL and Actiwatch were utilized to measure 24-hour activity patterns in cancer survivors, and examine the effect of reallocating time between sleep, PA, SB on QOL and BMI. With regard to QOL, reallocating time away from sedentary time or light PA to MVPA results in a clinically meaningful increase in QOL. This is in alignment with current research suggesting that MVPA is important for improving QOL in cancer survivors (Duncan et al., 2017). This study also found that reallocating time to sleep did not result in improvements in QOL, indicating that for survivors already obtaining adequate volumes of sleep (7-9 hours), sleep may not be a behavior target for interventions designed to improve QOL. The dissertation also provides evidence for reallocating time from sedentary time to light PA to improve BMI. Specifically, a statistically significant association with BMI was observed for cancer survivors when reallocating 30 minutes of sedentary time to light PA (i.e., lower BMI). Previous literature supports the role of light PA in cancer survivor health. Light PA prevents functional decline in older cancer survivors at higher risk for age or treatment-related declines,

regardless of MVPA (Blair et al., 2014). When removing 30 minutes from MVPA to sleep, sedentary time, or light PA, no significant associations were observed. When removing 30 minutes from sleep and reallocating it to sedentary time, a significant association arose, resulting in an increase in BMI. Similarly, cancer survivors that reallocate 30 minutes of sedentary time to sleep saw a significant association resulting in lower BMI.

LIMITATIONS

Study one found that the activPAL accelerometer does not estimate TIB similarly to the Actiwatch accelerometer, indicating the activPAL accelerometer is not a suitable choice alone when TIB measures are needed. Although these results are important for choosing accelerometers for lifestyle behavior measurement, it is not without limitations. For example, a gold-standard for measuring time in bed was not available. Due to this lack of measurement, it is not possible to validate the activPAL accelerometer to measure time in bed. In addition to the lack of gold-standard for reliability and validity, the activPAL accelerometer does not have the functionality to measure pertinent sleep-related behaviors including WASO and sleep latency. The activPAL is limited to measuring start time in bed and end time in bed to determine time in bed, not the actual amount of time spent sleeping. Measurements related to specific sleep behaviors may be beneficial when assessing the effects of 24-hour activity patterns on cancer-related outcomes (i.e., the quality and efficiency of sleep). Therefore, the necessity to continue utilizing the Actiwatch, a valid and reliable measure of free-living sleep, in addition to a physical activity accelerometer is warranted to measure the 24-hour day is likely to continue.

In studies two and three of this dissertation, additional analyses including bouted and non-bouted time, and subgroup analyses including those meeting MVPA/sleep guidelines versus those not meeting guidelines, those with high versus low BMI/QOL, and cancer type/staging, could not be done due to sample size limitations. Therefore, a larger sample size is necessary to improve generalizability to the population at large. Although the USDHHS no

longer provides recommends accumulating MVPA in a minimum of 10-minute bouts, there is still evidence to suggest that bouted sedentary time significantly effects cancer-related outcomes (Boyle et al., 2017; Vallance et al., 2017).

Despite a wide range of cancer diagnoses included in this sample, the sample was not racial/ethnically or economically diverse. This is important to consider since it limits generalizability to all cancer survivors. The majority of participants in these studies were obtaining adequate levels of sleep, which is not typical for cancer survivors (Fiorentino & Ancoli-Israel, 2007). The healthy sleep duration of this sample of cancer survivors may explain the results regarding reallocating time TO sleep. Since these survivors are already obtaining >7 hours of sleep per night, adding additional time to sleep may not be advantageous for improving QOL or BMI. This limits generalizability, making it difficult to transform the reallocation results into 24-hour activity guidelines suitable for all cancer survivors.

The use of BMI as an outcome measure can also be considered a limitation. Despite the known associations between BMI and health outcomes, it lacks specificity (i.e., fat mass and lean mass). For cancer survivors, skeletal muscle depletion is a known factor associated with morbidity and mortality (Martin et al., 2013). Additionally, muscle mass is associated with improved QOL in cancer survivors, indicating a more specific measure of body composition, such as DEXA, should be utilized to assess the effects of weight status on cancer-related outcomes (Derksen et al., 2020).

FUTURE DIRECTIONS

Findings from these studies indicate that additional research is needed to test and evaluate accelerometers to accurately measure activities conducted during the full 24-hour day (i.e., sleep, sedentary time, standing, light PA, and MVPA). Accurately capturing time spent in different waking behaviors as well as sleep is essential to better understanding how lifestyle

behaviors effect pertinent cancer-related outcomes. By developing or updating current devices to accurately capture all activities within the 24-hour day, research costs and burden will be decreased, allowing for more access to objectively measure PA and sleep measurements and the ability to include more participants (i.e., larger sample size).

Second, these findings may contribute to the development of lifestyle behavior modification interventions to improve QOL and BMI cancer survivors. Based on the evidence described in this dissertation, MVPA is still an essential part of lifestyle behavior prescription for cancer survivors. This is shown through the reallocation results for QOL which reveal that reducing sedentary time or light PA by 30 minutes and spending that time in MVPA was associated with a clinically meaningful improvement in QOL. However, these findings also elude to the idea that cancer survivors already obtaining acceptable levels of MVPA and meeting sleep guidelines may benefit from interventions designed to decrease sedentary time and increase light PA. Specifically, reducing sedentary time by 30 minutes and spending that time in light PA was associated with significantly lower BMI, revealing a potential intervention target for future studies.

Third, future studies can apply the Isotemporal substitution model to and should be utilized to evaluate the effects of wake and sleep behaviors on other cancer-related outcomes such as fatigue, depression, anxiety, and physical function. With a better understanding of how sleep, sedentary time, light PA, and MVPA work interdependently rather than in isolation, individualized exercise prescriptions based on the survivor's current patterns and abilities can be prescribed.

In summation, this dissertation moves the PA, sedentary time, and sleep research field forward in the cancer survivor population by exploring optimal measurement techniques for exploring associations between behaviors across the 24 hour cycle. Not only does this body of work introduce the need for more studies using gold-standard, objective measures of sleep

measurements cancer survivors, it explored an accelerometer frequently used in healthy and clinical populations to measure PA and assess its ability to estimate TIB compared to a well-validated free-living sleep accelerometer. This is important as accelerometer-based measurements can be difficult to acquire due to the high cost associated with using multiple accelerometers and the increased research burden for analyzing data from multiple devices. By exploring a well-validated PA accelerometer to measure TIB, researchers may gain increased access to objectively-measure lifestyle behaviors to assess the role of the 24-hour activity cycle on pertinent cancer-related outcomes including QOL and BMI.

Although this dissertation found that the PA accelerometer was not similar in estimating TIB, the 24-hour activity cycle was still able to be objectively measured to assess the role of interdependent lifestyle behaviors (i.e., sleep, sedentary time, light PA, and MVPA) on QOL and BMI in cancer survivors. By assessing these behaviors together, rather than in isolation, more specific recommendations can be ascertained for prescribing lifestyle behaviors to cancer survivors struggling with QOL and BMI.

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