DISSERTATION

THE TIME COURSE OF THE THERAPEUTIC INFLUENCE OF A SINGLE EXERCISE BOUT ON CANCER-RELATED FATIGUE

Submitted by

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ABSTRACT

THE TIME COURSE OF THE THERAPEUTIC INFLUENCE OF A SINGLE EXERCISE BOUT ON CANCER-RELATED FATIGUE

Introduction: Cancer-related fatigue (CRF) is a critical outcome for cancer survivors due to its high prevalence, impact on activities of daily living (ADLs), and quality of life (QOL). Non-pharmacological interventions, such as chronic exercise interventions, are a promising intervention target to improve CRF. However, the effect of these interventions is often only studied at the baseline and post-intervention period; therefore, it does not capture the dynamic nature of how CRF may change daily and even weekly within those intervention periods. Studying these within-day and weekly changes may have important implications on exercise motivation, especially when cancer survivors are experiencing severe CRF. Exploring these effects may lead to improved long-term exercise adherence in cancer survivors. To fill in the gap of how exercise affects CRF daily during a 12-week exercise program, additional research must be conducted to explore the acute effects of exercise on CRF and how factors such as exercise intensity may have a role in the impact of change. Therefore, the purpose of this dissertation is to (1) examine changes in CRF from immediately before to immediately after exercise sessions during an exercise program for cancer survivors, (2) changes in CRF up to 7-hours following a single-bout of exercise on an exercise and non-exercise day, and (3) how self-selected exercise intensity impacts CRF immediately following, and after up to 7-hours after an exercise session.

Methods: An observational, longitudinal cohort study of (n=25) cancer survivors was conducted to study within-day trends of CRF. Participants (for all studies) completed a 12-week exercise program in an outpatient cancer rehabilitation program. Exercise classes were held twice per week, and participants were assigned to a set day and time. CRF was assessed using a visual analog scale (0=no fatigue–10=worst fatigue), before, and immediately after exercise;

and 1-, 4-, & 7- hours following one exercise class per week and at the same times the following day on one non-exercise day per week via a phone application, ExpiWell. Finally, heart rate and rate of perceived exertion were collected once a week to capture participants' self-selected exercise intensity for each given session. Demographics were calculated using mean ± standard deviation or frequencies (%). Mixed effects models with random and fixed effects were used to evaluate CRF immediately after exercise and over the course of the day. Statistical significance for all studies was set at $p<.05$.

Results: This work examined changes in CRF from immediately before to immediately after exercise sessions. Overall, it did not demonstrate acute effects of exercise on CRF, and there was no difference in the magnitude of CRF change from week to week. When assessing CRF at hour 1-, 4 and 7-hours post exercise, findings revealed that on exercise days, CRF demonstrated a positive significant slope for CRF from immediately post-exercise through 1, -4, and -7 hours, with CRF levels remaining stable at 1- and 4-hours compared to post exercise before rising significantly by the 7-hour timepoint compared to post-exercise. On non-exercise days, CRF demonstrated a positive significant slope for CRF from the 1-hour timepoint through 4, and -7 hours; however, CRF levels at each timepoint (4 and 7 hours) were not significantly different than the 1-hour timepoint. Notably, comparisons between exercise and non-exercise days revealed no significant differences in CRF slopes, suggesting that CRF tends to follow a similar trend during the day, independent of exercising.

Conclusion: CRF did not significantly decrease following a single session of exercise, nor did categorizing exercise sessions by intensity level reveal differences in CRF outcomes. Across the course of the exercise day, CRF gradually increased, peaking at hour 7. Interestingly, this pattern was also observed on non-exercise days. However, the reported CRF remained below a moderate threshold, suggesting that while exercise did not alleviate CRF, it also did not lead to a statistically significant increase in CRF during or after the sessions. The

findings presented in this dissertation offer a vital perspective on the acute effects of a single bout of exercise on CRF. Future research should conduct randomized controlled trials that will aim to establish a causal relationship between exercise and immediate reductions in CRF, while allowing for consideration of several key CRF moderators. In addition, future studies should include the collection of biomarkers that examine the underlying physiologic mechanisms of the change in CRF immediately following a bout of exercise and over the course of a day.

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Chapter 1 – Introduction

INTRODUCTION

"Exercising has helped me have more stamina in my day when I leave, more energy to do the things I love, like working in my garden…. something I haven't been able to do since starting treatment" – Participant.

RATIONALE

As of January 2022, there were an estimated 18.1 million individuals living with and beyond cancer (i.e., cancer survivors) in the United States, with the number of cancer survivors now projected to increase to 22.5 million by 2032.[1] This increase in the number of cancer survivors can be attributed, in part, to a larger population of individuals over the age of 65 [2] and advancements in early detection and treatment(s) for cancer. With this large population of cancer survivors, it is essential to explore and implement strategies to improve the health span and quality of life (QOL) of these individuals.

Cancer survivors undergo a variety of different treatments, such as chemotherapy, radiation, and surgery, and although effective for improving survival from cancer, often result in symptoms and side effects (e.g., decreased physical and cognitive functioning, sleep impairments, pain, depressive symptoms, cardiotoxicity, etc.) which can negatively impact physical and mental well-being.[3] One of the most common, debilitating, and persistent symptoms reported is cancer-related fatigue (CRF).[4] CRF is often described as all-encompassing, affecting almost every aspect of daily life. The definition proposed by the National Comprehensive Cancer Network (NCCN) is that CRF is "a distressing, persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity that interferes with usual functioning".[5] Given the successes in cancer treatment in extending survival, healthcare

professionals are now likely to see cancer survivors with prolonged states of CRF persisting up to five years. [6]

CRF is multi-dimensional in nature and can interfere with employment, enjoyment of life, relationships, and motivation to continue treatment.[7] In addition, CRF severity may be a predictor of the ability to receive the full dose of treatment and overall survival,[8] illustrating a pressing need for strategies to mitigate CRF both during and after treatment.

Exercise has been established as one of the most effective strategies to reduce CRF, even when compared to pharmaceutical interventions.[9–11] Beneficial effects of exercise training on CRF have been shown in numerous systematic reviews,[6,12,13] pointing to several potential mechanisms such as decreased inflammation, improved immune function, and increased strength and aerobic capacity.[14] Engaging in thirty minutes of at least moderate-intensity aerobic exercise three days per week, plus two days per week of resistance training for at least twelve-weeks is recommended to reduce CRF,[3] however, cancer survivors are less likely than those without a history of cancer to report achieving these exercise recommendations with an estimated 14% regularly engaging in aerobic and resistance exercise.[15] Paradoxically, one of the most common barriers to exercise reported by cancer survivors is CRF, [16,17] and many cancer survivors report a lack of knowledge about the most beneficial exercise type and intensity for managing CRF.[16] Consequently, it can be daunting for cancer survivors experiencing moderate or high levels of CRF to begin or adhere to regular exercise when the benefit seems very distal (i.e., weeks or months before seeing reductions in CRF). This raises the question of whether exercise may result in more immediate, or “acute” reductions in CRF.

To date, there is little information about whether exercise may have an acute effect on CRF. The acute benefits of exercise (e.g., immediately following up to several hours after a bout of exercise) have been demonstrated in outcomes such as energy, mood, and state anxiety among healthy adults, yet it is unclear whether exercise can have a similar, positive impact on CRF, how long this effect might last follow a bout of exercise, and whether the intensity of the

exercise matters. To our knowledge, only three previous studies have examined the acute effects of exercise on CRF. Matsugaki et al. (2018)[18] examined CRF among N=18 cancer survivors before and after a single inpatient exercise session. Another study by Cohen et al. (2021) examined the immediate effects of aerobic exercise combined with relaxation training compared to aerobic exercise alone on CRF among N=40 breast cancer survivors. Finally, Siebert et al. (2022)[19,20] evaluated the effects of four intervention groups with varying exercise modalities and intensities on CRF. Examining the extent to which exercise can result in an immediate reduction or provide relief from CRF has important implications, such as providing an incentive to cancer survivors who perceive CRF as a barrier to adopting an exercise routine, emphasizing the need for more evidence on how a single exercise session can potentially decrease feelings of CRF. Thereby increasing motivation for long-term exercise adaptations and informing healthcare providers on how to incorporate acute exercise strategies into supportive care plans to improve overall symptom management.

Based on the literature summary presented above, the studies herein aim to examine (1) changes in CRF from immediately before to immediately after exercise sessions during an exercise program for cancer survivors, (2) changes in CRF up to 7-hours following a single-bout of exercise, and (3) how self-selected exercise intensity impacts CRF immediately following, and after up to 7-hours after an exercise session.

PROBLEM STATEMENT AND RESEARCH QUESTIONS

Problem Statement

Current exercise guidelines to reduce CRF are based on the effects elicited following regular exercise over the course of several weeks. However, the outcome of exercise for providing immediate relief or reduction in CRF has yet to be elucidated. Thus, there is a need to determine whether exercise can reduce CRF immediately following and several hours after a bout of exercise, and whether exercise intensity impacts this effect.

Overarching Research Questions

1. Is there a reduction in CRF from immediately before to immediately after an exercise session?

2. How does CRF change 1-, 4-, and 7-hours following an exercise session, and is it different than on a non-exercise day?

3. Does the intensity of an exercise session impact (a) the change in CRF from immediately before to immediately after an exercise session and (b) 1-, 4-, and 7-hours following an exercise session?

Specific Research Aims and Hypotheses

Study 1: The Acute Effects of Exercise on Cancer-Related Fatigue

Purpose: This study will examine changes in self-reported CRF from immediately before to immediately after exercise sessions during a 12-week outpatient cancer rehabilitation exercise program. CRF will be measured using a single-item visual analog scale from (0-10) immediately before and after one exercise session per week.

Hypothesis 1a: There will be an improvement (decrease) in CRF from immediately before to after exercise sessions.

Hypothesis 1b: There will be a decrease in the magnitude of change from immediately before to after exercise sessions from week 1 to week 12 of the exercise program.

Study 2: Time Course of Cancer-Related Fatigue during an Outpatient Exercise Program for Cancer Survivors

Purpose: This study will examine changes in CRF from immediately after exercise sessions to 1, -4, and -7 hours following the exercise session and differences in CRF measured at the same clock time on a non-exercise day within the same week. CRF will be self-reported via a mobile

phone app using a single-item visual analog scale from (0-10) at -1, -4, and -7 hours following one exercise session per week, and at the same times on a non-exercise day.

Hypothesis 2a: Compared to immediately after an exercise session, there will be no change in CRF at 1 hour following exercise, but CRF will be higher at hours 4 and 7. In addition, the slope of the line for CRF from immediately post-exercise through 1, -4, and -7 hours will be positive, reflecting increasing CRF over the three timepoints.

Hypothesis 2b: On a non-exercise day, CRF will be higher at hours 4 and 7 compared to the 1-hour timepoint. In addition, the slope of the line for CRF from hour 1 through -4 and -7 hours will be positive, reflecting increasing CRF over the three timepoints.

Hypothesis 2c: The slope of the line for CRF between the 1-, 4-, and 7-hour time-points will have a greater positive slope (i.e., CRF is higher) on non-exercise days compared to exercise days.

Study 3: Effects of Exercise Intensity on Cancer-Related Fatigue immediately and up to 7 hours following exercise

Purpose: This study will examine how exercise intensity impacts changes in CRF from immediately before to after an exercise session and 1-, 4-, and 7-hours following an exercise session. Heart Rate Reserve (HRR) and Rating of Perceived Exertion (RPE) will be used to categorize each exercise session into light (30-39% HRR, 9-11 RPE) or moderate-vigorous (40-89% HRR, 12-20 RPE). Exercise intensity will be self-selected by participants.

Hypothesis 3a: Exercise sessions that are categorized as moderate-high intensity will have a larger magnitude of decrease in CRF immediately following exercise compared to exercise sessions categorized as low intensity.

Hypothesis 3b: Exercise sessions that are categorized as moderate-high intensity will have a greater negative slope (i.e., a larger decrease) of CRF across the 1-, 4-, and 7-hour period following an exercise session, compared to exercise sessions categorized as low intensity.

Chapter 2 - Review of Literature

INTRODUCTION

This literature review intends to provide an overview of the current knowledge related to the acute effect of exercise on cancer-related fatigue (CRF). The primary components in this literature review are 1) cancer survivorship, cancer prevalence, and treatment-related side effects, 2) CRF definitions, mechanisms, impact, prevalence, and measurement, and 3) plausible mechanisms for exercise to have an acute effect on CRF. 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.

The persistent CRF in cancer survivors can have widespread adverse emotional, social, and physical consequences. Cancer survivors frequently report the negative impact of CRF on health-related quality of life, and the interfering effect on their ability to perform activities of daily living and maintain functional independence.[21] There is extensive evidence to support the benefits of regular exercise done over the course of several weeks to months to improve or alleviate CRF. However, to date, minimal research has delved into the potential for an acute bout of exercise to alleviate CRF. This literature review will emphasize the relevance of my dissertation research by outlining key exercise and CRF studies that justify the theoretical foundation and provide the necessary context for understanding the specific methodologies used in this project.

CANCER PREVALENCE

The term cancer can be used to describe a group of over 100 diseases. Specifically, neoplasm is used to describe the abnormal growth of cells, which develop because of damage to deoxyribonucleic acid (DNA). When the DNA is not repaired, it leads to the cells multiplying at an uncontrolled rate, eventually replacing normal cells in the body.[22] As cancer cells multiply uncontrollably, they can invade and damage surrounding tissues, leading to severe health

consequences. In 2024, there will be approximately 2,001,140 new cancer cases in the United States alone, and the probability of developing invasive cancer is currently 1:2 (416%) for males and 1:3 (39.6%) for women.[1] The rising participation in early detection and screening initiatives has greatly improved cancer prognosis. These advances have resulted in a continual decline in mortality rates and a steady rise in cancer survivors, with individuals living longer after primary treatment. For this reason, by 2040, there will be an estimated 26 million individuals living with and beyond cancer.[23] Improved prognosis has created a growing need to address the unique health issues that result from the disease, its treatment, and related comorbid conditions.

CANCER SURVIVORSHIP

According to the American Cancer Society and other organizations such as the National Comprehensive Cancer Network (NCCN) and the National Coalition for Cancer Survivorship (NCCS), survivorship starts at the time of diagnosis and lasts throughout the lifespan.[23] However, in oncology literature, the interpretations of a cancer survivorship definition vary widely depending on the focus of research, cancer survivors' perspectives, and the viewpoints of advocacy and policy groups that use the term. Survivorship is a constantly evolving concept to organize a body of knowledge that will improve over time and ideally impact the health and well-being of those diagnosed with and treated for cancer. In 2007, a Breast Cancer Symposium surveyed oncology healthcare professionals and cancer survivors, inquiring about the definition of a cancer survivor. The lack of consensus led the group to declare that cancer survivorship could be viewed (1) as a time frame, so it could be developed based on the type and stage of the disease (i.e., after 2, 5, or 10 years); (2) as an outcome like no evidence of disease, complete remission, or cured; (3) as a stage or phase and, in this case, we must consider if primary treatment has ended or if there is any recurrence; or finally (4) as a process where people live through different stages of illness.[24] For this dissertation, survivor will be defined in congruence with the National Cancer Institute (NCI), stating that survivorship starts at the time of diagnosis and lasts throughout the lifespan.

With the growing prevalence of cancer survivors, it is vital to assess appropriate treatments, resources, and interventions across the cancer continuum to best serve the unique needs and side effects that individual cancer survivors experience and address symptom burden.

TREATMENT AND SIDE EFFECTS

Treating cancer is a highly complex process; the most widely used traditional treatment methods are surgery, chemotherapy, and radiotherapy, while modern modalities include hormone therapy, anti-angiogenic therapy, stem cell therapies, immunotherapy, and dendritic cell-based immunotherapy.[25] However, with these advances in treatment also come increased treatment-related side effects and cancer survivors living longer after a diagnosis. These side effects can affect cancer survivors years after the completion of primary treatment. In the clinical setting, the toll of treatment-related side effects is distinguished by the term “symptom burden”. It is defined as the subjective, quantifiable prevalence, frequency, and severity of symptoms placing a physiologic burden on cancer survivors, and producing multiple negative, physical, and emotional cancer survivors responses. [26] The symptom burden imposed by cancer- and treatment-related symptoms can be substantial, resulting in a considerable impact on cancer survivors’ daily and working lives, affecting employment status and hours worked. Identifying and treating the side effects associated with cancer treatment can reduce their negative impact on cancer survivors’ daily lives and health-related quality of life.[26]

Cancer survivorship has become a significant area of focus as the prevalence and incidence of cancer continues to rise and more individuals are living with and beyond cancer. Managing the heavy symptom burden of treatment is the key component to enhancing quality and length of life for cancer survivors. This includes advancing research on the most reported treatment side effect, CRF. CRF is often described as more severe, persistent, and distressing than “typical” tiredness for fatigue, making it a critical focus in survivorship research. Addressing

CRF is not only vital for improving the quality of life but also ensuring that individuals can adhere to their full treatment plan on schedule and engage in healthy behaviors such as exercise, which has been shown to lower the risk of cancer mortality and reoccurrence.

Overview of Cancer-Related Fatigue (CRF)

CRF is the most commonly reported side effect of cancer treatment, which impacts nearly all individuals with cancer across the care continuum.[27] High incidence of increased CRF has been associated with depression, anxiety, physical symptoms, comorbidities, and higher rates of recurrence.[4]

CANCER-RELATED FATIGUE DEFINITIONS

NCCN defines CRF as a "distressing persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity that interferes with usual functioning".[5] In addition, other organizations have also defined CRF in a variety of ways, including the European Association for Palliative Care (EAPC), which defines CRF as a subjective feeling of tiredness, weakness, or lack of energy. [28] In addition, the Assessing the Symptoms of Cancer using Patient-Reported Outcomes (ASCPRO) developed a consensus definition of CRF as the perception of unusual tiredness that varies in pattern of severity and has a negative impact on the ability to function in people who have or have had cancer.[29] Despite the numerous definitions of CRF, each variation describes CRF as subjective in nature, indicating that the assessment of CRF should be individualized to each cancer survivor's needs. Cancer survivors report CRF as persistent and debilitating and is not alleviated by adequate rest or sleep.[30] A cancer survivor's level of CRF varies during the day, according to their treatment, and follows a pattern related to the course of the day. [31] To distinguish between general fatigue and CRF in a clinical setting, the NCCN has established four criteria to define the diagnosis of CRF for clinicians.[32] These criteria include: 1) 2 weeks or longer within the preceding month during which significant CRF or

diminished energy was experienced each day or almost every day along with additional CRF-related symptoms; 2) the experience of CRF results in significant distress or impairment of function; 3) the presence of clinical evidence suggesting that CRF is a consequence of cancer or cancer therapy; and 4) CRF is not primarily a consequence of a concurrent psychiatric condition, such as major depression. As the number of cancer survivors continues to grow, CRF continues to be an undermanaged and reported problem in clinical settings. CRF exerts a major burden on their life in the short and long term, impairing cancer survivors' physical, psychological, and/or occupational functions and limiting their ability to perform daily activities.[13] Along with the provided clinical guidelines listed above, cancer survivors should be screened for the presence and severity of CRF at their initial clinical visit, at appropriate intervals during and after cancer treatment, and as clinically indicated. The clinical CRF guidelines have four defined evaluation stages.[5] (i) During the first phase, screening, health care professionals screen for the presence of CRF and intensity level. (ii) During the primary evaluation step, clinicians conduct an in-depth CRF assessment with a focused history of current disease status, type, length of treatment, and physical examination. Evaluating CRF severity regarding the onset, pattern, duration, change over time, and interference with function. (iii) The intervention stage utilizes the cancer survivor's clinical status to suggest nonpharmacologic and pharmacologic interventions, which may include nutrition changes, education, and counseling. (iv) Reevaluation emphasizes that CRF is continuous, and the health care professional should continue to monitor CRF both throughout and after treatment.

CRF PREVALENCE

Comprehension of the prevalence of CRF among individuals living with cancer is crucial for the assessment, treatment, and management. It also plays a significant role in cancer survivors' care by physicians and cancer survivors' education and lifestyle management, as the

occurrence of CRF is associated with high mortality by predicting shorter recurrence-free survival (risk ratio 1.3; $p < 0.01$) and overall survival (risk ratio 1.2; $p < 0.01$).[33]

However, the current literature reports a large variability of overall CRF prevalence among studies with CRF as the primary outcome. A systematic review and meta-analysis demonstrated a pooled estimate of CRF prevalence of mixed cancer types was between 49%-62%[4,34,35] , with an aggregated prevalence of cancer survivors reporting high rates of CRF, 49%, 43%, and 52%.[34] This large variability in the range of the prevalence of percentages of CRF may be attributed to several reasons. First, multiple scales are used to measure CRF that differ in sensitivity and specificity. Second, studies have different sampling strategies that have led to a variety of estimates of prevalence. In addition, the estimates that are found in systematic reviews and clinical guideline papers are composed of various studies, with differing study protocols and inclusion criteria; therefore, the quality of these analyzed studies and sampling strategies may contribute to the variability in reporting. For example, many studies report a limitation is that participants were not included/excluded based on baseline CRF levels. Implying that individuals may be hitting the ceiling effect post-study, leading to the need for participants to hit a CRF criterion to be included in the study to test specific intervention effects on CRF outcomes. Third, there is not currently a universally accepted definition of CRF used by clinicians and health professionals, which hinders accurate reporting of CRF in different settings. Finally, CRF is a subjective experience that can be modulated by the availability of social support, physical exercise, and cancer survivors' emotions. [34] Thus, different individuals may experience CRF under different conditions, which may alter how two participants fill out the same questionnaire, leading to the variation in prevalence estimates.

CRF PREVALENCE ACROSS THE CANCER CONTINUUM

CRF may be elevated before treatment onset, and typically increases to the greatest severity during cancer treatment; however, elevated levels are often reported for up to 5-10

years post-treatment completion,[6] demonstrating the critical need to address screening and treatment across the cancer continuum. On an individual level, the goal of CRF management throughout the cancer continuum should include reducing CRF severity, lowering distress, and decreasing interference with daily or usual activities.[36]

The cancer continuum can be categorized into four phases: diagnosis/pre-treatment, treatment, post-treatment/survivorship, and palliative care (Figure 2.1). [1]

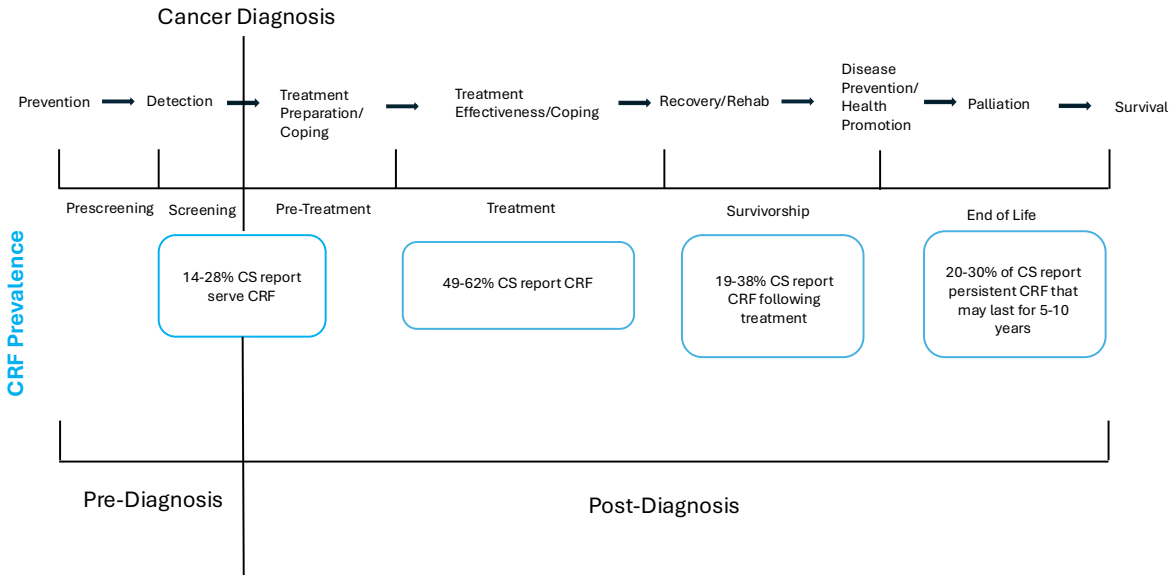

Figure 2.1. Cancer Continuum and CRF Prevalence

Diagnosis/Pre-treatment Phase: Pre-Treatment CRF

The pre-treatment phase encompasses the period between diagnosis and treatment initiation. Extreme or unusual tiredness without explanation is often an early warning sign for individuals to seek medical care, and can be an early warning sign of a cancer diagnosis.[37] Previous research investigated CRF levels in cancer survivors who were recently diagnosed, before initiation of treatment, and reported that 24% of the cancer survivors were severely fatigued, ranging from 14 to 28%. The presence of severe CRF was the lowest in cancer

[1] Continuum based on Yang et al. 2024

survivors with prostate cancer (14%), but higher in breast cancer survivors (20%) and gastrointestinal cancer survivors (28%). Factors that were found to influence the severe CRF levels were lower physical activity and depressive mood. In addition, more impaired sleep and rest appeared to be related to CRF before treatment.[38]

Treatment Phase: Treatment CRF

The treatment stage is between treatment initiation and completion, specifically for cancer survivors on primary treatment. There is a wide range of CRF prevalence reported during active treatment, with studies reporting 62% of cancer survivors experiencing CRF.[4] In the clinical setting, the goal for CRF during treatment is to mitigate the worsening of CRF severity across the course of treatment and provide counseling about the pattern of onset, duration, mood, physical function, and education on several interventions.

In cancer survivors with moderate to severe CRF, the presence of CRF contributing factors (eg, concurrent symptoms, emotional distress, sleep disturbances, anemia, nutritional alterations, inactivity/deconditioning, and comorbidities, such as hypothyroidism and cardiomyopathy) and the management plan to address these issues should be documented at regular intervals.[39] One meta-analysis compared pooled prevalence rates of CRF between cancer severity and found that 46.7% of cancer survivors with localized cancer and 60.6% of cancer survivors with advanced cancer reported CRF. [4]

Post-Treatment/Survivorship Phase: Post-Treatment CRF

Post-surgery consists of the time following the completion of primary treatment, during nonsurgical treatments (adjuvant and neoadjuvant). Although symptoms frequently improve following treatment completion, CRF persists in a substantial number of cancer survivors. It has been estimated that 19–38% of survivors experience significant levels of CRF following treatment.[40]

Palliative Care/Extended Survival Phase

The extended survival phase refers to the length of time someone lives following a cancer diagnosis, with exercise's focus on helping cancer survivors combat the psychological struggles of cancer and helping transition back to a "normal" lifestyle and support a return to the level of health experienced before treatment. Finally, the palliative phase includes cancer survivors who have a progressive, life-altering diagnosis, with a focus on symptom management and maintenance of quality of life. In a longitudinal study assessing CRF at two timepoints (1-5 years and 5-10 years) in a sample of 763 breast carcinoma survivors, it reported that 35% of women were fatigued at the 1–5-year assessment, 34% reported significant CRF at 5-10 years and 21% reported CRF at both assessment timepoints.[39] Another study utilized the Brief Fatigue Inventory to assess the estimates of CRF in head and neck cancer (HNC) survivors one year post-radiation therapy. The study found that 67% of HNC reported mild CRF and 18% reported moderate to severe CRF.[41] Literature shows that CRF may continue for years after treatment is completed and even when the cancer is cured. Although CRF typically abates in the year after cancer treatment, approximately 20–30% of cancer survivors report persistent CRF that may last for 5–10 years post-treatment and beyond.

CRF ASSOCIATED PATIENT AND CLINICAL CHARACTERISTICS

Across the cancer continuum, the prevalence rates of CRF can depend on a multitude of factors and severity levels, including type of cancer, treatment phase and type, sex differences, and assessment methods.[33] A systematic review reported that cancer survivors with brain cancer had the highest prevalence of severe CRF, followed by breast cancer survivors, with the lowest CRF prevalence reported by gynecologic cancer. Considering treatment modality, cancer survivors who underwent chemotherapy exhibited the highest prevalence of 'moderate to severe' CRF (54.5%), followed by the surgery (45.0%) and endocrine therapy groups (34.0%), meanwhile, the top three highest prevalence of 'severe' CRF were observed in those administered targeted therapy (37.1%), stem cell transport CT (34.7%) and chemotherapy

(33.1%). Research has also reported CRF prevalence variability with sex, as female cancer survivors(38.4%) exhibited a 1.4-fold higher prevalence than males (29.2%).[4] This sex difference may be due to men reporting CRF less frequently to their provider or that women are less likely to receive social support during their diagnosis. These findings suggest that future studies need to continue to identify factors that impact CRF levels from diagnosis into survivorship to identify distinct profiles of CRF over time, despite important implications for developing a more precise understanding of CRF and implementing personalized interventions.

The high incidence of CRF is coupled with distress; cancer survivors have reported CRF to be the most distressing symptom they have experienced, even more so than pain. CRF affects one's perceived overall QOL and has also been coupled with decrements in physical, psychological, and social functioning.[42] In addition to the multidimensional nature of the effects of CRF, CRF's multifactorial etiology is also rooted in complex physiological disruptions associated with cancer and its treatments.

ETIOLOGY OF CRF

The underlying cause of CRF remains unclear but has been linked to a variety of interconnected biological, behavioral, psychological, and treatment-related mechanisms (Figure 2.2). Al-Majid et al. have proposed a biobehavioral model that helps illustrate the complexity of CRF.[43] In summary, this model includes several factors:

(i) Biological mechanisms include decreased muscle mass and strength, anemia, immune system impairment, and elevated pro-inflammatory cytokines, such as IL-6 and TNF-α.

(ii) (ii) Psychologically, CRF correlates strongly with depression and anxiety, affecting treatment adherence and overall health management, thus impacting survival. In addition, CRF can also reduce the quality of life, diminish social support, and increase sleep disturbances.

(iii) (iii) Functional mechanisms include decreased physical functioning and functional capacity.

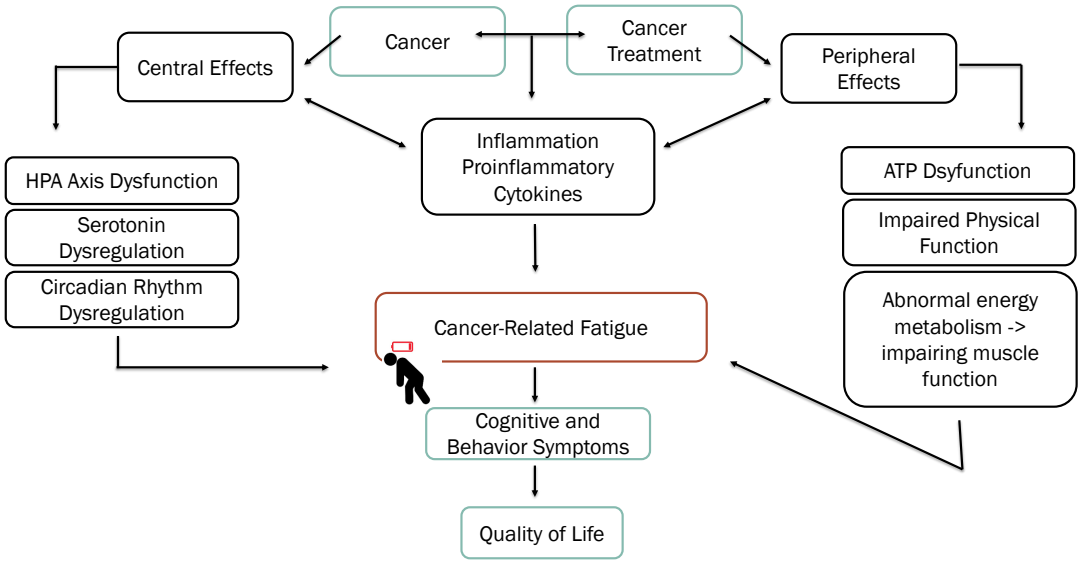

Figure 2.2 Hypothesized CRF Mechanisms

Understanding and addressing these multifaceted mechanisms in a clinical and research setting is crucial for improving the quality of life and survival rates of cancer survivors. The etiology of CRF is multifactorial, with varying degrees of contribution from biological cancer factors, cancer treatment, inflammation, immune system dysregulation, hypothalamic–pituitary-adrenal axis dysfunction, cachexia, and poor sleep quality.[42] Although the underlying physiological mechanisms for CRF have not been fully elucidated, researchers suggest that there may be some interconnected processes that are correlated with CRF levels in cancer survivors. Cancer and its treatment can have a profound effect on the brain and body, impacting multiple systems that may be relevant for CRF. CRF is comprised of both peripheral and central physiological aspects.

Peripheral and Central Fatigue

Cancer survivors frequently experience weakness or reduced energy, which may stem from peripheral fatigue, characterized by the muscle's inability to sustain performance despite

adequate neural stimulation. According to the ATP dysregulation hypothesis, cancer or its treatment may damage the sarcoplasmic reticulum, leading to elevated intracellular calcium levels and/or mitochondrial dysfunction. These changes can hinder skeletal muscle regeneration and compromise physical performance.[44] Cancer survivors often experience disruptions in energy metabolism, including reduced energy intake due to appetite changes and treatment-related side effects. These factors can contribute to anemia and nutritional deficiencies, ultimately impairing ATP production.[45] For instance, research has shown that cancer survivors with CRF tend to fatigue more quickly during motor tasks, suggesting impaired muscular endurance linked to energy metabolism deficits.[44] In contrast, central fatigue originates within the central nervous system (CNS), which is marked by an inability to sustain physical or mental tasks that rely on self-motivation and internal drive, despite the absence of observable cognitive impairment or motor weakness. [44]

While many mechanisms may contribute to CRF, the following sections will focus on those with both empirical support and relevance to physiological responses to exercise: inflammation and cytokine dysregulation, hypothalamic-pituitary adrenal (HPA) axis dysfunction, circadian rhythm disturbances, and loss of physical fitness. These mechanisms were selected to be discussed in this dissertation due to their potential bidirectional interaction with exercise and relevance to both central and peripheral CRF processes.

Inflammation and Cytokine Dysregulation

In current research, the CRF mechanism that has gathered the most empirical attention, and research is the role of inflammation/cytokine dysregulation. Different components of the pro-inflammatory cytokine network may be associated with different aspects of CRF, in different cancer survivor groups, at different stages of the cancer trajectory. Researchers have proposed that pre-treatment tumors may be a source of inflammatory cytokines. Additionally, during treatment, treatments used to eradicate a variety of cancer types can activate the pro-inflammatory cytokine network; for example, cytokines may be produced in response to tissue

damage from chemotherapy and radiation, both pathways leading to symptoms of CRF via cytokine signaling in the CNS.[30] Research has demonstrated that the tumor micro-environment contains elevated levels of proinflammatory cytokines such as IL-1, IL-6, and TNF-α and their receptors.[29] Cytokines such as C-reactive protein (CRP), interleukin-1 receptor antagonist (IL-1ra), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNFα) have been implicated in the development of both central and peripheral fatigue. These pro-inflammatory mediators may contribute to central fatigue through pathways involving anemia, cachexia, and depression, and to peripheral fatigue by impairing mitochondrial function and energy production.[44] Peripheral inflammation is communicated to the central nervous system (CNS) through multiple pathways, including the activation of sensory nerves. This signaling triggers the release of prostaglandins and pro-inflammatory cytokines.[40] These cytokines are linked to symptoms such as anemia, cachexia, anorexia, fever, infection, and depression, all of which can contribute to CRF. [46] Cachexia, in particular, has been associated with elevated levels of inflammatory cytokines, including various interleukins and TNF-α, and may also reflect underlying disruptions in energy metabolism.[47]

CRF is considered a key element of “sickness behavior”, which is driven by inflammatory signals that act on the brain to evoke feelings of fatigue.[40] Wang and colleagues investigated the relationship between inflammation and sickness symptoms in cancer survivors receiving combined radiation and chemotherapy. They observed acute elevations in inflammatory markers that were closely correlated with increases in CRF and other sickness-related symptoms.[30] Similarly, studies in ovarian cancer survivors assessed before surgery found a positive association between plasma IL-6 levels and CRF.[48,49] In another study involving individuals undergoing radiation therapy for early-stage breast or prostate cancer, elevations in CRP and IL-1 receptor antagonists were linked to increased CRF.[50] Among breast cancer patients receiving chemotherapy, changes in IL-6 throughout treatment were also associated with fluctuations in CRF.[30] These findings suggest that proinflammatory cytokines may

contribute to CRF independently or in conjunction with other mechanisms such as vagal afferent signaling, disruption of the HPA axis, or circadian rhythm disturbances that influence fatigue perception. [30]

HPA Axis Dysfunction

Alterations in the HPA axis have been proposed as a contributing mechanism to CRF. The HPA-dysfunction hypothesis suggests that cancer and its treatments, either directly or indirectly, disrupt normal HPA axis functioning, resulting in endocrine changes that may contribute to CRF.[47] Treatments such as glucocorticoids, radiotherapy, and certain chemotherapy agents can suppress the HPA axis, leading to a blunted stress response and reduced energy levels.[44] The HPA axis controls the release of the stress hormone cortisol in response to physical or psychosocial stress. Additionally, cortisol has important biological effects; these include the regulation of the cardiovascular system, including blood pressure, immune system function, metabolism, and inhibiting cytokine production. The HPA axis regulates inflammatory effects via a negative feedback loop at the level of the hippocampus, hypothalamus, and pituitary.[44] The HPA axis regulates the release of cortisol, a key stress hormone involved in maintaining cardiovascular function, immune regulation, metabolism, and the suppression of proinflammatory cytokines.[40] In terms of cortisol production, breast cancer survivors with persistent CRF show alterations in diurnal cortisol slope, with elevated levels of evening cortisol relative to non-fatigued controls.[30]

Cortisol production follows a diurnal rhythm, typically peaking in the morning and declining throughout the day. In individuals with CRF, particularly breast cancer survivors, this natural pattern is often disrupted. Studies have found that fatigued survivors exhibit flatter diurnal cortisol slopes, characterized by lower morning cortisol levels and elevated evening levels, in contrast to non-fatigued controls.[51] Fatigued breast cancer survivors had a significantly flatter cortisol slope than non-fatigued survivors, with a less rapid decline in cortisol levels in the

evening hours. At the individual cancer survivor level, survivors who reported the highest levels of CRF also had the flattest cortisol slopes.[52]

Circadian Rhythm Disruption

Another proposed mechanism contributing to CRF is circadian rhythm dysregulation, which is closely linked to HPA axis dysfunction. Circadian rhythms are internal, genetically, and physiologically regulated patterns that follow an approximately 24-hour cycle and are governed by the body's biological clock. [46] Disruptions in circadian rhythms in cancer survivors may result from multiple factors, including tumor-related inflammation and endocrine disturbances, cancer treatments such as chemotherapy and radiation, and behavioral changes like altered routines, stress, and medication use.[44]

Cancer survivors frequently report poor sleep quality and insomnia, leading to disrupted rest-activity patterns, such as excessive wakefulness during the night and prolonged sleep during the day. Individuals with CRF often exhibit flatter diurnal cortisol slopes, with less decline in cortisol levels during the evening. Additionally, greater CRF has been associated with lower daytime activity, more restless sleep, and dampened or inconsistent 24-hour rest-activity rhythms. [46] Together, these findings suggest that disrupted circadian regulation may significantly contribute to the persistence and severity of CRF.

Loss of Physical Fitness

Additional explanations for CRF among cancer survivors include loss of fitness, particularly due to sarcopenia, a common side effect of cancer and its treatments. Sarcopenia involves metabolic alterations in skeletal muscle that result in decreased muscle mass and contractile strength, which likely intensifies the physical sensation of fatigue.[40] Cachexia, a more severe form of muscle and fat wasting, is also prevalent in cancer populations. It is characterized by unintentional weight loss, anorexia, muscle atrophy, impaired physical function, and reduced survival. Cancer cachexia affects approximately 50% of all cancer survivors and up to 85% of those with certain malignancies, such as gastric or pancreatic

cancers. Cancer survivors also exhibit lower oxygen consumption, which, combined with decreased muscle strength, makes the relative intensity of daily living activities closer to the anaerobic threshold.[46] Alterations in autonomic nervous system function may also play a role in CRF. For example, studies in breast cancer survivors have found associations between CRF and elevated norepinephrine levels, suggesting decreased parasympathetic tone. These autonomic imbalances were observed both at rest and in response to psychological stress, further supporting their relevance to CRF.[30]

Given the multifactorial nature of CRF, measurement of CRF remains a challenge in the field. One of the barriers to the assessment and management of CRF may be a lack of information about the mechanisms underlying this symptom, risk factors, and effective treatments.

MEASUREMENT OF CRF

Given the multifactorial etiology of CRF, it is conceptualized as a multidimensional symptom comprising physical, emotional, and cognitive aspects, as well as a subjective phenomenon, appraised by the individual via self-report. In the current literature, there is no "gold standard" measure of CRF, and there is a lack of consensus for which of the available measures should be used in a given clinical or research context.[53] This has led to inconsistency in measures used for CRF in interventions, adding a layer of difficulty for researchers and clinicians to compare findings across studies or inform clinical practice.

Despite a lack of consensus on which measure to use, the most common form of measure for CRF is self-report questionnaires. Self-report questionnaires are one of the conventional ways of measuring CRF because CRF is a subjective condition involving a combination of symptoms and is experienced and reported differently by each person; therefore, the in-depth assessment must include the cancer survivor's self-assessment of CRF. A variety of questionnaires exist that have been tested for reliability and validity, including single-item and

multiple domain assessment tools.[53] Currently, in clinical practice, there are over 50 different measures that assess CRF.[36] Self-report questionnaires can be broken up further into two categories: (1) unidimensional and (2) multidimensional. Both measurement types are important in research; however, each has advantages and disadvantages.

Unidimensional Measures

Unidimensional measures may be appropriate if the main outcome of interest is a single outcome, such as CRF severity. In addition, unidimensional measures are typically shorter, easier to administer, and are more suitable for longitudinal data, as they are less burdensome for the participant and are often used in clinical settings to screen cancer survivors for CRF. However, they may oversimplify the complexity of CRF by focusing mainly on severity, which, conversely, makes these measures limited in their assessment of CRF domains.[53] Some of these measures include single-item tools such as the Brief Fatigue Inventory (BFI), Functional Assessment of Chronic Illness Therapy- Fatigue Scale (FACIT-F), NCCN Intensity Scale, Fatigue Intensity Scale, and the Visual Analogue Scale (VAS).[7] Each questionnaire measures CRF at a different time domain. For example, the BFI assesses CRF over the past 24 hours, the FACIT-F scale over the past seven days, and the VAS and NCCN scale, “in this exact moment”.

Multidimensional Measures

In addition to the cancer survivors’ self-report, using a multidimensional approach to elicit more information will enable the clinician to better manage the CRF. Descriptors beyond severity, such as onset, duration, interference in daily activities, exacerbating and palliative factors, and treatments tried, are helpful.[7] CRF is a multidimensional, patient-reported outcome that affects a cancer survivor’s physical, cognitive, and emotional well-being.

Multidimensional measures are better utilized for exploring impacts on various CRF domains. However, these questionnaires contain numerous questions, in turn making them lengthy and potentially burdensome to participants. Multidimensional measures include the Cancer Fatigue Scale (CFS), Fatigue Assessment Questionnaire (FAQ), Revised Piper Fatigue

Scale (PFS-R), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). The CFS and PFS-R assessed CRF in the time domain of "in this exact moment," and the FAQ and EORTC QLQ-C30 assessed CFF over the past week.

Self-Report Questionnaire Limitations

The limitation of self-reported questionnaires is that there is no clear recommendation regarding the most appropriate subjective measure. The prevalence of 'severe' CRF was the highest in the data assessed by the EORTC QLQ-C30 (EORTC, 40.9%) and Checklist Individual Strength (CIS, 34.6%), whereas total CRF prevalence was the highest when measured by the Brief Fatigue Inventory (BFI, 64.0%).[33] Other key considerations when deciding on a questionnaire are the intervention or research context in which CRF is being assessed. Additionally, the purpose of assessment, the relevant timeframe of interest, measuring the outcome of interest, and scoring guidelines (cut-off scores/MCIDs). An MCID is defined as the smallest change in a score considered to be clinically meaningful and is valuable for evaluating the effectiveness of interventions aimed at CRF management. Currently, only 32% of self-reported measures have an established cancer-specific MCID.[53] This is problematic as it limits the comparability of findings across studies, precluding robust conclusions about the relative effectiveness of different interventions to inform clinical practices.

CRF Questionnaire Development

To help guide researchers in determining what CRF self-reported measure to utilize in their intervention studies, researchers have compiled a review to evaluate the diverse range of patient-reported outcomes, consisting of two phases.[53] The first phase is content evaluation, assessed according to the NCCN's definition of CRF and whether the item content of each measure captured CRF that is (1) related to cancer and/ or cancer treatment; (2) distressing; (3) persistent; and captures (4) physical, (5) emotional, and (6) cognitive aspects of CRF; as well as CRF (7) that is not proportional to recent activity; and (8) interferes with usual functioning. Not a

single self-reported measure captured all aspects of the NCCN definition. Physical, emotional, and cognitive CRF were the most frequently assessed domains, captured by more than half of the measures. In contrast, very few measures assessed whether CRF was distressing, persistent, disproportionate to recent activity, and related to cancer and/or cancer treatment. Only five measures (Piper Fatigue Scale-Revised, Patient Reported Outcomes Measurement Information System [PROMIS] Fatigue Short Form, Multidimensional Fatigue Symptom Inventory Short Form, Modified Fatigue Impact Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-Related Fatigue) covered at least 50% of the conceptual domains specified by the NCCN definition of CRF.

The second phase was an appraisal of psychometric properties based on the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) Each measure was evaluated against the following COSMIN criteria: item generation (literature, cancer survivor interviews, clinician/expert interviews), item reduction (percentage of missing total scores, percentage of missing items, factor analysis), reliability (internal consistency and test0retest), content validity, item total correlations, convergent/divergent validity, known group validity, cross-cultural validity, and responsiveness. Only three measures (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life—Fatigue Questionnaire [EORTC QLQ-FA12], Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT/FACT-F], and Fatigue Symptom Inventory) had evidence for all eight psychometric properties.

Self-reported questionnaires provide valuable insight into the subjective and physiological dimensions of CRF. However, understanding strategies that can alleviate both the perceived and physiological burden of CRF in cancer survivors is vital. Additionally, cancer survivors' management is often complicated by the misconception held by cancer survivors, their caregivers, and even clinical staff that CRF is an inevitable and unavoidable consequence of cancer and its treatment. The following section discusses these interventions, with a

particular focus on exercise as a prominent non-pharmacological modality for mitigating CRF across the cancer continuum.

CRF MANAGEMENT

Numerous psychological, lifestyle, and pharmacological interventions have been tested to address the significant burden of CRF on cancer survivors. This includes pharmacological approaches such as psychostimulants, antidepressants, and erythropoietin-stimulating agents (ESAs), and non-pharmacological interventions including psychosocial and exercise. There is currently no effective pharmacological treatment that is recommended to alleviate CRF. In current research, the effectiveness of treating CRF varies among the different pharmacological treatments. With certain interventions showing CRF improvements, and others having a similar effect as a placebo. However, certain treatments target specific aspects of CRF, for example, ESA is used to improve anemia and antidepressants to fight depression;[54] therefore, the contributing factors of the cause of CRF should be considered, along with possible side effects for each survivor.

A seminal meta-analysis by Mustian et al. (2016) compared the effects of exercise, psychological, exercise plus psychological, and pharmaceutical interventions on CRF. Results showed that exercise and/or psychological interventions were more effective for improving CRF during and after treatment than pharmaceutical interventions.[11]

Psychological interventions include psychotherapy, psychoeducation, and mind-body. The main goals of these interventions are to help cancer survivors restructure their cognitive appraisal of CRF, change their coping strategies and behavior, and address self-help or self-care strategies.[55] Some interventions include elements such as relaxation techniques, energy conservation, and stress management, and there is some evidence showing that such strategies can improve QoL and reduce the subjective feeling of CRF. Specific interventions include mindfulness-based cognitive therapy and yoga. A systematic review evaluating

psychological interventions on CRF following treatment reported that 23 out of the 33 interventions included reported a significant effect of the interventions on CRF.[56] However, the overall quality of the evidence about psychological interventions for CRF after the completion of cancer treatment is low, and the limited generalizability of psychosocial interventions makes it difficult for researchers to examine the true effects of decreasing CRF. Another non-pharmacological intervention is stress management therapy (SMT). SMT provides cancer survivors with tools to manage stress and anxiety, modify negative thought patterns contributing to CRF, and is a non-invasive and low-risk intervention. A study of breast cancer survivors who participated in weekly sessions of SMT reported no significant differences in changes in CRF intensity after the intervention; however, there was a greater reduction in CRF-related daytime disturbances compared to the control group.[57] Additionally, other supplemental interventions for CRF include nutritional management to help manage deficiencies caused by anorexia, diarrhea, nausea, and vomiting. Another includes sleep management and sleep hygiene, which involves establishing a regular sleep schedule, avoiding physical or mental exercise close to bedtime, improving the bedroom environment, and acupuncture, which has been proven to be safe and effective for CRF management.[58]

EXERCISE FOR THE MANAGEMENT OF CRF

Exercise has become a widely recognized non-pharmacological intervention that is effective for managing CRF. Unlike pharmacological treatments, which often provide only temporary relief or come with unwanted side effects, exercise targets both physiological and psychological mechanisms and offers a sustainable, evidence-based approach to alleviating CRF across all stages of survivorship. Exercise as a management tool for CRF is a primary focus of this dissertation because numerous randomized controlled studies and meta-analyses have proven that exercise is safe for cancer survivors and has a systemic effect, targeting numerous side effects of treatment.[3] In addition, the modality of exercise is adaptable and can be personalized

to cancer survivors depending on treatment status, physical function, and personal factors based on the unique needs of cancer survivors.

Exercise (i.e., a subset of physical activity that is structured, planned, and intended to improve some aspect of health and/or fitness) has consistently been shown as an effective treatment for CRF.[59,60] Cross-sectional evidence has consistently demonstrated an inverse association between exercise and CRF, and a pivotal review found that exercise interventions were more effective for reducing CRF compared to pharmacological treatments.[11] Most recently, an umbrella review synthesizing 44 systematic reviews and meta-analyses also found consistent evidence to support the efficacy of exercise interventions for reducing CRF.[61] Taken together, this evidence suggests that "chronic exercise" (i.e., multiple exercise sessions done over several weeks or months) reduces CRF, In addition, there have been more than 100 clinical trials that have assessed the efficacy of exercise training to improve CRF, as appropriate exercise can improve cancer survivors' aerobic capacity, muscle strength, body composition, reduce CRF and improve QOL.[62] When compared to pharmacologic interventions, one meta-analysis noted a moderate effect size of 0.30 for 69 exercise trials compared with a nonsignificant effect size of 0.09 for 14 pharmacologic interventions for CRF.[62]

Based on this body of evidence, exercise recommendations and guidelines for the management of CRF have been established. The guidelines for the management of CRF in cancer survivors from the American Society of Clinical Oncology (ASCO) suggest that, given the benefit of exercise on broad dimensions of physical and emotional well-being, initiating or maintaining an exercise program should be helpful for all cancer survivors. The review did not identify an optimal type, dose, intensity, or duration of exercise that is maximally effective for reducing CRF; however, mentioned that benefits have been seen with interventions that combine aerobic and resistance training, as well as resistance-only interventions, offering maximal flexibility for survivors to choose a program that works for them.[63] The National Comprehensive Cancer Network (NCCN) suggests moderate-intensity exercise for at least 150

minutes per week and strength training 2-3 times per week.[64] And finally, the American College of Sports Medicine's 2019 Exercise Guidelines Roundtable recommends exercise programs that last at a minimum of 12 weeks and consist of 3x per week and 30 minutes of moderate-intensity aerobic exercise, plus 2x per week of resistance training.[3]

PLAUSIBLE PHYSIOLOGICAL MECHANISMS FOR THE EFFECTS OF CHRONIC EXERCISE TRAINING ON CRF

There are several possible mechanisms for how chronic exercise can reduce CRF. Exercise plays a crucial role in reducing CRF by improving physical fitness and counteracting inflammation. Chronic exercise enhances aerobic capacity and lean muscle mass, which helps combat physical deconditioning and increases the ability to complete activities of daily living.[40] Increased muscle strength and endurance may also help alleviate psychological stress and improve sleep, which both have the potential to be linked to CRF. Beyond increased fitness, exercise exerts anti-inflammatory effects to help reduce CRF.[40] Regular exercise decreases fat mass, particularly visceral fat, leading to a reduction in pro-inflammatory adipokines that contribute to chronic inflammation. Exercise has also been shown to increase levels of anti-inflammatory cytokines such as interleukin 10 (IL-10), while simultaneously reducing tumor necrosis factor-alpha (TNF- α) expression and C-reactive protein (CRP) levels.[14] Since chronic inflammation plays a central role in CRF, these anti-inflammatory effects directly impact peripheral and central CRF mechanisms, through reduced ATP production and changes in HPA axis activity.[14]

ACUTE EFFECTS OF EXERCISE ON CRF

Although the evidence base for exercise interventions (i.e., exercise training over weeks to months) to reduce CRF is well established, less is known about the immediate, or "acute" effects of exercise on CRF (i.e., reductions occurring after a single bout of exercise).

Despite the importance of exercise in managing CRF, current literature frequently reports this symptom as a major obstacle impacting patients' adherence to exercise.[16,17]

Therefore, there is currently an exercise paradox where it can be daunting for cancer survivors who are experiencing moderate or high levels of CRF to begin or adhere to regular exercise when the benefit is somewhat distal (i.e., weeks or months before seeing reductions in CRF). Educating patients about the effects of exercise and organizing the sessions according to the weekly fatigue patterns could be a potential solution to break this paradox. Therefore, acute bouts of exercise may be a necessary tool to reduce and manage CRF on a daily level and serve as a promising strategy to reduce the barrier of low engagement in exercise. Determining whether exercise has an acute effect on reducing CRF could have the potential to profoundly influence how oncology clinicians and exercise professionals discuss and prescribe exercise to cancer survivors with the intent of alleviating CRF.

In non-cancer populations (e.g., college students,[65] individuals with major depressive disorder,[66] and healthy adult men [67]), previous studies have examined the acute effect of exercise on fatigue and energy. In a systematic review summarizing these studies, Loy et al. reviewed 16 studies involving a total of 678 participants aged 18 to 55 years.[68] Fatigue and energy were self-reported, but specific definitions were not included in search terms, and the measures varied. Four studies focused on resistance exercise, while the remaining studies exclusively examined aerobic exercise. Exercise intensity varied across all studies and was measured using percentages of one-repetition maximum (RM) (15-80%), predicted heart rate max (40-80%), heart rate reserve, and oxygen consumption (VO_2). Findings demonstrated that energy increased immediately following a single exercise session; however, the effects of fatigue were inconsistent.[68] Interestingly, a significant three-way interaction was detected for changes in fatigue immediately after exercise that depended upon increases in energy, and the intensity and duration of exercise. When increases in energy were at least moderate, fatigue was reduced after light-to-moderate intensity exercise, but not after vigorous exercise lasting longer than 20 minutes. Although these studies in non-cancer populations (primarily college-age students) provide some support for the premise that exercise can reduce fatigue immediately

afterward, these findings may not be directly transferable to CRF, given the differences in the etiology of general fatigue (i.e., usually temporary; resolving with rest, recovery, and other lifestyle factors) vs. CRF (i.e., debilitating exhaustion that is not alleviated by rest and that can persist for months to several years[30]). Thus, this highlights and supports the need to further explore whether these relationships are similar for CRF.

In regard to the acute effects of exercise on CRF, only three previous studies have examined changes in CRF from immediately before to after at least one bout of exercise. A retrospective study by Matsugaki et al. (2018) examined CRF among cancer survivors before and after a single in-patient exercise session.[18] An RCT by Cohen et al. (2019) examined the immediate effects of aerobic exercise combined with relaxation training compared to aerobic exercise and relaxation alone on CRF,[20] and the other study, an RCT by Siebert et al. (2022) compared the effects of four exercise interventions with varying intensity and type.[19] Study details are described in Table 2.1.

Table 2.1 Summary of acute exercise and CRF studies

Citation	Participants Characteristics	Intervention Exercise Prescription	CRF Measurement And CRF Timepoints	Study Findings
Matsugaki et al. (2018)	N=18 Hematologic cancer Currently undergoing Treatment	Retrospective Study F; Single Session I: Rate of perceived exertion (RPE) of 4/10 T: 20-40 min T: standing, sitting and walking	Cancer Fatigue Scale (CFS) [69] "Immediately" before and after session	CRF domains of physical, affective, cognitive and total decreased following the exercise session, however only scores of physical (p=0.023) and total (p=0.006) fatigue were significantly reduced
Cohen et al. (2019)	N=40 Breast Cancer Not currently undergoing treatment	RCT Aerobic only: F: 3 sessions (≥24 hr apart) I: 50-70% age predicted HRmax T: 20 min each (40 total)	Piper Fatigue Scale (PFS) [70] Before and after session (exact timeframe not specified)	There was a significant reduction in CRF from pre- to post-exercise in the combined and relaxation group only, with a large effect (Cohen's d =0.91)

		T: Stationary bike and quiet seated rest Relaxation only: F: 3 sessions (≥24 hr apart) T: 20 min each (40 total) T: Technology-based MBSR and quiet seated rest Combined: F: 3 sessions (≥24 hr apart) I: 50-70% age predicted HRmax T: 20 min each (40 total) T: Stationary bike and Technology-based MBSR		
Siebert et al. (2022)	N=33 Various Cancer Types Not currently undergoing treatment	RCT Moderate Endurance: F: 3x for 4 weeks I: 50–60% of VO2max T: 30 min T: cross-trainer or bicycle ergometer Vigorous Endurance: F: 3x for 4 weeks I: 70–80% of VO2max T: 30 min T: cross-trainer or bicycle ergometer Moderate Strength: F: 3x for 4 weeks I: 50-60% of 1RM T: 30 min T: weight machines Vigorous Strength: F: 3x for 4 weeks I: 70-80% of 1RM	Numerical Rating Scale (NRS)[71] Before and after session + three additional times per day (unspecified)	Both strength groups had the largest decrease in fatigue over the daily fatigue timepoints. The change in CRF from before to immediately after each exercise session was not reported.

		T: 30 min T: weight machines		

Taken together, findings from these three studies provide preliminary support for the potential for the acute effect of exercise to reduce CRF, however, small sample sizes and the heterogeneity of exercise protocols and measures of CRF limited our ability to draw definitive conclusions. Additionally, the timing of CRF measures varied, with immediate post-exercise reductions reported in two studies, and the other which measured CRF throughout the day.

PLAUSIBLE PHYSIOLOGICAL MECHANISMS FOR AN ACUTE EFFECT OF EXERCISE ON CRF

One plausible mechanism for the acute effect of exercise on reducing CRF may be via anti-inflammatory pathways, specifically, transient increases in IL-6. Previous studies have examined acute IL-6 changes following exercise, finding patterns such as increased IL-6 immediately post-exercise, which is more pronounced with higher intensity and longer duration exercise, peaking within 1-2 hours post-exercise and declining towards baseline values within 24 hours.[72,73] This acute increase in IL-6 immediately following exercise could upregulate the production of anti-inflammatory cytokines, including IL-10, IL-1Ra, and transforming growth factor beta (TGF-β), dampening the inflammatory response, potentially leading to acute reductions in CRF.[74] Indeed, in a large meta-analysis of 18 studies,[75] evidence showed that acute moderate-intensity exercise led to an increase in anti-inflammatory cytokines, with a marked response observed after high-intensity exercise.

An additional hypothesis of how acute exercise may temporarily alleviate CRF through anti-inflammatory effects is through sickness behavior, which is a coordinated set of behavioral and psychological changes, such as fatigue, cognitive dysfunction, and reduced motivation, driven by pro-inflammatory cytokines acting on the central nervous system. These symptoms, while adaptive during acute illness, become maladaptive when inflammation is chronic, as is often the case during and after cancer treatment. Cancer therapies such as chemotherapy and

radiation can trigger persistent low-grade inflammation through tissue damage and immune activation, leading to elevated levels of cytokines such as IL-6, TNF-α, and IL-1β. This inflammatory state is believed to underlie, in part, the development and persistence of CRF as a manifestation of sickness behavior.[44] Acute exercise may interrupt this cycle through transient, exercise-induced increases in IL-6 derived from skeletal muscle, which, unlike inflammation-associated IL-6, acts in an anti-inflammatory capacity. This surge stimulates the release of anti-inflammatory cytokines (e.g., IL-10, IL-1Ra, TGF-β) and suppresses TNF-α, thereby temporarily reducing systemic inflammation. Through this mechanism, a single bout of exercise may dampen central inflammatory signaling and reduce sickness behavior, leading to acute decreases in CRF.[40] This pathway provides a biologically plausible explanation for the observed reductions in fatigue within hours following an exercise session in cancer survivors.

In contrast, cancer and its treatments (i.e., chemotherapy, radiation, immunotherapy, and/or hormonal therapy) can activate the pro-inflammatory cytokine network; for example, cytokines may be produced in response to tissue damage. This damage has been associated with chronically increased levels of pro-inflammatory cytokines (i.e., IL-6 and TNF-α), which have been linked to inflammation-induced conditions, including CRF.[46,47] Chronic exercise training has been shown to have anti-inflammatory effects, including increased IL-10 and reduced TNF-α expression.[40]

Another plausible mechanism that supports the potential for the acute effect of exercise on CRF is the endocannabinoid system (ECS). The ECS regulates many systemic physiological processes in the human body, including emotions, mood, and somatic perception (e.g., the subjective perception of pleasure and pain).[76] Emerging evidence suggests the ECS may be altered in the presence of cancer. A recent review reported that dysregulation of the ECS via changes in receptor expression and signaling has been documented in many cancer types, suggesting that the ECS system might be a target for anti-cancer therapies, including exercise.[76] Exercise has been shown to elevate circulating levels of endocannabinoids (eCBs), particularly anandamide (AEA), with increases observed as soon as 15 minutes post-exercise, and the highest levels (2–3x increase) observed 30–45 minutes following exercise.[77,78] The release of endocannabinoids following exercise has also been referred to as "runner's high", characterized by increased sensations of euphoria and decreased pain up to 30 minutes post-exercise. Therefore, given the positive emotional arousal that can result from the release of endocannabinoids immediately following exercise, there may be potential for this response to contribute to a feeling of reduced CRF (Figure 2.3). However, to our knowledge, there are no studies that have examined ECS responses to exercise among individuals living with and beyond cancer.

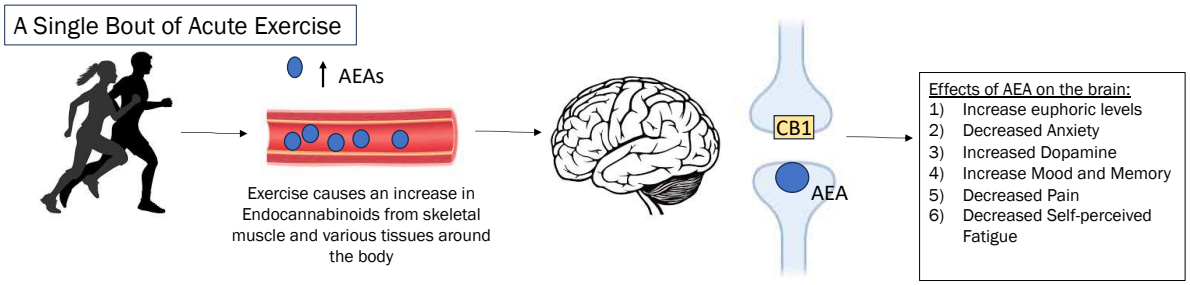

Figure 2.3

A third plausible mechanism for reduced CRF following an acute bout of exercise could be related to a positive psychological response. In healthy adults, prior research has shown that

exercise can enhance positive mood states, with effects occurring immediately after and lasting up to one day post-exercise.[79] Exercise has also been shown to increase levels of dopamine and serotonin immediately following exercise, which are linked to positive affect (i.e., the rewarding effect of exercise) and reduced feelings of depression and anxiety.[80] This positive emotional state immediately following exercise provides a plausible mechanism by which exercise could have an immediate effect on CRF because imbalances in neurotransmitters like dopamine and serotonin can contribute to fatigue. Exercise promotes the release and regulation of these neurotransmitters, enhancing mood and alleviating fatigue symptoms.[81]

SUMMARY OF GAPS IN THE LITERATURE

Although the effects of exercise interventions (i.e., exercise training over the course of weeks to months) on CRF have been well established, few studies have examined the acute effects of exercise on CRF. This leaves three major gaps in the literature that, if addressed, stand to contribute substantially to this body of evidence. First, there is a lack of studies that have established the efficacy of exercise in reducing CRF from immediately before to immediately after exercise. Second, the trend of CRF across the time course of the day following an exercise session is unknown. Third, it is unknown how self-selected exercise intensity may impact the acute effects of exercise on CRF pre-to-post exercise and across the time course of a day.

Exercise to reduce CRF from immediately before to immediately after exercise

There is currently a gap in the literature regarding the immediate impact of exercise on CRF, as current literature focuses on long-term (i.e., 8-12 weeks) exercise interventions for a reduction in CRF. In these studies, CRF is typically assessed only at baseline and post-intervention, failing to capture any acute effects of exercise on CRF. Understanding the acute effects of a bout of exercise could contribute to the literature base to support the use of exercise to alleviate CRF on a day-to-day basis and help promote exercise engagement among survivors

who perceive CRF as a barrier. This lack of information limits our understanding of whether exercise provides immediate CRF reductions or if a single bout increases self-reported CRF, which may influence motivation to engage in future exercise sessions.

The effect of an exercise session on CRF throughout the day

No previous studies have examined the effect of exercise on CRF at multiple time points within the same day following an exercise session. This is a significant gap in our understanding of the impact of exercise on the time course of fatigue throughout the day. The proposed study will address this gap by providing real-time, self-reported CRF measurements anchored around an exercise session to determine a potential "peak effect" of exercise on CRF and evaluate the time course of when CRF returns to pre-exercise levels.

Impact of exercise intensity on CRF

Cancer survivors are often given advice to exercise, but it is not clear how or with what intensity they should perform exercise for optimal benefits, as current exercise recommendations remain rather generic. Defining optimal intensity of exercise may help further improve the effectiveness of exercise programs to reduce CRF severity. Numerous chronic exercise studies have compared various exercise intensities on CRF in cancer survivors and have found mixed results. Despite the inconsistencies reported in chronic exercise interventions, there is no current knowledge on the impact of self-selected exercise intensity during a single exercise session on CRF. Exercise intensity may be a vital component to exercise prescription for highly fatigued cancer survivors, as different exercise intensities may have an effect in decreasing CRF, through reduced inflammation mechanisms. While low-to-moderate intensity may be preferred by most cancer survivors,[82] one study found that moderate-to-high-intensity exercise during cancer treatment was beneficial for physical CRF compared to low-intensity exercise.[83] Therefore, this is the first study to explore the impact of self-selected exercise intensity on CRF immediately following and several hours after a bout of exercise.

POTENTIAL IMPACT OF STUDYING THE ACUTE EFFECTS OF EXERCISE ON CRF

Studying the acute effects of exercise on CRF will make a significant impact on the field of exercise oncology in three ways: 1) exercise motivation and adherence, 2) symptom management, and 3) future exercise prescription.

Exercise Motivation and Adherence

Potential reductions in CRF immediately following exercise may provide cancer survivors with positive feedback or emotional arousal (i.e., affect), leading to greater motivation to continue to exercise even when an individual may not feel well beforehand. A large body of research has suggested that physical activity can boost emotional well-being (i.e., the "feel good" effect).[84] Accordingly, cancer survivors would be expected to engage in continued physical activity over time if they experienced a boost in positive affect but to exercise less across time if negative affect resulted. Positive affect refers to feelings that reflect a level of pleasurable engagement with the environment, such as happiness, joy, excitement, enthusiasm, and contentment, and contains both activated states, such as excitement, and non-activated states, such as peace. Longitudinal evidence suggests the relationship between physical symptom distress and depression and anxiety in cancer survivors may be mediated by changes in positive affect.[85] Thus, positive affect may indirectly impact important health and psychosocial outcomes among cancer survivors.

To understand the complex framework that combines physiological, psychological, and behavioral determinants of acute exercise and CRF, this research adapted a transdisciplinary model from prior research in exercise behavior. Bryan et al. hypothesized that the physiological effects (e.g., changes in body temperature, heart rate) of exercise influence the subjective experience of exercise (e.g., mood changes, perceived exertion, perceived reward), which in turn are important determinants of motivation to exercise (e.g., higher self-efficacy for exercise behavior and higher intentions to exercise) and of future exercise behavior.[86] The implications of this model are that individuals who are better able to cope with exercise physiologically (e.g.,

better modulation of body temperature) will experience more of the immediate positive benefits of exercise (e.g., increases in positive mood, less perceived exertion) and develop higher motivation to exercise (e.g., greater intentions). Finally, this motivation is translated into future exercise behavior, and future exercise behavior recapitulates the model, thereby reinforcing positive experiences of exercise behavior, more positive attitudes, greater intentions, and greater self-efficacy. Parallel to Bryan et al., this research hypothesizes that subjective experiences of exercise (e.g, positive affect, motivation) will influence decreased physiological effects (e.g, CRF). Perhaps the most well-documented immediate benefit of exercise is psychological; acute exercise increases positive mood and decreases negative mood.[87] The effects on mood are observed with as little as 10 min of exercise, although most studies involve approximately 30 min of exercise. It stands to reason that individuals who perceive an immediate mood benefit of exercise might be more likely to exercise. [88]

Symptom Management

Research has found that cancer survivors who do not regularly engage in exercise during chemotherapy may experience a greater magnitude of an acute increase in symptoms.[89] One study in breast cancer survivors examined the patterns of daily CRF in women with breast cancer who did and did not exercise while receiving the first three cycles of adjuvant chemotherapy and found that women who adopted exercise experienced fewer bad days of CRF and demonstrated decreasing CRF over the three courses of chemotherapy when compared to a non-exercisers group.[90] This is important because some cancer survivors have reported continually worrying about CRF, and they perceive exercise as a CRF trigger and rest as a reliever, in turn making them more prone to physical inactivity. This behavior results in the absence of perceived benefit from exercise by the cancer survivors, physical deconditioning consequences, and increased CRF and decreased activity may further predispose a cancer survivor to extreme CRF.[13]

CRF often interferes with the performance of daily activities, and qualitative studies have reported that the experience of CRF and its consequences have created negative limitations in cancer survivors' daily lives, resulting in an altered, in some cases deteriorated, quality of life.[91] On average, CRF tends to increase during cancer treatment and remit within one year after treatment completion. However, these averages mask considerable individual variability in the severity and course of CRF**.** This daily symptom burden emphasizes the critical need for exercise interventions to assess how exercise could be utilized to reduce CRF on a week-to-week or daily basis. The majority of studies to date have focused on average levels of CRF, which may obscure important individual differences in the severity and course of CRF over time.[92] For example, chemotherapy treatment for cancer survivors is typically delivered by a series of infusions separated by one, two, or three weeks, known as a cycle. The pattern of onset, duration, and intensity of side effects after chemotherapy infusions varies from cancer survivor to cancer survivor. In the first seven days after each infusion, increased feelings of CRF and depression, as well as elevated resting heart rate, reduced blood pressure, and sleep disturbances have been reported. During this time, a cancer survivor's physical capacity and willingness to engage in exercise may also be reduced.[93] Schwartz et al. (2000) concluded that CRF peaked two to five days after chemotherapy and resolved over time but never reached pretreatment status. [90]

Collecting CRF immediately before and after exercise also provides an educational component for cancer survivors. Since participants are asked to regularly rate their CRF on a scale of 0-10, they can learn to relate to how they feel and how CRF may be impacting their everyday activities. This new knowledge can also assist cancer survivors in self-selecting what intensity or dose of exercise they may want to participate in that day while factoring in other treatment-related side effects, sleep quality from the night before, and current nutrition status. For example, a study in hematological cancer following a bone marrow transplant[94] utilized a traffic light screening system (Figure 2.4) before each session to gauge how participants were

feeling that day, and it was used to guide exercise intensity and timing of intervals for that individual session.

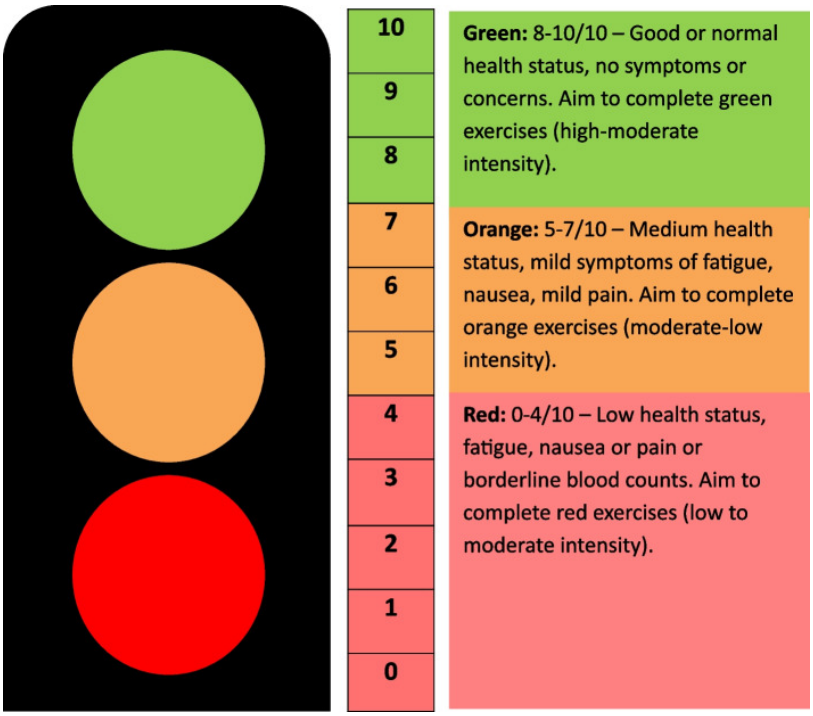

Figure 2.4 Traffic light screening system

Having the self-reported rating of CRF may help cancer survivors continue to adhere and show up for exercise sessions if they know they can base it on where they are that day, supporting cancer survivors to adopt and sustain exercise.

Undergoing treatment(s) that result in CRF may initiate declines in physical activity, and for these survivors, knowledge of the immediate benefits of exercise to alleviate CRF may provide an incentive to prevent or ameliorate a post-diagnosis drop-off in physical activity levels.

Future exercise prescription

Understanding that a single bout of exercise can lead to improvements in CRF has significant implications for healthcare and exercise professionals, particularly in the development of more targeted exercise prescriptions for cancer survivors. This evidence

provides oncology healthcare clinicians with a concrete, immediate benefit of exercise that can be communicated to cancer survivors who may be hesitant to engage in exercise due to CRF concerns. This is vital as a recent study identified that cancer survivors prefer to receive information about exercise through discussion with their clinicians and that if exercise was unmentioned by their oncology clinician, survivors perceived exercise to be unimportant.[95] Additionally, it enables cancer exercise specialists to tailor exercise recommendations based on CRF responses, optimizing exercise session timing and intensity to maximize benefits while minimizing potential exacerbations of symptoms. By integrating these findings into a clinical setting like an outpatient rehabilitation exercise program, this knowledge can help reach survivors who have a clinical level of CRF.

Outpatient rehabilitation exercise programs effectively support cancer survivors by improving function, managing treatment-related side effects, providing emotional support, and enhancing quality of life.[96] These programs, often embedded in healthcare settings, primarily focus on chronic exercise interventions, demonstrating long-term benefits for CRF [97]. However, with emerging evidence suggesting that acute exercise may help manage daily CRF symptoms, addressing this effect of a single exercise bout gap, these programs could enhance exercise prescriptions by incorporating strategies that offer both short- and long-term CRF management, helping survivors stay engaged in structured exercise programs.

SUMMARY

This literature review outlines the known effects of exercise interventions for reducing CRF and the potential impact of increasing our understanding of the acute effects of exercise on CRF. Importantly, exploring the acute effects of exercise on CRF may help cancer survivors and clinicians better understand how to utilize exercise to manage CRF daily. Currently, only three studies have measured CRF immediately before to immediately after exercise, and no studies have explored the time course of CRF following an exercise session, nor how exercise intensity

may impact these acute effects on CRF. The knowledge gained from these proposed studies will have a profound impact on how oncology rehabilitation and exercise professionals prescribe exercise and may also help cancer survivors overcome CRF as a barrier to engaging in exercise.

MANUSCRIPT I: THE ACUTE EFFECTS OF EXERCISE ON CANCER-RELATED FATIGUE

Introduction

The number of people living five or more years after a cancer diagnosis is projected to increase by upwards of 30%, resulting in an estimated 22.2 million cancer survivors by 2030 in the United States.[1] Advancements in treatment(s) are implicated in this improved survival rate, but many of these treatments are accompanied by negative side effects such as which can significantly impact day-to-day physical functioning and quality of life (QOL).[6] One of the most prevalent and distressing side effects reported by cancer survivors is cancer-related fatigue (CRF). CRF is a subjective experience in nature and has physical, behavioral, cognitive, and affective components. CRF is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and that interferes with usual daily activities and functioning.[55,98]

One of the most salient therapeutic modalities for reducing CRF is exercise.[3,9–11,99] Randomized controlled trials of exercise interventions have demonstrated reductions in CRF that are greater than a non-exercise control group[11,12] and pharmacological therapy. This evidence base has resulted in exercise guidelines, which suggest 150 minutes of moderate or 75 minutes of vigorous aerobic exercise, and 2-3 days of resistance training, focusing on all major muscle groups, to attain health benefits.[3] To improve CRF severity, the American College of Sports Medicine's 2019 Exercise Guidelines Roundtable recommends that cancer survivors should participate in exercise training programs that last at a minimum of 12 weeks, performing moderate intensity exercise, with a combination of aerobic and resistance training exercises.

More specifically, 3x per week and 30 minutes of moderate intensity aerobic exercise, plus 2x per week of resistance training, including two sets of 12-15 reps of the major muscle groups.

However, this evidence is almost exclusively based on changes in CRF following several weeks to months of regular exercise. This leaves a gap in the literature in understanding the extent to which exercise has an immediate, or "acute" benefit for improving CRF among survivors of cancer. Understanding the acute effects of exercise on CRF (i.e., occurring after a single bout of exercise) may help individuals surviving cancer overcome barriers to exercising when feeling fatigued and/or low energy, due to a more proximal benefit and/or attention to the positive affective response.[86] CRF is associated with low motivation for physical activity and negative attitudes toward exercise.[20,100] This may lead to decreased activity levels, further exacerbating negative side effects of cancer treatment(s) such as deconditioning, frailty, and poor quality of life.[100] Thus, finding ways to provide immediate relief for high CRF could be an important tool for improving survivorship.

To our knowledge, few studies have examined the acute effects of exercise on CRF and other self-reported outcomes among survivors of cancer. Only four previous studies have examined the acute effect of exercise on CRF. Two studies were randomized controlled trials (RCTs), one was a retrospective study, and one was a pre-post single-arm study. The retrospective study by Matsugaki et al. (2018) examined CRF among cancer survivors before and after a single inpatient exercise session.[18] One RCT by Cohen et al. (2019) examined the immediate effects of aerobic exercise combined with relaxation training compared to aerobic exercise and relaxation alone on CRF,[20] and the other RCT by Siebert et al. (2022) evaluated the effects of four exercise interventions with varying intensity and type.[19] The pre-post study by Gomes et al. (2024) examined the acute effects of exercise on self-reported CRF and energy scores during a virtual exercise program.[101] Taken together, findings from these studies provide preliminary support for the potential for the acute effect of exercise to reduce CRF; however,

small sample sizes and the heterogeneity of exercise protocols and measures of CRF limited our ability to draw definitive.

The purpose of this study was to examine changes in CRF from before to immediately after exercise sessions completed during an outpatient cancer rehabilitation program for adult survivors of cancer. We hypothesized that there would be a decrease in the magnitude of change from immediately before to after exercise sessions from week 1 to week 12 of the exercise program.

Methods

Design and Setting

This study was an observational, longitudinal cohort design, enrolling adult cancer survivors who were participating in an existing outpatient cancer rehabilitation exercise program at a regional cancer center. The exercise program is available to all cancer survivors who are currently undergoing or have completed cancer treatment at the cancer center. The program is 12 weeks long and includes pre- and post-program assessments with a physical therapist, and twice-weekly group exercise classes supervised by a Clinical Cancer Exercise Specialist.

Participants

To be eligible for this study, participants had to be 1) between the ages of 18 and 85 years old, (2) diagnosed with any type of cancer, (3) currently enrolled in the outpatient cancer rehabilitation program, and (4) have clinically relevant levels of cancer-related fatigue (CRF). To meet this inclusion criterion, individuals had a score ≤43 on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire.[102] A score ≤43 indicates a level of CRF greater than the general population, and thus, individuals not meeting this criterion were excluded to reduce the likelihood of a ceiling effect.[103] Exclusion criteria were: (1) does not have a IOS or Android smart phone with internet access, (2) deemed not eligible for the exercise program (i.e., not medically stable or cognitively capable to participate in the program from a safety or mobility standpoint, (3) is not able to speak or read English,(4) pregnant or planning to

become pregnant and (5) Participants were enrolled in the study between March 2024 and March 2025. All participants who were enrolled in the study provided consent for their data to be collected and used for research purposes. The University of Colorado Institutional Review Board (IRB#23-1789) approved this study. Informed consent was obtained from all individual participants included in this study, and study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado.[104]

Outpatient Cancer Rehabilitation Program Description

Participants were referred by oncology clinicians via the electronic medical record system. Potential participants received an initial evaluation and treatment visit with a physical therapist. This visit includes the FACIT-Fatigue questionnaire [102] and a series of physical function assessments. At the end of this visit, the physical therapist introduced the study procedures and asked permission to provide the study staff with their contact information. Additionally, participants met with the physical therapist the following week to go over exercise session procedures and meet exercise staff before officially starting the 12-week program the following week. The program has been described previously and has demonstrated a reduction in CRF from pre- to post-program [97].

Exercise Sessions

The program consisted of exercise sessions twice per week. Participants were given the choice of days (either Monday and Wednesday or Tuesday and Thursday) and time (hourly between 8:00 am – 3:00 pm). Depending on which classes had space available. Once selected, these days and times remained consistent for the duration of the program. Exercise sessions lasted approximately one hour and included aerobic, resistance, and balance exercises, guided by rating of perceived exertion. Exercise duration and modality were determined individually for each participant by the physical therapist based on results from the initial assessment, participant medical and treatment history, and presence of any functional limitations or comorbidities. Aerobic exercise was performed for 10 to 20 minutes using a NuStep (ie,

recumbent elliptical trainer), cycle or arm ergometer, or treadmill. The remainder of the session consisted of resistance exercise, targeting all major muscle groups and using body weight, resistance bands, and dumbbells, with a goal of 3 sets of 10 repetitions for each exercise.

Study Procedures

Following the initial visit with the physical therapist, participants were contacted by study staff via phone to give additional study details and answer any questions. When study staff confirmed participants' interest in the study, the participant met with study staff at the end of the participant's second physical therapy appointment to review study procedures and sign the informed consent.

Measures

Cancer-Related Fatigue (CRF)

CRF was assessed immediately before and immediately after (within 5 minutes) one exercise session per week. Participants were asked to rate their self-perceived level of CRF using a visual analog scale from 0-10 (0 = no fatigue, 10 = high fatigue) on a tablet in person. Along with the visual analog scale (Figure 3.1), participants were provided with the National Comprehensive Cancer Network (NCCN) definition of CRF, "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning".[5] A recent analysis suggests that the 10-point rating scale is the most efficient method to screen for the presence of CRF, and the nature of the question belies the strength of psychometric properties and demonstrates good test-retest reliability (r=.88) and convergent validity with the FACIT-F measure.[105]

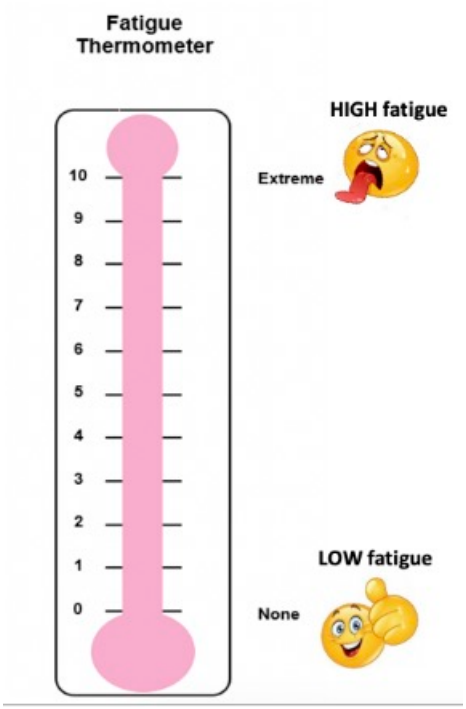

Figure 3.1 CRF Visual Analog Scale

Demographic and clinical data

Basic demographic information was self-reported at baseline, including age, sex, race, ethnicity, and employment status. Clinical information was collected from electronic health records by the physical therapist. Data included cancer diagnosis, stage, treatment status and tumor type. Treatment status was defined as “on treatment” if participants were undergoing chemo and/or radiation therapy at the time of program enrollment (Table 3.1).

FACIT-Fatigue

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire.[102] This measure was repeated by the physical therapist at the post-program assessment. The FACIT-Fatigue (version 4) is a 13-item questionnaire on a scale of 0 to 52, with a higher score indicating less fatigue, and a change of 3 points is considered and MCID.

Statistical Analyses

Participants were included in analyses if they had pre-post CRF data for at least one exercise session. Descriptive statistics (means and standard deviations) were calculated for

demographic, clinical, and CRF data. To estimate the difference between CRF from pre- to post-exercise sessions, a mixed effects model was used, with a fixed intercept that represents the overall mean CRF difference scores (post-pre) across all participants with random effects for each participant (model 3.1) (pre-post exercise CRF was observed across multiple days across multiple participants). To examine the magnitude of change from immediately before to after exercise sessions from week 1 to week 12 of the exercise program, we then added the week of study as a fixed predictor (model 3.2). All sets of analyses were conducted using linear mixed-effects models, which account for the correlation among repeated measurements within subjects over time.[106] A post-hoc power analysis was conducted with 24 measurement timepoints; a minimum sample size of n=12 was required to detect a moderate effect size with α = .05 and β = 0.95 (G*Power 3.1.9.7) using a repeated measures test to detect a within-factors effect. Both models were estimated using restricted maximum likelihood (REML) to account for missing data and provide unbiased parameter estimates. No outliers were removed to preserve the true variability both between and within participants.

Results

A total of *N*=31 individuals were screened for eligibility, and *N*=29 (93%) signed the consent form and enrolled in the study. Of those, *N*=18 (62%) completed all 12 weeks of exercise sessions, and *N*=8 (27%) withdrew. A total of *N*=25 participants completed pre- and post-measures of CRF for one exercise session and were included in analyses. Flow through the study and reasons for withdrawal/dropout are shown in Figure 3.2. Participants represented a variety of cancer types, including breast (*n*=4, 16%), colorectal (*n*=3,12%), and pancreatic (*n*=3,12%), and other (60%). The average age was 62±12 years, and *n*=19 (76%) were receiving chemotherapy at the time of enrollment. The average number of exercise sessions attended was 7.00±3.26 (range = 2-12). Additional participant characteristics are shown in Table 3.1.

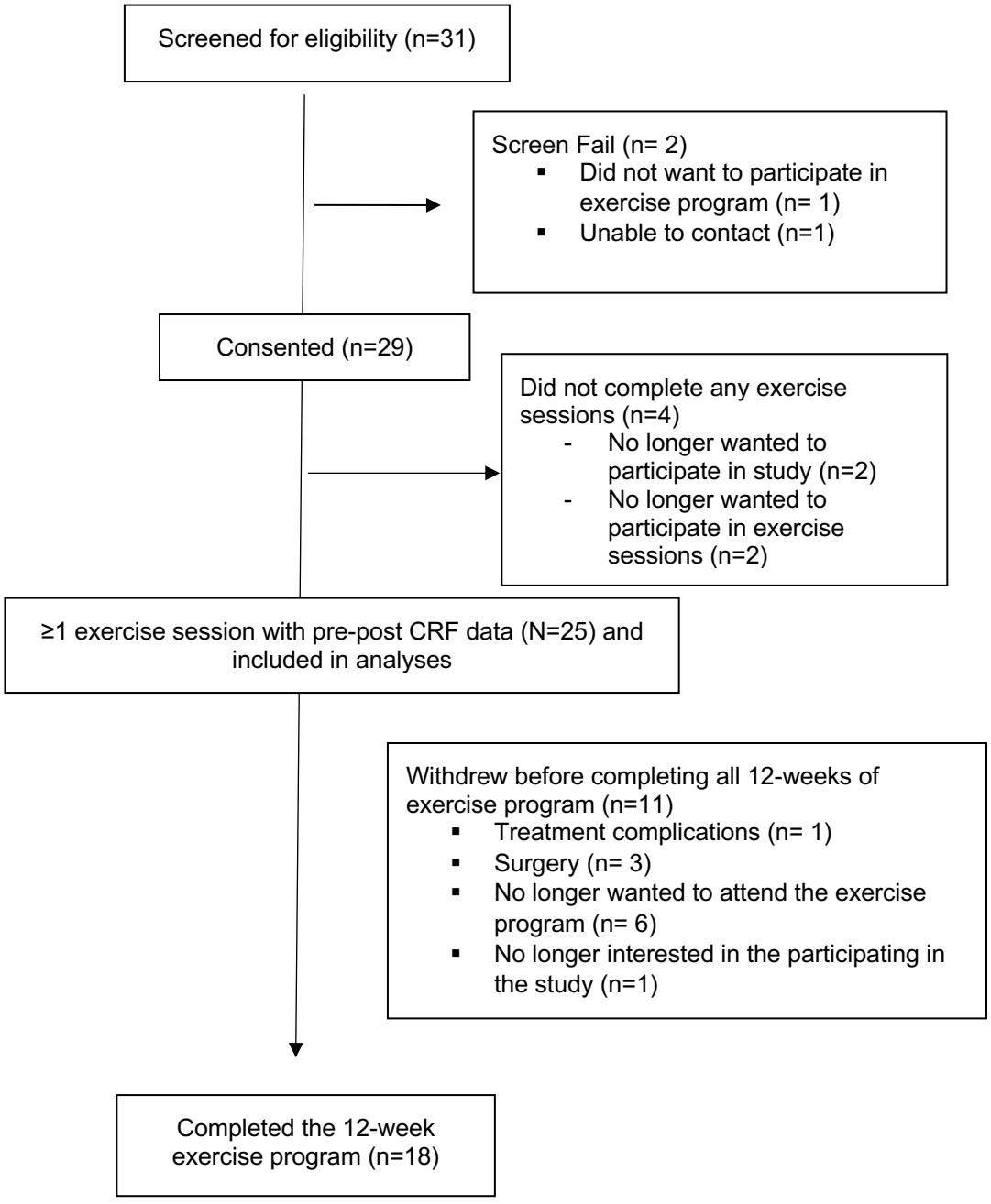

Figure 3.2 CONSORT Flow Diagram

Table 3.1 Demographics

N=25	Mean±SD
Age Years	62±12
	N (%)
Sex	
Female	21 (84%)
Male	4 (16%)
Ethnicity	
White	25 (100%)
Current Work Status	
Working full time	4 (16)
Working part time	6 (24)
Not working	5 (20)
Retired or disabled	9 (36)
Cancer Diagnosis	
Breast	4 (16)
Colorectal	3 (12)
Lung	2 (8)
Lymphoma	2 (8)
Prostate	1 (4)
Pancreatic	3 (12)
NET	1 (4)
Endometrial	2 (8)
Peritoneal	1 (4)
Adrenal	1 (4)
Singlet Ring Cell	1 (4)
Multiple Myeloma	1 (4)
Ovarian	1 (4)
Myelodysplastic Syndrome	1 (4)
Cholangiocarcinoma	1 (4)
Cancer Stage	
Stage I	4 (16)
Stage II	5 (20)
Stage III	1 (4)
Stage IV	11 (44)
N/A[2]	4 (16)
Receiving chemotherapy upon enrollment?	

[2] Four cancer types use alternative staging systems, N=4 (N/A)

No	6 (24%)	
Yes	19 (76%)	
Receiving radiation upon enrollment?		
Yes	2 (8%)	
No	23 (92%)	
Total Number of Exercise Sessions with pre-post CRF data	N=187	
	Mean±SD,	Median (Range)
Baseline FACIT scores	25.56±11.26	26 (5-43)
Post FACIT scores	35.73± 8.18	35 (23-49)
Number of Exercise Sessions Completed	7.00±3.26	8 (2-12)

Pre- and Post-Exercise CRF

Overall, pre-exercise session CRF was (M = 3.19, SD = 1.61), and average post-exercise CRF was (M = 3.13, SD = 1.61). Average pre- and post-exercise CRF by week is shown in Table 3.2. The change in CRF from pre-to-post exercise session did not differ significantly from zero (Model 3.1. b_0 = -0.10, SE = 0.20, p = 0.62). See Figure 3.3 and Figure 3.4. Approximately 25% of the variance in CRF pre-post difference scores was attributable to differences between participants, indicating that some participants experienced a greater magnitude of CRF changes than others. The magnitude of change from immediately before to after pre-to-post exercise sessions from week 1 to week 12 was not significant from zero (Model 3.2 b_0 = 0.05, SE = 0.03, p = 0.14). After accounting for the effect of week, approximately 23% of the variance remained between participants, suggesting that individual differences combined to play a substantial role even after controlling for week. Trends in weekly pre- and post-session CRF are shown in Figure 3.5. The average heart rate and RPE of the exercise session are shown in Table 3.3.

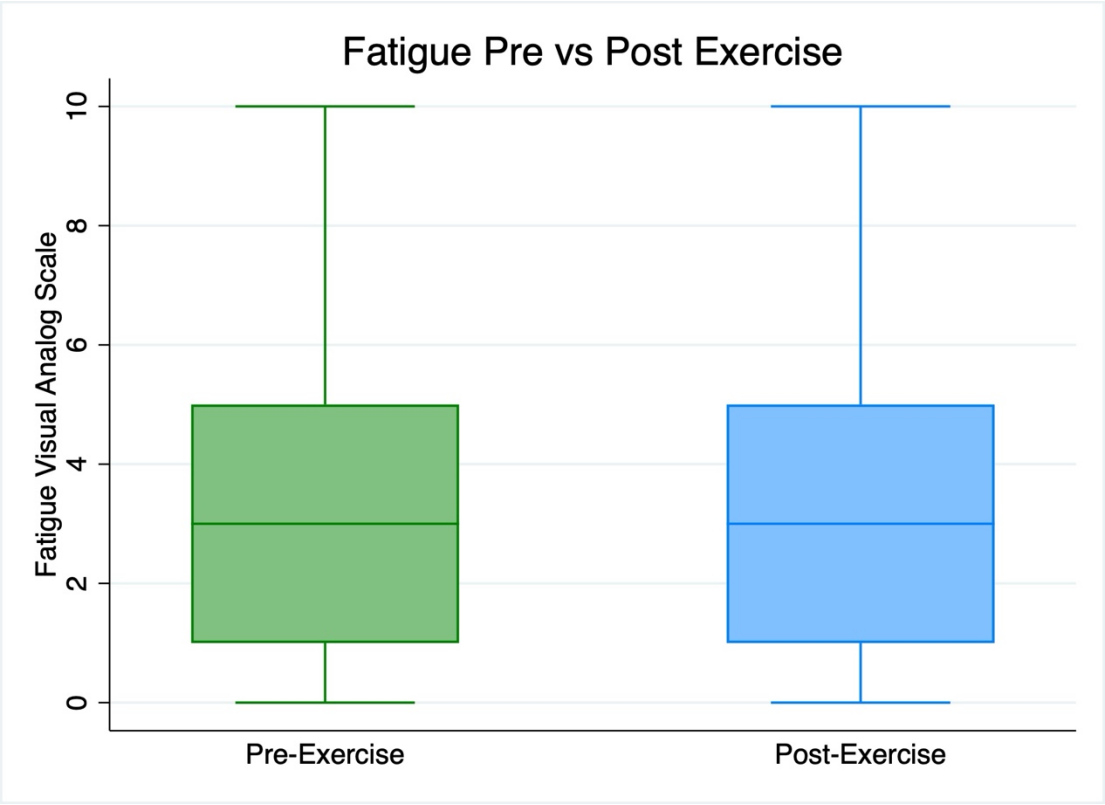

Figure 3.3 Boxplot of Pre-to-Post CRF Scores

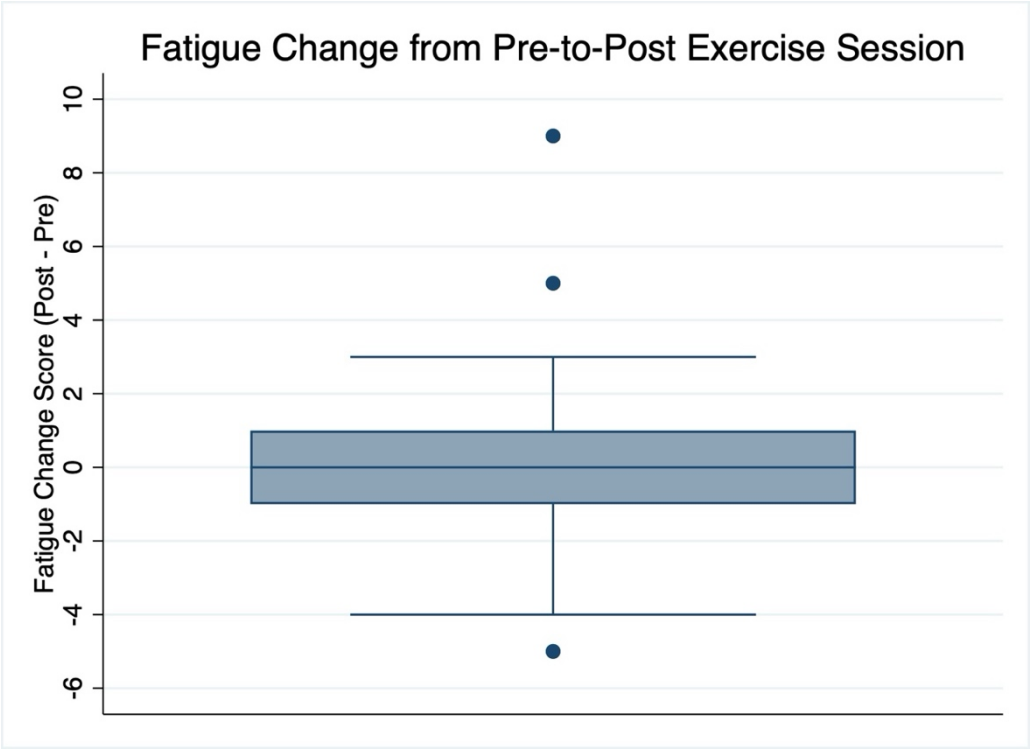

Figure 3.4 Exercise CRF Pre-and-Post Change Scores

Table 3.2 Average CRF Across 12 Weeks

Week	Pre-Exercise Mean±SD (Range)	Post-Exercise Mean±SD (Range)	Mean Change Score	Number of exercise sessions (1 per participant)
1	3.46±2.61 (0-8)	3.06±2.54 (0-9)	-0.40	N=15
2	4.09±2.68 (0-10)	3.71±2.57 (0-8)	-0.38	N=21
3	4.16±3.01 (0-10)	3.83±2.25 (0-8)	-0.33	N=18
4	2.72±2.53 (0-8)	2.44±1.85 (0-6)	-0.28	N=18
5	3.11±2.52 (0-8)	2.91±1.72 (0-6)	-0.20	N=17
6	3.50±2.42 (0-9)	3.31±2.30 (0-8)	-0.19	N=16
7	3.46±2.06 (0-7)	3.40±1.88 (0-7)	-0.06	N=15
8	2.38±1.75 (0-5)	3.00±2.49 (0-10)	+0.62	N=18
9	2.87±1.96 (0-7)	3.37±2.47 (0-8)	+0.50	N=16
10	2.50±2.12 (0-6)	3.00±2.16 (0-6)	+0.50	N=10
11	2.66±2.30 (0-7)	2.58±2.06 (0-7)	-0.08	N=12
12	1.90±1.51 (0-5)	2.00±7.69 (0-5)	+0.10	N=11
Overall	3.15±2.39 (0-10)	3.11±2.21 (0-10)	-0.04	N=25

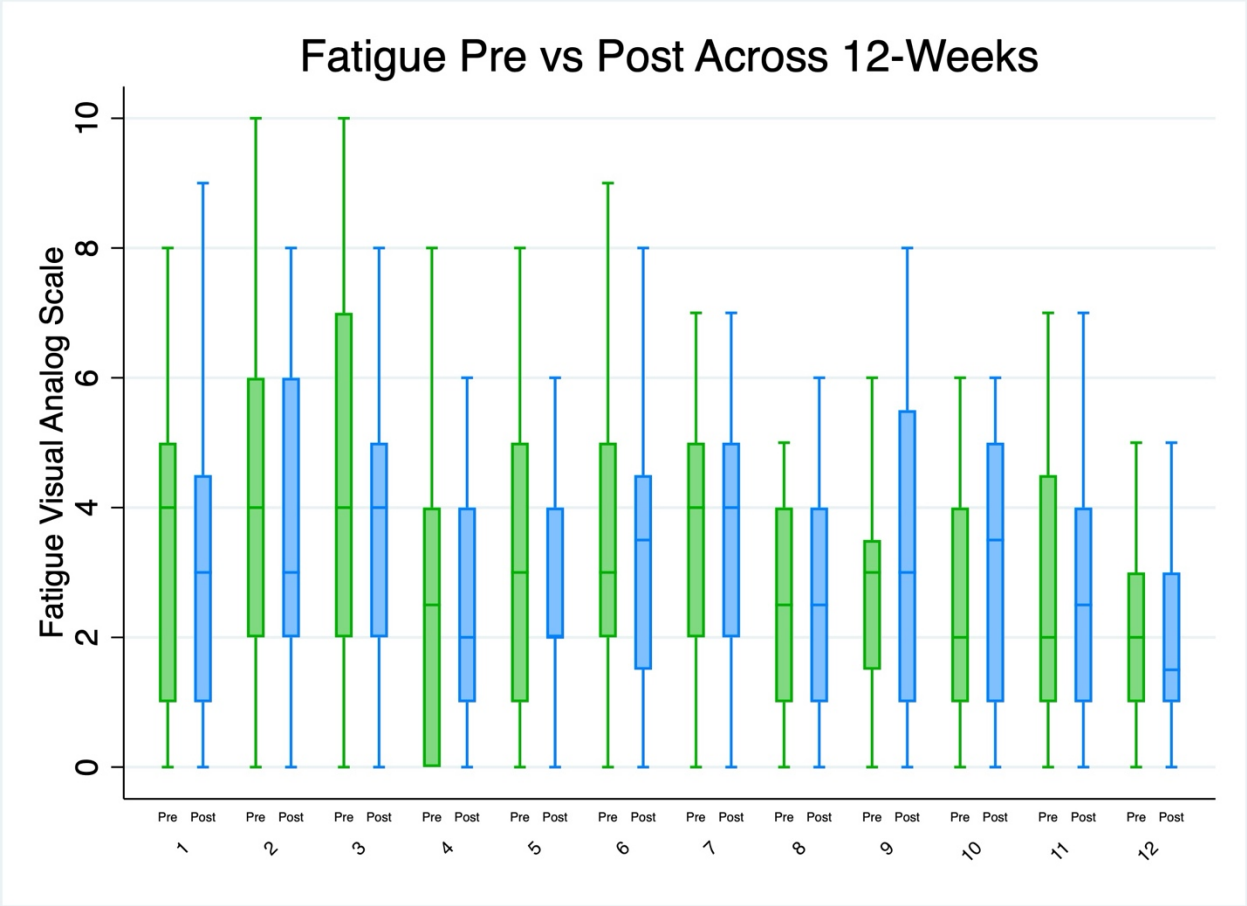

Figure 3.5 Average Pre- and Post-Exercise Session CRF by Week

Table 3.3 Average Heart Rate and RPE for Each Exercise Session

	Aerobic		Resistance	
Exercise Session	Average Heart Rate (bpm)	RPE (6-20)	Average Heart Rate (bpm)	RPE (6-20)
1	96±33	12±2	92±35	13±2
2	103±16	12±2	103±17	13±2
3	103±19	12±1	103±36	13±2
4	104±18	12±2	104±20	13±2
5	103±15	12±2	101±14	12±2
6	105±21	12±2	98±17	12±2
7	109±18	12±1	93±16	12±2
8	102±21	12±2	94±31	12±2
9	113±19	12±2	94±32	12±3
10	99±12	12±2	104±16	12±2
11	94±18	12±2	94±10	12±2
12	104±22	12±2	93±15	12±2

Discussion

This study examined changes in CRF from immediately before to immediately after exercise sessions during an outpatient exercise rehabilitation program. This study contributes novel information to the exercise oncology literature regarding the immediate effects of exercise on CRF among survivors of cancer. Findings did not demonstrate acute effects of exercise on CRF from before to immediately after exercise sessions, and no difference in the magnitude of CRF change from week to week.

Given that many cancer survivors report CRF as a persistent, distressing symptom or side effect of cancer and treatment(s),[55] a common concern is engaging in activities that may worsen their perceived fatigue.[91] Although CRF was not reduced immediately following exercise, finding no change in CRF (i.e., CRF did not increase following exercise) may have important and promising clinical implications. Cancer survivors have reported feeling like exercise could worsen CRF, and that rest could provide relief, making them more prone to physical inactivity. For example, a previous qualitative study found that cancer survivors reported having to reduce their activities to cope with symptoms of CRF, expressing "I don't know until the morning of the same day if I can do anything at all that day".[91] Over time, this inactivity can result in physical deconditioning and subsequent worsening of CRF.[13]

Our results contrast with those of three prior studies that examined change in CRF immediately before and after a single exercise session. Matsugaki et al. found that physical (d=.59) and total (d=.74) CRF were significantly reduced following a single bout of exercise; however, cognitive and affective domains of fatigue were not.[18] Cohen et al. showed a decrease in CRF with a large effect (d=.91) of combined aerobic exercise and relaxation pre-to-post across three sessions of exercise on CRF.[20] Finally, Gomes et al. found a reduction in CRF from immediately pre- to immediately post-exercise sessions conducted as part of an 8-week videoconference exercise program.[101]

Potential reasons why our study did not observe similar reductions in CRF immediately following exercise include differences in sample characteristics, the number of exercise sessions, and the exercise setting. For example, Cohen et al. studied only breast cancer survivors who had completed chemotherapy within the last five years, measured CRF after just three exercise sessions, and found a large effect size only in the combined aerobic a relaxation group, not the aerobic-only group. In contrast, 76% of our diverse sample of participants with advanced cancer were actively undergoing chemotherapy, and we assessed CRF pre- and post-exercise across 12 weeks. Participant characteristics may contribute to differing CRF responses to exercise. For example, Cohen et al. studied a homogeneous sample of BCS further out from treatment, a period when CRF is typically less severe and may be more responsive to exercise.[107]

In contrast, the current study included participants with advanced cancer stages, which are associated with higher symptom burden and more persistent CRF, potentially limiting the immediate benefits of exercise.[108] Matsugaki et al evaluated CRF in in-patient cancer survivors after a single exercise session. Measuring CRF after one exercise session compared to multiple sessions may lead to differences in findings because measuring CRF after a single session may make the measurement time point vulnerable to momentary factors of a single day, whereas assessing CRF across multiple sessions allows for the evaluation of within-person patterns. Lastly, while Gomes et al. used the same CRF VAS scale across an 8-week intervention with a combination of aerobic and resistance exercises, they also collected energy ratings (0-10 scale) at the same timepoints. It is possible that higher post-exercise energy scores influenced participants' perceptions of lower CRF. In our study, energy levels were not measured pre- and post-exercise, which may explain the different findings. Finally, differences in exercise setting, such as the controlled nature of exercise intervention-based sessions versus the more variable and real-world context of an outpatient rehabilitation setting, influence pre-to-post CRF responses. Participants in a clinical setting may view exercise sessions as a necessary step to

recovery with greater ability for individualized exercise prescription,[109] compared to highly motivated cancer survivors who may seek out an exercise[110] study, leading to differences in CRF responses due to the motivation for the exercise sessions.

The current study contributes to a growing body of literature examining the acute effect of exercise on CRF. Notably, while our findings did not demonstrate acute effects of exercise on CRF immediately following exercise, no change in CRF provides empirical support that both during and after treatment does not result in an immediate increase in CRF (i.e., feeling worse) after exercise.

Strengths and Limitations:

Strengths of the current study include the inclusion of multiple exercise sessions per participant, which increased the number of observations and enhanced statistical power, as well as the ability to explore acute changes in CRF longitudinally (i.e., one exercise session per week, across the course of a 12-week program). Another strength of this study is the observational design utilizing an existing outpatient rehabilitation program. This decreased selection bias (i.e., decreased the likelihood that only motivated, already active individuals would volunteer for an exercise study)[110] and ensured a more diverse and representative sample of cancer survivors (i.e., cancer type and stage). Another strength was the inclusion criteria of a clinical cut-off for fatigue, which reduces the likelihood of a ceiling effect and represents an enrollment of cancer survivors who are experiencing clinically significant CRF.

Limitations of this study include the lack of racial/ethnic and socioeconomic diversity of our sample, and a sample consisting of a majority of female cancer survivors. However, previous research has reported that female cancer survivors exhibit a 1.4-fold higher prevalence of severe CRF compared to males.[33] Despite the inclusion criteria of <43 on FACIT-Fatigue completed at the initial visit with the physical therapist, pre-exercise session CRF was relatively low (3 out of 10), which potentially caused a floor effect as it was difficult to detect improved CRF, if only low levels were present at pre-exercise. Finally, this study only utilized a single-item

measure of CRF at pre- and post-exercise timepoints, collecting CRF severity, which may not be as sensitive for collecting subtle changes in CRF in just 60 minutes, as there is currently no Minimal Clinically Important Difference (MCID) cutoff for clinical change for the VAS. Additionally, there is a lack of validated tools in the current literature for measuring acute changes in CRF, making it unclear whether existing measures accurately capture CRF in the short term.

Future Directions

Further research is needed to identify which factors, such as exercise intensity, cancer type, sleep, and behavioral components, influence why some cancer survivors self-report decreases in CRF immediately following exercise while others do not. Additionally, future studies should consider using alternative CRF measurement tools that may be more sensitive to detecting acute changes following a single exercise session. A deeper understanding of the mechanisms underlying post-exercise changes in CRF could help inform the development of optimized exercise perspiration to better manage CRF symptoms in cancer survivors.

Conclusion

This study did not demonstrate acute effects of exercise on CRF from immediately before to immediately after exercise sessions during a 12-week outpatient cancer rehabilitation exercise program. However, it also did not find that CRF worsened following a single bout of exercise. This suggests that the acute effects of exercise on CRF have important implications for the daily functioning of cancer survivors, which may help survivors overcome the misnomer of worsening CRF as a barrier to engaging in exercise. Findings from this study provide important evidence that participating in exercise, even during active treatment, does not exacerbate CRF. This evidence can support recommendations from cancer rehabilitation and exercise oncology professionals, helping to reassure survivors that exercise is safe and will not worsen their CRF.

MANUSCRIPT II: TIME COURSE OF CANCER-RELATED FATIGUE DURING AN OUTPATIENT EXERCISE PROGRAM FOR CANCER SURVIVORS

Introduction:

Recent advances in cancer screening and treatment have resulted in a greater number of individuals living with and beyond cancer (i.e., cancer survivors). As of January 2019, there were an estimated 16.9 million cancer survivors in the United States, with the number of cancer survivors now projected to increase to 22.2 million by 2030.[1] Cancer survivors frequently experience a range of side effects throughout their illness, stemming from cancer itself or diverse treatments. These side effects encompass physical deconditioning, cognitive impairment, and psychological changes.[3] Notably, cancer-related fatigue (CRF) ranks as one of the most prevalent and prominent issues associated with cancer and remains a persistent and distressing side effect of cancer. This cancer survivor reported that outcomes can arise from peripheral and central components and can be devastating and negatively affecting cancer survivors' performance and emotional well-being, reducing their quality of life.[30]

According to the definition of the National Comprehensive Cancer Network, CRF is a distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[5] CRF is associated with decreased survival and significantly impacts daily life, interfering with employment, enjoyment of life, and motivation to continue treatment.[55] Studies have shown that CRF is reported in 49% -62% of cancer survivors.[4,34,35] Remarkably, 62% of cancer survivors[4] report CRF during active treatment, with 19-38% reporting CRF following treatment.[40] More critically, CRF can impair the ability of cancer survivors to receive their full dose of treatment. In some cases, it may even lead to dose reductions.[8] Therefore, a reduction in CRF has gained increasing focus, posing an urgent

concern for clinicians and survivors. Currently, ambiguity remains regarding the etiology of CRF. It has been suggested that inflammation, dysregulation of the hypothalamic-pituitary-adrenal axis, and activation of the autonomic nervous system have been advocated as potential mechanisms of CRF.[111]

Among non-pharmacological therapies, exercise is widely acknowledged as a beneficial treatment for CRF.[9,10] It not only decreases CRF symptoms, but it also addresses other cancer-related outcomes, such as quality of life and muscle loss.[3] Findings from numerous systematic reviews and meta-analyses support the important role exercise plays in improving CRF. These reviews conclude that CRF improved in cancer survivors who participated in exercise interventions, as compared to usual care controls.[11,61] While a growing body of evidence supports the role of exercise training in alleviating CRF, little is known about how an exercise session can impact CRF throughout the day. We have previously shown that cancer survivors can self-report decreases in CRF from immediately before to immediately after a 60-minute session of exercise in a community-based program, but it is unclear if this immediate benefit is sustained for several hours following exercise.[101] Previous studies have established that there are acute effects of exercise that may impact physiologic systems implicated in CRF. For example, Koivula et all. 2023 examined changes in immune cell counts in newly diagnosed breast cancer survivors and found that acute exercise led to a significant increase of total leukocyte (CD45+), CD8 + T cell, CD19+ B cell, total Natural Killer (NK) cell, CD56+CD16+ NK cell, and CD14+CD16+ monocyte counts in the bloodstream after short acute exercise. The percentages of NK cells and $CD8^+$ T cells decreased back to baseline at 30 min post-exercise, but the percentage of $CD14^+CD16^+$ monocytes remained elevated at 30 min post-exercise.[112] Evan et al. reported similar findings in breast cancer survivors, showing that NK cell counts did significantly increase immediately postexercise compared with pre-exercise levels, and then decreased toward pre-exercise levels at 2 hours and 24 hours post-exercise.[113] Taken together, these studies suggest that acute bouts of exercise do elicit a physiological change immediately

after a single session. This acute exercise response is important when examining potential physiological mechanisms that potentially affect CRF immediately following exercise and throughout the day. This knowledge will provide insight to clinicians and exercise professionals as to how cancer survivors will respond to acute bouts of exercise and how they recover in terms of managing side effects such as CRF.

The extent to which exercise can reduce CRF for the remainder of the day has important clinical implications. CRF is a frequently reported barrier to participating in activities of daily living, and survivors often report difficulties in performing routine tasks such as household chores, employment responsibilities, and social interactions.[5] Persistent CRF can contribute to this cycle of inactivity, further exacerbating physical deconditioning. If a single exercise session can provide relief from CRF throughout the rest of that day, it could enhance day-to-day well-being and is essential for overall quality of life.

Despite growing interest and knowledge regarding treatments of CRF, the time course of CRF following an exercise session remains largely unexplored, and to our knowledge, there are no previous studies that have investigated the trajectory of CRF following an exercise session. This study aimed to examine CRF on an exercise day at 1-, 4-, and -7 hours post-exercise to CRF immediately post-exercise and examine the slope of the line for CRF from immediately post-exercise through 1-, 4-, and -7-hours post-exercise. On non-exercise days, we will examine CRF at 4- and 7-hours to CRF at 1-hour and examine the slope of the line for CRF from 1-hour through 4-and 7-hours. We will also compare the slope of the line to the CRF measured at the same clock time on a non-exercise day within the same week.

Methods

Design and Setting

This study was an observational, longitudinal cohort design, enrolling adult cancer survivors who were participating in an existing outpatient cancer rehabilitation exercise program

at a regional cancer center. The exercise program is available to all cancer survivors who are currently undergoing or have completed cancer treatment at the cancer center. The program is 12 weeks long and includes pre- and post-program assessments with a physical therapist, and twice-weekly group exercise classes supervised by a Clinical Cancer Exercise Specialist.

Participants

To be eligible for this study, participants had to be 1) between the ages of 18 and 85 years old, (2) diagnosed with any type of cancer, (3) currently enrolled in the outpatient cancer rehabilitation program, and (4) have clinically relevant levels of cancer-related fatigue (CRF). To meet this inclusion criterion, individuals had a score ≤43 on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire.[102] A score ≤43 indicates a level of CRF greater than the general population, and thus, individuals not meeting this criterion were excluded to reduce the likelihood of a ceiling effect.[103] Exclusion criteria were: (1) does not have a IOS or Android smart phone with internet access, (2) deemed not eligible for the exercise program (i.e., not medically stable or cognitively capable to participate in the program from a safety or mobility standpoint, (3) is not able to speak or read English,(4) pregnant or planning to become pregnant and (5) Participants were enrolled in the study between March 2024 and March 2025. All participants who were enrolled in the study provided consent for their data to be collected and used for research purposes. The University of Colorado Institutional Review Board (IRB#23-1789) approved this study. Informed consent was obtained from all individual participants included in this study, and study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado.[104]

Outpatient Cancer Rehabilitation Program Description

Participants were referred by oncology clinicians via the electronic medical record system. Potential participants received an initial evaluation and treatment visit with a physical therapist. This visit includes the FACIT-Fatigue questionnaire[102] and a series of physical function assessments. At the end of this visit, the physical therapist introduced the study

procedures and asked permission to provide the study staff with their contact information. Additionally, participants met with the physical therapist the following week to go over exercise session procedures and meet exercise staff before officially starting the 12-week program the following week. The program has been described previously and has demonstrated a reduction in CRF from pre- to post-program. [97]

Exercise Sessions

The program consisted of exercise sessions twice per week. Participants were given the choice of days (either Monday and Wednesday or Tuesday and Thursday) and time (hourly between 8:00 am – 3:00 pm). Depending on which classes had space available. Once selected, these days and times remained consistent for the duration of the program. Exercise sessions lasted approximately one hour and included aerobic, resistance, and balance exercises, guided by rating of perceived exertion. Exercise duration and modality were determined individually for each participant by the physical therapist based on results from the initial assessment, participant medical and treatment history, and presence of any functional limitations or comorbidities. Aerobic exercise was performed for 10 to 20 minutes using a NuStep (ie, recumbent elliptical trainer), cycle or arm ergometer, or treadmill. The remainder of the session consisted of resistance exercise, targeting all major muscle groups and using body weight, resistance bands, and dumbbells, with a goal of 3 sets of 10 repetitions for each exercise.

Study Procedures

Following the initial visit with the physical therapist, participants were contacted by study staff via phone to give additional study details and answer any questions. When study staff confirmed participants' interest in the study, the participant met with study staff at the end of the participant's second physical therapy appointment to review study procedures and sign the informed consent.

Measures

Cancer-Related Fatigue (CRF)

CRF was assessed immediately before and immediately after (within 5 minutes) one exercise session per week. Participants were asked to rate their self-perceived level of CRF using a visual analog scale from 0-10 (0 = no fatigue, 10 = high fatigue) on a tablet in person. Along with the visual analog scale (Figure 4.1), participants were provided with the National Comprehensive Cancer Network (NCCN) definition of CRF, "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning".[5] A recent analysis suggests that the 10-point rating scale is the most efficient method to screen for the presence of CRF, and the nature of the question belies the strength of psychometric properties and demonstrates good test-retest reliability (r=.88) and convergent validity with the FACIT-F measure.[105]

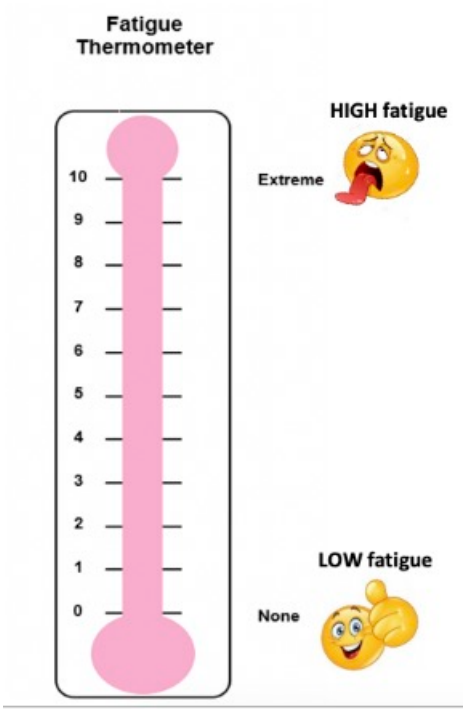

Figure 4.1 CRF Visual Analog Scale

Time Course of Cancer-Related Fatigue (CRF)

To examine the time course of CRF following each exercise session, we utilized Ecological Momentary Assessment (EMA). EMA involves repeated real-time assessment of

individuals' experiences and behaviors in their real world and natural environments, which do not require participants to recall extended periods, helping to reduce participant recall biases and increase ecological validity.[114] EMA has been previously used to capture real-time self-reported CRF levels in participants' natural environments,[115] including in cancer populations.[116] EMA notifications were sent via ExpiWell, a secure, widely used experience sampling smartphone application that participants downloaded. Participants received smartphone notifications to complete CRF assessments via ExpiWell at three timepoints following exercise and three timepoints on the following non-exercise day. The EMA protocol consisted of signal-contingent, fixed scheme notifications anchored around the participant's exercise time that included the same CRF visual analog scale and CRF definition used at the pre- and post-exercise measurement timepoints (Figure 4.2). We hypothesize that CRF will vary across the day following exercise, due to the dynamic nature of psychological, biological and environmental factors,[89,117] Therefore, our timepoints were chosen to balance a representative sampling method, while also minimizing participant burden, we chose three measurement timepoints at varying intervals of time to collect a within hour effect, afternoon and evening effect of exercise on CRF. Participants received notifications to answer the CRF question at the start of the hour at 1-, 4-, and 7 hours following their exercise session and at the same times on the non-exercise day. Participants were given a 30-minute time frame to respond to the prompt and were aware when the notifications were set to arrive, and if not completed, received an additional reminder prompt at 10 minutes past the top of the hour. The one non-exercise day CRF collection was added to account for potential daily variability in CRF. The compensation for the EMA surveys was prorated based on compliance level and ranged from $25 - $50.

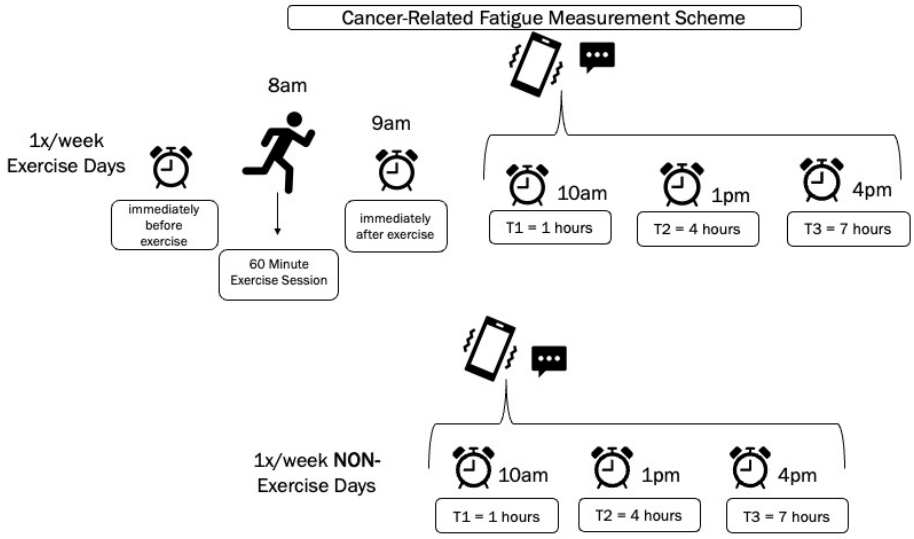

Figure 4.2 CRF Measurement Scheme

FACIT-Fatigue

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire.[102] This measure was repeated by the physical therapist at the post-program assessment. The FACIT-Fatigue (version 4) is a 13-item questionnaire on a scale of 0 to 52, with a higher score indicating less fatigue, and a change of 3 points is considered and MCID.

Demographic and clinical data

Basic demographic information was self-reported at baseline, including age, sex, race, ethnicity, and employment status. Clinical information was collected from electronic health records by the physical therapist. Data included cancer diagnosis, stage, treatment status, and tumor type. Treatment status was defined as “on treatment” if participants were undergoing chemo and/or radiation therapy at the time of program enrollment (Table 4.1).

Statistical Analyses

Participants were included in the analysis if they had CRF data at each time-point on a day with an exercise session and a non-exercise day. Descriptive statistics (means, standard deviations, medians, and ranges) were calculated for demographic, clinical, and CRF data.

Compliance with EMA notifications was defined as the ratio of the number of EMA measurement occasions participants completed divided by the maximum number of measurement occasions in the EMA protocol. Overall response rates were calculated for the entire sample; the total possible responses per week were 6 x 12 weeks, for a total of 72 responses throughout the study for N=18 (completers), for N=7 participants who did not complete the full 12 weeks, possible responses were individually calculated. If a participant did not show up to the exercise session in a given week, CRF was not recorded at 1-, 4-and 7-hours post-exercise. In addition, an EMA prompt on the non-exercise day at hour 1 asked participants, “Did you participate in structured exercise today?” If a participant answered “yes”, that individual day was excluded from the non-exercise day analyses to attempt to capture the true exercise effect on CRF.

To examine the effects of an exercise session on the time course of CRF, we constructed three mixed effects models:

(1) Model 4.1 examined changes within exercise days with timepoints included either as continuous variable (model 4.1a) to examine the slope of the line for CRF from immediately post-exercise through 1, -4, and -7 hours or categorical variable (model 4.1b) to examine change in CRF from immediately post-exercise to each individual follow-up timepoint (1, -4, and -7 hours). Both models included each subject as a random effect. For Model 4.1b, each timepoint measurement was centered around the CRF value for post-exercise.

(2) Model 4.2 examined changes within non-exercise days with timepoints included either as continuous variable (model 4.2a) to examine the slope of the line for CRF between 1, -4, and -7 hours or categorical variable (model 4.2b) to examine change in CRF from 1-hour following exercise to the -4-, and -7-hour timepoints. Both models included each subject as a random effect. For Model 2b, each timepoint measurement was centered around the CRF value for timepoint hour 1.

(3) Model 4.3 examined the change of slopes between exercise and non-exercise days with timepoints included as a continuous variable and the interaction term of day and timepoint.

All three models were estimated using restricted maximum likelihood (REML) to account for missing data and provide unbiased parameter estimates. No outliers were removed to preserve the true variability both between and within participants. Coefficients and accompanying statistics, including standard error and p-values ($p < .05$), were reported for each model. All sets of analyses were conducted using linear mixed-effects models, which account for the correlation among repeated measurements within subjects over time.[106] A post-hoc power analysis was conducted with 72 measurement timepoints; a minimum sample size of n=7 was required to detect a moderate effect size with $\alpha = .05$ and $\beta = 0.95$ (G*Power 3.1.9.7) using a repeated measures test to detect a within-factors effect.

Results

A total of *N*=31 individuals were screened for eligibility, and *N*=29 (93%) signed the consent form and enrolled in the study. Of those, *N*=18 (62%) completed all 12 weeks of exercise sessions, and *N*=8 (27%) withdrew. A total of *N*=25 participants who completed pre- and post-exercise measures of CRF and had data for 1-, 4-, and 7-hour timepoints on one exercise day and one non-exercise day were included in analyses. Flow through the study and reasons for withdrawal/dropout are shown in Figure 3.2. Participants represented a variety of cancer types, including breast (*n*=4, 16%), colorectal (*n*=3,12%), and pancreatic (*n*=3,12%), and other (60%). The average age was 62±12 years, and *n*=19 (76%) were receiving chemotherapy at the time of enrollment. The average number of exercise sessions attended was 7.00±3.26 (range = 2-12). Additional participant characteristics are shown in Table 4.1.

Table 4.1 Demographics

N=25	Mean±SD
Age Years	62±12

	N (%)
Sex	
Female	21 (84%)
Male	4 (16%)
Ethnicity	
White	25 (100%)
Current Work Status	
Working full time	4 (16)
Working part time	6 (24)
Not working	5 (20)
Retired or disabled	9 (36)
Cancer Diagnosis	
Breast	4 (16)
Colorectal	3 (12)
Lung	2 (8)
Lymphoma	2 (8)
Prostate	1 (4)
Pancreatic	3 (12)
NET	1 (4)
Endometrial	2 (8)
Peritoneal	1 (4)
Adrenal	1 (4)
Singlet Ring Cell	1 (4)
Multiple Myeloma	1 (4)
Ovarian	1 (4)
Myelodysplastic Syndrome	1 (4)
Cholangiocarcinoma	1 (4)
Cancer Stage	
Stage I	4 (16)
Stage II	5 (20)
Stage III	1 (4)
Stage IV	11 (44)
N/A[3]	4 (16)
Receiving chemotherapy upon enrollment?	
No	6 (24%)
Yes	19 (76%)
Receiving radiation upon enrollment?	
Yes	2 (8%)
No	23 (92%)

[3] Four cancer types use alternative staging systems, N=4 (N/A)

Total Number of Exercise Sessions	187	
	Mean±SD,	Median (Range)
Baseline FACIT scores	25.56±11.26	26 (5-43)
Post FACIT scores	35.73± 8.18	35 (23-49)
Number of Exercise Sessions Completed	7.00±3.26	8 (2-12)

EMA Compliance

Compliance was 68% on exercise days and 59% on non-exercise days. Compliance with each time point is shown in Table 4.2. Overall, these results suggest that participants answered more EMA prompts on exercise days, particularly at the 4- and 7-hour timepoints (Figure 4.3). There was a recorded N=22 non-exercise days where participants reported completing structured exercise; therefore, 66 responses were removed from analyses.

Table 4.2 EMA Compliance at each Timepoint on Exercise vs Non-Exercise Days

EMA Timepoint	**1 Hour**	**4 Hour**	**7 Hour**	**Average across 3 timepoints**
Exercise Day	65% (127/198)	69% (138/200)	69% (139/202)	68%
Non-Exercise Day	57% (151/265)	61% (161/263)	57% (155/263)	59%
Average at each Timepoint	61%	65%	64%	

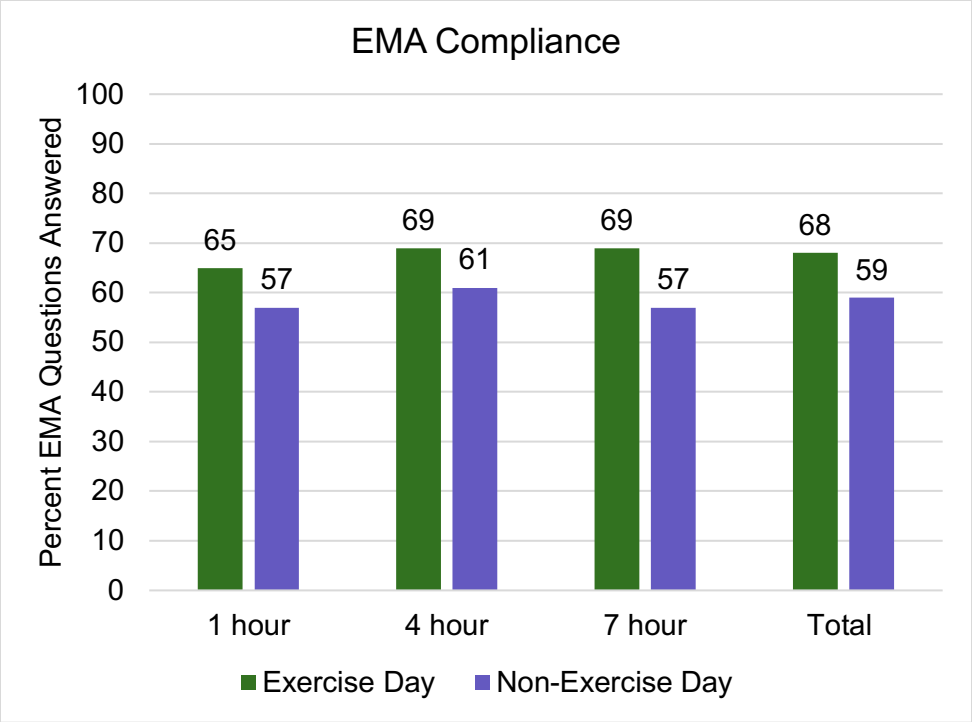

Figure 4.3 EMA Compliance

CRF on Exercise Days

CRF at each time point is shown in Table 4.3. On exercise days, treating time post-exercise as a continuous predictor (model 4.1a), we observed a significant positive slope of the line for CRF from immediately post-exercise through 1, -4, and -7 hours (b = 0.29, SE = .09, p = 0.001). On exercise days, treating time post-exercise as a categorical predictor (model 4.1b), we observed non-significant changes in CRF (relative to post-exercise) at hour 1 (b = -03, SE = 0.13, p=0.78) and 4 (b = 0.1, SE = 0.13, p =0.92) but a significant increase at hour 7 (b = 0.36, SE = 0.13, p = 0.006).

CRF on Non-Exercise Day

On non-exercise days, treating time as a continuous predictor (model 4.2a), we observed a significant positive slope in CRF across the 1-, 4-, and 7-hour timepoints (b = 0.09, SE = 0.02, p < .0001). On non-exercise days, treating time as a categorical predictor (model

4.2b), we observed non-significant changes in CRF (relative to hour 1 timepoint) at hour 4 (b = -0.002, SE = 0.14, p = 0.98) and 7 (b = .20, SE = 0.14, p = 0.50) timepoints.

Trend of CRF Across Timepoints Between Exercise and Non-Exercise Days

When assessing the slope of the line across the 1-, 4-, and 7-hour timepoints between an exercise day and non-exercise day (model 4.3), we did not see a significant difference (b = 0.20, SE = 0.18, p = 0.25). Trends shown in Figures 4.4 and 4.5.

Table 4.3 Average CRF Levels at Each Timepoint

Timepoint	Mean ± SD	Median (Range)		Mean±SD	Median (Range)
Pre-Exercise	3.19±1.61	3 (0-10)	Non-exercise day	n/a	n/a
Post-Exercise	3.13±1.61	3 (0-10)	Non-exercise day	n/a	n/a
Exercise Day Hour 1	3.02±1.66	3 (0-9)	Non-Exercise Day Hour 1	3.18±1.64	3 (0-8)
Exercise Day Hour 4	3.13±1.65	3 (0-8)	Non-Exercise Day Hour 4	3.18±1.63	3 (0-8)
Exercise Day Hour 7	3.65±1.66	4 (0-10)	Non-Exercise Day Hour 7	3.39±1.64	3 (0-10)

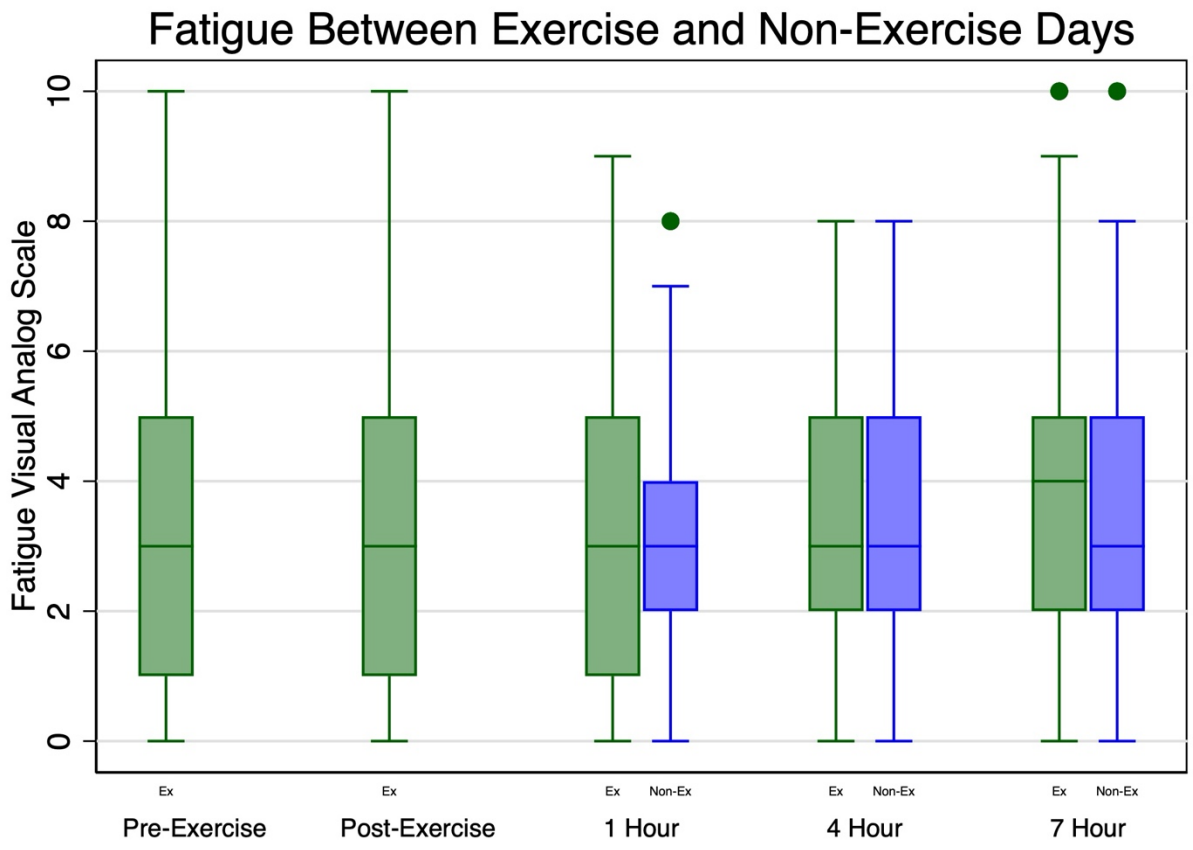

Figure 4.4 Boxplot CRF Compared on Exercise and Non-Exercise Days

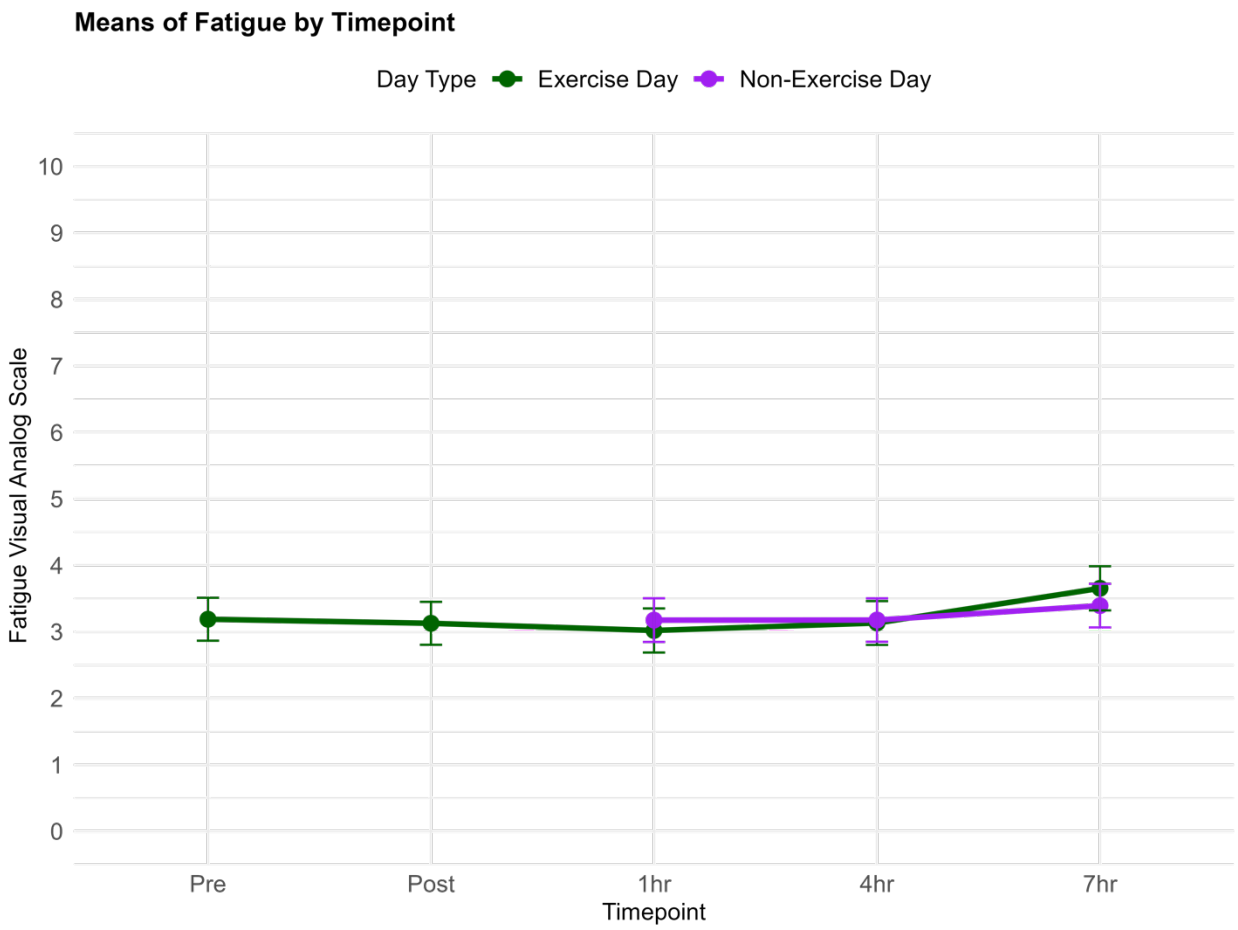

Figure 4.5 Line Graph of CRF Compared on Exercise and Non-Exercise Days

Discussion

This study sought to examine the effect of exercise on CRF at 1, -4, and -7 following an exercise session and determine whether CRF differed at these timepoints on a non-exercise day within the same week.

On exercise days, CRF demonstrated a significant slope for CRF from immediately post-exercise through 1, -4, and -7 hours. When examining the post-exercise timepoints individually, CRF levels remained stable at 1- and 4-hours compared to post-exercise, before rising significantly by the 7-hour timepoint compared to post-exercise. On non-exercise days, CRF demonstrated a positive significant slope for CRF from the 1-hour timepoint through 4, and -7 hours. When examining the 4- and 7-hour timepoints individually, CRF levels were not significantly different than the 1-hour timepoint.

Taken together, comparisons between exercise and non-exercise days revealed no significant differences in CRF slopes, suggesting that CRF tends to follow a similar trend during the day, independent of exercising.

To our knowledge, this is the first study to assess CRF at multiple time points within the same day following an exercise session. One previous study in breast cancer survivors has examined the effect of a single exercise session immediately and three hours after an exercise session on self-reported energy, stress, nausea, and pain, [118] and found that energy and stress levels were improved immediately following exercise but returned to baseline at the three-hour timepoint. However, nausea and pain did not improve immediately following exercise or at the three-hour time point.[118] Findings from this study offer valuable context for interpreting our results because they highlight the varying nature of cancer-related symptoms following exercise. Showing that while some symptoms like energy and stress may improve immediately following exercise, the effect of exercise on these symptoms may diminish within a few hours.

On exercise days, our hypothesis was partially supported; CRF at the 7-hour timepoint was significantly higher compared to post-exercise; however, CRF was not significantly higher at the 4-hour timepoint compared to post-exercise. These findings could be encouraging, as they suggest that exercise does not negatively impact CRF throughout most of the day; while CRF levels at 1- and 4-hours post-exercise were not significantly different from immediately post-exercise, an increase in CRF was observed at the 7-hour timepoint. Although CRF was higher at the 7-hour timepoints compared to immediately post-exercise, this timepoint also represented the highest CRF level on the non-exercise day. Importantly, CRF remained within the clinically mild range (0-3) [55] across both exercise and non-exercise days, never reaching the threshold for moderate CRF. In addition, an increase in CRF at hour 7 may be expected and beneficial on exercise days, as it may improve sleep, a likely mechanism of exercise effects on CRF.[47]

Although the absence of significant differences in CRF between exercise days and non-exercise days contradicted our original hypothesis, it may alleviate concerns for worsening CRF in the hours following an exercise, which is a common barrier to exercise participation.[16] This is important because even though the current study didn't see an immediate improvement in CRF following exercise, removing the barrier to exercise (i.e., fear that CRF will get worse) can help ensure long-term benefits on CRF. One possible mechanism explaining why CRF did not differ between exercise and non-exercise is that cancer survivors often exhibit a flattened diurnal cortisol slope and elevated evening cortisol levels compared to healthy individuals. [51,52] Elevated evening cortisol has been associated with factors such as work-related stress, sleep disturbances, disrupted res-activity cycles, and reduced social support,[119] all of which may contribute to persistent CRF regardless of exercise participation.

Strengths and Limitations

Strengths of this study include the measurement of CRF in real-time collected via EMA via a phone application, which reduced recall bias and ensured standardized data collection within a fixed response window for each participant. Another strength of this study is the novelty. To date, no previous studies have examined the time course of CRF anchored around an exercise session, with repeated measures of CRF. This results in the ability to track trends in CRF longitudinally across the 12 weeks. Additionally, we included a non-exercise day as a control condition to strengthen internal validity by isolating the effects of exercise and accounting for natural daily variation in CRF. Another strength of this study is the observational design utilizing an existing outpatient rehabilitation program. This decreased selection bias by (i.e., decreased the likelihood that only motivated, already active individuals would volunteer for an exercise study)[110], ensuring a more representative sample of cancer survivors that would be found in a clinically supervised setting, which included diversity in terms of cancer type, stage and varying timepoints of treatment. In addition, an exclusion criterion included a clinical cut

point of fatigue with a score of 43 on the FACIT-Fatigue questionnaire at baseline, representing enrollment of highly fatigued cancer survivors.

Limitations of this study include the lack of racial/ethnic and socioeconomic diversity of our sample, and a sample consisting of a majority of female cancer survivors. However, previous research has reported that female cancer survivors exhibit a 1.4-fold higher prevalence of severe CRF compared to males.[33] Therefore, there was a considerable amount of missing weekly data for each participant, which has the potential for this study to have missed certain CRF trends that may appear with additional data. This study only utilized a single-item measure of CRF at all measurement timepoints that collected CRF severity, which may not be as sensitive for collecting subtle changes in CRF in a single day, as there is currently no minimal clinically important difference (MCID) cutoff for clinical change for the VAS. Additionally, there is a lack of validated tools in the current literature for measuring acute changes in CRF, making it unclear whether existing measures accurately capture CRF in the short term. Another limitation was participant compliance with EMA messages, with compliance rates of 68% on exercise days and 59% on non-exercise days. However, there is currently a lack of standardized EMA compliance benchmarks in oncology literature, as many studies fail to report compliance rates and differ in the number of timepoints and days of data collection, making comparisons challenging. In a similar study assessing CRF before and after intensive cancer treatment, participants completed CRF ratings at three timepoints over three days, achieving an overall compliance rate of 87%.[120] Additionally, an EMA study in cancer survivors undergoing a stem cell transplant asked participants to rate CRF five times per day over the course of one week and reported a compliance rate of 80%.[121] Therefore, we had a lower compliance rate compared to similar studies.

In summary, this study suggested that CRF levels remained stable for up to four hours post-exercise when compared to post-exercise CRF, and CRF response did not differ between exercise and non-exercise days. These findings have important implications for exercise

prescription in cancer rehabilitation. Given that CRF remains stable rather than worsening, survivors may be more confident in incorporating exercise into their routines without fear of immediate exhaustion. By utilizing daily and weekly CRF data collection, more extensive and detailed conclusions can be drawn regarding the time course of the therapeutic influence of a single exercise bout on CRF, a critical cancer-related outcome. Future research should control for specific exercise variables, for example, if exercise modalities, intensities, or durations yield different CRF responses, and whether long-term adherence to exercise with stable CRF levels following exercise leads to greater overall improvements in CRF management.

MANUSCRIPT III: EFFECTS OF EXERCISE INTENSITY ON CRF IMMEDIATELY AND UP TO 7 HOURS FOLLOWING EXERCISE

Introduction:

Cancer is the second leading cause of death in the United States, with over 2 million new cases estimated to be diagnosed in 2025, with approximately 693,000 cancer survivors.[122] With a growing number of cancer survivors comes a large burden of numerous side effects associated with cancer, and/or treatments such as surgery, chemotherapy, and radiation. Cancer survivors experience a range of adverse effects, including fatigue, disrupted sleep, neuropathy, chronic pain, loss of physical function, impaired cognition, depression and anxiety, and decreased quality of life.[123] Numerous randomized controlled trials have shown that regular exercise can help reduce cancer and cancer treatment-related side effects such as anxiety, depression, health-related quality of life, lymphedema, and physical function.[124–128] Studies also suggest that higher levels of physical activity are associated with decreased all-cause mortality as well as cancer-specific mortality in breast, colorectal, prostate, lung, and ovarian cancer survivors.[129–131] Dose response for exercise is also important, as a recent systematic review found that 17 out of the 30 reviewed studies reported a significantly lower risk of cancer-specific mortality and all-cause mortality among cancer survivors with higher exercise levels.[132] Despite these benefits, reduced physical activity contributes to a decline in individuals with cancer during their first six months of treatment.[133] Loss of lean muscle mass accompanied by a decrease in muscle strength and endurance also impacts heavily on the physical functioning of cancer survivors.[134]

Low levels of physical activity can in part be explained by potential barriers that could hinder cancer survivors' engagement in physical activity. Previous studies have reported that common barriers to exercise participation are tiredness, weakness, fatigue, and psychological

barriers such as lack of motivation, depression, and lack no awareness of exercise programs.[16,17,108] Cancer-related fatigue (CRF) is one of the most prevalent and distressing cancer and treatment-related side effects reported by 49-62% of cancer survivors. CRF has been defined in the literature as a distressing, persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning.[4,32,34,35] The exact mechanisms of CRF are unknown and may be influenced by demographic, medical, psychological, social, behavioral, and biological factors. Potential biological mechanisms include dysregulation of cytokines, hypothalamic pituitary axis (HPA), 5-hydroxytryptophan (5-HT), and changes in muscle metabolism.[30,32,135,136]

Consequently, it can be daunting for cancer survivors who are experiencing moderate or high levels of CRF to begin or adhere to regular exercise when the benefit is somewhat distal (i.e., weeks or months before seeing reductions in CRF). In addition to CRF being reported as one of the main barriers to exercise among cancer survivors, a majority of past studies failed to recruit cancer survivors who were experiencing CRF or failed to report whether they were experiencing CRF at the time the research was conducted.[137–139] Therefore, ways to engage fatigued cancer survivors in a long-term exercise program remain a challenge.

One way to potentially combat this exercise barrier is for cancer survivors to participate in an outpatient rehabilitation program that is located in a healthcare facility and is medically supervised. A study examining exercise facilitators found that almost all participants emphasized that an exercise program should be supervised by a trained health care professional, where they have a health care professional's knowledge, guidance, and feedback, in addition to motivational support.[109] Most participants stated they would prefer to exercise with other individuals with cancer, as they would have undergone a similar path since diagnosis and treatment, and be of similar fitness levels. These factors would provide an opportunity for peer

support, shared experiences, a sense of belonging, and subjective norms. These facilitators are important as, after exercise, many participants reported experiencing improvements in treatment side effects such as nausea, pain, and CRF, which was a key motivator to continue participating in exercise and physical activity during cancer treatment.[17] Reinforcing the concept that, given cancer survivors' difficulties in maintaining a long-term exercise program, a single session may be more achievable if immediate improvements in patient-reported side effects are present. A study by Mas et al. suggested that psychological factors might be better at determining whether cancer survivors are physically active or not, whereas physical factors, on the contrary, might influence intensity, regularity, and the duration of exercise.[140] For example, participants with motivation for exercise seem to be more likely to overcome their reported barriers.[108] Emphasizing the need for more evidence on how a single exercise session can potentially decrease feelings of CRF, in turn increasing exercise motivation for long-term exercise adaptations.

Another way to potentially combat this exercise barrier is the concept that feelings of positive affect may play a role in these immediate benefits following a single bout of exercise. For this reason, a facilitator in increased exercise effect might be allowing participants to self-select exercise intensity for the exercise session that day based on the severity of treatment-related side effects they are experiencing. Previous research in healthy adults reported that self-selection of aerobic exercise intensity may provide superior benefits for affective responses compared to imposed intensity.[141] Exercise intensity may be a vital component to exercise prescription for highly fatigued cancer survivors, as different exercise intensities may have an effect in decreasing CRF, through reduced inflammation mechanisms. While low-to moderate intensity may be preferred by most cancer survivors,[82] one study found that moderate-to-high-intensity exercise during cancer treatment was beneficial for physical CRF compared to low-intensity exercise.[83] Additionally, a systematic review comparing exercise intensities on inflammation markers found that pro-inflammatory cytokine TNF-α and anti-inflammatory IL-10

only increase after intense exercise, and pro-inflammatory cytokines IL-6 and IL-1β increase more with intense than with moderate exercise.[142] Further research is needed to determine optimal exercise prescription for cancer survivors to reduce CRF during a single exercise session, with more robust reporting of the FITT principles used.

This study aimed to examine the effect of self-selected exercise intensity on CRF from (a) immediately before to immediately after an exercise session, and (b) 1-, 4 -, and 7-hours following the exercise session. We hypothesized that exercise sessions that are categorized as moderate-high intensity will have a larger decrease in CRF immediately following exercise and a greater negative slope of CRF from immediately to 7-hours hours post-exercise compared to exercise sessions categorized as low intensity.

Methods

Design and Setting

This study was an observational, longitudinal cohort design, enrolling adult cancer survivors who were participating in an existing outpatient cancer rehabilitation exercise program at a regional cancer center. The exercise program is available to all cancer survivors who are currently undergoing or have completed cancer treatment at the cancer center. The program is 12 weeks long and includes pre- and post-program assessments with a physical therapist, and twice-weekly group exercise classes supervised by a Clinical Cancer Exercise Specialist.

Participants

To be eligible for this study, participants had to be 1) between the ages of 18 and 85 years old, (2) diagnosed with any type of cancer, (3) currently enrolled in the outpatient cancer rehabilitation program, and (4) have clinically relevant levels of cancer-related fatigue (CRF). To meet this inclusion criterion, individuals had a score ≤43 on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire.[102] A score ≤43 indicates a level of CRF greater than the general population, and thus, individuals not meeting this criterion were

excluded to reduce the likelihood of a ceiling effect.[103] Exclusion criteria were: (1) does not have a IOS or Android smart phone with internet access, (2) deemed not eligible for the exercise program (i.e., not medically stable or cognitively capable to participate in the program from a safety or mobility standpoint, (3) is not able to speak or read English,(4) pregnant or planning to become pregnant and (5) Participants were enrolled in the study between March 2024 and March 2025. All participants who were enrolled in the study provided consent for their data to be collected and used for research purposes. The University of Colorado Institutional Review Board (IRB#23-1789) approved this study. Informed consent was obtained from all individual participants included in this study, and study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado.[104]

Outpatient Cancer Rehabilitation Program Description

Participants were referred by oncology clinicians via the electronic medical record system. Potential participants received an initial evaluation and treatment visit with a physical therapist. This visit includes the FACIT-Fatigue questionnaire[102] and a series of physical function assessments. At the end of this visit, the physical therapist introduced the study procedures and asked permission to provide the study staff with their contact information. Additionally, participants met with the physical therapist the following week to go over exercise session procedures and meet exercise staff before officially starting the 12-week program the following week. The program has been described previously and has demonstrated a reduction in CRF from pre- to post-program. [97]

Exercise Sessions

The program consisted of exercise sessions twice per week. Participants were given the choice of days (either Monday and Wednesday or Tuesday and Thursday) and time (hourly between 8:00 am – 3:00 pm). Depending on which classes had space available. Once selected, these days and times remained consistent for the duration of the program. Exercise sessions lasted approximately one hour and included aerobic, resistance, and balance exercises, guided

by a rating of perceived exertion. Exercise duration and modality were determined individually for each participant by the physical therapist based on results from the initial assessment, participant medical and treatment history, and presence of any functional limitations or comorbidities. Aerobic exercise was performed for 10 to 20 minutes using a NuStep (ie, recumbent elliptical trainer), cycle or arm ergometer, or treadmill. The remainder of the session consisted of resistance exercise, targeting all major muscle groups and using body weight, resistance bands, and dumbbells, with a goal of 3 sets of 10 repetitions for each exercise.

Study Procedures

Following the initial visit with the physical therapist, participants were contacted by study staff via phone to give additional study details and answer any questions. When study staff confirmed participants' interest in the study, the participant met with study staff at the end of the participant's second physical therapy appointment to review study procedures and sign the informed consent.

Measures

Cancer-Related Fatigue (CRF)

CRF was assessed immediately before and immediately after (within 5 minutes) one exercise session per week. Participants were asked to rate their self-perceived level of CRF using a visual analog scale from 0-10 (0 = no fatigue, 10 = high fatigue) on a tablet in person. Along with the visual analog scale (Figure 5.1), participants were provided with the National Comprehensive Cancer Network (NCCN) definition of CRF, "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning".[5] A recent analysis suggests that the 10-point rating scale is the most efficient method to screen for the presence of CRF, and the nature of the question belies the strength of psychometric properties and demonstrates good test-retest reliability (r=.88) and convergent validity with the FACIT-F measure.[105]

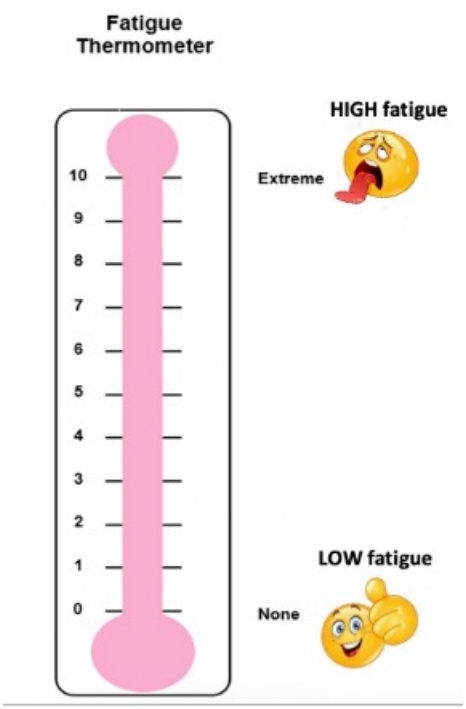

Figure 5.1 CRF Visual Analog Scale

Time Course of Cancer-Related Fatigue (CRF)

To examine the time course of CRF following each exercise session, we utilized Ecological Momentary Assessment (EMA). EMA involves repeated real-time assessment of individuals' experiences and behaviors in their real world and natural environments, which do not require participants to recall extended periods, helping to reduce participant recall biases and increase ecological validity.[114] EMA has been previously used to capture real-time self-reported CRF levels in participants' natural environments,[115] including in cancer populations.[116] EMA notifications were sent via ExpiWell, a secure, widely used experience sampling smartphone application that participants downloaded. Participants received smartphone notifications to complete CRF assessments via ExpiWell at three timepoints following exercise and three timepoints on the following non-exercise day (Figure 5.2). EMA protocol consisted of signal-contingent, fixed scheme notifications anchored around the participant's exercise time that included the same CRF visual analog scale and CRF definition used at the pre- and post-exercise measurement timepoints. We hypothesize that CRF will vary across the day following

exercise, due to the dynamic nature of psychological, biological and environmental factors,[89,117] Therefore, our timepoints were chosen to balance a representative sampling method, while also minimizing participant burden, we chose three measurement timepoints at varying intervals of time to collect a within hour effect, afternoon and evening effect of exercise on CRF. Participants received notifications to answer the CRF question at the start of the hour at 1-, 4-, and 7 hours following their exercise session and at the same times on the non-exercise day. Participants were given a 30-minute time frame to respond to the prompt and were aware when the notifications were set to arrive, and if not completed, received an additional reminder prompt at 10 minutes past the top of the hour. The one non-exercise day CRF collection was added to account for potential daily variability in CRF. The compensation for the EMA surveys was prorated based on compliance level and ranged from $25 - $50.

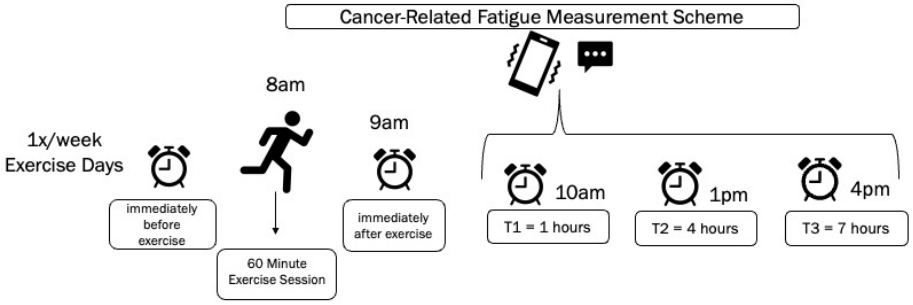

Figure 5.2 CRF Measurement Scheme

Exercise intensity

Exercise intensity of each exercise session was determined based on heart rate (HR) and rate of perceived exertion (RPE). Participants were given a heart rate wrist monitor (M200) to measure heart rate continuously throughout each exercise session, and RPE was self-reported using the Borg Scale of 6-20. RPE and HR were self-reported twice during each exercise session; once within the last two minutes of the aerobic component, and once within the last two minutes of the resistance component. The two recordings were averaged for each

session. Exercise intensity was classified: light, or moderate-vigorous, according to American College of Sports Medicine cutoffs for Heart Rate Reserve (HRR) and RPE (i.e., light =HRR 30-39%, RPE <12, moderate/vigorous = HRR >40%, RPE >12.[143] Resting heart rate was collected using a pulse oximeter at the beginning of each exercise session. Heart rate max was estimated using the age-predicted method of (220-age) for each participant. If the HR and RPE were incongruent (i.e., one was in the light category and one was moderate), HR was used, with the exception of a participant who was taking a medication that would alter HR response (i.e, beta blocker) then RPE was used as the default to determine intensity category.

FACIT-Fatigue

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire.[102] This measure was repeated by the physical therapist at the post-program assessment. The FACIT-Fatigue (version 4) is a 13-item questionnaire on a scale of 0 to 52, with a higher score indicating less fatigue, and a change of 3 points is considered and MCID.

Demographic and clinical data

Basic demographic information was self-reported at baseline, including age, sex, race, ethnicity, and employment status. Clinical information was collected from electronic health records by the physical therapist. Data included cancer diagnosis, stage, treatment status, and tumor type. Treatment status was defined as “on treatment” if participants were undergoing chemo and/or radiation therapy at the time of program enrollment (Table 5.1).

Statistical Analysis:

Participants were included in the analysis if they had complete data for a minimum of one exercise day during the 12-week study (N=25). Descriptive statistics (means, standard deviations, medians, and ranges) were calculated for demographic, clinical, and CRF data.
To examine the effect of exercise intensity on CRF from immediately before to immediately after an exercise session, we estimated CRF across pre-to-post timepoints as a function of exercise intensity using a mixed effects model. Model 5.1 included a fixed intercept representing the

average CRF score at pre-exercise, a fixed slope for the effect of time (i.e., pre vs. post exercise), a fixed slope for the effect of intensity (light vs. moderate-vigorous), and an interaction between time and intensity. The model included a random intercept to account for repeated measures between participants. To examine the effect of exercise intensity on CRF at 1-, 4 -and 7-hours following an exercise session, we constructed Model 5.2a and 5.2b, which were similar to model 5.1, except replacing the pre-to-post time variable with the fixed intercept of the 1-, 4- and 7-hours as either a continuous (5.2a) or categorical variable (5.2b).

All three models were estimated using restricted maximum likelihood (REML) to account for missing data and provide unbiased parameter estimates. No outliers were removed to preserve the true variability both between and within participants. Coefficients and accompanying statistics, including standard error and p-values ($p < .05$) were reported for each model. Linear mixed-effects models were selected to account for the correlation among repeated measures within subjects over time.[106] A post-hoc power analysis was conducted with 60 measurement timepoints; a minimum sample size of n=7 was required to detect a moderate effect size with $\alpha = .05$ and $\beta = 0.95$ (G*Power 3.1.9.7) using a repeated measures test to detect a within-factors effect.

Results

Participant Characteristics

A total of *N*=31 individuals were screened for eligibility, and *N*=29 (93%) signed the consent form and enrolled in the study. A total of *N*=25 participants completed pre- and post-measures of CRF for one exercise session and 1-,4-, and 7-hour timepoints and were included in analyses. A total of *N*=18 completed all 12 weeks of exercise sessions. Flow through the study and reasons for withdrawal/dropout are shown in Figure 3.2. Participants represented a variety of cancer types, including breast (*n*=4, 16%), colorectal (*n*=3,12%) and pancreatic (*n*=3,12%) and other (60%). The average age was 62±12 years, and *n*=19 (76%) were receiving

chemotherapy at the time of enrollment. Additional participant characteristics are shown in Table 5.1. The average number of exercise sessions attended was 7.00±3.26 (range = 2-12), and the HR and RPE for light and moderate-vigorous exercise sessions are shown in Table 5.2.

Table 5.1 Demographics

N=25	Mean±SD
Age Years	62±12
	N (%)
Sex	
Female	21 (84%)
Male	4 (16%)
Ethnicity	
White	25 (100%)
Current Work Status	
Working full time	4 (16)
Working part time	6 (24)
Not working	5 (20)
Retired or disabled	9 (36)
Cancer Diagnosis	
Breast	4 (16)
Colorectal	3 (12)
Lung	2 (8)
Lymphoma	2 (8)
Prostate	1 (4)
Pancreatic	3 (12)
NET	1 (4)
Endometrial	2 (8)
Peritoneal	1 (4)
Adrenal	1 (4)
Singlet Ring Cell	1 (4)
Multiple Myeloma	1 (4)
Ovarian	1 (4)
Myelodysplastic Syndrome	1 (4)
Cholangiocarcinoma	1 (4)
Cancer Stage	
Stage I	4 (16)
Stage II	5 (20)
Stage III	1 (4)

Stage IV	11 (44)	
N/A[4]	4 (16)	
Receiving chemotherapy upon enrollment?		
No	6 (24%)	
Yes	19 (76%)	
Receiving radiation upon enrollment?		
Yes	2 (8%)	
No	23 (92%)	
Total Number of Exercise Sessions	187	
	Mean±SD,	Median (Range)
Baseline FACIT scores	25.56±11.26	26 (5-43)
Post FACIT scores	35.73± 8.18	35 (23-49)
Number of Exercise Sessions Completed	7.00±3.26	8 (2-12)

Effect of Exercise Intensity on CRF from pre to post-exercise session

CRF at each time point, separated by light and moderate-vigorous intensity exercise sessions, is shown in Table 5.2. The average HRR and RPE between each exercise intensity group are shown in Table 5.3. The moderate-vigorous group (2.56±1.47) had overall lower pre-exercise CRF levels compared to the light intensity group (3.75±1.45). The moderate-vigorous group had an increase in CRF from pre-to-post exercise (+0.27), compared to the lower intensity group which had a slight decrease in CRF pre-to-post exercise (-0.19) (see Figure 5.3), but this difference was not statistically significant (b= -0.45, SE = 0.24, p = 0.06).

[4] Four cancer types use alternative staging systems, N=4 (N/A)

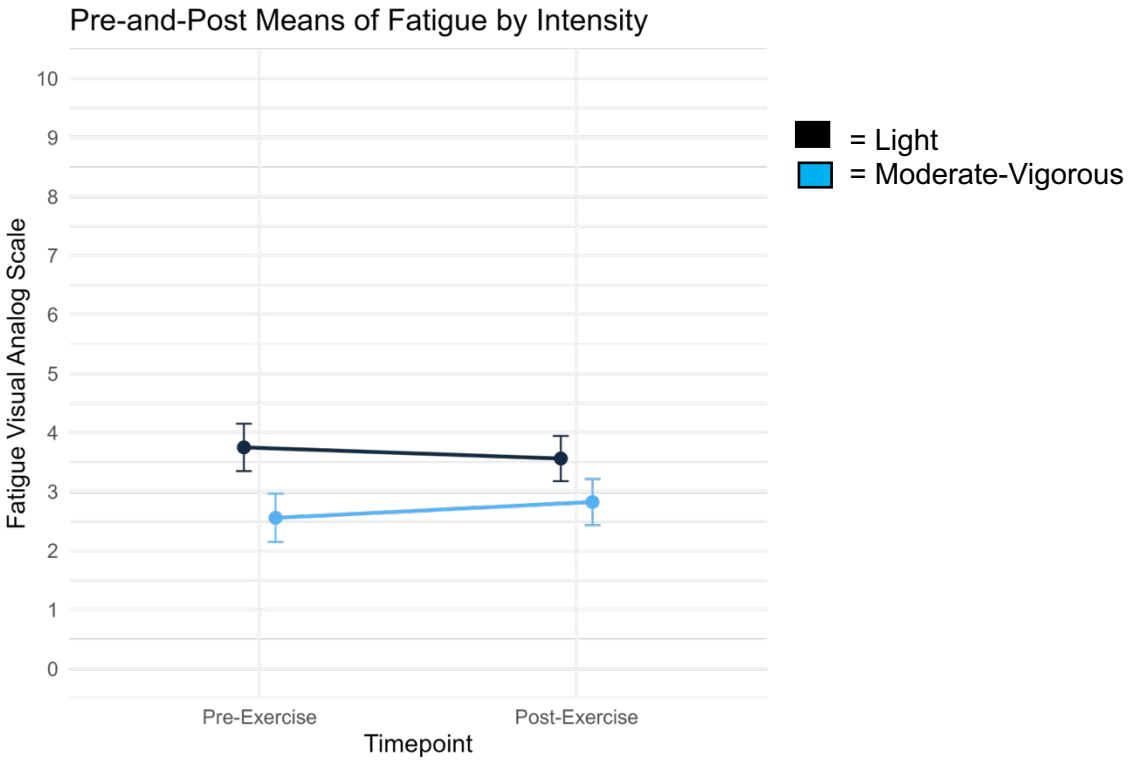

Figure 5.3 CRF by Pre- and Post-Exercise Timepoints and Intensity

Table 5.2 CRF between Exercise Intensities at Each Timepoint

	Light			**Moderate-Vigorous**		
Timepoint	Adjusted Mean±SD	SE	CI	Adjusted Mean±SD	SE	CI
Pre-Exercise	3.75±1.45	0.40	2.93-4.57	2.56±1.47	0.40	1.72-3.39
Post-Exercise	3.56±1.38	0.38	2.77-4.35	2.83±1.40	0.38	2.03-3.62
1-hour	3.43±1.48	0.41	2.59-4.26	2.48±1.54	0.42	1.62-3.34
4-hour	3.57±1.47	0.40	2.75-4.40	2.65±1.52	0.42	1.80-3.50
7-hour	3.82±1.48	0.41	2.99-4.66	3.36±1.54	0.42	2.49-4.22

Table 5.3 HRR and RPE of Light and Moderate-Vigorous

N=187		**Light**	**Moderate-Vigorous**
Mean±SD	HRR	30.41±4.51	49.91±11.42
	RPE	11.49±2.31	12.5±2.04

Median (Range)	HRR	30% (30-36%)	48% (40-89%)
	RPE	11 (6-14)	12 (8-16)
% of Sessions		55.50%	44.50%

Effects of exercise intensity at 1-, 4-, and 7-hours following the exercise session

Treating time post-exercise as a continuous variable (model 5.2a), we observed an increase in CRF across 1-, 4-, and 7-hour post-exercise timepoints for both intensity groups (b = 0.05, SE = 0.03, p = 0.01). However, the moderate-vigorous group retained lower overall CRF levels across all three time points compared to the light intensity group. (Figure 5.4 and Figure 5.5). Additionally, when treating time as a categorical predictor (Model 5.2b), there was no difference in CRF between intensity groups at hour 1 (b = -0.05, SE = 0.30, p=0.84), 4 (b = -0.03, SE = 0.29, p =.90) or at hour 7 (b = 0.42, SE = .31, p = 0.17).

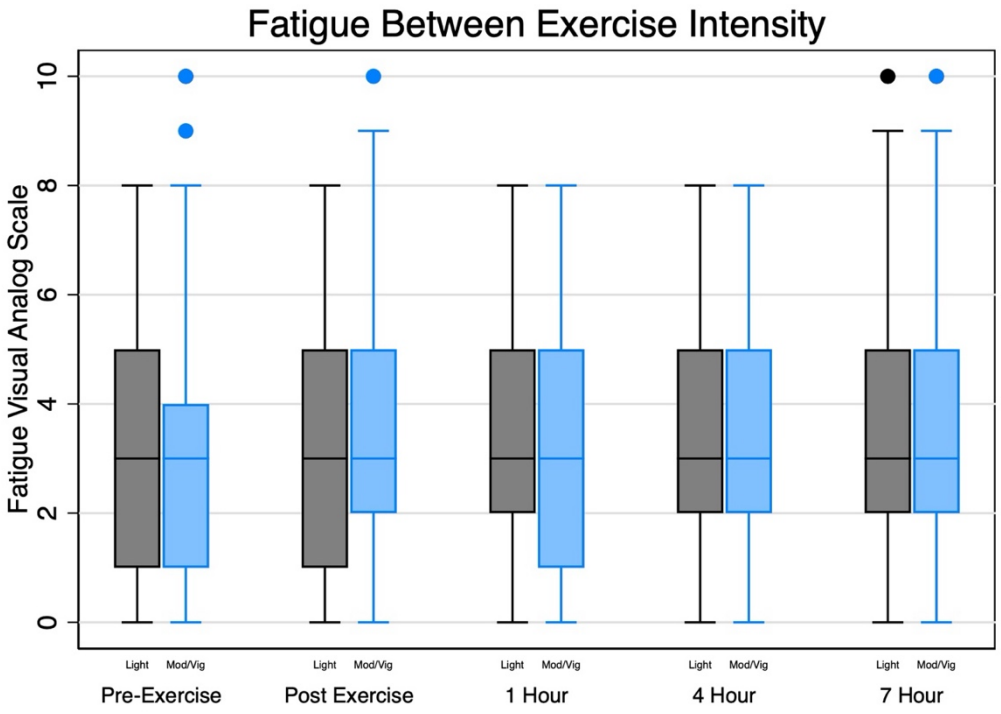

Figure 5.4 Boxplot between Timepoints and Intensity

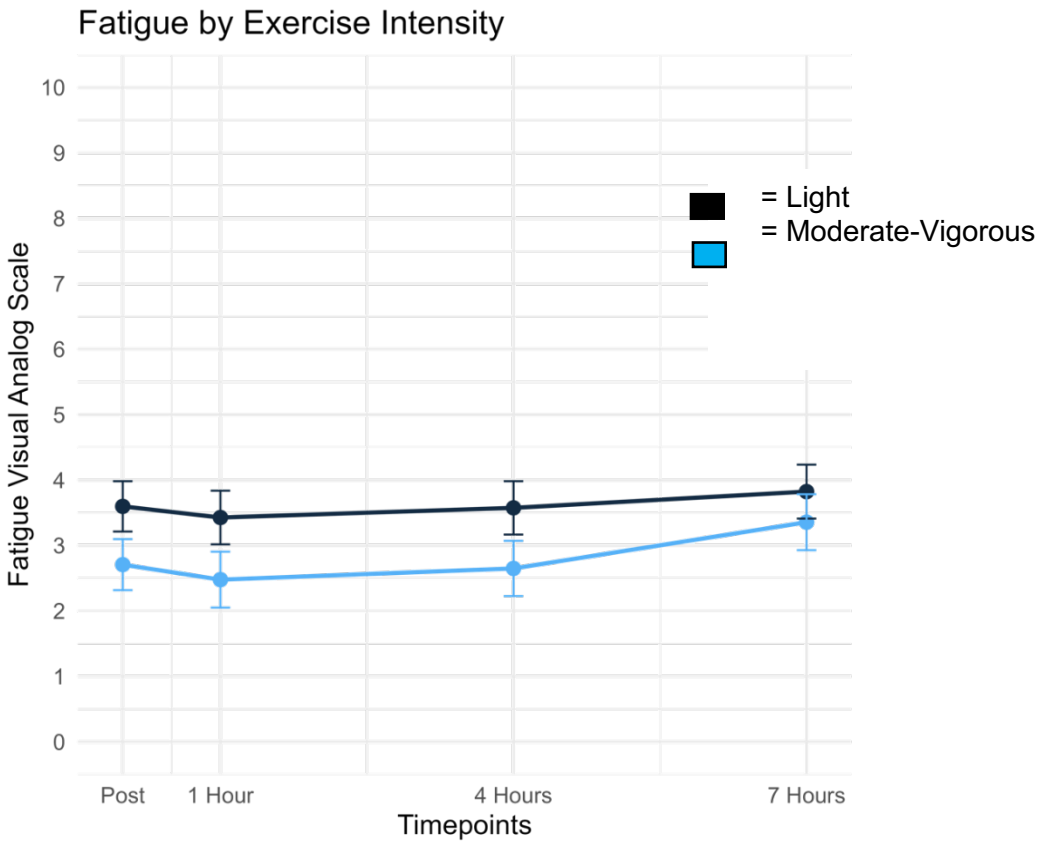

Figure 5.5 CRF by Post-Exercise Timepoints

Discussion

This study examined the effect of self-selected exercise intensity on CRF from immediately before to immediately after an exercise session, and 1-, 4 -, and 7-hours following the exercise session. Findings indicate no difference in CRF change from pre- to post-exercise between the intensity groups. The slope of CRF levels from post-exercise to the 7-hour timepoint increased (i.e., CRF got worse) for both intensity groups.

To our knowledge, this is the first study to examine how exercise intensity impacts CRF from before to immediately after and for several hours following an exercise session. Previous studies have examined the effect of exercise intensity on fatigue from before to immediately after exercise in non-cancer populations (e.g., college students, individuals with major

depressive disorder, and healthy adult men). A systematic review summarizing these studies found that fatigue was reduced after light-to-moderate intensity exercise, but not after vigorous exercise lasting longer than 20 minutes.[144] These findings contrast with our study, as we found no difference in CRF changes between light and moderate-vigorous sessions. The lack of CRF differences between exercise intensities in our study compared to findings in other populations may reflect the unique physiological and psychological context of CRF. Unlike in healthy individuals, where post-exercise fatigue may be predominantly influenced by muscular fatigue, CRF is often persistent and may be less responsive to changes in exercise intensity, potentially due to a stronger cognitive or emotional component influenced by factors such as stress, emotional burden, or disturbed sleep. [55]

Although no previous studies have directly compared the effect of exercise intensity on CRF immediately following exercise sessions, previous studies among cancer survivors that have measured CRF pre-to-post exercise found reductions in CRF, and exercise intensities ranged from RPE 3-6 and/or 50-70% age predicted heart rate max.[18,101,140] This indicates that moderate intensity exercise tends to reduce CRF, with limited information about exercise performed at lower intensities. One potential reason that the current study did not find a difference in the effect of exercise intensity on CRF could be that participants were able to self-select exercise intensity at each session based on how they felt that day. Our findings showed that exercise sessions where participants self-selected moderate-vigorous exercise also reported lower pre-exercise CRF levels. This may have resulted in a self-regulating effect, where participants chose an exercise intensity based on pre-exercise CRF, thereby minimizing the observable differences in CRF outcomes between intensities. Future studies using a prospective design could randomize participants to light or moderate-vigorous intensity, resulting in a more controlled assessment of how exercise intensity independently influences post-exercise CRF, regardless of pre-exercise CRF levels.

Additionally, for the moderate-vigorous group, the average heart rate reserve (HRR) was 49% which is at the lower end of the range of 40-89%, which may not have been a large enough difference from the average HR of 30% in the light intensity group to see a meaningful difference in effect on CRF.

Although the absence of significant differences in CRF between exercise intensity groups contradicted our original hypothesis, it does challenge the common misconception that participating in higher intensity exercise can increase CRF afterwards.

To our knowledge, no previous studies have examined the impact of exercise intensity on the time course of CRF following an exercise session. Optimizing exercise intensity may be a vital component in exercise prescription for highly fatigued cancer survivors, as different exercise intensities may have varied effects in reducing objective CRF in a single bout of exercise, through reduced inflammation mechanisms. For instance, a systematic review comparing exercise intensities in chronic exercise interventions on inflammation markers found that pro-inflammatory cytokine TNF-α and anti-inflammatory IL-10 only increased after intense exercise, while pro-inflammatory cytokines IL-6 and IL-1β increased more with intense than with moderate exercise.[142] These findings suggest that exercise intensity can influence inflammatory processes, which are known to affect CRF levels in chronic exercise. Therefore, further research is needed to understand how exercise intensity impacts CRF in a single exercise session to strengthen recommended acute exercise prescriptions for cancer survivors.

Strengths and Limitations

Strengths of the current study include the inclusion of multiple exercise sessions for pre- and post-CRF data, and CRF data over the course of a day across 12 weeks. This results in the ability to track trends in CRF longitudinally, to identify patterns of CRF, and capture session-to-session variability across the 12 weeks. Another strength of this study is the observational design utilizing an existing outpatient rehabilitation program. This decreased selection bias by (i.e., decreased the likelihood that only motivated, already active individuals would volunteer for

an exercise study)[110], ensuring a more representative sample of cancer survivors that would be found in a clinically supervised setting, that included diversity in terms of cancer type, stage and varying timepoints of treatment. Another strength was the inclusion criteria of a clinical cut-off for fatigue, which reduces the likelihood of a ceiling effect and represents an enrollment of cancer survivors experiencing CRF. A strength in our study design was the real-world relevance of allowing participants to self-select exercise intensity each session, which may reflect how cancer survivors participate in exercise outside of structured programs, improving generalizability. Our study used an objective and subjective measurement of exercise intensity by capturing heart rate and rate of perceived exertion. Finally, a major strength in our study was the within-subject design, as participants had the potential to complete both light and moderate/vigorous intensity sessions, which reduced between-subject variability.

Limitations of this study include the lack of racial/ethnic and socioeconomic diversity of our sample, and a sample consisting of a majority of female cancer survivors. However, previous research has reported that female cancer survivors exhibit a 1.4-fold higher prevalence of severe CRF compared to males. Since our findings from pre-to-post exercise CRF between groups showed a marginally significant effect, we believe that a larger sample size may have shown a significant difference. Self-selected exercise intensity was measured each session utilizing a Polar M200 wristwatch to collect heart rate instead of the Polar H10 chest strap due to the strap causing skin irritation on cancer survivors who were undergoing radiation treatment. The H10 chest strap or arm band is preferred due to its high validity with ECG, which is the gold standard for measuring exercise heart rate.[145] In addition, taking the averages of heart rate across aerobic and resistance sessions may have the potential to underestimate true intensity levels, as heart rate is not an ideal measurement to capture resistance training intensity.

In conclusion, the results of the current study provide evidence that both light and moderate/vigorous exercise intensity do not increase CRF following exercise but rather help maintain CRF across the day. These findings highlight the value of a single exercise session in

managing treatment-related side effects and promoting exercise motivations and adherence among cancer survivors, regardless of exercise intensity. They also highlight the importance of monitoring CRF beyond the immediate post-exercise period, particularly when prescribing exercise intensity in outpatient rehabilitation settings. Understanding how CRF evolves throughout the day may inform strategies to support activities of daily living and improve overall function. This study contributes to real-world clinical exercise recommendations by examining whether exercise intensity moderates CRF responses. Future studies should investigate the mechanisms underlying this relationship, where exercise intensity is controlled and standardized across exercise sessions to understand the true effect of exercise. Additionally, future studies should measure this exercise intensity effect on CRF across additional weeks/months of exercise to test if prescribed moderate-vigorous intensity exercise can maintain a lower overall CRF level across time.

Chapter 6 - Conclusions

SUMMARY

CRF is closely associated with quality of life in cancer survivors, making this highly prevalent symptom a critical target for survivorship care. Many cancer treatments have a negative impact on CRF; thus, exercise interventions that target this prominent patient-reported outcome are necessary. However, with CRF being a multi-dimensional concept, we need more information on how to utilize exercise to target how to improve self-reported CRF for cancer survivors. Although multiple randomized control trials have been conducted to assess long-term exercise interventions on CRF, many of these studies only target baseline and post-measurements of CRF, despite the ability of CRF to be altered day-to-day for many cancer survivors. Additionally, CRF is not often measured throughout the day following a single exercise bout. To understand how exercise affects CRF, subjective CRF following that bout needs to be collected to account for studying the impact of a single exercise bout on CRF. Without considering the day-to-day changes of CRF, it is difficult to understand its effects on exercise motivation and adapting long-term exercise behaviors. Therefore, this dissertation sought to better understand how a single bout of exercise could impact CRF immediately before and after a session and throughout that same day in a diverse sample of cancer survivors.

Currently, only four studies analyzing the acute effects of exercise and CRF are available in cancer survivors (Matsugaki et al. 2018, Cohen et al. 2019, Siebert et al. 2022, Gomes et al. 2024). Taken together, findings from these studies provide preliminary support for the potential for the acute effect of exercise to reduce CRF; however, small sample sizes and the heterogeneity of exercise protocols and measures of CRF limited our ability to draw definitive conclusions. Additionally, the timing of CRF measures varied, with immediate post-exercise reductions reported in three studies, and the other which measured CRF throughout the day. Even though one study studied CRF throughout the day, the study did not report the

outcome of this measure; therefore, gaps still exist on how CRF changes after a single bout of exercise. Therefore, another purpose of this dissertation was to advance the science of measuring CRF at three timepoints following a single exercise session and three timepoints on a non-exercise day. In addition, this dissertation has the potential to inform clinical exercise recommendations for cancer survivors from a real-world outpatient rehabilitation setting. Specifically, we wanted to determine whether exercise intensity moderates CRF responses, providing insights into individual variability and potential optimization of exercise prescriptions.

Findings from this work that examined changes in CRF from immediately before to immediately after exercise sessions did not demonstrate acute effects on CRF, as there was no difference in CRF, and no difference in the magnitude of CRF change from week to week. When assessing CRF at hours 1-, 4, and 7-hours post-exercise, findings revealed that on exercise days, CRF demonstrated a positive significant slope for CRF from immediately post-exercise through 1, -4, and -7 hours, with CRF levels remaining stable at 1- and 4-hours compared to post-exercise before rising significantly by the 7-hour timepoint compared to post-exercise. On non-exercise days, CRF demonstrated a positive significant slope for CRF from the 1-hour timepoint through 4, and -7 hours; however, CRF levels at each timepoint (4 and 7 hours) were not significantly different from the 1-hour timepoint. Notably, comparisons between exercise and non-exercise days revealed no significant differences in CRF slopes, suggesting that CRF tends to follow a similar trend during the day, independent of exercise.

Finally, when assessing the effect of self-selected exercise intensity on CRF from immediately before to immediately after an exercise session, and 1-, 4 -and 7-hours following the exercise session, findings revealed that there was no significant change in CRF from pre- to post-exercise between the light or moderate-vigorous exercise intensity groups, however, the slope of CRF levels over the day following exercise increased for both groups.

Taken together, findings from these three studies offer insight into the short-term patterns of CRF between baseline and post-intervention assessments. Although our study did

not demonstrate an acute effect of exercise on CRF, the absence of significant increases suggests that acute bouts of exercise, both during and after treatment, do not appear to exacerbate fatigue symptoms.

Furthermore, if cancer survivors report similar levels of CRF on exercise and non-exercise days, they can still achieve the benefits and physiological adaptations of exercise[9] without experiencing a worsening of CRF, helping to reduce avoidance around exercise. Finally, our study results suggest that if both light and moderate-vigorous exercise sessions result in similar CRF trajectories throughout the day, cancer survivors may not need to avoid higher intensities out of the fear of worsening CRF. However, if survivors experience benefit from a single exercise session at any intensity, they may be more likely to perceive exercise as a manageable and beneficial activity. This is particularly important for individuals unable or unwilling to engage in higher-intensity exercise due to treatment-related side effects.

Being conducted in an outpatient cancer rehabilitation setting allowed for limited research control over certain intervention methods; however, conducting this research in a real-world setting allowed for the enhancement of the generalizability and clinical applicability of this research. The data collected will provide cancer survivors and oncologists with proven evidence that exercise continues to be safe and feasible during and after treatment and that a single exercise session will not significantly increase CRF levels after or over the day, regardless of what exercise intensity is self-selected. Our results also showed variability within cancer survivors in terms of self-reporting CRF, which could depend on a variety of external factors such as sleep quality, employment status, current blood levels, and nutritional status that were not able to be collected in the current study. Strengths of this study include the use of real-time self-reported CRF measurements collected via EMA via a phone application, which reduced recall bias and ensured standardized data collection within a fixed response window for each participant. Another strength of this study is the novelty. To date, no previous studies have examined the time course of CRF anchored around an exercise session, with repeated

measures of CRF. This results in the ability to track trends in CRF longitudinally across the 12 weeks. Additionally, we included a non-exercise day as a control condition to strengthen internal validity by isolating the effects of exercise and accounting for natural daily variation in CRF. Another strength of this study is the observational design utilizing an existing outpatient rehabilitation program. This decreased selection bias by (i.e., decreased the likelihood that only motivated, already active individuals would volunteer for an exercise study)[110], ensuring a more representative sample of cancer survivors that would be found in a clinically supervised setting

Although these results are important for adding to the acute effects of the exercise literature base, they are not without limitations. This study only utilized a single-item measure of CRF at all measurement timepoints that collected CRF severity, which may not be as sensitive for collecting subtle changes in CRF in a single day, as there is currently no minimal clinically important difference (MCID) cutoff for clinical change for the VAS. Another potential limitation was that participants may not have shown up to an exercise session if they were extremely fatigued that day; however, we were not able to capture if CRF was a barrier to exercise in this study. Despite a wide range of cancer diagnoses included in this sample, the sample was not racially/ethnically or economically diverse. This is important to consider since it limits generalizability to all cancer survivors. The timing and amount of EMA CRF questions as a study method can also be considered a limitation. Despite the lack of current literature to determine what EMA timepoints and how many to send are unknown in the cancer population, there is still a possibility that we were not able to capture the true exercise effect on CRF with our chosen timepoints. Additionally, our EMA method required participants to have access to a smartphone and be aware that notifications were appearing. Many participants would often attend additional appointments, treatments, or naps following exercise sessions, therefore missing EMA notifications. Also, since all participants' messages had to be anchored around the exercise session, afternoon participants received their 7-hour timepoint message quite late, making it difficult to capture that last timepoint for a handful of participants.

FUTURE RESEARCH DIRECTIONS

A substantial literature base exists to support the benefits of exercise interventions (i.e., "chronic exercise") for reducing CRF. However, whether exercise can provide immediate relief of CRF remains a pressing scientific question, with substantial practical and clinical implications. Currently, few previous studies have examined the acute effect of exercise on CRF, but promising findings from my dissertation studies, including the absence of significant increases in CRF following a single exercise bout and up to 4-hours, along the presence of plausible underlying physiological mechanisms for this phenomenon support the need for further investigation, and a promising direction of research in the field of exercise oncology. Below are suggested future directions that will build upon the information provided in this dissertation.

Establishing the efficacy of exercise to reduce CRF from immediately before to after exercise

While my first study did not find an increase in CRF from immediately before to immediately after exercise, it also did not see a decrease in self-reported CRF like previous studies.[18,20] Therefore, to more definitively determine the acute effect of exercise on CRF, additional studies with a randomized control trial (RCT) design are needed. RCT's will establish a causal relationship between exercise and immediate reductions in CRF, and will allow for consideration of several key moderators, such as treatment(s) received, demographics (e.g., age and sex socioeconomic), and baseline level of CRF, as these factors may influence the magnitude of effect for exercise on CRF. This could be achieved in several ways, including multiple studies of specific subpopulations that control for heterogeneity in factors hypothesized to influence the CRF response, or stratifying randomization based on one or more of these factors. In addition, understanding how these factors impact acute CRF response to exercise may help inform exercise personalization.

Additional considerations for future RCTs that aim to determine the acute effect of exercise on CRF include careful selection of CRF measures and the impact of exercise type, intensity, duration, and timing. First, in order to detect meaningful reductions in CRF immediately

following exercise, the appropriate CRF measure is of vital importance. My dissertation studies utilized the fatigue visual analog scale (VAS), which was a low-burden option for assessing CRF before and after exercise sessions and has also been tested for reliability and validity to measure CRF.[55,105] However, due to findings suggesting no decrease in CRF, this measure may not be sensitive enough to capture acute or immediate changes in CRF. Even though many widely tested, valid, and reliable instruments exist,[146] these tools typically have 6 or more questions, and have been used to assess CRF either cross-sectionally or to capture changes over weeks to months. Thus, it is unclear whether these instruments would be too burdensome to assess CRF before and after exercise. Therefore, additional testing of the psychometric properties for the VAS for sensitivity to change and clinical meaningfulness of this change is needed. Second, given that our study did not find any significant differences in CRF based on exercise intensity, predetermined exercise prescription is vital for further studies. For example, future RCTs should be attentive to exercise prescriptions and potentially consider comparisons across exercise type (e.g., aerobic vs. resistance), duration, or assigned exercise intensity. Finally, in my dissertation studies, participants exercised at numerous timepoints across the day (e.g., in the morning and afternoon); therefore, the time-of-day exercise is completed should be considered. When exercise is performed has been shown to have important implications for its effects on metabolic outcomes (e.g., obesity, type 2 diabetes, dyslipidemia, and hypertension),[147] suggesting that this may also be a factor to consider when designing future RCTs that examine the acute effect of exercise on CRF (i.e., standardizing the timing of exercise sessions within and across participants).

Additional considerations for future studies should include recording reasons why participants miss exercise sessions, to tease out if they missed because of an appointment or family obligation, or if it was because of treatment-related side effects. This information would provide insight into ongoing barriers to exercise for cancer survivors. Future studies should also

consider additional factors that can impact CRF throughout the day, such as sleep, nutrition, and treatment schedules.

Elucidating underlying Mechanisms for the acute effect of exercise on CRF

In order to understand how exercise can immediately reduce CRF both immediately and over the course of a day, future studies that examine the underlying physiologic mechanisms are also needed. Although the mechanisms by which exercise can acutely reduce CRF are unclear, an exciting and emerging area of future research may include exploring the role of the endocannabinoid system (ECS) in how exercise may provide immediate relief of CRF.[76] Adaptations in the ECS system may induce positive emotional arousal following exercise,[148] yet no studies have explored the ECS responses to exercise in a cancer population, and the subsequent impact on CRF. Thus, future studies are needed to determine a direct link between ECS activation during exercise and the effect on CRF, which may include biomarker assays of circulating eCB levels. Based on previous studies that evaluated the relationship between a runner's high following endurance exercise and eCB levels,[78] future studies seeking to examine this response among cancer survivors experiencing CRF may consider measuring circulating levels of eCBs (e.g., anandamide (AEA)) before and 15 - 60 minutes post-exercise. Therefore, the EMA timing of future studies should be adapted to measure CRF to align with the mechanistic timeline of the ECS system.

CONCLUSION

The acute effect of exercise on CRF is an understudied area of research with many important practical and clinical implications. Only four studies have examined the acute effects of exercise on CRF, and despite promising results, limitations in sample size and variability of intervention type and CRF measure prevent drawing definitive conclusions. My dissertation research significantly contributed to the field of exercise oncology by demonstrating how exercise can enhance motivation and adherence, improve symptom management, and inform more effective exercise prescriptions in the clinical setting. Finding stable levels in CRF

following exercise in this study had the potential to provide cancer survivors with positive emotional feedback, which may have increased their motivation to continue exercising, even on days when they did not initially feel well. We hope that the regular collection of CRF ratings before and after exercise also serves as an educational tool, helps survivors better understand how CRF affects their daily functioning, and empowers them to self-select exercise intensity based on factors such as treatment side effects, sleep quality, and nutrition status. Importantly, this evidence offered oncology clinicians a tangible and concrete benefit of exercise to share with cancer survivors who may have been hesitant to engage due to CRF concerns.

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