Using Exercise Based Interventions for the Treatment of Cancer Related Fatigue: A Meta Analysis

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"I am a magnet. I attract what I feel. I see in my mind only the positive. I focus with passion until my thoughts become real. This is my path to an abundant life."

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ABSTRACT

Background: Cancer Related Fatigue (CRF) is recognized as the most prevalent and distressing symptom affecting cancer patients and survivors. Although the study of CRF is a new field of research, many studies have investigated the role of exercise for the management of CRF. Results from these studies are inconsistent and difficulties interpreting the literature make it impossible to draw accurate conclusions regarding its effectiveness. **Purpose:** The purpose of this study is to apply Glassian meta–analytic procedures to primary study findings from studies testing the effects of physical exercise interventions on patients and survivors with CRF to determine the efficacy of exercise interventions for CRF. **Search Strategies:** Electronic databases with key word searches, hand searches of popular journals reporting on CRF and the reference lists of previously conducted meta analyses, reviews and eligible studies were searched to identify all possible published and unpublished articles, abstracts, theses and dissertations for the inclusion in the meta analysis. **Inclusion Criteria:** Published and unpublished literature quantitatively investigating the use of exercise based intervention used to treat CRF as an outcome in adult samples were included. **Data Collection and Analysis:** One author independently assessed each candidate study and extracted the appropriate data based on predefined criteria. With the available data, a meta analysis was performed using the fixed effects model to allow for investigation into potential heterogeneity using theoretically derived moderator variables. **Main Results:** 19 studies were identified for inclusion into the meta analysis (n = 2026). A meta analysis of the effects of exercise on CRF indicated that at the end of the exercise intervention period, exercise was significantly more effective in reducing CRF than the control intervention (SMD 0.27, 95% (CIs) 0.144 to 0.395). **Conclusion:** Exercise can be regarded as an effective treatment possibility for patients and survivors with CRF during and

after various treatments. Further investigation is needed to determine the most effective type and timing of exercise interventions. In addition, better understanding of the biological and physiological adaptations underlying these results is needed to develop the most effective treatment for individuals with CRF.

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CHAPTER 1

INTRODUCTION

In Canada, 39% of males and 45% of females will develop cancer in their lifetime with 24% of females and 29% of males dying from the disease (Canadian Cancer Society, 2008). Although these rates are high, advancements in medical technology and research have resulted in longer survival rates and even cures to many cancers (van Weert et al., 2008). However, as the number of patients living with cancer and as the side effects of adjuvant therapies continue to increase, parallel efforts to maintain or improve quality of life (QOL) have been insufficient.

Cancer and cancer treatments are accompanied by negative side effects that deteriorate psychological and emotional wellbeing as well as physical functioning. Common psychological and emotional side effects include depression, anxiety, loss of self control, stress, fatigue, decreased body image and decreased self esteem (Courneya, Mackey, & Jones, 2000; Knobf, Musanti, & Dorward, 2007; Mitchell, Beck, Hood, Moore, & Tanner, 2007). Physical and functional side effects of cancer and cancer treatment include diminished cardiovascular functioning, reduced pulmonary function, decreased muscular strength, cachexia, asthenia, atrophy, fatigue, weight changes, vomiting, pain, and difficulty sleeping (Courneya et al., 2000; Knobf et al., 2007; Mitchell et al., 2007; van Weert et al., 2008). A common side effect to both psychological and physical parameters of QOL is fatigue. In cancer patients this is known as cancer related fatigue (CRF). Cancer Related Fatigue is often reported as the most debilitating and distressing symptom of all cancer and cancer treatment side effects, even more so than pain, nausea or vomiting (Ryan et al., 2007).

Due to the limited success and the presence of many adverse side effects of pharmaceutical trials, non-pharmaceutical options such as psychotherapy and physical exercise have become an attractive possibility (Portenoy & Itri, 1999). Psychotherapy interventions have been successful; however this form of rehabilitation only offers benefit to one aspect of a multidimensional syndrome. Psychological treatments can improve psychological and emotional parameters but neglects the overwhelming physical parameters associated with CRF (Courneya et al., 2000).

Physical exercise is a treatment method that has only recently been investigated. Since the first trial testing the effects of a cycle ergometer program on cancer patients by Winningham in 1983, research on exercise as a treatment modality for CRF is rapidly expanding. Although the notion of exercise to improve fatigue is counter intuitive to many patients and medical staff, exercise has been documented to exert positive effects on both physical and psychological parameters of CRF and overall QOL. However, the literature regarding exercise interventions for patients with CRF commonly reports inconsistent results and has been scrutinized for the use of notoriously weak methodologies (Jacobsen et al., 2007; McNeely et al., 2006; van Weert et al., 2008). Therefore, the understanding of the role exercise in reducing CRF is not well understood.

STUDY RATIONAL AND PURPOSE

With cancer survival rates increasing, the need to develop effective rehabilitation strategies and programs to restore and increase patient QOL is of paramount importance. Previous research on the effects of exercise on CRF and its underlying etiologies has declared mixed results and is the target of much criticism. To date, a number of reviews

have investigated the effects of a variety of physical activity interventions on cancer patients and survivors highlighting specific outcome variables such as: QOL, fatigue, psychological well being, physical functioning and select potential etiologies (Schmitz et al., 2005). Results from pre – post studies, quasi experimental studies, and random controlled trials in addition to qualitative reviews generally conclude that exercise is a beneficial intervention for oncology patients suffering from CRF regardless of the type or stage of cancer or treatment. However, due to the many definitions of CRF, multiple assessment instruments, variety of exercise prescriptions and inconsistent results presented in the current body of experimental literature, drawing accurate conclusions on the effects of exercise on CRF in terms of magnitude and direction is difficult, and thus generalized conclusions declared by qualitative literature reviews should be carefully considered. For example, Schmitz et al. (2005), state that existing qualitative reviews may conclude that physical exercise can consistently exert positive effects on CRF where the magnitude of this effect may be too small to be of meaningful value to the oncology patients with CRF (Schmitz et al., 2005). Therefore, the rationale to this study is due to the preliminary nature of this rapidly expanding field of research. There is a need to quantitatively synthesize the results of experimental trials investigating exercise for the management of CRF in order to assist interprofessional health care teams in making accurate decisions regarding the overall efficacy of exercise as a treatment for CRF. The purpose of this study is to apply Glassian meta analytic procedures to primary findings from studies testing the effects of physical exercise interventions on patients and survivors with CRF.

RESEARCH QUESTIONS

The research questions are as follows: First, what is the overall effect of physical exercise interventions on CRF? Second what is the optimal exercise type (aerobic, resistance or mixed) used to reduce CRF? Third, does the effectiveness of exercise interventions differ based on cancer and cancer treatment characteristics? Fourth, what effect does exercise have on the underlying etiologies contributing to CRF?

STUDY LIMITATIONS

The following limitations of our meta analysis have been considered. First, there may be heterogeneity present within our mean effect size distributions due to differences in exercise prescriptions, cancer diagnosis, cancer treatment characteristics or small sample sizes. This heterogeneity may indicate that the mean is not representative of the population being investigated. Secondly, because of the diverse range of parameters we wish to study within our subgroups, small study numbers may occur. Third, there will be one primary investigator that will pass studies through the process of inclusion and coding; therefore, a bias may occur. However, in order to reduce a natural bias, inclusion criteria have been defined and coded in a manual to reduce bias and ensure equality of inclusion throughout all eligible studies (Appendix A). Fourth, methodological quality will not be used as inclusion criteria. Methodological data was coded for further qualitative analysis and was decided that by including weaker methods and designs such as pre – post contrast studies it would provide a better overall picture of the effects of exercise on CRF from all available data.

A confounder of the present study is that not all studies may present adequate data to calculate an effect size. Cramp and Daniel (2008), suggest that those studies that do not find favourable outcomes are more likely to withhold all the data (Cramp & Daniel, 2008). Therefore, data that are present may cause an upward bias. Also, due to strict inclusion criteria, small sample sizes of independent studies may be present. Unfortunately a limitation to the meta analysis is that sample sizes can become small and it is not possible to increase these numbers unless the inclusion criteria are revised.

DEFINITIONS

Cancer Related Terms

Cancer Related Fatigue: A persistent and subjective sense of tiredness that can occur with cancer or cancer treatment that interferes with usual functioning (de Nijs et al., 2008).

Cancer Treatment Terms

Adjuvant Therapy: is the use of a treatment in addition to primary surgical treatment of cancer (McKinnell et al., 1998).

Biological Response Modifiers: heterogeneous group of chemicals that influence cells of the immune system and affect other cells. Include interferons, interleukins, and tumour necrosis factors (King & Robins, 2006).

Chemotherapy: a treatment of cancer with chemical agents (McKinnell et al., 1998).

Radiotherapy: a treatment of disease with radiation (McKinnell et al., 1998).

Etiology Terms

Anemia: a condition in which hemoglobin concentration is lower than 12g/dL (Jager et al., 2007)

Apoptosis: also known as programmed cell death, is a highly conserved biological process that plays an important role in controlling tissue development, homeostasis, and arChitecture by eliminating redundant, dysfunctional or injured cells (Quadrilatero & Rush, 2006)

Cancer Cachexia: is a syndrome characterized by a marked weight loss, anorexia, asthenia and anemia, often associated with the presence of a tumour and leads to a status of malnutrition due to induction of anorexia or decreased food intake (Argiles et al., 2006)

Circadian Rhythms: are endogenous genetically and physiologically based patterns that are controlled by the body's "biological clock" (Ryan et al., 2007)

Cytokines: are hormone–like peptides that play a very important role in the cellular interactions; include Tumour Necrosis Factor–Alpha (TNF-a) and members of the Interleukin family (IL-1, IL-6, IL-8) (Adamopoulos et al., 2006)

Hypothalamic Pituitary Axis: is the central regulatory system controlling release of the stress hormone cortisol (Ryan et al., 2007)

CHAPTER 2

LITERATURE REVIEW

The aim of the literature review is to develop an understanding of the theory regarding CRF. The review of literature will focus on defining CRF and assessing CRF, identifying the prevalence of CRF and identifying the potential etiologies of CRF as well as investigating current treatment strategies of CRF. Following the chapters regarding CRF theory, a description of the meta analysis as it relates to the current research will be presented.

WHAT IS CANCER RELATED FATIGUE

Cancer Related Fatigue is a common symptom in patients with cancer as well as disease free survivors. The study of fatigue itself is complicated due to a number of possible etiologies, physical and psychological factors, and varied patient perceptions of the experience (Lucia et al., 2003). The study of physical fatigue in the study of exercise physiology defines fatigue as the decline in muscle tension capacity with repeated stimulation (Lucia et al., 2003). This definition focuses on the physical effects of fatigue without mention to the psychological parameters. In contrast, the clinical definition of fatigue acknowledges the psychological and emotional parameters but does not refer to any physical effects. For example, clinical fatigue is defined as a patient's feeling of lack of energy, weariness or tiredness (Lucia et al., 2003). Contrary to the previous two definitions of fatigue, the term CRF takes on a more multidimensional approach. For example, Portenoy and Itri (1999), define CRF as an inherently subjective and multidimensional condition. This definition illustrates fatigue as a subjective symptom

that does not just affect psychological or physical function alone, but diminishes the function of both. Furthermore, CRF has been more specifically defined as a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion, creating an unrelenting overall condition which interferes with the individual's ability to function to their normal capacity (de Nijs, Ros, & Grijpdonck, 2008). In efforts to unify the definition of CRF, the National Comprehensive Cancer Network (NCCN) defines CRF as a persistent and subjective sense of tiredness that can occur with cancer or cancer treatment that interferes with usual functioning (de Nijs et al., 2008; Watson & Mock, 2004). Although there are a variety of definitions proposed for this condition, the many definitions highlight similar key features such as a subjective experience, multidimensional symptoms, unrelenting fatigue, and reduced QOL. Fatigue can be described and defined in a number of different ways due to its many different etiologies and wide range of symptoms. However, a definition of CRF must be one that incorporates a subjective multidimensional experience with consideration for a variety of etiologies and symptoms.

Recently, CRF has been accepted by the International Classification of Diseases 10th Revision Clinical Modification as a diagnosis. According to this classification fatigue is characterized as a multidimensional phenomenon that develops over time, diminishing energy, mental capacity, and the psychological effects of cancer patients (Portenoy & Itri, 1999). For CRF to be acknowledged as a clinically diagnosable symptom allows differentiation between CRF, normal fatigue and other pathological forms of fatigue. CRF is a separate entity from other types of fatigue experienced by those with depression, multiple sclerosis, and arthritis and is much more disruptive and debilitating when

compared to these diseases (Lucia et al., 2003). Regardless of the type of cancer, the fatigue associated with this disease influences all aspects of the patient's QOL and aggravates other symptoms such as pain, nausea, vomiting and depression (Lucia et al., 2003). In contrast to other forms of fatigue, whether psychological fatigue, physical fatigue or the fatigue associated with other disease, CRF incorporates a wide variety of symptoms ranging from physical to psychological, cannot be relieved with rest and is much more disruptive and enduring (Windsor et al., 2004).

When patients describe their symptoms, they are inclined to describe what they feel as a diversely negative experience and an inability to perform some aspects of normal functioning (Windsor et al., 2004). Complaints of weakness, fatigue, constant exhaustion, poor sleep, depression, subtle cognitive impairments, and difficulty concentrating may be expressed. Due to CRF being a multi dimensional condition with a variety of symptoms, using the term CRF alone may be misleading (Winningham, 2001). Since CRF is characterized by a diverse collection of experiences and symptoms, Winningham (2000) proposes the use of the medical term "syndrome" as a more accurate and appropriate term for CRF. Therefore, CRF would be better suited and more accurately identified as Cancer Related Fatigue Syndrome. By expanding the term to a syndrome we can enhance the awareness of the diverse symptoms of CRF and generate more accurate and improved ways of assessing, evaluating and reporting the condition.

The diverse nature of CRF has resulted in a variety of working definitions. Studies on CRF are notoriously difficult to interpret and synthesizing the results is also a challenge to researchers. The lack of a standardized or consistent definition of CRF is one reason for this (Franklin & Packel, 2006). A consistent and standardized definition

used for CRF research would improve methodological strength, validity and reliability of CRF research and thus provide a stronger understanding of this debilitating syndrome.

ASSESSMENT AND EVALUATION OF CANCER RELATED FATIGUE

Assessing Cancer Related Fatigue

CRF as a subjective multidimensional condition should be assessed by an inventory that includes measures of each distinct dimension involved in the syndrome through a self-report style questionnaire (Portenoy & Itri, 1999). The use of a comprehensive assessment will provide the clinician or researcher a detailed characterization of the fatigue the patient is experiencing.

In a comprehensive CRF assessment tool a variety of characteristics must be identified. First, an effective fatigue inventory should include a description of the patient's fatigue experience (Portenoy & Itri, 1999). By measuring items such as fatigue severity, daily patterns of fatigue severity, course of fatigue over time and exacerbating factors, the clinician could map out the patient's experience and indentify the most appropriate timing of intervention. Second, a fatigue investigation should include a description of the patient's medical history (Portenoy & Itri, 1999). Key information such as type of cancer, stage of cancer, types of cancer therapy taken, stage of adjuvant therapy and prescription of cancer treatments must be integral in the evaluation (Jereczek-Fossa et al., 2002; Portenoy & Itri, 1999). These parameters will provide the clinician with clues to determine possible etiological mechanisms resulting in or exacerbating the patient's fatigue experience. Third, a medical examination should be taken to evaluate different biological correlates of CRF. A medical examination should

describe factors such as the presence of anaemia, cytokines, dehydration, electrolyte disturbances and metabolic and energy disorders (Jereczek-Fossa et al., 2002; Portenoy & Itri, 1999; Ryan et al., 2007). Understanding of the biological parameters contributing to the patient's experience may provide support for specific prescriptions of pharmaceutical and exercise interventions. Fourth, an evaluation of physical functioning should be included in the assessment protocol. Physical function examinations determining cardiovascular fitness, pulmonary function, flexibility and muscular strength should also be included. These items are crucial for patient's overall QOL (Knobf et al., 2007). The level at which the patient is capable of performing on these assessments of physical function may determine safe integration back into the work place, determine any ergonomic changes that must be made at home or at a place of employment and provide areas of concern which the patient and rehabilitation experts must address. Finally, psychological and emotional health status should be addressed. Assessments in this area could illustrate anxiety levels, depressive disorders, emotional disturbances, self esteem issues and sense of control issues (Courneya et al., 2000; Jacobsen et al., 2007). Psychological and emotional evaluation would provide a base from which clinicians could prescribe or suggest specific interventions or involvement in appropriate support services and programs. The data established from an inventory with both subjective and objective measures like the ones mentioned above may allow for plausible hypotheses concerning pathogenesis and in turn an appropriate therapeutic intervention strategy (Franklin & Packel, 2006; Portenoy & Itri, 1999; Stone & Minton, 2008). The next section will describe common CRF assessment instruments which use a variety of the above topics to diagnose CRF.

Cancer Related Fatigue Assessment Tools

Screening for cancer related fatigue can take on two distinct approaches: the use of a uni-dimensional assessment tool or a multidimensional assessment tool. The uni-dimensional tool is the simplest level at which fatigue can be measured (Stone & Minton, 2008). These instruments include single item questionnaires or single item visual analog scales. Uni-dimensional assessment tools can be used independently or more commonly, as a supplement to additional larger scale assessment tools (Schmitz et al., 2005). Independently, the uni-dimensional tools may be best suited for fatigue screening, monitoring changes over time due to interventions and illustrating the degree or severity of fatigue (Portenoy & Itri, 1999; Stone & Minton, 2008). A limitation of the uni-dimensional fatigue assessment tools is that fatigue is defined and perceived as a multidimensional experience. Uni-dimensional assessment tools are limited therefore, in the extent that they can detect the full range of subtleties of this complex syndrome (Stone & Minton, 2008). Due to this limitation, assessment of fatigue by single item scales and questionnaires have commonly underestimated the fatigue in cancer patients (Jereczek-Fossa et al., 2002).

In contrast, multidimensional tools have been designed to assess a variety of characteristics involved with the CRF experience. The multidimensional fatigue assessments have been designed to capture the multiple characteristics and related manifestations of fatigue as well the impact they have on the patient's ability to function (Portenoy & Itri, 1999). These assessment tools can provide insight not only to the fatigue changes over time but which etiologies may be exerting the greatest influence on the syndrome. Data derived from multidimensional assessments are much more

informative than the uni-dimensional counterparts and provide greater insight into the pathology of CRF (Portenoy & Itri, 1999)

Prior to the use of CRF assessment tools the NCCN advocate that screening be done to ensure the subject is indeed diagnosed with CRF. The NCCN uses a single item, 11 point, numerical rating scale describing the fatigue being experienced. NCCN guidelines recommend that patients with a score of 0 – 3 should be considered to have none to mild fatigue, those with scores 4 – 6 or 7 – 10 should be considered to have moderate to severe fatigue respectively (Stone & Minton, 2008). Prior to CRF assessment a diagnostic interview for CRF should be taken (Stone & Minton, 2008). According to Stone and Minton (2008), in order to be identified as a patient in need of CRF treatment or inclusion to CRF research an individual should have experienced significant fatigue, lack of energy or an increased need to rest every day or nearly every day for 2 weeks in the last month. Additionally, subjects should experience 5 out of 9 other CRF symptoms and should have had fatigue cause a significant impact of functional abilities (Stone & Minton, 2008). By evaluating and screening patients prior to applying treatment protocols we can distinguish those who truly have CRF from those who are experiencing fatigue more common to the general population.

Many different types of CRF assessment tools have been used in the literature. This has contributed to some of the variability in results across studies. Each study differs slightly from the next depending on the definition of CRF used. The definition used will determine the constructs being evaluated thus producing different results between studies. An outline of commonly used CRF assessment tools are presented in Table 1.0 and Table 1.1.

Table 1.0 Cancer Related Fatigue Assessment Instruments

Assessment Instrument	Description
NCCN CRF Screening Tool	• Single item, 11 point numerical scale • Detects the presence of CRF
Multidimensional Fatigue Inventory (MFI-Q20)	• 20 point self report questionnaire • Designed for assessing fatigue during radiotherapy
Fatigue Assessment Questionnaire (FAQ)	• 19 item self report questionnaire • Binary and visual analogue scales • Assess physical, affective and cognitive parameters of fatigue
Fatigue Questionnaire (FQ)	• 11 item self report questionnaire • 7 items regarding physical parameters • 4 items on mental parameters
Piper Fatigue Scale (PFS)	• 42 item self report questionnaire • Composed of visual analogue scales • Measures temporal, sensory and affective aspects of fatigue
PFS Revised	• 22 item self report questionnaire • 4 dimensions assessed include behavioural/severity, affective meaning, sensory and cognitive/mood

Table 1.1 Cancer Related Fatigue Assessment Instruments

Assessment Instrument	Description
Functional Assessment of Cancer Therapy – Fatigue Subscale (FACT-Fg)	• 13 item self report questionnaire • Assesses physical, functional, emotional, and social aspects of daily life and contributions to CRF
European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQc30	• 3 item subscale measures tiredness weakness and lack of energy
Brief Fatigue Inventory (BFI)	• 9 item self report questionnaire • Measures intensity of fatigue over past 24 hours on a 10 point scale
Medical Outcomes Study 36 – Item Short Form Health Survey fatigue subscale	• Measures physical, emotional and social well parameters of QOL • 4 item fatigue subscale to measure fatigue within the last week
Functional Assessment of Cancer Therapy – Fatigue Subscale (FACT-Fg)	• 13 item self report questionnaire • Assesses physical, functional, emotional, and social aspects of daily life and contributions to CRF

The CRF assessment tools illustrated in tables 1.0 and 1.1 are a sample of the commonly used tools in the field of CRF research (Franklin & Packel, 2006). Although there are a variety of instruments to choose from, the researcher must adopt the instrument based on the nature of the research question and the explicit or implicit definition of CRF which they are working from (Franklin & Packel, 2006). A variety of

instrumentation used to assess CRF is one of the causes of a notoriously consistent critique within the body of CRF literature. As a result of a broad range of CRF definitions, a broad range of CRF assessment tools have been produced. Each tool differs on each various parameters or the weighting of importance of the item being measured. Due to these individualities, results from CRF studies are inconsistent and difficult to interpret.

PREVALENCE OF CANCER RELATED FATIGUE

The prevalence of CRF is likely to vary depending on the assessment tool used and the threshold criteria that are established by the researcher (Stone & Minton, 2008). Regardless of the instrument used to assess the presence of CRF, fatigue is one of the most prevalent symptoms that is experienced by oncology patients (Courneya et al., 2000; Hofman et al., 2007; Ryan et al., 2007). Cancer Related Fatigue is commonly found within the range of 70 – 100% in cancer patients (Hofman et al., 2007). Unfortunately there is little information regarding the prevalence of fatigue prior to diagnosis. However, reports of CRF by oncology patients suggest that fatigue is present throughout the entire course of the disease (Hoffman et al., 2007). For example, fatigue has been identified as one of the first symptoms causing the patient to seek medical attention even prior to diagnosis of cancer (Brown et al., 2004; Wang, 2008). From time of diagnosis to survival and remission, fatigue is most commonly experienced by 40 – 100% of patients undergoing cancer therapies (Courneya et al., 2000; Stone & Minton, 2008). CRF is commonly described throughout the full cancer experience, from diagnosis, during therapy, and for months to years following completion of therapy and

into remission (Hoffman et al., 2007). This section of the review will identify the scope of CRF by exploring the prevalence of CRF with regards to cancer types and cancer treatments.

The Presence of Cancer Related Fatigue Depending on Cancer Types

There is evidence suggesting that fatigue is more common in certain cancer populations (Stone & Minton, 2008). For example, Servaes and colleagues (2001), discovered that in a mixed sample of cancer patients, the prevalence of severe fatigue was most common among patients with inoperable non–small cell lung cancer patients with fatigue occurring in 50% of the sample. In contrast, CRF occurred in 16% of recently diagnosed patients with prostate cancer. In addition, CRF has been found to affect 15% of patients with newly diagnosed breast cancer (Servaes et al., 2002). This may suggest that differing cancer diagnoses may induce greater risk factors for fatigue. It is possible that the location of the cancer may inhibit healthy organ function which may explain the different degree of fatigue and what the predominant causes may be between cancer diagnoses. For example, patients with hemotological malignancies often experience the greatest fatigue (Cella et al., 2004). This may be due to the effect of the cancer on haemoglobin production or even the intensity of chemotherapy treatments. In addition to location of the cancer, different intensities of CRF are felt based on type of adjuvant therapy.

Cancer Related Fatigue during Adjuvant Radiotherapy and Chemotherapy

Radiotherapy has been reported to induce fatigue early on during the treatment, or shortly after, in up to 80% of patients (Jereczek-Fossa et al., 2002). Radiation therapy, although producing high overall rates of CRF affects a variety of cancer types to different

degrees. For example, CRF is common in 30% of patients with brain tumours undergoing irradiation therapy is common in 30% of patients (Jereczek-Fossa et al., 2002). In contrast, 90% of breast cancer patients undergoing radiation therapy experience CRF during radiation therapy (Jereczek-Fossa et al., 2002). Fatigue is also an extremely common side effect during adjuvant chemotherapy (Lucia et al., 2003). It is commonly reported that 75% to 90% of oncology patients receiving chemotherapy will experience CRF (Hofman et al., 2007)

Regardless of the type of cancer, fatigue following radiation therapy and chemotherapy is a typical and expected, acute, as well as potentially enduring, side effect. Although short term radiation and chemotherapy induced fatigue may be present early within the first treatments, subsequent treatments do not seem to cause additional increases of fatigue. For example, one study found that 82% of women receiving chemotherapy for breast cancer experienced fatigue following the first cycle whereas the sample experienced a reduction of fatigue to 77%, during the second cycle. This non-linear incline of fatigue with cumulative radiation dose may suggest an adaptation within the patients to the stresses of the first treatment (de Nijs et al., 2008; Jereczek-Fossa et al., 2002). Although fatigue symptoms seem not to be cumulative following each treatment dosage, the resulting fatigue present may last from months to years following the completion of adjuvant chemo or radiation therapy (Courneya et al., 2000). For example, in 30% of patients receiving radiation therapy, fatigue can continue for a long time following completion of treatment (Jereczek-Fossa et al., 2002).

Cancer Related Fatigue Following Adjuvant Therapy

In as many as 40% of patients following completion of cancer related therapies, CRF is still present from months to years following treatment (Courneya et al., 2000). The majority of research on this phenomenon is done on breast cancer populations. Hofman and colleagues (2007) report that in a study of 763 women who survived breast cancer, fatigue was reported in 35% of the sample 1 – 5 years following completion of treatment and in 34% of patients even 5 – 10 years following completion of therapy (Hofman et al., 2007). Long term CRF is the most commonly reported symptom in 76% of women with breast cancer who had participated in adjuvant radiotherapy 2 – 10 years before the completion of the study (Lucia et al., 2003). In addition to these findings, it has been reported that 68% of the sample who received adjuvant chemotherapy 2 – 10 years previously reported fatigue (Lucia et al., 2003). The presence of long lasting CRF for advanced or palliative care patients is not well established since fewer controlled studies have investigated this area. However, fatigue in palliative care patients has been found to be significantly higher than the fatigue in the general population with 78% of palliative care patients experiencing fatigue symptoms (Stone & Minton, 2008).

Chemotherapy and radiation therapy are both associated with the induction and exaggeration of CRF. The severity may depend on the age of the patient, the type of cancer and or the intensity of the treatment protocol. The prevalence of CRF is difficult to accurately examine due to poorly established inclusion criteria and assessment instruments (Stone & Minton, 2008). For example, in a review of CRF interventions, it is reported that few studies applied diagnostic criteria rigorously enough to establish CRF from the fatigue felt in the general population (de Nijs et al., 2008). This may cause an

over estimation of the problem. In future studies, the inclusion of rigorous diagnostic criteria will produce a more valid and reliable illustration of the prevalence of CRF overall and in different populations and cancer types. In spite of the possible errors of interpretation, CRF still remains an ongoing concern. Improved clarity into CRF epidemiology will lead to more successful investigations into CRF risk factors and thus stimulate stronger etiology hypotheses.

POTENTIAL CAUSES OF CANCER RELATED FATIGUE

The pathophysiology of CRF has not been completely identified even though several causes and potential mechanisms have been proposed. Currently, studies have investigated factors that contribute to CRF arising from the malignancy itself or cancer treatments. Also, common comorbid conditions such as depression, anxiety, sleep disturbance, anemia and cachexia have been studied in hopes to explain possible etiologies responsible for the CRF phenomena (Ryan et al., 2007; Wang, 2008). Due to the multifactorial and multidimensional nature of CRF, the developments of methodologies to evaluate its underlying etiologies have been delayed (Ryan et al., 2007; Wang, 2008). It is currently suggested that CRF is most likely caused by multiple risk factors and underlying mechanisms as opposed to a single mechanism or factor. This complex interplay seen between etiological agents has been referred to as a web of causation, meaning that the pathogenesis may reflect an interaction of etiologies and host susceptibilities (Wang, 2008). In attempts to unravel this web, investigations of CRF etiology using triangulation methods have identified components of CRF that are similar

to other diseases, syndromes and comorbid conditions. This section of the review will first address the potential causes of CRF due to the malignancy and cancer related treatments. Next, we will identify and describe the proposed underlying mechanisms of CRF.

Potential Tumour Related Causes of Cancer Related Fatigue

Fatigue is common during cancer treatment. However, prior to cancer related therapy, significant fatigue is also reported and is one of the first symptoms that cause individuals to seek medical care (Brown et al., 2004; Wang, 2008). This suggests that fatigue may arise due to the changes occurring to the body in response to the malignancy itself. It is not understood how the malignancy causes fatigue. One possibility is that the location of the malignancy and metastases may induce mechanical changes on the organ system and its function. For example, cancer of the lungs can lead to shortness of breath, decreased total lung capacity, decreased total inspiration capacity, decreased oxygen diffusion capacity and reduced carbon dioxide removal (Schneider et al., 2007). These symptoms are directly related to the physical presence of the malignancy on the lungs. The location of this type of tumour will result in a reduction in the oxygen carried by the blood and thus reduce the ability to perform physical work which is associated with fatigue. Second, renal dysfunction caused by renal cancer or leukemia can lead to anemia and also reduced oxygen transport (Burnham & Wilcox, 2002; Lucia et al., 2003; Portenoy & Itri, 1999). Third, cancer affecting endocrine organs may induce fatigue by altering serotonin regulation resulting in depression and sleep disturbances and reduced central nervous system afferents (Ryan et al., 2007; Wang, 2008). In addition to the

physical impact exerted by the location of the tumour, host defence mechanisms may also induce symptoms of CRF.

It is hypothesized that the malignancy process can directly affect several organ systems through changes to the host's biological and physiological processes (Wang, 2008). Common links between many of the changes seem to biological and physiological systems involve the role of proinflammatory cytokines. In response to malignant cancer, host defence systems issue an inflammatory attack on the tumour. As a result, increased levels of circulating cytokines are present. A meta analysis by Schubert et al. (2006) found a significant positive correlation between fatigue and circulating levels of inflammatory markers and various cytokines (Schubert et al., 2007).

The process of cancer, even prior to treatment, has been identified to cause symptoms of fatigue by reducing the functional properties of different organs and altering biological and physiological processes. Experimental and correlation evidence points to the location and or the changes introduced to the patient's biology by the malignancy as a cause of CRF. Although CRF is present prior to treatment cycles, cancer treatments such as radiation therapy and chemotherapy commonly increase patient's levels of fatigue (Servaes et al., 2002).

Potential Treatment Related Causes of Cancer Related Fatigue

Cancer Related Fatigue is dramatically increased following cancer related treatments (Servaes et al., 2002a). Although chemotherapy and radiotherapy are most commonly associated with increases in fatigue, therapies such as surgery, and biological response modification have also been documented to increase fatigue and diminish

overall quality of life (Servaes et al., 2002a; Wang, 2008; Winningham, 2001). This section will describe the potential relationships between surgery, radiotherapy, chemotherapy, biological response modification therapy and CRF.

Surgery and CRF

Fatigue following surgery may be related to the receipt of anaesthesia, the type of analgesic used, decrease in pulmonary capacity, the invasiveness of the procedure, anxiety, infection and or prolonged bed rest (Nissen et al., 2001;Wang, 2008; Winningham, 2001). There are two theories on the cause of fatigue following surgery. Both suggest that increases in fatigue and reduction in QOL are a result of the physical responses to the surgery and emotional response prior to and following surgery (Wang, 2008). The first theory suggests that somatisation is the mechanism underlying this CRF following surgery. Immediately following surgery the sensations typically described involve tiredness, lethargy, sluggishness, desire to sleep or rest and change in emotional states (Rubin et al., 2004). Many studies indicate that the emotional state of the patient before and following surgery is strongly correlated to postoperative fatigue and QOL (Salmon & Hall, 1997). In support of the somatisation theory, Rubin and colleagues (2004) found that post operative fatigue shows significant associations with negative moods during four follow-up stages ($p < 0.001$) and was significantly predicted by a patient's history of mood disorders ($p = 0.02$). At 6 months post surgery the preoperative belief in physical capacity was positively associated with reduced fatigue ($p < 0.001$). This finding leads into the second hypothesis of postoperative fatigue which involves the physical response to surgery.

Self reported breathlessness was used as an indicator of physical functioning and cardiovascular conditioning in the study by Rubin et al. (2004). At six months post operation, self reported breathlessness was reported to significantly predict fatigue ($p = 0.02$) (Rubin et al., 2004). This indicates that cardiovascular conditioning may be an important determinant in fatigue in late stages of surgical recovery. A common recommendation to patients following surgery is to rest. However, this suggestion may impose greater harm to the patient if not integrated with attempts to maintain functional capacity. National Aeronautics and Space Administration (NASA) investigations have demonstrated that bed rest and chair rest results in rapid loss of physical functioning which may have profound emotional and psychological implications related to fatigue (Winningham, 2001). Results of Rubin's study indicate that both emotional and physical parameters can influence postoperative fatigue. However, it seems that within the first few weeks following surgery emotional status and somatisation may be the greatest influence whereas physical functioning may be more influential in latter stages in determining recovery success and fatigue levels (Rubin et al., 2004; Wang, 2008).

Radiation Therapy and Cancer Related Fatigue

Common side effects of radiotherapy include myelosupression, diarrhea, malnutrition, dehydration, electrolyte disorders, dyspnea, nausea/vomiting, hormonal and immune insufficiencies and changes in weight (Jereczek-Fossa et al., 2002). These radiotherapy complications have been correlated with fatigue and fatigue severity and may provide avenues to investigate underlying biological mechanisms involved with the production of these side effects (Servaes et al., 2002a; Servaes et al., 2002b). In addition, pre-existing comorbidities such as anemia, anorexia, mood disturbances, functional

disabilities and pain resulting from previous adjuvant therapies for cancer itself can exacerbate and even predict the degree of severity of CRF during and following radiation therapy.

Although common side effects of radiotherapy have been identified, the etiologies related to CRF from radiotherapy are not well defined. CRF due to radiotherapy is however, suggested to arise due to alterations to immunologic and hematologic alterations. For example, peripheral blood cell levels declined significantly during therapy and were still low 2 months after treatment. Lymphocytes are also reduced by 50% from their initial values but returned to baseline values by week 5. These findings suggest that fatigue experienced by patients receiving radiotherapy may be due to underlying changes to the oxygen carrying capacity of the blood and immune function. In contrast, it was found that the changes to cytokines TNF-a and IL-6 were not significantly altered in this study. Other biochemical agents that have been hypothesized as potential causes of radiotherapy induced CRF include increased serum interleukins, and reduction in neuromuscular efficiency (Jereczek-Fossa et al., 2002).

Chemotherapy Related Causes of Cancer Related Fatigue

Possible mechanisms and associated conditions underlying fatigue due to adjuvant chemotherapy have been studied. Strong evidence has pointed to the possibility of low and high dose chemotherapy affecting mean haemoglobin content. For example, Nieboer et al. (2005) demonstrated that high dose chemotherapy induces a reduction in haemoglobin content. Also, in the same study a relationship was found between a higher haemoglobin concentration and a reduction in fatigue ($p = 0.0006$). The exact

mechanisms causing anemia in patients undergoing chemotherapy is not fully understood. However, certain theories have been established. For example, chemotherapy can damage bone marrow and produce renal toxicity which may inhibit the function of erythropoietin, the hormone that stimulates maturation of red blood cells. In addition, anemia present at the time of chemotherapy exacerbates the fatigue experienced by patients with cancer following therapy (Wang, 2008).

Cardiovascular, pulmonary and neurotoxicity are additional effects of chemotherapy which may contribute to chemotherapy fatigue. Cardiotoxicity in conjunction with pulmonary toxicity results in a reduction of oxygenated blood to working muscles due to reduced cardiac output and altered ventilation perfusion ratios (Lucia et al., 2003). This results in a decreased ability to perform physical work which is highly associated with CRF. In addition, chemotherapy drugs may cross blood brain barriers and induce neurotoxicity which may cause fatigue (Wang, 2008). Chemotherapy may also induce fatigue through the accumulation of end products from cell destruction. An increase in apoptotic and damaged cells results in increased cytokines and inflammation. An increase in the presence of cytokines can result in sickness behaviour which presents with similar symptoms as CRF and may aggravate already existing CRF and related symptoms (Wright et al., 2005).

The severity of fatigue may differ depending on the chemotherapy regiment. For example, de Jong et al. (2004) discovered that a group of breast cancer patients treated with doxorubicin experienced a large, direct increase in fatigue in contrast to a second group of patients who were being treated with cyclophosphamide, methotrecate and 5 – fluorouracil (CMF) who only experienced a moderate direct increase in fatigue (de Jong

et al., 2004). Always, in the CMF group, a delayed strong increase in fatigue was present. In the same study, declines in physical functioning were the strongest predictors of chemotherapy induced fatigue in both groups (de Jong et al., 2004). The effects of chemotherapy and radiotherapy are the most commonly researched therapy type with regards to CRF. However, the role of biological response modification therapy and hormonal therapy has also been found to induce CRF and should be investigated.

Biological Response Modification and Hormone Therapy

Biological–response modification and hormone therapy options are also available for patients with cancer. Biological response modification treatments such as proinflammatory cytokines induce fatigue in 70% - 100% of patients and may cause hypothyroidism which can further increase fatigue by up to 20% (Kirkwood et al., 1985). Administration of cytokines results in the activation of an innate immune system response which is commonly accompanied by fever, chills, and headaches and fatigue cumulatively known as cytokine induced "sickness behaviour". This sickness behaviour is associated with negative mood and CRF (Wright et al., 2005). Hormonal treatment is often underestimated in terms of side effects. In patients with prostate carcinoma with pre established CRF, hormonal ablation was found to double the reported fatigue (Wang, 2008). Common symptoms related to hormonal therapy include lethargy and a lack of energy (Wang, 2008).

In summary, surgical, radiation, chemo, biological and hormonal therapies are suspected and documented to increase the risk of fatigue through potential effects on various biological processes. CRF is reported as the most distressing symptoms as a

result of cancer therapies during treatment phases. The literature shows that fatigue may persist for years after the treatment is complete even if cancer has been cured; however, the pathological mechanisms for CRF still remain unknown making efficient and effective treatment strategies difficult to prescribe (Wang, 2008).

POTENTIAL ETIOLOGIES OF CANCER REALTED FATIGUE

Presently the mechanisms of CRF are unclear and the unique processes contributed by the malignancy and cancer therapy are not well understood (Ryan et al., 2007). The current hypothesized CRF etiologies are based largely on evidence from different conditions in which fatigue is also present. For example, chronic fatigue syndrome and exercise induced fatigue have provided a theoretical framework to base future CRF research and hypotheses. Currently, the proposed hypothesises underlying CRF include serotonin dysregulation, hypothalamic pituitary adrenal axis deregulation, increased vagal afferents, circadian rhythm disturbances, cytokine dysfunctions, anemia, and metabolic alterations. This section of the review will investigate these major proposed mechanisms of CRF by first illustrating their homeostatic physiological roles and processes. Next we will describe their pathological role in other conditions reporting fatigue where possible. This will be followed by the potential role in the pathogenesis of CRF.

Serotonin (5 – HT) Dysregulation Hypothesis

Research from healthy human and animal studies suggests that an increase in 5-HT levels in the brain stem and hypothalamus can result in central fatigue which may be linked to CRF symptoms (Lucia et al., 2003). The mechanisms behind central fatigue are hypothesized to begin with the competition between branched chain amino acids (BCAA) and tryptophan for the entrance through brain blood barriers. The competition is the rate limiting step for the production of 5 – HT in the brain and thus a possible regulator of the effects of 5 – HT on fatigue (Ryan et al., 2007; Yamamoto et al., 1997). In addition, the concentration of free tryptophan and bound tryptophan (to albumin) may also control the rate of entry of 5 – HT across the blood brain barrier. An increase in plasma concentration ratio of free tryptophan/BCAA could lead to an increase in the amount of free tryptophan entering the brain thereby causing an increase in brain 5 – HT concentration (Yamamoto et al., 1997). This increase in 5 – HT concentration may increase the activity of selective 5 – HT neurons in the brain that results in: sleep, decreased somatomotor drive, and a sensation of reduced capacity to perform physical work (Ryan et al., 2007; Wright et al., 2005; Yamamoto et al., 1997).

5 – HT Regulation in Exercise Induced Fatigue

Investigations studying the expected 5–HT regulation and function have developed a baseline of expected observations. These observations are then compared to pathological conditions. In CRF one hypothesis is that the cancer or cancer therapies cause an increase in brain serotonin levels and or up-regulation of 5 – HT receptors. Research from studies based on exercise fatigue and chronic fatigue syndrome have been

used to link the role of brain serotonin metabolism and neurotransmission in the pathogenesis of CRF (Wang, 2008).

Research has identified that 5 – HT concentrations increase during exercise until they reach maximum concentration which is reached at fatigue (Yamamoto et al., 1997). One hypothesis for this phenomenon suggests that an increase in free plasma tryptophan is enhanced by a reduction of circulating BCAAs which allows greater concentrations of tryptophan through the blood brain barrier (Ryan et al., 2007). The reduced BCAA results from greater uptake by working muscles (Wright et al., 2005). In addition, the concentration of plasma free fatty acids increases with exercise which has been found to displace tryptophan from albumin; therefore, producing even greater concentrations of free plasma tryptophan. Documented results of increased brain 5 – HT production include decreased exercise capacity measured in time to exhaustion (W. M. Wilson & Maughan, 1992; Yamamoto et al., 1997). In support of these findings, Blomstrand et al (1991) administered BCAA during prolonged exercise and reported that supplementation with BCAA delays physical fatigue and reduces perceived exertion during exercise (Blomstrand, Hassmen, & Ekblom, 1991).

5 – HT regulation in Chronic Fatigue Syndrome

The role of 5 – HT in chronic fatigue syndrome (CFS) has provided many possible etiological concepts that are currently used in CRF research. Preliminary studies in CFS research found that an increased level of 5 – HTAA, the breakdown product of 5 – HT, is commonly located in the cerebrospinal fluid and in the plasma of CFS patients which suggested an increase in central turnover of 5 – HT in the brain (Cleare et al.,

2005). In addition, research has discovered that patients with CFS have an increase in plasma levels of free tryptophan as well as altered 5 – HT receptor function compared to healthy controls (Badawy et al., 2005; Sharpe et al., 1997). This may be a result of 5 – HT1a receptors being compromised. In support of this theory, reported evidence of decreased 5 – HT 1a receptor number affinity or numbers is common in patients with CFS (Ryan et al., 2007). It is also suggested that alterations to the 5 – HT regulation may inhibit or alter hypothalamic pituitary adrenal axis (HPA – axis) function which is hypothesized to contribute to the pathophysiology of CRS as well as CRF (Ryan et al., 2007; Stone & Minton, 2008).

5 – HT Regulation in Cancer Related Fatigue

The 5 – HT dysregulation witnessed in patients with CFS is thought to be similar in the pathogenesis of CRF. In a group of heterogeneous cancer patients serum tryptophan concentrations were lowest in patients with progressive disease. These levels of serum tryptophan were related to a decrease in QOL ($r^2 = 0.256$, $p < 0.01$) and increased fatigue ($r^2 = -0.179$, $p < 0.05$). In this study tryptophan was predictive for impaired QOL and fatigue in univariate regression analysis (Schroecksnadel et al., 2001). These results suggest that tryptophan, a precursor to 5 – HT, may contribute to CRF. The underlying mechanisms for this correlation are uncertain.

Huang and colleagues suggest that the immune system may influence QOL parameters including fatigue by interacting with serum tryptophan (Huang et al., 2002). Evidence that proinflammatory cytokines such as TNF – *a,* can influence 5 – HT metabolism have been established (Ryan et al., 2007). For example, studies have

discovered that a possible feedback loop exists between TNF – *a* and central 5 – HT (Ryan et al., 2007; Wang, 2008). Peripherally synthesized TNF – *a* causes an increase in the release of 5 – HT into the synaptic space, conversely 5 – HT can decrease TNF – *a* synthesis. This feedback loop may become deregulated in patients with cancer. In addition, TNF – *a* can increase 5 – HT transportation which will result in an increased clearance of 5 – HT from synaptic spaces (Ryan et al., 2007; Wang, 2008). Another mechanism in which 5 – HT regulation may partake in the pathogenesis of CRF is by altering the function of the HPA – axis (Portenoy & Itri, 1999).

Hypothalamic Pituitary Adrenal – Axis Dysfunction Hypothesis

The HPA – axis is the central regulating system for the release of stress hormones such as cortisol. Corticotropin releasing hormone (CRH) is secreted from the paraventricular nucleus of the hypothalamus in response to physical or psychological stress. Acting in conjunction with arginine vasopressin (antidiuretic hormone [ADH]) it releases corticotropin (adrenocorticotropic hormone [ACTH]) from the anterior pituitary. ACTH then stimulates the release of cortisol from the adrenal cortex (Ryan et al., 2007). Cortisol is used in the regulation of blood pressure, cardiovascular function, carbohydrate metabolism and immune function. Cortisol also inhibits HPA – axis function through a negative feedback loop at the level of the hippocampus, hypothalamus, and pituitary (Ryan et al., 2007). The HPA dysfunction hypothesis suggests that cancer and or its treatment directly or indirectly induces alterations in normal HPA function. This could lead to endocrine changes that may cause or contribute to CRF (Ryan et al., 2007; Stone & Minton, 2008; Wang, 2008). In this section we will review causes of HPA dysfunction

found in patients with cancer related fatigue and discuss the possible mechanism involved in HPA axis dysfunction in cancer patients.

HPA – Dysfunction in Cancer Related Fatigue

Fatigue in cancer patients along with CFS and rheumatoid arthritis have been linked to an adverse HPA-axis function causing either hypercortisolemia or hypocortisolemia (Ryan et al., 2007). Patients with cancer presenting with hypocortisolemia have been found to have increased fatigue symptoms (Schmiegelow et al., 2003). A state of hypocortisolemia suggests that the HPA – axis is not producing adequate concentrations of cortisol in response to the stress stimulus. Reduced HPA-axis function has been documented in patients with cancer. For example, Bower et al (2002) studied cortisol production in patients with breast cancer by administering a social stress test to induce a psychological challenge. Bower and colleagues indicated that women with fatigue had a reduced cortisol response to stress test questions as measured by salivary cortisol levels when compared to health controls (Bower, Ganz, & Aziz, 2002). This reduction of cortisol as a function of psychological stress may be initially asymptomatic however; failure to mount the appropriate response to stressors may lead to deleterious consequences and fatigue (Ryan et al., 2007; Schmiegelow et al., 2003).

Increases in cortisol levels have also been documented in patient with advanced cancer. According to Lundstrom and Furst (2003) the level of endogenous cortisol has significant positive correlations to appetite loss, fatigue and nausea and vomiting. They indicate that these findings provide support of a chronic stress condition in patients with advanced cancer. In a chronic stress condition, properly functioning HPA – axis would

be crucial considering the role of cortisol in stress management processes. The previous two studies indicate that cancer may cause alterations to the HPA – axis and thus impact the patient's ability to cope with stressful stimuli.

How HPA – axis Dysfunction Arise in Cancer Patients

How these alterations occur is unclear. Alterations to the HPA – axis may arise from treatment effects. In our first example, Schmiegelow and colleagues (2003) suggest that irradiation may induce ACTH secretion abnormalities due to changes to the HPA – axis or as a result of atrophy of the adrenal cortex. They found that Children who underwent cranial irradiation treatment for brain tumours had significantly lower basal cortisol levels ($p = 0.0099$) as well as significantly lower cortisol levels in response to an ACTH concentration test ($p = 0.0002$). Second, the use of high dose steroids has been suggested to lead to deficiencies in ACTH production and HPA – axis suppression. A study by Priore et al (1995) concluded that steroid regimes prescribed with chemotherapy induce transient decreases in HPA-axis function but do not seem to induce long term inhibition of HPA axis function. In addition, Priore found that the HPA function may be suppressed for approximately 8 days following chemotherapy cycles involving dexamethasome (DEX). The effects of cancer treatments have been found to suppress HPA – axis function. An additional hypothesis is that HPA – axis suppression or alterations may be a function of the tumour burden itself.

In response to the neoplastic disease host defence mechanisms are engaged. As a result, there is a release of proinflammatory cytokines. Interleukin – 6 (IL-6), Interleukin – 1 (IL-1) and TNF – a, are potent stimulators the HPA-axis. Cytokines effect HPA axis

function through feedback links between immune cells to HPA – axis. This feedback loop may in turn regulate cortisol production (Ryan et al., 2007). Conversely, HPA – axis function also influences immune cell development, maturation, and cytokine production. Cortisol released by the HPA – axis has a suppressive effect on the immune system by reducing the production of cytokines. As a function of tumour burden, reduced 5 – HT concentrations, glucocorticoids, radiation therapy and or chemotherapy reductions of cortisol would allow cytokine levels to rise thus inducing sickness behaviours, fatigue and other cytokines associated comorbidities (Ryan et al., 2007; Wang, 2008).

Currently HPA – axis dysfunction is thought to arise from reduced 5 – HT receptor signals, adjuvant therapies, or as a result of tumour burden. Reduced cortisol levels have been correlated with increased fatigue and other comorbidities such as depression. Due to the rhythmic nature of cortisol release, mechanism upsetting the timing of cortisol release may also be involved with HPA – axis dysfunction and fatigue.

Circadian Rhythm Disruption

Circadian rhythms are genetically and physiologically based patterns that are controlled by the bodies "biological clock". They typically have 24 hour cycles that are sensitive to a variety of environmental and psychological factors (Ryan et al., 2007). It is hypothesized that cancer fatigue is associated with disruption of this biological clock. Types of rhythm alterations include diminished amplitudes, phase shifts, period changes, and erratic peaks and troughs throughout the 24 hour cycle (Ryan et al., 2007). Alterations to circadian function witnessed in patients with cancer may be due to changes

in endocrine rhythms, rest-activity patterns and immune system. As a result consequences may include sleep disruption which can contribute to CRF.

Potential Causes of Circadian Rhythm Disruption in Cancer Patients

The understanding of potential alterations in endocrine rhythms originates from studies focusing on cortisol secretion timing. Typically serum cortisol concentrations show diurnal variation throughout the day with concentrations being highest after waking then declining throughout the day (Ryan et al., 2007). Bower et al (2005), showed that cancer patients with fatigue had a significantly flatter diurnal cortisol slope than the group of non-fatigued cancer patients. In addition, they also found that an increase in fatigue severity is correlated with a flatter slope (Bower, Ganz, & Dickerson, 2005). The direct causes for alterations in diurnal patterns of cortisol may be due to alterations in timing of 5 – HT secretion, HPA – axis dysfunction or timing and release of proinflammatory cytokines (Rich et al., 2005).

An increase of inflammatory cytokines in response to tumour burden or treatment has also been linked to CRF through the disruption of circadian rhythms. Rich and colleagues investigated the association between cytokines interleukin – 6 (IL-6), TNF – a, and transforming growth factor – alpha (TGF – *a*). In their study they found a strong association between TGF – *a*, poor QOL and increased fatigue (Rich et al., 2005). Of particular interest is the finding of an association between TGF – *a* and fatigue. This is because TGF – *a* is a ligand of epidermal growth factor receptor which mediates hypothalamic signalling for circadian regulation of motor activity, sleep and body temperature (Wang, 2008). The association between cytokines and fatigue and circadian

rhythm may be explained by the potential role of TGF – *a*. In addition, these potential causes of altered endocrine rhythms may also have implications in altered rest/activity and sleep patterns.

Potential Consequences of Circadian Rhythm Defects

Sleep disorders are commonly observed in patients with cancer and may result from altered circadian activity/rest cycles. These alterations are proposed to induce fatigue (Wang, 2008). For example, Berger and Farr (1999), discovered that an inverse correlation exists between fatigue and daily activity levels and that a positive correlation exists between fatigue and restless night time sleep (Berger & Farr, 1999). It was also observed that patients had greater fatigue associated with inconsistent or dampened circadian rhythms in contrast to those with more well defined circadian rhythms (Berger & Farr, 1999; Wang, 2008).

These changes to sleep patterns and rest/active cycles may be induced by cancer therapies. In the study by Berger (2000), patients experienced fluctuating patterns of lowered activity, disturbed as well as and fatigue at the highest levels for the first four days following a third drug cycle. Another proposed mechanism underlying rhythmic disturbances causing poor sleep quality include, shifts of regular cytokine secretion from daytime to night time. Vgontzas et al. (2002) studied the association between poor sleep quality and the effect of two cytokines. They found a significant shift of peak IL-6 secretion from night time (4 am) to evening (7 pm) in patients with insomnia compared to controls ($p < 0.05$). In the same study TNF showed a distinct circadian rhythm with a peak close and prior to the offset of sleep in controls. However, patients with insomnia

did not have this distinctive rhythm. From these results they concluded that fatigue and performance decrements are associated with the shifting of the rhythmic cycles of IL-6 and TNF secretion (Vgontzas et al., 2002). The cause of cancer related circadian dysregulation may include genetic factors, psychosocial, environmental and behavioural influences along with immune functions. Despite the origin of altered circadian rhythms, changes to the biological clock have been found to result in mood disturbances, sleep disorders, and fatigue in patients with cancer.

Vagal Afferent Activation Hypothesis

Vagal nerves are comprised largely of afferent fibers which communicate signals from the viscera to areas of the brain stem. In response they send efferent responses through parasympathetic fibers to visceral organs such as the heart and stomach. The vagal afferent activation hypothesis suggests that cancer or its treatment result in a peripheral release of neuroactive substances such as inflammatory markers or 5 – HT which in turn activate vagal afferent nerves thus suppressing somatic muscle activity and inducing sickness behaviours (Ryan et al., 2007; Wang, 2008). In this section we will discuss the effects of vagal activation and how it may be associated with CRF.

Role of Activated Vagal Afferents in Cancer Related Fatigue

Activation of vagal nerves may reduce physical capacity and in turn contribute to CRF. One way in which vagal activation can reduce work capacity is by causing an inhibition of somatomotor activity. This has been termed the vagosomatic inhibitory reflex. An example of this reflex was witnessed during a study by Schweitzer and Wright in 1937. Schweitzer and Wright demonstrated that through electrical stimulation of the

vagal nerve at the central terminus a reduction in the knee jerk reflex is a end result (Schweitzer & Wright, 1937). In addition to these findings, research demonstrates that activation of vagal afferent nerve fibers from the lungs and abdomen result in the inhibition of somatomotor activity including reflex activation of skeletal muscle and exercise induce electromyogram activity (Ryan et al., 2007). The resulting reduction in muscular tone would be perceived with great weakness resulting in an inability to complete physical tasks which is a common symptom of CRF. In addition to a vagosomatic inhibitory reflex, vagal nerves may mediate the induction of sickness behaviour in patients experiencing acute or chronic inflammation.

The vagus nerve mediates the induction of IL-6 into the brainstem, hippocampus and hypothalamus which is thought to be a cytokine which has the greatest effects on sickness behaviours (Ek et al., 1998; Ryan et al., 2007; Wang, 2008). Of particular interest here is the location of cytokine IL-6 production within the hypothalamus. Given the possible role of HPA axis dysfunction and the effects of cytokines on the HPA – axis, vagal regulation of IL-6 may be a potential cause of cytokine induced HPA axis dysfunction. The vagal nerve also acts as a regulator for inflammatory responses (Sloan et al., 2007; Tracey, 2007). Sloan et al (2007), reported that Heart Rate Variability (HRV) is strongly and inversely related to IL – 6 ($p < 0.001$) and CRP ($p < 0.001$). This finding supports the role of the vagal nerve as an anti-inflammatory system. When inflammation is present cytokines can stimulate vagal afferents to suppress inflammation responses by reducing cytokine production (Sloan et al., 2007), which may in turn induce sickness behaviour or reduce somatomotor reflex (Tracey, 2007; Wang, 2008; Wright et al., 2005) In contrast, if vagal dysfunction occurs in cancer patients then there may be an

increase cytokines and greater inflammation. Studies reporting on the neural profile of cancer patients experiencing fatigue with HRV investigations may clarify the role of the vagus nerve in inflammation and cytokine production.

Cytokine Dysregulation Hypothesis

Cytokines are biologically active proteins that are expressed in response to noxious events such as tissue damage or infection (Panju et al., 2008). Their primary biological role is to signal an inflammatory response. Common families of cytokines related to CRF include TNFs, interleukins (IL), and chemokines. One of the proposed etiologies of CRF is that a dysregulation of cytokine production exists (Panju et al., 2008; Ryan et al., 2007; Stone & Minton, 2008; Wang, 2008). This malfunction of cytokine regulation may occur in response to tumour burden or as a response to cancer therapies. Wang (2008), suggests that the insult of cancer therapy, including chemo and radiation modalities produce an increase of inflammatory cytokines, particularly IL-6 and TNF variants (Wang, 2008). In this section we will illustrate correlations of cytokine productions and involvement in CRF, expand on additional roles of cytokines in common co morbidities/symptoms associated with CRF and suggested possible roles of cytokines in system changes occurring in CRF.

Correlations of CRF and Cytokines

Correlation studies have identified cytokines as potential mechanisms of CRF and reduced QOL in cancer populations with colorectal, breast, prostate and acute myeloid leukemia (AML). A study by Panju et al (2008), found that clinically significant correlations between global QOL and cytokines exist. The cytokines investigated in this

study include interferon – y (IFN-y) which had a correlation of r = 0.376 (p = 0.031), IL – 2 with a correlation of r = -0.34 (p = 0.053), IL – 5 with a correlation of r = 0.368 (p = 0.035), IL – 8 with a correlation of r = 0.312 (p = 0.077), TNF – a with a correlation of r = - 0.326 (p = 0.064) and IL – 6 with a correlation of r = 0.332 (p = 0.059). The findings presented in this study suggested that IFN – y, IL-5, IL-10 and TNF – a were of greater importance in the relationship between cytokines and overall QOL where as cytokines IL-5, IL-6 and IL-10 appeared to most likely play a role in regulating fatigue in cancer patients (Panju et al., 2008). Schubert and colleagues investigated the association between fatigue and inflammatory markers in a quantitative analysis of 18 studies on inflammation and CRF with high methodological quality. They reported that an overall positive correlation between CRF and inflammatory markers is present ($r = 0.11$, $p < 0.0001$). Individual correlations produced several significant positive correlations between fatigue and IL-6 ($r = .12$, $p = 0.004$), IL- 1ra ($r = .24$, $p = 0.0005$) and neopterin ($r = 0.22$, $p = 0.0001$). However, they also illustrated that IL – 6 and TNF – a were not significantly correlated with fatigue in cancer patients (Schubert et al., 2007). Correlation studies examining the relationship between cytokines and fatigue are limited and results have been inconsistent. Although evidence is inconsistent cytokines have been linked to a variety of other conditions such as CFS and rheumatoid arthritis which also presents fatigue as a common and debilitating symptom.

Cytokines and CRF Symptoms and Comorbidities

Cytokines have been linked to psychological symptoms and comorbidities related to CRF. Meyers (2005) studied the relationship between certain cytokines and executive function in patients with AML experiencing CRF. Results indicate that higher levels of

IL-6 were associated with poor executive function and high levels of IL-8 were associated with better memory performance (Meyers, Albitar, & Estey, 2005). These results indicate that cytokines may play a role in the cognitive consequences appearing in patients with CRF which include reduced memory. In addition, cytokines have been found to play a role in depression. Depression is a comorbid condition associated with CRF. However, patients with depression present similar symptoms as patients with CRF (Stone & Minton, 2008). Wilson and Warise (2008) describe that patients who are administered proinflammatory cytokines to treat medical diseases often report signs of depression. They also state that patients diagnosed with depression tend to have higher levels of cytokine activity and dysfunctional immune responses when compared to controls (Wilson & Warise, 2008).

Physical manifestations of cytokine involvement in CRF symptoms and comorbidities can be observed via sickness behaviour and cachexia. As discussed previously, cytokines can induce sickness behaviour which presents with symptoms of fatigue, increased sleep, inability to concentrate, fever and poor appetite (Ryan et al., 2007). Sickness behaviour is a result of dysregulated inflammatory processes and its downstream toxic effects (Wilson & Warise, 2008). Sickness behaviours are a significant basis for the subjective feelings of CRF and related closely to other CRF comorbidities such as depression (Wang, 2008; Wilson & Warise, 2008).

Cachexia is a wasting disease which is presented in up to 85% of patients with cancer (Ryan et al., 2007). Cachexia involves the loss of both adipose tissue and skeletal muscle tissue resulting in anorexia, weight loss, fatigue, impaired physical functioning and shortened survival time (Ryan et al., 2007). Although the etiologies of cachexia are

complex and varied, the tissue catabolism associated with this disorder is thought to be mediated by cytokines (Ryan et al., 2007). Physical and psychological effects of CRF and associated cancer comorbidities involve and may be explained through the role of cytokines.

Role of cytokines in possible CRF etiologies

CRF, as highlighted in previous sections may be a result of or a combination of several possible etiologies. Cytokines may play a common underlying role in five of the discussed etiologies. First, serotonin dysregulation is one of the proposed mechanisms of CRF. It has been found that cytokines can influence neurotransmission of serotonin as well as interfere with serotonin metabolism in a manner which may lead to reduced physical function and depression (Wilson & Warise, 2008; Wright et al., 2005). Second, cytokines may also impact cortisol production and induce changes to the HPA – axis (Ryan et al., 2007; Wilson & Warise, 2008). As a result of cytokine damage to HPA – axis, inability to cope with stress may result, leading to increased risk of fatigue. (Ryan et al., 2007; Wilson & Warise, 2008). Third, alterations to circadian function resulting in increased fatigue and poor quality of sleep are associated to the regulation of cytokines and other inflammatory mediators. Four, cytokines have been postulated to affect vagal regulation which is associated with sickness behaviour and reduced physical capacity. Fifth, cytokines may play a role in inducing cancer related anemia. This topic will be discusses in greater detail in the next section. The role of cytokines in the etiology of CRF is very complex. The mediating role of cytokines can been associated with many of the psychological and physical symptoms related to CRF and therefore present a potential common biological cause to this condition. Further investigation into the cytokine theory

of CRF may provide affective anti-fatigue treatments which may have additional benefits to other debilitating conditions contributing to CRF.

Anemia Hypothesis

Anemia is defined as a deficiency of haemoglobin (Hb), more specifically a haemoglobin level of <12 g/dl. Anemia is a condition in which up to 50% of all cancer patients will experience regardless of their treatment or diagnosis (Mercadante et al., 2000). Fatigue has been described as a cardinal symptom of anemia and is also a common condition accompanying or contributing to CRF (Jager et al., 2008). Anemia results in a decrease in oxygen delivery to working tissue which in turn compromises organ function (Dicato, 2003; Jager et al., 2008; Ryan et al., 2007). The effect of overall hypoxia on organ tissue is suspected to result in both psychological and physical fatigue in cancer patients (Shasha, George, & Harrison, 2003). In this section we will review the role of anemia in cancer patient QOL, potential causes of cancer anemia, followed by contributions of anemia to CRF.

Cancer Anemia and Quality of Life/Cancer Related Fatigue

A direct relationship exists between increases in haemoglobin, decreased fatigue and increase QOL in adult patients with chronic anemia and cancer (Wang, 2008). For example, Glaspy and colleagues (1997), investigated the effects of epoetin alfa on 2,342 patients with malignancies undergoing cytotoxic chemotherapy. 1,047 participants completed the 4 month study. They concluded that epotin alfa was associated with a significant increase in subjective measures of energy levels, activity levels and overall

QOL. These findings correlated with the magnitude of haemoglobin increase of 1.8 g/dl from baseline, $p < 0.001$ (Glaspy et al., 1997).

In addition to overall QOL, anemia may affect CRF by influencing physical or psychological parameters. Functional capacity is a major component determining the level of fatigue experienced by the patients with cancer. Anemia is has been found to reduce exercise capacity which may lead to increased risk of CRF. For example, Clyne et al (1994), illustrated that a significant correlation exists between total haemoglobin and maximal exercise capacity ($r = .27$, $p < 0.05$) (Clyne et al., 1994). These findings suggest that anemia may be a potential cause of reduced functional capacity. In support, Dimeo et al. (2003) found that exercise training in patients with cancer anemia reduced the loss of haemoglobin and preserved physical performance following chemotherapy (Dimeo et al., 2003).

In addition to the effects of anemia on physical parameters, psychological factors may also be affected by anemia. Kallich et al (2002), studies the relationship between psychological variables, haemoglobin levels and fatigue in patients with solid state tumours. Their team found that patients who had improvements in FACT – F scores reported significantly greater improvements in each psychological variable ($p < 0.0001$). Interestingly, they identified that patients with haemoglobin response of at least 2 g/dl increase were more likely to experience a significant improvement in the FACT-F and improvements in additional psychological parameters (Kallich et al., 2002). Further research has been done to identify the haemoglobin level at which QOL is optimized. Cleeland and colleagues applied an incremental analysis on two clinical studies of 4383 anemic cancer patients who were receiving Epoetin alfa and chemotherapy. Results

suggest that incremental improvement in QOL per 1 g/dl haemoglobin increase occurred when haemoglobin concentrations rose from 11 to 12 g/dl (Cleeland et al., 1999). These findings will help to identify the optimal management strategies for improving QOL in anaemic cancer patients receiving chemotherapy.

Potential Causes of Anemia in Cancer Patients

Anemia can occur in cancer patients as a direct result of the malignancy process or as a result of cancer treatments such as chemotherapy. In addition, solid tumours can invade bone marrow which reduces available bone marrow space and creates a fibrotic reaction which disrupts the marrow environment and inhibits its normal functions (Mercadante et al., 2000). In regards to the direct effects of the malignancy, metastases within the bone marrow can destroy and displace the stem cells needed to ensure adequate haematopoietic cell production as well as destroy and displace progenitor cells. This consequently inhibits the production of hematopoietic growth factors which are essential for regulating the proliferation, differentiation and survival of haematopoietic cells (Mercadante et al., 2000). Another direct cause of anemia in cancer may be due to blood loss. Gastrointestinal, head and neck, genitourinary and uterine cancers are commonly associated with chronic and acute blood loss (Mercadante et al., 2000). Sarcomas, melanomas, hepatomas, ovarian cancer and adrenocortical cancers may cause anemia due to bleeding into the tumour itself (Mercadante et al., 2000). Other causes of cancer induced anemia may result from haemolysis, renal, hepatic or endocrine disorders and nutritional deficiencies. Essential nutrients such as B12, folate and iron are paramount for normal proliferation and differentiation of erythroid progenitor cells and

are often found to be less abundant in cancer patients (Gilreath et al., 2008; Mercadante et al., 2000).

Cancer may directly induce anemia in patients, however, cancer anemia present is also often associated with cancer treatments. First, radiotherapy has been found to increase anemia from pre-existing levels. For example, Varlotto and Stevenson found that prior to radiotherapy; anemia was present in 48% of patients with cancer. In contrast, following completion of radiotherapy it was found that anaemia increased to 57% of the participants. It is possible that the radiation also causes stem cell damage. Stem cells have a poor capacity to repair radiation damage which may be a reason for the increase in anaemia in patients undergoing radiation treatment (Mercadante et al., 2000). In addition to radiation therapy, chemotherapy related anemia has been found to occur in up to 100% of patients (Varlotto et al., 2005). Incidence rates may vary depending on chemotherapeutic regimen (Varlotto & Stevenson, 2005). Drug induced anemia caused by chemotherapy may be due to stem cell death, blockage or delayed haematopoietic factors, oxidant damage to mature haematopoietic cells, long term myelodyplasia or immune – mediated haematopietic cell destruction (Mercadante et al., 2000). Hormonal therapy may also induce anemia. Hormonal therapy has been found to reduce haemoglobin levels by 75% (Varlotto et al., 2005). Varlotto and colleagues (2005) documented that a 2 g/dl reduction of haemoglobin was found in the same sample even after 2 months of combined androgen blockade (Varlotto et al., 2005). Radiation, chemical, and hormonal treatments can induce a variety of mechanisms which in turn cause anemia. However, biological agents such as cytokines produced by the host response to cancer its self may also stimulate anemia.

Cytokines produced through tumour interactions may be involved in the chronic anemia experienced during cancer (Mercadante et al., 2000; Panju et al., 2008; Wang, 2008). The over production of cytokines in cancer may inhibit erythropoiesis in a variety of ways. First, cytokines may shorten red blood cell survival time (Mercadante et al., 2000). Second, cytokines can reduce the iron availability by producing hepcidin in live cells which reduced liberation of iron form duodenal cells and reticulo – endothelial cells (Dicato, 2003; Jager et al., 2008). Third, cytokines may also interfere with the proliferation of progenitor cells (Mercadante et al., 2000). Finally, cytokines may diminish erythropoiesis by inducing apoptosis of erythroid precursor cells thus, decreasing erythropoietin production (Dicato, 2003; Jager et al., 2008). Inflammatory cytokines TNF – a, TGF – b, Il-6, Il-1 and interferon-gama are thought to be the most prevalent inflammatory cytokines inducing cancer related anemia (Dicato, 2003). Anemia in cancer patients can be caused by a variety of ways. Regardless of the mechanism behind cancer induced anemia, anemia has a powerful influence of overall QOL and fatigue in cancer patients.

Treatment for anemia in cancer patients produce significant positive side effects in both physical and psychological variables and should be considered when designing an intervention. The mechanisms by which anemia might cause fatigue in patients with cancer is unclear; however, hypoxic conditions causing impairments to healthy organ function in addition to alterations to muscle energetic have been suggested and warrant further research.

Muscle Energetic/Metabolic Dysfunction Hypothesis

Perceptions of CRF described by patients often involve feelings of weakness and lack of energy as well as an inability to perform physical work (Brown et al., 2004). The mechanisms underlying this occurrence is postulated to be multi dimensional however, the understanding of these mechanisms has not been identified. However, it is hypothesized that cancer and or its treatments most likely interfere with ATP production through a variety of mechanisms (Winningham, 2001). The proposed mechanisms responsible for the lack of energy, feelings of weakness and poor physical capacity may be caused by one of, or the interaction between the following: First, insufficient oxygen transport to muscle tissue second, insufficient blood pumping to muscle tissue and third, cancer induced muscle wasting. In this section we will illustrate how these three possibilities may individually or cumulatively contribute to the overall dysfunction of muscle energetics and force production.

Insufficient Oxygen Transport

Patients with cancer may acquire a variety of specific conditions that result in the inability to supply sufficient oxygen to meet the oxygen demands of working muscle (Lucia et al., 2003). First, tumour burden and or adjuvant therapy can reduce the oxygen carrying capacity of blood by damaging the bone marrow and producing renal toxicity which in turn reduces the amount of mature red blood cells and impairs the function of haemoglobin. As a result delivery oxygen to working muscles is compromised (Lucia et al., 2003; Dimeo et al., 2001). Second, in lung cancers or radiotherapy of pleural regions can inhibit lung function for example, loss of lung volume due to primary pulmonary

tumours, pulmonary metastasise, pleural effusions or pleural fibrosis would subsequently reduce the overall vital capacity of the lungs (Abratt et al., 2002; Lucia et al., 2003; Dimeo et al., 2001; Winningham et al., 2001). In addition, oxygen saturation of arterial blood supply is severely compromised due to damage of the capillary alveolar membrane (Lucia et al., 2003; Mehta et al., 2005). To compound the work limiting effects of reduced oxygen carrying capacity, reduced blood flow as a function of deteriorated cardiovascular system may also occur.

Insufficient Blood Pumping to Muscle Tissue

Chemotherapy and radiation treatments can affect cardiac dynamics consequently affecting blood transport to body tissues including the lungs and muscles (Lucia et al., 2003). Cardiotoxic medication such as anthracyclines, cyclophosphamide and doxorubicin can cause reduction of cardiac output. The affects of doxorubicin on cardiac dysfunction can still be present even after 6 years post treatment (Lipshultz et al., 2005). For example, Lipshultz and colleagues (2005) found that the left ventricle fractional shortening was significantly reduced after doxorubicin therapy. They concluded that inadequate ventricular mass with chronic after load excess was associated with the progressive contractile dysfunction and a possible cause of reduced cardiac output and restrictive cardiomyopathy (Lipshultz et al., 2005).

In addition to the effects of chemotherapy on cardiovascular function, radiation treatment also can negatively affect cardiac dynamics. For example, Hardenbergh et al. (2001) investigated the prevalence and dose dependence of regional cardiac perfusion abnormalities in patients with left side breast cancer treated with radiation therapy with

and without doxorubicin. They found that 60% of patients had visible perfusion defects 6 months post radiation therapy. Also, 1 of 20 patients had a decrease in left ventricle ejection fraction (greater than 10%) and 2 patients had developed pericarditis at 6 months post treatment. They concluded that radiotherapy can cause cardiac perfusion defects in most patients (Hardenbergh et al., 2001). Chemo and radiation therapy can induce myocardial defects which contribute to a reduction of cardiac output. However, these are not the only mechanisms effecting myocardial function in cancer patients.

Reduced myocardial function occurring in patients with cancer often occur as a result of long term bed rest which can lead to cardiac atrophy and deterioration of left ventricular function (Lucia et al, 2003). A study by Perhonen et al. (2001) found that head down bed rest resulted in ventricular remodelling. Overall, a reduction in cardiac output, regardless or the origin, leads to insufficient blood volume and circulation which reduces the ability of the blood to adequately perfuse working tissues with nutrients needed to fuel the production of high energy substrates. As a result, oncology patients may experience symptoms of weakness, lack of energy and poor physical function may present which can contribute to overall CRF and reduced QOL.

Muscle Wasting/ Cancer Cachexia

Muscle wasting is a common occurrence in patients with cancer in which 50% of patients experience significant wasting (Al-Majid et al., 2001). It may seem intuitive to rest if fatigue is present. However, prolonged bed rest may paradoxically increase fatigue by causing muscle wasting as well as cardiopulmonary deconditioning. Severe muscle atrophy can result from the catabolic effects of a sedentary habits and prolonged bed rest.

For example, Brooks et al (2008) reported an 11% decrease in thigh muscle area after 28 days of bed rest (Brooks et al., 2008). In addition, powerful immunosuppressive drugs such as glucocorticoids, cyclosporine or cyclophosphamide may reduce myofibrillar mass and muscle capillarisation (Winningham et al., 2001; Lapier et al., 1997). The tumour can also induce the activation of factors that produce an inflammatory response within the muscles (prostaglandin E2) which can also result in muscle wasting (Winningham et al., 2001; Lapier et al., 1997). Associated with this inflammatory response are cytokines that may mediate cancer cachexia.

Cancer cachexia is a wasting disease that involves the loss of both adipose tissue and skeletal muscle, leading to anorexia, weight loss, fatigue, impaired physical functioning and poor prognosis (Ryan et al, 2007; Al-Majid et al., 2001). Cancer cachexia induces protein catabolism as well as inhibits protein metabolism through a multi factorial process that is mediated by reduced nutrient intake, proinflammatory cytokines and proteolysis factors. In contrast to anorexia, which was thought to be the sole cause of wasting in cancer, it has been found that cancer cachexia causes differing metabolic perturbations leading to dramatic loss of mass. For example, patients with cancer have been found to report a greater loss of lean body mass compared to patients with anorexia nervosa (Al-Majid et al., 2001). In addition, if reduced food intake is the only cause of muscle wasting during cancer cachexia then supplementation would reverse the symptoms. However, nutritional supplementation and appetite stimulants increase body fat and water contents and do not have a significant effect on muscle tissue (Al-Majid et al., 2001). Cancer cachexia cannot solely be explained by reduced food intake but reduced energy intake does play a role in the overall effect of cachexia.

Another potential mechanisms eliciting cancer cachexia may be the effects of proinflammatory cytokines TNF – a, IL-1, IL-6. For example Fong et al. (1989) discovered that treatment of healthy rats with TNF – a or IL-1 recombinants result in a decrease in muscle protein content. The decrease was also found to be associated with a decrease in muscle mRNA levels for myofibrillar proteins (Fong et al., 1989). Cytokines may induce muscle wasting in a variety of ways. One way in which cytokines may be responsible for cachexia is by the induction of proteolysis through the activation of ubiquitin proteasome pathways. Ubiquitin is a protein that is involved in targeting proteins that are undergoing cytosolic ATP – dependent proteolysis. In addition, proteolysis inducing factor can also stimulate muscle wasting through the activation of the ubiquitin proteasome pathway. A second role of cytokine induced muscle wasting included the role of TNF – *a* in activating the transcription factor called nuclear factor kappa B (NF – kB). The activation of NF – kB inhibits the differentiation of muscle cells by suppressing the synthesis of transcription factors that are essential for muscle cell differentiation and repair (Al-Majid et al., 2001).

Cytokine induced muscle wasting and damage can causes a self propitiating cycle. As muscle cell damage occurs, the injured cells greater TNF – a directly or through inflammatory pathways. Muscle cells, under exposure of TNF – a have been found to increase the exposure of cytokine receptors which in turn will amplify the cytokine response at the level of the muscle cell thus activating further ubiquitin pathways, protein degradation and metabolic inhibition (Al-Majid et al., 2001). The pathophysiology of cachexia includes interrelated roles of decreased energy intake and inflammatory

responses. When combined with impaired oxygen transport systems and insufficient blood kinetics, weakness, lack of energy and reduced physical capacity is an outcome.

Resulting Metabolic/Energetic Dysfunctions

Insufficient oxygen transportation, altered blood pumping mechanics and muscle wasting causes a need for, increased pulmonary, cardiac and muscular work in order to maintain physical work and cellular metabolism (Winningham, 2001). Simple tasks under these conditions can overwhelm the oxygen transport system and energy producing pathways which will result in a shift from aerobic metabolism to less efficient anaerobic pathways. As a result of the metabolic distress in cancer patients, fatigue may be experienced during low intensity activities. For example, Dimeo (2001) found that while patients are walking on a treadmill at a submaximal speed of 5 km/h for 3 minutes they had a dramatic increase in heart rate in addition to a high sub maximal lactic acid concentration (2.6 mmol.l) (Dimeo et al, 2001). As a consequence of a shift in metabolic processes, from aerobic to anaerobic; elevated heart rate, increased respiratory rate, poor rate of recovery, less efficient energy production and metabolic acidosis was present. The combined burden of these results can exacerbate fatigue, reduce stamina and decrease the ability of the patients to sustain long term physical exertion which can severely impede QOL parameters.

Summary of Hypothesized Mechanisms of CRF

Research devoted to understanding the mechanisms underlying CRF requires a multidisciplinary approach. With the knowledge acquired from studying similar conditions and diseases presenting with fatigue new insights and stronger theories

regarding the pathophysiology of CRF will be and have been developed. Specifically, efforts need to be directed at understanding the role of serotonin regulation, HPA – axis function, circadian rhythm alterations, vagal afferent activation, cytokine regulation, anemia and metabolic dysfunction.

Special attention to the role of cytokines in CRF pathology is needed. Cytokines may be a common biological factor in the regulation of all proposed mechanisms of CRF. Further investigation into potential treatments aimed at cytokine regulation may produce effective treatments having beneficial effects on all the hypothesized CRF mechanisms. Cumulatively, a strong understanding of the factors that cause CRF combined with subjective and objective measures will lead to the most appropriate management strategies.

STRATEGIES FOR MANAGING CANCER RELATED FATIGUE

The etiologies of CRF involve a multidimensional and complex integration of adverse biological contributions which consequently presents patients with a diverse spectrum of symptoms. Due to the lack of understanding of CRF etiologies and symptoms, CRF remains under recognized and undertreated (Carrol et al., 2007; Portenoy & Itri, 1999). Current NCCN guidelines for CRF recommend that clinician frequently screen patients for CRF and possible contributing factors. Once the presents of CRF and possible contributing etiologies are identified, an appropriate intervention can then be designed.

Currently, pharmaceutical treatments have been investigated with low to moderate success and are associated with high risk to benefit ratios (Carrol et al., 2007; Portenoy &

Itri, 1999). In addition to pharmaceutical options, psychological therapies have been used with moderate success in alleviating psychological symptoms of CRF but have neglected attention to the physical parameters (de Nijs et al., 2008). In contrast to both pharmaceutical and psychological options, exercise therapies have been used with successful results on both psychological and physiological parameters of CRF with limited side effects (de Nijs et al., 2008; Dimeo, 2001; Dimeo et al., 2003; Friedenreich & Orestein, 2002; Knobf et al., 2007; Lucia et al., 2003). In this section we will discuss pharmaceutical al, psychological and exercise based interventions on the underlying mechanism of CRF.

Pharmaceutical Treatment for Cancer Related Fatigue

Due to a greater understanding of the pathophysiology of CRF, increased research has begun to focus on identifying pharmaceutical interventions suited to intervene with the potential biological pathways of CRF. We will review the effects of 4 commonly used drug interventions in order of drug class.

First, as described previously, anemia is experienced by up to 50% of cancer patients and can contribute to CRF. Drug treatment of anemia with hematopoietics has provided beneficial results in relieving CRF (Carrol et al., 2007; Dicato, 2003; Gilreath et al., 2008). Commonly used hematopoietics include epoetin alpha and darbepoetin alpha. The use of hematopoietics has been found to revive haemoglobin concentration back to levels associated with better health and functioning. For example, Shasha and colleagues evaluated the effectiveness of a once weekly recombinant human erythropoietin in anemic cancer patients receiving radiation therapy with concomitant or sequential

chemotherapy. As a result of treatment, Hb increased more than 2 g/dl in 74% of 442 participants which resulted in Hb levels above 12 g/dl ($p < 0.05$). They also found that epoetin – alpha significantly improved QOL ($P < 0.05$) and was found to be well tolerated. The use of epoetin has been found to benefit CRF patients similarly to patients with anemia. In summary, treating anemia in cancer patients with CRF is well tolerated and has minimal side effects (Mitchell et al., 2007; Shasha et al., 2003).

Second, a class of central nervous system stimulants called psychostimulants have been prescribed to alleviate sleep disorders in patients with insomnia and excess daytime sleepiness (Carrol et al., 2007). They have also been found to enhance a patient's alertness, attention and reduce fatigue in cancer patients (Carrol et al., 2007). Common psychostimulants prescribed to patients with cancer include methylphenidate, dexmethylphanidate and modafinil. Mitchell and colleagues (2007) investigated the effects of four clinical trials using methylphenidate to reduce CRF. They stated that all four studies reported some improvement in fatigue; however, in one study over half of the participants experienced adverse side effects. These included agitation, anorexia, nausea and vomiting (Mitchell et al., 2007). Further evaluation into the use of psychostimulants for patients with CRF is needed due to limited controlled studies, small sample sizes and adverse side effects.

Third, antidepressants such as Bupropin and Paroxetine (a serotonin reuptake inhibitor) have been used in efforts to treat depression in cancer patients and patients with CRF. Antidepressents have been used in other diseases such as multiple sclerosis with positive results (Carrol et al., 2007). Carrol et al., (2007) identified two case studies in which bupropin was used to treat CRF. The studies indicated that antidepressents such as

bupropin may be useful in the treatment of CRF since patients had reduced fatigue levels within 2 – 4 weeks of treatment (Carrol et al., 2007). However, serotonin reuptake inhibitor Paroxetine was found to improve depressive symptoms in CRF patients but was unable to reduce overall fatigue scores (Roscoe, Morrow, & Hickok, 2005). Although not effective for CRF, this treatment further distinguishes the difference between causal mechanisms between CRF and depression. Antidepressant may benefit CRF patients by reducing depression, a common comorbidity, which in turn may elevate stress from the fatigue. However, further research is needed into the role of antidepressant treatment in CRF.

Fourth, corticosteroids such as prednisone, methylprednisolone, and megestrol acetate have been found to improve symptoms of pain, increase energy and reduce fatigue. For example, the use of an oral dose of methylprednisolone was able to cause significant reductions in pain severity in comparison to a placebo group within 14 days (Bruera, Roca, & Cedaro, 1985). Although corticosteroids have been used to positively affect a variety of aspects related to CRF, it is suggested that they only be used for short durations or for patients that are in terminal stages of cancer with severe pain (Bruera et al., 1985; Carrol et al., 2007). This is because corticosteroids, although helpful, can cause side effects such as muscle wasting which drastically deteriorates QOL and contributes strongly to CRF (Bruera et al., 1985; Carrol et al., 2007).

In summary, several pharmaceutical interventions have been proposed for the treatment of CRF. The most researched and potentially beneficial medicinal agents effective in the treatment of CRF have been epoetin alfa and darbepoetin alfa (Carrol et al., 2007). Results supporting or negating the use of CNS stimulants, antidepressants and

corticosteroids are inconsistent (Carrol et al., 2007). Further investigation into these drug classes using double blinded randomized controlled designs would help solidify the potential role in CRF treatment. It has been suggested that pharmaceutical treatment of CRF may be most effective when combined with nonpharmaceutical interventions such as psychotherapy and exercise (Carrol et al., 2007; Mitchell et al., 2007).

Psychologically Based Interventions for Cancer Related Fatigue

Conditions which arise from the malignancy or cancer treatments such as anxiety, difficulty coping, sleep disturbances, attention deficits and depression have been found to contribute to CRF and diminish QOL. The last two decades has seen an increase in knowledge regarding the benefits of psychosocial intervention for cancer patients and survivors (Mustian et al., 2001). In this section we will review findings from psychotherapy, psychoeducational interventions.

Psychotherapy includes education, stress management, coping strategy training and behavioural interventions. Results from psychotherapy interventions on CRF are inconsistent due to a variety of outcome measures and lack of control groups (Jacobsen et al., 2007; Mustian et al., 2001). Fawzy and colleagues (1990) evaluated the immediate and long term effects on psychological distress and coping mechanisms during a 6 week long psychological group intervention for patients completed surgery. They incorporated health education, enhancement of problem solving skills and stress management as well as psychological support into the intervention. Results indicated that the patients of the intervention group experienced greater vigour, and increased use of behavioural coping mechanisms when compared to controls. In addition they found in a 6 month follow up

study the same patients showed significantly lower fatigue, depression, confusion and mood disturbances (Fawzy, Cousins, & Fawzy, 1990).

Efforts to educate the patients regarding anticipated symptoms of fatigue and the effects of the disease processes help give the patient anticipatory guidance about fatigue. Educational designs help promote emotional and instrumental coping skills as well as behaviours that can be applied after completion of the intervention. For example, Fawzy (1995) designed a study to determine if a psychoeducational nursing intervention could enhance coping behaviour and overall state of stage I/II malignant melanoma patients. In this study Fawzy reported that the treatment group had significantly decreased their scores on the POMS – fatigue subscale. In a follow up treatment group members were using less ineffective passive coping strategies then controls at 3 months post intervention (Portenoy & Itri, 1999).

Psychological and cognitive impairments can contribute to CRF as well as to produce problems in social and family relationships; independent living, self care and employment therefore psychological and cognitive parameters must be attended to. Psychological and cognitive based interventions focusing on stress management, coping skills, behavioural change strategies and education of CRF and contributing conditions may provide beneficial long lasting effects for cancer patients (F. I. Fawzy et al., 1990; N. W. Fawzy, 1995; Jacobsen et al., 2007; Mustian et al., 2001; Portenoy & Itri, 1999). Debate on the effectiveness of psychological designed therapies in assisting patients with CRF is present due to a small number of studies, small sample sizes, lack of randomized controlled experiments and inconsistency in results. However, Mustain et al. (2007) suggests that altogether the results of psychological interventions seem to lower CRF

(Mustian et al., 2001). In addition to psychotherapy, it is suggested that the addition of exercise to a psychologically based intervention may improve outcomes related to fatigue when compared to psychological treatments alone (Courneya et al., 2003; Mustian et al., 2001). Psychotherapy methods have been found to improve psychological aspects of CRF; however, physical symptoms greatly contribute to the overall CRF experience are not attended to in this type of treatment. Therefore, it has been suggested that psychological interventions incorporate the use of physical exercise sessions.

Current Attitudes Regarding Exercise for Cancer Related Fatigue

Current Recommendations

The results of exercise interventions, in contrast to psychological therapies and pharmaceutical treatments, are first not unidimensional and second have fewer negative side effects respectively. In addition, exercise has been established as an effective treatment for physiological impairments such as depression and anxiety and can induce biochemical adaptations which provide similar results to debilitating pharmaceutical interventions. (Winningham, 2001). However, for many years a common recommendation for patients with CRF was to rest and avoid physical efforts (Court et al., 2001). These recommendations seem intuitive. Since cancer and its treatment result in the reduction of physical functioning through cardiovascular, pulmonary and metabolic insults it seems logical that exercise would exacerbate fatigue and aggravate the set of symptoms present. Therefore, it was thought that avoiding physical activity would result in greater comfort from fatigue and other symptoms (Lucia et al., 2003). However, a reduction in the amount of exercise and physical activity seems to have paradoxical

outcomes. The recommendation for sedentary lifestyles actually causes further progression of symptoms such as inflammation, muscle wasting, reduced cardiovascular and pulmonary capacity, and metabolic dysfunction consequently; worsening symptoms, increasing fatigue and reducing overall QOL (Courneya et al., 2000; Dimeo, 2001). Therefore, the lack of exercise and physical activity actually causes a self perpetuating continuum of diminished activity leading to increased fatigue and vice versa. However, due to the fragility of both physical and psychological attributes of oncology patients concerns about the use of exercise for this population logically arise.

Potential Risks of Exercise

Due to the invasiveness and potential dangers associated with exercise, concerns about its application in oncology rehabilitation have been expressed. As described by Courneya et al. (2000) these concerns include: first, the potential immunosuppressive effects of vigorous exercise. Second, the increased likely hood of pathological bone fractures due to compromised bone density and overall integrity. Third, possible exacerbation of cardiotoxicity from chemotherapy and or radiotherapy is thought to occur. Fourth, exercise may induce pain, nausea and fatigue. Fifth, cancer patients may be unwilling to tolerate exercise given a weakened physical and or emotional condition (Courneya et al., 2000). However, current research has begun to put many speculation and concerns regarding safety of exercise to rest. For example, Schmitz et al. (2005) studied the safety and efficacy of a resistance training program in recent breast cancer survivors in which the team found that a twice weekly weight training regime is well tolerable with an injury rate of 10.5% over the first six months and a total of 22.5% over a full year. These injury rates are comparable with the healthy population normative data

on injury rate during exercise. Injury rates in apparently healthy humans are 14.4% over the first 6 months and 28.8% over the full year (Schmitz, Ahmed, & Hanna, 2005). Although injury rates in this study were only slightly above healthy population norms, extra attention to safety while developing exercise prescriptions and supervising exercise sessions must be considered.

If prescribed with appropriate supervision and attention to pathological contraindications, exercise is a potentially powerful treatment for CRF (Winningham, 2001). The exact process in which exercise may reduce CRF is not fully developed. The first step in this investigation is to identify the potential pathological causes associated with CRF. Currently a variety of potential etiologies have been proposed. Of these etiologies, exercise has been found to improve serotonin regulation, HPA – axis function, circadian rhythms, chronic inflammation, cardiopulmonary function, and energy/muscle metabolism (Lucia et al., 2003; McNeely et al., 2006; Schwartz, Mori, Gao, Nail, & King, 2001; Winningham, 2001).

The Role of Exercise Based Interventions on Cancer Related Fatigue Etiologies

For patients with similar symptoms and etiologies as CRF, the use of physical exercise has consistently been used as a central rehabilitation method. It has been well documented that exercise improves fatigue experienced by patients with rheumatoid arthritis, multiple sclerosis, cardiovascular disease, chronic fatigue syndrome, depression, and conditions presented with sickness behaviours resulting from chronic inflammation (Lucia et al., 2003; McNeely et al., 206; Schwartz, Mori, Gao, Nail, & King, 2001; Winningham, 2001). Primarily through the investigation of the above mentioned

conditions, it has also been proven that exercise induces adaptive changes in the physiological systems that may contribute to the web of CRF etiologies. These adaptations are similar to those witnessed as a result of pharmaceutical interventions; however, exercise therapies have considerably less risk and side effects (Mustian et al., 2001; Winningham, 2001).

In this section we will describe the role that exercise plays in the physiological adaptations to the potential biological mechanism resulting in CRF starting with the effects of exercise on serotonin dysregulation resulting in increased fatigue, mood disturbances and depression. Second we will uncover the effects of exercise on HPA axis function and altered cortisol production during stress responses. Third, we will illustrate the effects of exercise on circadian rhythm irregularities which cause sleep disturbances. Fourth, we will investigate the effects of exercise on immune function and cytokine production in oncology patients. Fifth, we will address the effects of exercise on cardiovascular and pulmonary dysfunction in cancer patients. Finally, we will investigate the effects of exercise on ATP production and metabolism dysfunction in oncology populations.

Effects of Exercise on Serotonin Regulation

Cancer and or its treatment has been hypothesized to increase brain serotonin and or increase the density of 5 – HT receptors, leading to reduced somatomotor drive, altered HPA function, increased sensitivity to physical work, depression and poor mood states (Ryan et al., 2007). The study of fatigue from the perspective of exercise physiology has investigated the effects of serotonin in generating central and peripheral fatigue and the

effects of exercise on the regulation of the underlying mechanisms. Dwyer and Browning (2000), investigated the effects of aerobic exercise training on serotonin receptor sensitivity is wistar rats. They found that a significant difference in the time to exhaustion from base line to post training (increased by 406 seconds) was present in the treatment group (treated with 5 – HT1a angonist) ($p = 0.004$). In contrast, the control group's time to exhaustion was relatively unchanged. Their team concluded that exercise training decreases the sensitivity to 5 – HT1a receptor agonist which may be caused by a decrease in 5 – HT1a receptor sensitivity.

In addition to a reduced 5 – HT receptor sensitivity, exercise may reduce or delay the onset of an increased concentration of serotonin thus, increasing time to fatigue. For example, Langfort et al., (2006) found that endurance training significantly lowered 5 – HT content in all brain regions except the cerebellum when compared to untrained controls following non exhaustive aerobic exercise (Langfort et al., 2006). As a result of endurance training, sub maximal concentrations of brain serotonin were decreased allowing for greater sub maximal performance. Therefore, it is possible that endurance training may improve the ability of the oncology patient in carrying out sub maximal activities of daily living without fatigue.

As described in previous sections, CRF is associated with psychological distress such as memory impairments. While serotonin has been speculated to impair learning and memory, it is suggested that exercise may be able to improve 5 – HT regulation and thus improve memory and overall learning (Chen et al., 2008). Chen et al., (2008) investigated the effects of a 4 week treadmill intervention on levels of 5 – HT and its metabolite (5 – HIAA) as well as the protein expression of 5 – HT1a. They demonstrated

that the exercise intervention improved learning performance, decreased 5 – HT levels in the hippocampus and decreased 5 – HT1a expression. These results show that exercise may improve memory and learning by reducing serotonin levels in the brain as well as reducing the expression of serotonin receptors.

An increase of 5 – HT concentration and density of 5 – HT1a receptors in conditions such as CFS have identified (Payne, Held, Thorpe, & Shaw, 2008; Ryan et al., 2007). It is postulated that the same expression of serotonin activity may be present in patients CRF (Ryan et al., 2007). The use of exercise interventions for the improvement of serotonin concentration, receptor expression, physical capacity and psychological functioning has been well documented. These result suggest that exercise may improve the physical and psychological functioning of patients with CRF in part by reducing serotonin concentrations and inhibiting the over expression of 5 – HT1a receptors.

Effects of Exercise on HPA Axis

Fatigue in cancer patients is associated with reduced HPA function resulting in defective cortisol production in response to physical and psychological stresses (Ryan et al., 2007; Wang, 2008). The dysfunction to the HPA axis may induce physiological distress, poor ability to cope, risk of depression and altered mood states; all of which have been associated with the severity of fatigue and QOL in oncology patients.

It has been documented that animals and humans who engage in regular moderate physical exercise show improved coping abilities and better overall mood (Droste et al., 2003). Dorste et al., (2003) studied the effects of a 4 week treadmill exercise intervention in male rats on HPA function and secretion of ATCH. In comparison to controlled rats

who received no treadmill exercise, the treatment group displayed augmented glucocorticoid responses to physical stress. This is critical in order to meet enhanced metabolic needs. Also, exercised rats were found to release less ATCH in response to environmental stress. This evidence is consistent with findings that exercised mice and humans show reduced anxiety to psychological stress (Droste et al., 2003). This study provides evidence which supports the notion that exercise is able to regulate HPA abnormalities to produce appropriate cortisol responses.

In addition to Dorste's findings, Kim et al., (2008) established a state of hypoactivated HPA axis in rats by administering corticosterone for 19 days. They then studied the effects of exercise on the hypoactivated rat models in which they found that the treadmill exercise recovered the deregulated HPA axis to normal functioning (Kim et al., 2008). These results suggest that exercise may aid in the recovery of hypoactive HPA axis function which is common in psychological disorders such as post traumatic stress syndrome. In contrast, hyperactive HPA axis function is associated with psychological conditions such as depression. Based on the findings of the previous two studies, it can be hypothesize that the effect of exercise may regulate HPA axis function in both directions (Droste et al., 2003; Kim et al., 2008).

The role of exercise on HPA axis function in patients with cancer is not well understood. HPA axis function plays a dominant role in many physiological systems including the cardiovascular system, immune system and circadian rhythm (Ryan et al., 2007; Wang, 2008). Therefore, exercise may be a valuable option to aid in the appropriate functioning of the HPA axis and thereby enhancing the function of both cardiovascular and immune systems in addition to circadian rhythm.

Effects of Exercise on Circadian Rhythm and Sleep Disturbances

A potential process in which cancer may cause fatigue is through the disruption of circadian rhythms (Ryan et al., 2007; Wang, 2008). Patients with cancer have been found to have endocrine abnormalities, alterations in metabolic processes, dysfunctional immune responses and deregulated sleep wake cycles all thought to arise from or initiate irregular circadian rhythms (Ryan et al., 2007). The role of exercise has been investigated throughout the scope of these potential mechanisms; however, sleep disturbances have been studies most extensively. It has been found that exercise can improve sleep quality in women receiving hormonal therapy for breast cancer. In addition the exercise can cause less movement and shorter wake times (Payne et al., 2008).

The role of exercise in regards to sleep hygiene is endorsed by the American Sleep Disorders Association as a non-pharmacological intervention to improve sleep (Hauri, 1993; Payne et al., 2008). The exact mechanisms are not fully understood however, exercise has been found to beneficially influence the role of many physiological systems to promote quality of sleep in patients with insomnia which may suggest an improvement in circadian rhythm function (Hauri, 1993; Payne et al., 2008). Further investigation into the mechanisms leading to the improvement in constructs related to circadian rhythm such as sleep quality is warranted.

Role of Exercise in Immune System Function

Elevated and prolonged inflammation is suggested to play a mechanistic role in CRF (Wang, 2008). The use of exercise in conditions, in which a prolonged inflammatory state is present, such as cardiovascular disease, has been shown to reduce levels of inflammation (Das, 2004). Das (2004), suggests that exercise has the ability to induce an anti–inflammatory effect on patients with chronic of prolonged inflammation (Das, 2004). A review of literature by Falrey (2002), investigates the overall effects of exercise on immune function in cancer survivors. In general, they found that the effect of exercise training on the immune system in cancer survivors reported favourable outcomes. Four of the six studies examined reported statistical significance for improvements in Natural Killer (NK) cell cytolytic activity, monocyte function, circulating granulocytes, and duration of neutropenia (absolute neutrophil count < 1200) (Falrey, Courneya, Fleld, & Mackey, 2002).

More specifically, Timmeram et al (2008), studied the effects of regular exercise training on inflammatory monocytes, CD14+ and CD16+. They found that 12 weeks of moderate exercise (aerobic and resistance training) significantly decrease levels of circulating monocytes by 64% (Timmerman, Michael, Coen, Markofski, & Pence, 2008). C14+, C16+ and related monocytes are highly "inflammatory" due to their affinity to produce high amounts of inflammatory cytokines. Immune cells such as monocytes, NK cells, macrophages and granulocytes have all been found to be highly active in cancer patients. These cells all have the ability to produce high levels of cytokines which induces greater proliferation of immune cells and further cytokine production. Therefore,

it is of interest to reduce the concentration of cytokines in effect to reduce the immune response.

Elevated proinflammatory cytokines such as interleukins (IL – 1, IL – 1b, IL – 2, IL – 6), interferons (INF – y), and tumour necrosis factors (TNF – a) are released by proinflammatory immune cells and damaged organ cells as a part of the host response to the tumour or in response to tissue damage resulting from adjuvant therapies (Bower, Ganz, Aziz, & Fahey, 2002). Das, illustrated that exercise reduces the production and activity of immune cells known to release large amounts of cytokines. In response to the reduced monocyte activity, Timmerman found exercise training lead to a significant decrease in TNF – a when stimulated with an LPS – stimulant (Timmerman, Michael, Coen, Markofski, & Pence, 2008).

The role cytokines play in the production of CRF may be related to their involvement cardiovascular dysfunction, cachexia, HPA regulation and ANS regulation. For example, C – reactive protein (CRP) is a common cytokine associated with CRF and cardiovascular risk. In a study by Fairey et al., (2005), they investigated the effects of exercise on CRP in postmenopausal breast cancer survivors. They found that a 15 week exercise intervention three times a week at 70 – 75% of individual peak oxygen consumption decreased CRP by 1.39 mg/L in comparison to the controlled group where CRP increased by .10mg/L. This increase provided a twofold benefit for patients. One, it reduces the risk of cardiovascular disease in addition to reducing the overall inflammation which in turn diminished sickness behaviour and fatigue.

Second, cachexia, a muscle wasting disease is common in CRF and may be moderated by cytokines. It is proposed that cytokines such as TNF – *a* play a large role in inducing the catabolism of muscle tissue resulting in loss of muscle mass. However, exercise has been shown to reduce this function. For example, Greiwe and colleges (2001) illustrate that levels of TNF – a mRNA and TNF – a protein content in the muscle is significantly decreased following resistance exercise training in frail elderly compared to matched controls (Greiwe, Cheng, Rubin, Yarasheski, & Semenkovich, 2001). The role of exercise in reducing the inflammatory and catabolic effects of TNF – a on skeletal muscle is thought to be induced in part by an increased anti–inflammatory cytokines such as IL- 4, IL – 10, and TGF by up to 36% (Das, 2004).

The exact mechanism in which exercise reduces proinflammatory immune cell activity and cytokine proliferation is not understood. Third, current hypotheses state that exercise may provide anti–inflammatory properties through regulating HPA axis function, improving oxidant buffering capability and enhancing vagal response to inflammation. First we will discuss the anti-inflammatory role of exercise through cortisol regulation and HPA axis activity. Under normal conditions immune cells are tightly regulated by glucocorticoids. As described previously, in some cases the level of glucocorticoids and cortisol can be dramatically attenuated during cancer (Bower, Ganz, & Aziz, 2002). This may result in the dysregulation of immune function and augmentation of immune activation (Bower, Ganz, Aziz, & Fahey, 2002). It has been found that exercise can improve the regulation cortisol and glucocorticoids in patients with cancer and other conditions (Bower, Ganz, & Aziz, 2002; Droste et al., 2003; Kim et

al., 2008). Therefore, exercise may in fact inhibit chronic inflammation by improving HPA axis regulation of glucocorticoids and cortisol.

A second possible mechanisms in which exercise may exert an anti-inflammatory effect is by improving the anti-oxidant status of the patient. Exercise has been found to produce anti–inflammatory cytokines and enhance the expression of anti-oxidants such as super oxide dismutase (SOD) which neutralizes the damaging effects of free radicals (Das, 2004). The damage that free radicals initiate is followed by an inflammatory response and subsequent inflammation. Therefore, a reduction of free radical injury due to increased presence of anti oxidants, such as SOD, will lead to a reduction in inflammation and cytokine production.

A third possibility in which exercise may induce reduction in inflammation is through the autonomic nervous system (ANS). Exercise may increase the parasympathetic hegemony in patients with inflammatory conditions such as heart disease (Das, 2004). This parasympathetic dominance is attributed with anti-inflammatory effects due to a suppression of immune activation and the release of acetylcholine which increases the expression of endothelial derived nitric oxide (eNOS) (Das, 2004). eNOS is a powerful anti-oxidant which may inhibit the production of cytokines.

In summary, exercise can reduce the chances of inflammation by improving cortisol and glucocorticoid production, increase production of anti oxidants and promote parasympathetic hegemony for further anti–inflammatory effects. The end result is a reduction to chronic inflammation by attenuating immune cell production and activity

and cytokine proliferation. Due to the involvement of cytokines and inflammation in many of the proposed etiologies of CRF, exercise may provide a holistic and potent treatment to a variety of etiologies.

Effects of Exercise on Cancer Induced Cardiopulmonary Dysfunction

Exercise is a well established modality for the improvement of cardiovascular and pulmonary performance in healthy individuals (Lucia et al., 2003). In patients with cancer, the severity of fatigue and reduction in physical ability due to cardiovascular and pulmonary dysfunctions are highly related (Dimeo et al., 1997). Insults to the cardiovascular and pulmonary systems may originate from tumour burden or cancer treatment (Wang, 2008).

Chemotherapy regimens have been found to cause cardio toxicity which lead to disabled function of the cardiovascular system. However, it has been found that improved physical functioning through regular exercise can protect the myocardium against toxic anthracyclines and myeloablative therapies (Lucia et al., 2003). Chicco et al (2006) found that exercise was associated with an increase in eNOS, myocardial heat shock protein content, and prevention of myocardial lipid peroxidation (Chicco, Schneider, & Hayward, 2006). These results suggest that exercise may protect myocardial function by increasing anti-oxidant and anti-inflammatory activity to protect against the inflammatory effect of these drugs.

In addition to protecting the myocardium from the toxic effects of cancer treatments, exercise can also improve overall cardiorespiratory function. For example, a 10 week low to moderate intensity aerobic exercise prescription for a heterogeneous

sample of cancer patients undergoing different types of treatments resulted in significant improvements to aerobic capacity ($p < 0.001$) (Burnham & Wilcox, 2002). Also, Quist and colleges investigate the effect of aerobic and resistance training on cardiovascular and muscular strength variables in cancer patients. They found that over a 9 hour per week, 6 week intervention period, muscular strength improved by 41.3% ($p <0.001$) and aerobic capacity increased significantly by 14.5% ($p< 0.001$) (Quist et al., 2006). The results from these studies suggest that aerobic and resistance exercise can improve overall function of the myocardium, vasculature and skeletal muscle.

Improvements in aerobic capacity are not only reflective of myocardial function, it but are also indicative of the efficiency and functioning of the pulmonary system. Cancer and cancer related treatments can induce a variety of insults to pulmonary function and geometry causing reduction in overall pulmonary efficiency (Wang, 2008). Reliable variables indicative of pulmonary function include forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) (Schneider et al., 2007). Schneider et al., (2007) studied the effects of an individual exercise prescription over six months on cardiopulmonary function and fatigue in breast cancer patients during and after treatment. The team found that aerobic exercise for 6 months improved FVC by 2.8%, FEV1 increased by 4.0% and overall maximal oxygen consumption increased by 15.1% (Schneider et al., 2007).

In summary, improvements in cardiopulmonary function with endurance and resistance training during and after cancer therapy are associated with significant increases in overall functional capacity and reduction in CRF (Lucia et al., 2003). The efficiency of these systems is an integrative indicator of the maximal capacity of different

bodily tissues including the lungs and heart but also of the blood, and skeletal muscle. The functional capacity of blood and muscle tissue relies on an effective chain of events including oxygen transport, ATP production and waste removal. In the next section will describe the role of exercise in cancer patients in relation to metabolic properties underlying an improved function capacity.

Effects of Exercise on Metabolic Abnormalities in Cancer Patients

Metabolic insufficiencies found in oncology patients stem from reduced oxygen uptake and transportation, as well as altered blood pumping mechanisms (Winningham, 2001). As a result light activities are not met with adequate energy production through aerobic pathways. This causes a shift to anaerobic derived energy production which in turn increases heart rate, lactic acidosis and breathlessness making simple tasks such as activities of daily living fatiguing for the patient to complete. As stated previously, exercise can promote beneficial increases to cardiovascular and pulmonary capacity, which reflects an improvement in the underlying metabolic systems regulating their functional status. Improved metabolic efficiency is one of the main adaptations caused by exercise training (Lucia et al., 2003).

Cancer and or its treatment may cause cancer related anaemia. Patients with cancer induced anemia have difficulty carrying out activities of daily living and other sub-maximal efforts due to the inability to transport sufficient oxygen to working tissues. One way in which exercise may enhance oxygen transport in cancer patients with anemia is by stimulating erythropoiesis (Lucia et al., 2003). For example Dimeo, et al (1997) showed that an endurance exercise program following chemotherapy was able to increase

haemoglobin concentration from 10.1 g/dL at base line to 13.1 g/dL ($p < 0.05$). As a result, patients undergoing the exercise intervention experienced reduced fatigue and improved ability to carry out activities of daily living (Dimeo, Tilmann et al., 1997).

Furthermore, exercise can also improve physical functioning and metabolic efficiency by increasing the proportion of oxidative fibers and reducing the proportion of glycolytic fibers (Fitts & Widrick, 1996; Lucia et al., 2003). For example, Carter et al (2001) found that endurance training in males and females increased oxidative muscle fibers which correlated with VO_2 Max ($r^2 = 0.52$, $p < 0.05$) (Carter, Rennie, Hamilton, & Tarnopolsky, 2001). These result support the notion that exercise training can enhance the capacity of physical work by increasing oxidative muscle fibers

An increase in oxygen delivery and a high proportion of oxidative muscle fibers will improve the functional capacity of patients. However, patients with cancer related fatigue commonly are associated with high rates of muscle atrophy or muscle catabolism which in turn reduces proportion of muscle fibers both oxidative and glycolytic. Increased ratios of protein degradation over protein synthesis can occur from the increased bed rest and reduced physical activity, by cancer induced processes (cytokines), or by cancer related treatments. Regardless of the cause of muscle wasting, the deleterious results are imparted on metabolic function and overall physical capacity. Resistance training has been a long known countermeasure for muscle metabolism in a variety of health and diseased individuals ((Al-Majid & McCathy, 2001). For example, protein synthesis rate of the biceps braChii muscle of in human subjects increased by 50% to 109% in 4 hours and 24 hours (choose numbers or letters) respectively following a single bout of resistance exercise compared to non-exercised controls (Chen et al.,

2008). In addition to resistance exercise, endurance exercises can also initiate an enhanced?! protein synthesis. For example, Deuster and colleges (1985), study the effects of endurance training modification of cachexia in rats with malignant tumours. They found that voluntary endurance training for four weeks resulted in a 15% increase in muscle protein synthesis and increased the muscle body weight ratio by 10% (Deuster, Morrison, & Ahrens, 1985). Muscle wasting contributes to substantial weakness and fatigue in cancer patients (Al-Majid & McCathy, 2001). As results indicate, exercise intervention incorporating both resistance and endurance exercise modalities would be beneficial to the overall functional abilities of cancer patients and improve metabolic efficiency by preserving and creating oxidative muscle fibers while increasing the ability to transport nutrients and oxygen.

In summary, cancer and its treatment have negative consequences on metabolic and muscle functions in cancer patients. Regular exercise of both aerobic and resistance modes have been suggested and proven to induce beneficial changes to haemoglobin content, oxidative muscle fibers and protein synthesis. As a result of enhanced metabolic efficiency, improved cardiopulmonary function, reduced inflammation, regulated circadian rhythms, appropriate HPA – axis responses or improvements in serotonin production through exercise, exercise has been suggested to improve the QOL and fatigue experienced by oncology patients. Exercise influences a broad spectrum of biological parameters causing multidimensional adaptations to physiological systems. Therefore, exercise may induce beneficial changes to a variety of etiologies simultaneously thus making it an efficient and holistically beneficial intervention strategy. However, its clinical acceptance has been delayed due to a lack of recognition of exercises benefits on

CRF etiologies in addition to concerns regarding the risk of exercise and an overall poor understanding of the current body of literature.

DIFFICULTIES UNDERSTANDING THE CURRENT LITERATURE

The recognition of the effects of exercise on pathological underpinnings of similar condition presenting with fatigue has lead to two and a half decades of research into the effects of exercise on the syndrome of CRF. The first study done by Winningham et al., (1983) first established the positive effects of exercise on CRF. In this study Winningham tested a therapeutic bicycle ergometry exercise protocol over ten weeks for breast cancer patients undergoing chemotherapy. The results of this study indicated an overall improvement of functional capacity as well as increasing the patient's sense of control. In subsequent studies using similar exercise programs, this team indicated improvements in many measures related to QOL including; reduced depression, increased vigor, and decreased fatigue (Winningham, 2001). Since this study, hundreds of studies have investigated the effects of exercise on CRF and QOL in cancer patients with fatigue as a secondary measure. In addition, many literature reviews have been published in attempts to draw a common conclusion from this large and diverse body of evidence. Many narrative and systematic literature reviews generally support the use of exercise in CRF and state that exercise is a safe and effective treatment option to decrease CRF and improve overall QOL (Courneya et al., 2000; de Nijs et al., 2008; Dimeo, 2001; Knobf et al., 2007; Lucia et al., 2003; Mitchell et al., 2007; Mustian et al., 2001; Portenoy & Itri, 1999; Stone & Minton, 2008; Watson & Mock, 2004; Winningham, 2001).

Although the majority of the literature consistently supports the use and efficacy of exercise intervention and the management of CRF during and after treatment as Mustain and colleges declare this field and the respective body of literature to be in its preliminary stages (Mustian et al., 2001). Many criticisms have originated from the preliminary status of the present literature. First, the lack of a unified and standardized definition of CRF has resulted in many studies investigating a variety of differing aspects of the syndrome as a whole. Thus, making the results of a sample of studies difficult to interpreted and draw appropriate conclusions (Franklin & Packel, 2006). As a consequence the lack of a standardized definition has lead to a wide variety of assessment tools. Second, inconsistent use of CRF assessment makes it difficult or even impossible to make interpretations and conclusion across studies (Franklin & Packel, 2006; Jereczek-Fossa et al., 2002; Mustian et al., 2001; Portenoy & Itri, 1999; Stone & Minton, 2008). Furthermore, CRF measures are subjective and at times can be difficult to identify differences between patients with CRF and patients with non CRF. Third, the lack of any objective measures for the diagnosis of CRF may cause an overestimation of the prevalence of the syndrome (Jereczek-Fossa et al., 2002; Mustian et al., 2001). In addition, many studies do not apply rigorous inclusion criteria or establish a threshold in which the participant must meet in order to be included. This may also lead to an inflated prevalence of CRF (Jereczek-Fossa et al., 2002; Mustian et al., 2001).

Although criticisms arise from lack of a unified definition and varied assessment protocols, additional criticism is contributed due to methodological weaknesses. For example, weaknesses in CRF literature commonly occur due to small sample sizes (Watson & Mock, 2004). A problem with small sample sizes is the difficulty in

aChieving significant results in addition to the difficulty in accurately inferring results to a larger population. Small sample sizes are notorious in CRF literature and commonly linked to a questionable reliability of CRF and exercise results ((Mustian et al., 2001; Watson & Mock, 2004). A second criticism of CRF literature is based on the limited amount of studies with true experimental designs (Mustian et al., 2001; Watson & Mock, 2004). The validity of less strenuous designs such as pre post designs or quasi experimental design is often questioned. However, in areas of research that are in their preliminary states, less stringent study designs are common (Conn, Hafdahl, Porock, McDaniel, & Neilson, 2006). Regardless, in order to improve the validity and reliability of CRF research and results, more experimental designs with larger sample sizes are needed (Watson & Mock, 2004). In addition, true controls and placebos are required in order to begin establishing theories of pathological mechanisms underlying CRF (Watson & Mock, 2004). A third methodological weakness is the lack of standardized exercise prescriptions (Mustian et al., 2001; Watson & Mock, 2004). This limitation makes it difficult to establish appropriate and effectively tailored exercise prescriptions that will meet the needs of the patients (Mustian et al., 2001; Watson & Mock, 2004). Furthermore, a lack of detail in describing exercise prescriptions used for participants is a common critique in CRF literature (van Weert et al., 2008). This makes it difficult to identify specific components of the exercise program that may be most effective or least effective. In addition, a general lack of understanding of the effects of different exercise interventions provides extra challenges for inter professional health care teams in terms of clinical application and patients education.

A thorough understanding of the pathophysiology of CRF may drastically improve the quality of the exercise prescription. However, an additional critique about CRF research is the lack of understanding regarding the pathological mechanisms contributing to the syndrome (Ryan et al., 2007; van Weert et al., 2008; Wang, 2008).

In spite of much criticism, CRF is a promising and rapidly growing body of literature. CRF research to date has provided consistent preliminary support to the efficacy of exercise as an intervention for CRF. In order to advance the existing state of literature on CRF, a unified or common definition of CRF is required. Furthermore, standardized subjective and objective measurement instruments are required to establish the presence of CRF and to accurately measure the effects of interventions. In addition, more rigorous study designs are needed to improve the validity and reliability of results in order to make more accurate inferences to the larger population. Finally, clear descriptions of exercise prescriptions and greater focus on prescribing exercise to identify the underlying mechanism contributing to CRF will enhance the potency of treatment for patients with CRF. Thus, generating greater results and further establishing exercise as a powerful intervention for CRF patients.

THE META ANALYSIS

Traditional literature reviews simply summarize findings over a specified topic of interest and draw conclusions about the state of knowledge in that given area (Bordens & Abbott, 2005). However, the drawn conclusions are subjectively derived from critical interpretation. Therefore, it is possible that the conclusions do not accurately reflect the

magnitude of the relationship under examination (Bordens & Abbott, 2005) (Conn et al., 2006; Schmitz et al., 2005). In order to avoid the possibility of misinterpretation, Glass (1977) suggests that the accumulated findings of studies should be regarded as complex data points, no more comprehensible without statistical analysis than hundreds of data points in a single study. This process of analyzing the results of independent studies is called the meta analysis.

Using a Meta Analysis to Investigate the Effects of Physical Activity on CRF

The meta analysis is a way to quantitatively synthesize and interpret a selected domain of research. Constraints of the meta analysis procedure include the following: first, the meta analysis applies to empirical studies only and cannot be used to summarizes review or theoretical papers. Second, the meta analysis can only be applied to quantitative research findings, ruling out qualitative findings. Third, in order for the findings of the meta analysis to be meaningfully compared, findings incorporated in the analysis must first be conceptually comparable and second be from a similar statistical form and study design (Lipsey & Wilson, 2001). In other words, it would not be appropriate to investigate the effects of distinctively different study topics within the same meta analysis. In order for the meta analysis to meaningfully synthesize and integrate the findings from a body of research, the studies investigated must deal with conceptually similar constructs, relationships and study designs (Lipsey & Wilson, 2001).

The Effect Size

The meta analysis procedure applies a set quantitative statics to the research findings of independent studies across a field of research in order to allow the researcher to combine and compare results in a non subjective, statistically quantifiable way. In general, the two outcomes from a meta analytic procedure include significance levels and effect sizes (Mullen & Rosenthal, 1985). Due to the purpose and nature of the present research questions, the present study will utilize the standardized effect size statistic. The standardized effect size is a statistic that encodes the critical quantitative information for each relevant study (Lipsey & Wilson, 2001). The effect size statistic produces a standardization of the study findings in a way that study findings can be interpreted across all the variables and measures involved in each individual study (Lipsey & Wilson, 2001). Standardization is a feature of the meta analysis which allows the effect sizes of various research studies to be compared. In this context, the standardized effect size statistic is similar to z scores and percentiles. The effect size (d) derived from a single research hypothesis indicates the magnitude and direction of the observed effect. In summary, the key to the meta analysis is to identify the effect size statistic that will represent the quantitative findings of the set of research studies under investigation in a standardized form, in order to permit meaningful numerical comparison and analysis across the studies.

The Fixed Effects Model

The current meta analysis will use the fixed effects model. The fixed effects model assumes that differences between the included studies are important and therefore

if heterogeneity of the effect size distribution making up the mean effect size is found, then pooling an overall mean is not recommended without investigation of the differences between studies (Helfenstein 2005). The benefit of a fixed effect size analysis is that it acknowledges this potential variability within the effect size distribution and between each independent study as something more than just subject level sampling error and that the observed variance may be derived from identifiable differences between studies such as interventions, diagnoses, treatment and demographic variables (Lipsey & Wilson, 2001). The fixed effects model best suits our research question based on theoretical understanding of the literature and purpose of the study in general. Since we believe that differences between studies can be attributed to differences in study characteristics such as exercise intervention and cancer characteristics, the fixed effects model is best suited. These differences are termed moderator variables. However, the fixed effects model does not call for an investigation of potential moderator variables if a Chi square test of homogeneity is accepted.

Homogeneity Analysis

When conducting a meta analysis an important question to investigate is whether the mean effect size produced is composed of effect sizes that estimate the same population. In a homogeneous effect size distribution the deviation of effect sizes around the mean is no greater than that which is expected from sampling error alone (Lipsey & Wilson, 2001). To test for homogeneity of the effect size distribution, a Chi square goodness of fit test of homogeneity will be conducted. If the null hypothesis for the test of homogeneity is rejected, this indicates that the variability in the effect size distribution

is larger than what was expected from sampling error alone and that differences among effect sizes originate from something other than sampling error, possibly differences among study characteristics (Lipsey & Wilson, 2001). In meta analysis these differences between study characteristics can be called moderators.

The Moderator Analysis

If the null hypothesis of the Chi square test is rejected then moderators are suspected to be involved in the effect size data (Arthur et al., 2001). In the context of the meta analysis the moderator variable can be defined as a variable that, by inclusion in the analysis accounts for, or helps explain more variance than would otherwise be the case (Arthur et al., 2001). This is different than the moderator variables used in multiple regressions. For example, moderators in a regression analysis interact with other variables to increase the predictability of the criterion variable (Cohen & Cohen, 1983). In the meta analysis, the moderator variable can be based on empirical or theoretical knowledge. Based on a review of the literature we feel that difference between study results may result from different types exercise interventions, different cancer diagnoses, different treatment regiments and differences between patients and survivors.

CHAPTER 3

METHODS

The meta analysis of the effects of exercise based interventions on CRF was conducted to evaluate first, the overall effectiveness of exercise interventions on CRF.

Second, determine the effects of different exercise types on CRF. Third, to determine the effect of exercise on CRF under different cancer characteristics (cancer types, treatments and status). Finally, to identify the overall effect of exercise on potential etiologies reported in the literature.

The study was conducted based on the recommendations of numerous narrative and systematic reviews (Conn et al., 2006; Courneya et al., 2000; McNeely et al., 2006; Mitchell et al., 2007; Schmitz et al., 2005; Schubert et al., 2007; van Weert et al., 2008; Watson & Mock, 2004). The research questions were designed to address the need to integrate the findings of exercise and CRF to help members of interprofessional health care teams make the appropriate treatment choices for oncology patients. The following chapter will discuss the steps used to conduct the current meta analysis. First, a description of the form of research collected will be provided. Second, a description of the comprehensive review of the literature will be illustrated. Third, the inclusion and exclusion criteria used will be addressed. Fourth, the analysis procedures used to code the study level and effect size level data as well as addressing the analysis of the effect size data will be described. Finally, we will describe the procedures used to interpret the results.

Identifying the form of research being analyzed

The quantitative research findings of importance to the present meta analysis are those presented as differences between pre and post means and between post intervention group means originating from either pre – post contrast or group contrast study designs respectively. The first type of research findings that will be investigated are those

derived from pre – post study designs. Although single group pre – post study designs are scrutinized due to the absence of a control group, pre – post designs are commonly found in newer areas of research and may yield valuable information (Conn et al., 2006). The second form of research findings that will be investigated are those derived from group contrast studies (quasi experimental and true experimental). As the study forms have been identified, the next step is to propose the literature search strategies that will be used to identify, locate and retrieve relevant research reports.

Comprehensive Review of Literature

One of the main goals of the meta analysis is to attempt to identify and retrieve every study within the defined population rather than a sample of that population (Lipsey & Wilson, 2001). The first step for this procedure is to develop a system to organize the search for potentially eligible studies. Second, the meta analysis must actively search and retrieve relevant citations.

Development of an Organization Strategy

The first step in organizing a search for eligible studies is to develop a meticulous accounting system to record search progress, status of search for each report, and indication of the outcome of completed searches (Lipsey & Wilson, 2001). For the present meta analysis RefWorks was used. RefWorks is a personalized data base that allows you to organize your data. RefWorks allowed us to set up a bibliography with fields of information regarding the search status for each item. Additionally, RefWorks has allowed us to encode useful information such as the source of citation, type of report and search progress on specific studies. In early stages of study retrieval, prior to the

application of eligibility criteria, retrieved studies were placed in specified folders. In later stages, when determining inclusion, studies were separated and filed based on inclusion of exclusion status. The next step in retrieving research reports was to develop search strategies and identify key terms (Lipsey & Wilson, 2001).

Search Strategies

The search process itself was divided into three sections. The first step was to identify where candidate studies were to be located. Second, defining specific search terms that were used was decided and finally the organization candidate studies was conducted. To locate potential studies multiple relevant sources available within the references of the Lakehead University library and RACER were searched. First, we investigated computerized and electronic databases such as; Pub Med, SportsDiscus, Dissertation Abstracts, PsyChiNFO, ProQuest and CIHNAL. These data bases have commonly been use in previous systematic reviews and meta analysis reports investigating related topics (Conn et al., 2006; Courneya et al., 2000; McNeely et al., 2006; Mitchell et al., 2007; Schmitz et al., 2005; Schubert et al., 2007; van Weert et al., 2008; Watson & Mock, 2004).

Second, we defined our appropriate search terms to effectively identify relevant studies. Specific search terms used for the present meta analysis were those related to exercise interventions such as: exercise, physical activity, exercise therapy, exercise training, aerobic exercise, resistance exercise, physical training, exercise prescription, physical capacity, and exercise capacity. Specific search terms related to cancer included: cancer, oncology, neoplasm, cancer treatment, chemotherapy, radiotherapy,

hormonal therapy, biological response therapy, and bone marrow transplant. Where search limitations and filters were not available, the search terms used to identify the appropriate study designs included: experimental design, quasi experimental design, randomized controlled trail, controlled trails, clinical trial, intervention study, pilot design and or pre – post design/study. These search terms have been used frequently to identify similar studies in previous meta analyses and systematic reviews (Conn et al., 2006; Courneya et al., 2000; McNeely et al., 2006; Mitchell et al., 2007; Schmitz et al., 2005; Schubert et al., 2007; van Weert et al., 2008; Watson & Mock, 2004).

In addition to computerized databases, hand searches were conducted. The journals involved in the hand search were those that commonly identified relevant articles. Also, relevant review articles and clinical trial and pre – post study bibliographies were examined. This process is called treeing backwards and was previously conducted by Conn et al. (2001) and suggested by Lipsey and Wilson (2001).

Third, during the collection period of this study each study was identified and organized into a folder titled "candidate studies" within the RefWorks database and had a separate electronic backup. In addition, each article retrieved was filed with the author name and year. Also, each study was filed with reference to the source from where it was retrieved (electronic source, hand searched, references and journal name). Once all databases had been searched and candidate studies had been retrieved and organized, each study was passed through inclusion criteria prior to meta analysis.

Study Eligibility and Inclusion Criteria

A characteristic of a good meta analysis is that the inclusion criteria are very explicit about the population of research studies whose findings are to be analyzed and summarized (Lipsey & Wilson, 2001). The inclusion criteria have to be based on a literature search of previously completed meta analysis article related to exercise and CRF (Conn et al., 2006; Courneya et al., 2000; McNeely et al., 2006; Mitchell et al., 2007; Schmitz et al., 2005; Schubert et al., 2007; van Weert et al., 2008; Watson & Mock, 2004). The themes of the inclusion criteria were adopted from Lipsey & Wilson, 2001.

Inclusion Criteria Manual

The inclusion criteria manual was developed in order to address any potentially ambiguous cases, thereby reducing subjective bias and allowing consistent interpretation. The inclusion manual for the current study is located in Appendix A. The inclusion form which was be filled out with each candidate study to determine eligibility can also be found in Appendix A. In the case of potentially ambiguous cases where inclusion criteria may become difficult, the inclusion manual was consulted to insure consistency in study inclusion. All studies that met the inclusion criteria were entered into a new electronic folder and hard copy folder. All eligible studies were then coded for variables of interest and effect size information.

Coding Study and Effects Size Level data

The coding procedure for the meta analysis is a procedure that allowed us to extract the specific variables of interest from each eligible study (Lipsey & Wilson,

2001). The purpose of the coding scheme is to build a database for statistical analysis. In order to proceed with this task the coder read through each study report and filled out the coding form with the appropriate responses for the study under investigation. For ease of later analysis, study level information was coded separately from effects size coding information as suggested by Lipsey & Wilson (2001). We will first present a brief discussion on the processes of developing our study level coding scheme. Secondly, we will describe the processes of developing our effect size coding scheme.

Study Level Coding

In the study level coding scheme we were able to code the study characteristics. In the present meta analysis we logged the following study level characteristics; study characteristics/vehicle descriptors, methodological features, participant characteristics, intervention characteristics and etiological variables investigation as well as CRF assessments used. For further detail into each characteristics and an illustration of the study level and effect size coding forms please refer to Appendix B. Each eligible study was surveyed for the relevant study characteristics and recorded in the study level coding form. These data were be used to assist in our analysis and to define sub categories used in moderator analysis procedures.

Effect Size Coding

The effect size coding form used for the present meta analysis can be found in Appendix B. In order to code the effect size information, standard error, and the inverse variance weight; the specific data needed are listed Appendix C. The equations used to

produce the effect size data are also located in Appendix C. Each study was surveyed for effect size data (sample size; means and SD; F-values and SD; t-scores and SD; Chi square values with SD). Once the appropriate values were located, they were recorded in the respective cells of the effect size coding form. Using the calculations presented in Appendix C; the standardized mean difference effect size, the standardized mean difference corrected effect size, the standard error and the inverse variance weight, were computed and also recorded in the appropriate cells located in the effect size coding forms. Although single group pre – post comparison studies contributed many studies to the initial search results, in order to calculate the standardized mean gain effect size for latter analysis, correlation data is required. Because none of the single group pre – post studies presented the required correlation data, they were excluded from the meta analysis. Once all effect sizes for each study were completed, we preceded with the analysis of the collected effect size results.

Analysis

Analysis of the Coded Effect Sizes

The overall analysis of the effects of exercise on CRF was carried out using the fixed effects model to allow us to investigate the potential for moderator variables. Fixed effects moderator analyses will allows us to compare the amount of effect size variability among levels of study level moderators with the amount of variability in the observed effect sizes that would be expected alone with subject level sampling error (Conn et al., 2006). In addition to the effect size statistic computations, a test of homogeneity was performed. The Chi square test of homogeneity was used to assess and test for the

presence of moderator variables (Arthur et al., 2001). If the Chi square test of homogeneity was significant this indicates that the distribution of independent effect sizes used to compose the standardized weighted mean effect size is significantly different from chance.

Research question two asks to determine which mode of exercise is the most effective in reducing CRF. To test the effect of different modes of exercise on CRF, variables such as aerobic, resistance and mixed regiments were pooled by their respective groupings and separate standardized weighted mean effect statistics were produced.

Research question three asks to investigate the potential role of cancer characteristics on the effectiveness of exercise interventions for CRF. To test the influence of cancer characteristics on the overall effectiveness of exercise for CRF a separate analysis was performed on the standardized mean effect size statistic identifying the overall effect of exercise on CRF. The variables that were pooled in the moderator analysis were divided into three categories, cancer type, cancer treatment, and cancer status. For each construct, the variables were pooled and investigated with the standardized weighted mean effect size.

Research question four inquires about the effects of exercise on potential etiologies related to CRF. In order to investigate the effectiveness of exercise on potential etiologies hypothesized to underlie CRF, a standardized mean effect size was calculated for each potential mechanism recorded. A test of homogeneity was conducted to identify the presence of potential moderators. Theoretical moderators that may influence the effect of exercise on potential etiologies include exercise type and cancer

characteristics. Therefore, moderator analysis was conducted on heterogeneous etiology effect sizes given sufficient sample sizes were available.

Once the standardized mean effect sizes have been calculated for each research question we created the confidence interval around the mean effect size to assess the accuracy of our mean effect size (Arthur, Bennett, Huffcut, 2001). The confidence interval for a mean effect size is based on the standard error of the mean effect size. The standard error of the mean effect size is the square root of the sum of the inverse variance weight (Hedges & Olkin, 1985). To construct the confidence intervals, we multiplied the standard error by the critical z – value of 1.96. Next, we added the product to the mean effect size for the upper limit and subtracted the product to form the lower limit. To directly test the statistical significance of the mean effect size derived from each analysis we computed a Single Sample t test. Due to the small number of studies we did not test the significance between groups from our suggested moderators.

CHAPTER 4

RESULTS

The results of the meta analysis will be present in the following order: First the results from the literature search, second, the results on the study characteristics of interest and third, the presentation of the findings from the quantitative meta analysis in the order of the research questions.

Literature Search Results

The search strategies resulted in a total of 260 potentially eligible studies. A breakdown of the location where the studies were found is presented in Table 2.0. Of the 260 candidate studies, 242 studies did not provide the appropriate study and or effect size level data required for inclusion. Therefore, 18 independent research reports met the inclusion criteria and provided sufficient data for the calculation of the appropriate effect size Figure 1.0.

Of the eighteen research reports included for meta analysis one of the studies provided data on the effects of an exercise treatment on CRF but did not report the SD in association with the mean and therefore, effect size data for this study was not calculated. However, this study provided data on the effects of the intervention on haemoglobin concentration and therefore was included in the analysis on CRF etiologies. This resulted in the total sample size of research reports for analysis being 17 data points. However, two studies included multiple treatments and contributed multiple dependent effect sizes within the category of the overall effects of exercise on CRF. As a result, the total data set for the overall effects of exercise on CRF is composed of 19 effect sizes data points. Similarly, of the 18 studies included in the meta analysis, 4 studies provided data on multiple etiologies. As a result, the data set for the overall effects of exercise on CRF etiologies is composed of 20 effect sizes.

Table 2.0: Source of Journals

Method	Source	Number of References Located
Electronic Databases		
	Pub Med	91
	CINHAL	68
	Psych INFO	49
	Pro Quest	29
	Sports Discus	12
Hand Searches		
	International Journal of Sports Medicine	1
	Oncology Nursing Forum	5
	Journal of Sport Science and Medicine	4
Treeing Backwards		
	Cramp & Daniel, 2008	1
		Total References Retrieved = 260

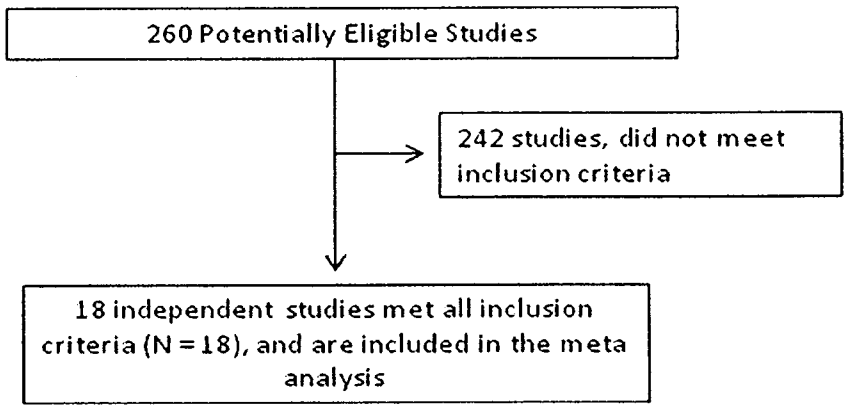

Figure 1.0: Study Inclusion Flow Diagram

Study Characteristics

All of the 18 eligible studies were published in peer reviewed research journals. Only one study was published in 1999, and the remaining 17 studies were published after 2000. Due to the lack of sufficient correlation data in single group pre – post data, all studies included in the meta analysis are group contrast designs with a control or placebo group. Control groups were most often reported as care as usual (*k=16).* Only two studies used a placebo comparison group. The placebo groups were treated with light stretching and print materials. Sample sizes were generally modest; however, seven studies (*k*=7) had sample populations over 100 participants. The average sample size was n=96. The smallest group studied is n=21 and the largest was n=242. The average age of participants was 56.8 years. The minimum age recorded was 40 years and the max was 69 years old.

The majority of studies tested the effects of supervised exercise interventions (*k*=13) as opposed to home based unsupervised interventions (*k*=5). The interventions most commonly took place over 12 weeks (*k*=7). The longest intervention recorded was

24 weeks (k=2). The shortest intervention duration was 4 weeks (k=1); however, in one study the exact duration was not stated but took place from hospital admission to discharge. The frequency of exercise per week ranged from 3 to 7 sessions of exercise per week. However, the majority of studies prescribed exercise at least 3 times a week (k=12). The highest reported frequency was 7 sessions per week (k=1). Most of the studies prescribed a moderate intensity exercise within the range of 30 – 70% maximum oxygen consumption, heart rate or one repetition maximum (1RM) (k=16). Of the 16 studies within this range, intensities that ranged above 70% were found in 6 studies. In addition, 2 studies prescribed all exercises at intensities greater than 70%. An exercise intensity ranging to maximal exertion was present in 1 study. The most commonly reported exercise type was aerobic exercise (k=16). One study used a mixed aerobic and resistance training exercise intervention. Resistance training alone contributed only 1 study to the analysis. However, 3 studies had both independent aerobic and resistance based exercise interventions. This allowed us to perform analyses on 4 studies using resistance exercise interventions

The most frequently occurring cancer type was breast cancer, contributing 8 studies to the analysis. The second most commonly reported cancer was prostate cancer with 4 studies contributing to the analysis. Also, with 4 studies included were those that investigated CRF in heterogeneous cancer cohorts. Colorectal and acute myelogenous leukemia (AML) both contributed one study. In regards to cancer treatment, the majority of studies began exercise as an intervention for CRF following completion of treatment (k=6). Chemotherapy was the second most common concurrent treatment among studies (k=4). Radiation therapy and mixed therapies each had 3 studies contributing to the

analysis. Darbepoetin alpha and Androgen deprivation therapies accounted for 1 study each. Zero studies investigated the effects of exercise prior to adjuvant therapy.

The most common potential etiology investigated was cardiopulmonary dysfunction (k=9). Second to cardiopulmonary dysfunction, musculoskeletal function was the most common potential etiology investigated (k=4). Only 2 studies investigated the change in haemoglobin concentration. Other than cardiopulmonary dysfunction, musculoskeletal dysfunction and haemoglobin concentration, no other potential CRF etiologies were investigated in the studies included in the meta analysis. All clinical characteristics of the studies included in the meta analysis are presented in Appendix E.

Meta Analysis Results

The effect size data for the overall effects of exercise interventions on CRF, the effects of exercise on CRF based on exercise type, cancer type, cancer treatment, cancer status and results of the Chi square tests can be found in Appendix F. Effect size data related to the effects of exercise on CRF etiologies is summarized in table 3.0 and 3.1. The standard weighted mean effect size (d) presented in tables 3.0 and 3.1 represents the observed difference between the experimental and the control groups in standard deviation units (Arthur et al., 2001). According to Cohen (1992) effect sizes with scores of 0.20, 0.50 and 0.80 represent a small, medium and large effect respectively.

Table 3.0 Results of the Meta Analysis

Variable	No. of Data Points	Total Sample Size	Sample Weighted Mean *d*	S^2	SD	% of Variance due to Sampling Error	95% CI		X^2
							L	*U*	
CRF	19	2026	0.27***	0.08	0.28	48.6	0.144	0.395	39.1**
Exercise Mode									
Aerobic	15	1451	0.25***	0.06	0.24	71.00	0.128	0.37	21.10
Resistance	3	518	0.17	0.01	0.08	100.0	0.079	0.260	0.82
Mixed	1	7	1.34	0	0	.	-	-	-
Cancer Type									
Breast	9	1289	0.29*	0.09	0.29	32.35	0.101	0.478	27.8**
Heterogeneous	4	204	0.16	0.03	0.17	100.00	-0.007	0.326	1.38
Prostate	4	418	0.27	0.08	0.28	51.10	-0.004	0.544	7.82*
AML	1	22	0.57	0	0	-	-	-	-
Colorectal	1	93	0.06	0	0	-	-	-	-
Cancer Treatment									
Post Treatment	6	454	0.29	0.17	0.42	31.64	-0.045	0.625	18.9**
Chemotherapy	5	724	0.13*	0.01	0.09	100.00	0.051	0.208	1.47
Radiotherapy	3	263	0.37	0.10	0.31	46.75	0.019	0.720	6.41*
Chemo/Radio	3	375	0.51*	0.02	0.12	100.00	0.374	0.645	1.34
DPA	1	55	0.10	0.0	0.0	-	-	-	-
ADP	1	155	0.13	0.0	0.0	-	-	-	-
Cancer Status									
Patient	15	1665	0.26***	0.05	0.22	75.33	0.150	0.369	19.91
Survivor	4	361	0.30	0.22	0.47	21.16	-0.160	0.760	18.89**

Table 3.1: Results of Meta Analysis of Etiologies

Variable	No. of Data Points	Total Sample Size	Sample Weighted Mean *d*	S^2	SD	% of Variance due to Sampling Error	95% CI		X^2
							L	*U*	
CRF Etiologies									
Cardiopulmonary	12	1299	0.42***	0.26	0.17	57.24	0.323	0.516	20.9*
Musculoskeletal	6	804	0.27	0.07	0.21	66.70	0.103	0.436	8.99
Anemia	2	120	1.79	1.61	1.27	5.98	0.029	3.550	33.4**

Effects of Exercise on Cancer Related Fatigue, Exercise Type and Cancer Characteristics

Overall Effects of Exercise on CRF

The overall influence of exercise on CRF resulted in a small but significant effect size which indicated a reduction in overall CRF ($d = 0.27$, $p < 0.001$). The Chi square test was significant ($X^2_{(18)} = 39.1$, $p < 0.05$), and therefore moderator variables may be operational. Based on research hypothesis, we have decided to investigate exercise type, cancer type, treatment and stage as potential moderator variables.

Exercise Type

Exercise type may be a potential moderator causing the heterogeneity within the overall effect size distribution of exercise on CRF. Results from the breakdown of exercise type into aerobic, resistance and mixed interventions indicate that a mixed

exercise program (k = 1), composed of both resistance and aerobic exercise, had the largest effect on reducing CRF. Although the effect size from this single study is large, the effect size did not meet statistical significance (d = 1.34, $p > 0.05$). This large effect size should be carefully considered since it was the product of one sample. In contrast, aerobic exercise (k = 15) had a small but statistically significant effect size suggesting that aerobic exercise reduced CRF (d = 0.25, $p < 0.001$). Resistance training regiments (k = 3) also had a small effect size. While the effect of resistance training was in a positive direction it was not significant (d = 0.17, $p > 0.05$). In summary, aerobic exercise, resistance exercise, and mixed exercise prescriptions all seem to be able to reduce CRF. However, aerobic interventions were the only regiment that produced statistical significance. Results from aerobic, resistance and mixed regiments all reported non-significant Chi square tests ($p > 0.05$) which indicated that there may be no further moderators operating on these effect sizes.

Cancer Type

Results on the effectiveness of exercise interventions on CRF pooled by cancer type indicate that improvements in CRF may also differ depending on the type of cancer. One study on the effect of exercise on patients with AML found a large effect size, indicating that exercise for AML patients did reduce CRF (d = 0.57). However, this effect size did not reach statistical significance at $p > 0.05$. The effects of exercise in breast cancer patients reduced CRF as illustrated from a small but significant effect size (d = 0.29, $p < 0.05$). As a result of exercise interventions, patients with prostate cancer also reduced CRF, but this reduction did not reach statistical significance (d = 0.27, $p >$

0.05). Studies investigating the effects of exercise treatments on heterogeneous samples reported a small non-significant effect size ($d = 0.16$, $p > 0.05$). However, the effect size still suggests a reduction in CRF. One study on colorectal cancer produced a small effect which did not attain significance ($d = 0.06$ $p > 0.05$). Results reported for the individual studies investigating AML and colorectal cancer must be reviewed carefully since they both had a sample size of 1. Overall, exercise seems to have a small effect on reducing CRF in populations of breast, prostate, AML and colorectal cancer patients. Of the studies investigated, breast cancer was the only one to reach statistical significance.

Chi square analyses for the different cancer populations were significant for breast cancer ($X^2_{(8)} = 27.8$, $p < 0.05$) and prostate cancer ($X^2_{(3)} = 7.82$, $p < 0.05$) subgroups, suggesting potential moderators. However, due to the small sample sizes, a moderator analysis on these variables was not conducted.

Cancer Treatments

Results on the effectiveness of exercise interventions on CRF, stratified by cancer treatment types, suggest that the effectiveness of exercise may also depend on the treatment being received by the patients. The effects of exercise on patients during chemotherapy combined with radiation treatments resulted in a medium reduction in CRF and statistically significant effect size ($d = 0.51$, $p < 0.05$). Effect size data on exercise in patients receiving radiation treatments was found to produce a small reduction in CRF but did not reach statistical significance ($d = 0.37$, $p > 0.05$). The use of exercise interventions following completion of treatment was found to also result in a small reduction in CRF but a non significant effect size ($d = 0.29$, $p > 0.05$). The effects of

exercise on patients undergoing chemotherapy resulted in a small and significant effect size indicating a reduction in CRF ($d = 0.13$, $p < 0.05$). In summary, exercise was able to reduce CRF as illustrated by the small effect sizes in populations undergoing a variety of cancer treatments; however, only patients undergoing chemotherapy and radiation along with chemotherapy approached statistical significance.

Results of the Chi square test indicated significant results in post treatment ($X^2_{(5)} = 18.9$, $p < 0.05$) and radiotherapy subgroups ($X^2_{(2)} = 6.41$, $p < 0.05$). Moderators may be operating on these subgroups, but due to the low sample sizes a moderator analysis was not done.

Cancer Status

The results of exercise interventions on CRF also seemed to differ between patient and survivor populations. The effects of exercise on CRF in survivors resulted in a reduction of CRF but was found to be insignificant with a small effect size ($d = 0.30$, $p > 0.05$). In contrast, exercise interventions used to reduce CRF in patient populations resulted in a small but statistically significant effect size indicating a reduction in CRF ($d = 0.26$, $p < 0.001$). These results indicate that exercise does have a small effect in reducing CRF. However, this effect was only significant in patient populations with active malignancies.

Results from Chi square analyses found that moderators may be acting on the effectiveness of exercise in survivor populations. This was indicated by a significant Chi square test ($X^2_{(3)} = 18.98$, $p < 0.01$). However, due to small sample sizes a moderator

analysis on the effects of exercise on CRF in survivors will not be completed. The Chi square analysis on patient populations was not significant suggesting that moderators may not be in play.

CRF Etiologies

The etiologies available for investigation within the eligible studies were cardiopulmonary (k = 12), musculoskeletal (k = 6), and anemia (k = 2). The results of exercise on haemoglobin concentration resulted in increases in haemoglobin concentration as illustrated by a large effect size but were found to not reach statistical significance (d = 1.79, $p > 0.05$). Once again caution is warranted when interpreting this result since it was derived from a small sample size (k = 2). Exercise interventions were able to produce a small but significant effect size indicating an overall improvement in cardiopulmonary function in patients with CRF (d = 0.42, $p < 0.001$). In addition, musculoskeletal function resulted in small improvements but did not reach statistical significance (d = 0.27, $p < 0.05$). Overall, exercise seems to have the ability to improve cardiopulmonary and musculoskeletal function as well as haemoglobin concentration which are considered to be potential etiologies of CRF. However, of the etiologies investigated, only improvements in cardiopulmonary function reached statistical significance.

Chi square tests were significant for cardiopulmonary and anemia samples ($X^2_{(11)}$ = 20.9, $p < 0.05$: $X^2_{(1)}$ = 18.9, $p < 0.001$). However, due to small sample sizes potential moderators were not investigated. Therefore, the effect sizes should be interpreted carefully.

CHAPTER 5

DISCUSSION

Methodological Features

The extensive search strategies resulted in 260 potentially eligible studies reporting on the effect of exercise on cancer patients with fatigue as an outcome. Of the 260 potentially eligible studies, 242 studies were excluded leaving 18 studies to be analyzed. In order to attain the most studies possible, an assessment of the studies methodological quality was not conducted. However, information on methodological features was recorded in the study level coding schemes in order to allow further qualitative investigation to develop suggestion for future research.

Upon review of the methodological features, three primary limitations arose. First, a large amount of intervention trials were reported without sufficient data to calculate the effect size. As a result, a large amount of potentially eligible studies were excluded therefore reducing the statistical power of our results. For example, in order to calculate effect size values for pre and post study designs, which contributed 30 eligible studies to our analysis, correlation data representing the relationship between pre and post intervention results is needed. However, no correlation data was presented. Furthermore, to calculate the effect size statistic for group comparisons using the group means, the standard deviations associated with the means are required. An additional 10 eligible studies did not report the standard deviations along with the means and therefore were excluded from the analysis. As a requirement for publication, successful defence or

dissemination of theses all means and measure of variability as well as correlation data should be included. It has been suggested that authors may not divulge statistical findings in the case of non significant results (Cramp & Daniel, 2008). However, these results are of great importance for the quantitative synthesis of the literature. In addition, sufficiently detailed statistical information about the results is vital for the reader's interpretation, practical applications and implications for further research.

A second concern and continued limitation of CRF research involves the heterogeneity of instruments used to assess CRF. In the present study, there were 10 different assessment instruments identified to assess CRF. They included the FACT-An ($k = 3$), FACT-F ($k = 3$), POMS ($k = 3$), BFI ($k = 2$), FS ($k = 1$), PFS ($k = 1$), PFS revised ($k = 1$), LASA ($k = 1$), EORTC – QOL30 ($k = 1$) and the FACT-C ($k = 1$). The variety of instrumentation used to assess CRF found in this synthesis further supports a common critique and limitation of CRF research. This wide variety of both unidimensional and multidimensional assessment tools prevents the direct comparisons between study findings. Therefore, there is a need for the research community involved with CRF to agree on a measure to be used. Although more time consuming, the use of multidimensional assessment tools has been suggested by previously done meta analyses and reviews (Cramp & Daniel, 2008; Portenoy & Itri, 1999; Schmitz et al., 2005). The advantages of the multidimensional assessment tool over the unidimensional counterpart is that the multidimensional fatigue assessments have been designed to capture the multiple characteristics and related manifestations of fatigue as well as the impact they have on the patient's ability to function in daily life situations (Portenoy & Itri, 1999). For example, an exercise intervention may produce noteworthy changes to symptoms

clustered with CRF within the psychological and emotional parameters. A multidimensional tool will be able to assess these changes whereas a unidimensional assessment would not capture this valuable information.

The third comment on the present literature is in regards to methodological weaknesses. In the study level coding scheme we were interested in reporting on the use of CRF inclusion criteria. Of the studies included no study assessed for the presence of CRF as inclusion criteria. By evaluating and screening patients prior to applying treatment protocols researchers can distinguish those who truly have CRF from those who are experiencing fatigue common to the general population. Without adequate screening for CRF prior to inclusion for interventions it is possible that some participants were experiencing little or no fatigue at the time of inclusion. This would result in a limitation of the study to detect true intervention effects on CRF (Jacobsen et al., 2007). In attempts to remedy this complication common in the literature the NCCN has designed CRF inclusion criteria. The NCCN uses a single item, 11 point, numerical rating scale describing the fatigue being experienced. NCCN guidelines recommend that patients with a score of 0 – 3 should be considered to have none to mild fatigue, those with scores 4 – 6 or 7 – 10 should be considered to have moderate to severe fatigue respectively (Stone & Minton, 2008). The assessment of CRF prior to inclusion for intervention would allow the results to describe, more accurately, the changes caused by the interventions.

In addition to the lack of CRF inclusion criteria, more commonly reported weaknesses were also observed. First, a large amount of research on the effects of

exercise on CRF is reported in the form of weaker, less reliable pre – post study designs. However, this trend seems to be changing. It was noted that in comparison to the 1990`s, more studies in the 2000`s have been using group contrast designs and Random Control Trials. This is a finding shared by a recently completed meta analysis by Cramp and Daniel (2008). Second, as commonly observed by previously done meta analyses and systematic reviews, the finding that the literature is still limited by inconsistent exercise prescriptions, diverse populations of cancer patients, and heterogeneous cancer treatment stages is also shared by our results. This heterogeneity within these methodological features makes the application of the findings for practice difficult. However, the aim of the present meta analysis is to help understand the effects of exercise on CRF as a result of different exercise interventions, cancer types and treatment characteristics.

Effect of Exercise on Cancer Related Fatigue

This review found that overall; exercise is able to significantly reduce CRF. The findings suggest that exercise interventions were able to produce small but significant reductions in CRF compared to controls ($d = 0.27$, $p < 0.001$). This finding is similar to the findings in the meta analysis done by Cramp and Daniel (2008).

The effects of exercise seen here on CRF may be explained by a variety of hypothesis. CRF has been hypothesized to originate from multiple etiologies including alterations to serotonin production and cortisol responses, increased vagal afferents and cytokine production, reduced quality of sleep and cardiopulmonary function as well as reduced haemoglobin concentration and musculoskeletal function (Al-Majid & McCarthy, 2001; Dicato, 2003; Jager et al., 2008; Ryan et al., 2007; Wang, 2008).

Exercise interventions have been found to mitigate these potential etiologies in patients with CRF and other conditions presenting with similar symptoms and etiologies. First, exercise training has been used to lower serotonin concentration and delay the production of serotonin in all brain regions leading to increased time to physical exhaustion (Langford et al., 2006). Second, exercise has been found to promote the proper response of cortisol following psychological and physical stress stimuli (Kim et al., 2008). Third, exercise has been found to improve the neural profile of patients with dysfunctional sympathetic and parasympathetic regulation (Levy et al., 2008). Fourth, increased exercise has been found to improve the regulation of cytokines and improve the overall immune system function in cancer patients (Fairey et al., 2002; Fairey et al., 2004). Fifth, exercise has been shown to improve quality of sleep in cancer patients (Payne et al; 2008). Sixth, exercise has been found to improve anemic status of cancer patients undergoing adjuvant therapies. For example, Dimeo et al. (1997) used an exercise intervention to mitigate CRF and improve physical functioning and found that the intervention increased haemoglobin concentrations by 3.2g/dL. Seventh, cardiopulmonary conditioning has been found to be dramatically improved in patients with cancer following involvement in exercise treatments. For example, Quist et al. (2006) used an aerobic exercise intervention for oncology patients and found a 14.5% increase in aerobic fitness. In addition, Schneider et al. (2007) found that an aerobic exercise intervention can improve FVC by 2.8% and FEV1 by 4.0%. Finally, exercise intervention programs have been found to maintain or improve musculoskeletal strength and lean muscle tissue in patients with cancer and CRF (Courneya et al., 2007; Milne et al., 2007; Segal et al., 2009). The results indicating that exercise is effective in reducing

CRF may be explained by the many positive effects exercise has on the potential etiologies of CRF.

Although the results of our analysis on the overall effects of exercise on CRF suggest that exercise is an effective treatment strategy to reduce CRF, the Chi square analysis indicated that the sampling distribution of coded effect sizes used to produce the sample weighted mean effect size statistic for the overall mean effect of exercise on CRF deviates significantly from chance ($X^2 = 39.1$, $p < 0.05$). This limitation suggests that the effect size found may not be an accurate representation of the population and therefore, careful interpretation is required and further attention should be directed at the confidence intervals for interpretation. The heterogeneity may be partially explained due to the relatively small number of studies making up the mean effect size ($n = 19$). In addition, the heterogeneity within this effect size may be attributed to the heterogeneity observed between study level variables such as heterogeneous exercise prescriptions, cancer types, treatment types, and cancer status. The following sections will elaborate on the effects of exercise on CRF in regards to these potential moderator variables.

Effects of Various Exercise Interventions on Cancer Related Fatigue

Aerobic Exercise

Exercise types of interest from meta analysis were aerobic, resistance, and mixed training regiments. Aerobic exercise interventions contributed 15 studies to the meta analysis and reported a small but significant effect size ($d = 0.25$, $p < 0.001$). This result suggests that aerobic exercise is significantly effective in making small reductions in

CRF compared to controls. However, due to the variation in study populations, designs, timing of intervention, and relatively small number of studies, it was not possible to identify differences in effectiveness between various programs. However, results of our study level coding revealed that on average, participants exercised 3 – 4 times per week. Most programs used a moderate to high aerobic intensity with training heart rate zones at 50 – 80% of maximal heart rate, 50 – 80% of VO2 max, 50 – 80% of heart rate reserve and 60 – 100% of maximal exercise capacity. The most common volume of aerobic exercise per session, excluding the common 5 minute warm up and cool down, were between 10 – 35 minutes a day (k = 8) and 35 – 60 minutes a day (k = 6). Aerobic training programs on average were carried on for 11 weeks. The majority of aerobic programs took place under supervised conditions (k = 11).

Unfortunately, the data used to analyze the effects of aerobic exercise on CRF did not report on the changes to many potential biological etiologies to justify the mechanisms of their results. Therefore, it is difficult to state why aerobic exercise is an effective technique to manage CRF. However, assessments of comorbidities and symptoms such as depression, anxiety, body image concerns, mood and vigour were commonly presented via the results of the multidimensional assessment instruments used to assess fatigue. For example, it was often found that CRF was highly related to symptoms of depression, sleep quality and pain (Fleishman 2004; Segal et a., 2008). This set of interrelated symptoms has been defined as a symptom cluster (Fleishman, 2004). In CRF, reductions in symptoms such as depression, pain and improved sleep quality have been found to promote reductions in CRF and vice versa. Within the studies that composed our overall standard weighted mean effect of aerobic exercise on CRF, 5

studies reported on depression as a primary or secondary end point. Within these studies their results all favoured the reduction of depressive symptoms as well as reduction in fatigue. One possible mechanism responsible for the reduction of CRF witnessed in patients undergoing aerobic exercise interventions is the effects of aerobic exercise on symptoms clustered with CRF such as depression. This is because with treatment for one of these symptoms such as CRF or depression an overlapping may occur which may have beneficial effects on reducing the other related symptoms (Fleishman, 2004).

In addition to treating symptom clusters such as depression, pain and sleep quality, improvements in cardiopulmonary fitness and physical function have also been highly correlated to reductions in overall fatigue. For example, it has been documented that the degree of physical disability following adjuvant therapy and surgical methods is strongly related to CRF (Rubin et al., 2004). Aerobic exercise training in patients with cancer and CRF have been found to improve cardiopulmonary function and therefore may be a potential mechanism involved in the difference of CRF between exercise groups and controls. For example, Dimeo et al. (2004) used a high intensity aerobic exercise intervention in a heterogeneous sample of cancer patients and found that the intervention produced a significant increase in cardiopulmonary function (Dimeo et al., 2004). In addition, Dimeo and college also observed a reduction in CRF. This result indicates that improvements to cardiopulmonary function may be in part responsible for reducing CRF. Improvements in overall cardiopulmonary fitness may exert beneficial effects on CRF because an improved cardiopulmonary system provides a greater capacity for physical functioning. For example, Dimeo et al. (1998) measured the effect of an aerobic exercise intervention on classic physiological variables related to functional capacity (heart rate

and lactate concentration at submaximal intensities). There results reported that the aerobic intervention was effective in reducing submaximal heart rate and lactate concentration. This was concluded to reflect an improved functional status and increased metabolic efficiency. CRF has been found to increase with decreased physical capacity. Therefore, these findings suggest that a potential reason why our meta analysis indicated that aerobic exercise is effective in managing CRF is because this intervention style is able to increase or preserve physical functioning.

Similar to the overlapping beneficial effects of treating one symptom involved in a symptom cluster, improvements in aerobic function and increased physical functioning can have a similar overlapping effect on many potential biological etiologies related to CRF. Of the studies included for the meta analysis of aerobic exercise interventions on CRF, the only potential biological mechanism investigated following aerobic training was haemoglobin ($k = 2$). It is has been found that adjuvant therapies such as chemotherapy and radiotherapy can disrupt the production and maturation of red blood cells and reduce haemoglobin concentration and cause anemia (Windsor et al., 2004). For example, Nieboer et al. (2005) demonstrated that high dose chemotherapy induced a reduction in haemoglobin content which was related to reduced QOL and increased fatigue. The effects of aerobic activity in the studies included in the meta analysis of aerobic interventions for CRF all reported significant improvements on haemoglobin concentration along with improvements in CRF and overall QOL (Courneya et al., 2007; Windsor et al., 2004). In addition to improve haemoglobin concentration, other potential biological mechanisms have been suggested to be alleviated with aerobic exercise.

First, aerobic exercise has been found to reduce the rate of serotonin production and improve 5 – HT 1a receptor sensitivity which decreases the time to fatigue during physical exertion (Dwyer & Browning, 2000). The effect of aerobic exercise on serotonin production and receptor sensitivity would allow oncology patients to carry out more activities of daily living without a premature onset central fatigue due to increased serotonin production and increase receptor sensitivity. Patients with CRF, in addition to having increased serotonin production also have been found to be characterized with increased vagal afferent outflow. Li, Wu and Owyang (2004) found that one way that vagal afferent outflow may be augmented is through vagal interactions with serotonin. Therefore, the increased serotonin may also increase fatigue and sickness behaviours through the activation of vagal afferents.

Aerobic exercise, in addition to its effects on serotonin, has been found to improve the regulation of vagal and sympathetic afferents. For example, aerobic exercise was found to improve the overall ratio of parasympathetic and sympathetic tone as indicated by low frequency (LF) and high frequency (HF) spectral components of heart rate variability (HRV) in standing positions (Zoppini et al., 2006). These results indicate that increased aerobic exercise can produce the appropriate withdrawal of vagal tone and allow the appropriate sympathetic response in situations of increased work. Therefore, is may be possible that aerobic exercise can in part reduce CRF by causing a reduction vagal afferents which would result in increased physical performance and reduced sickness behaviours.

The vagal nerve has been found to have anti-inflammatory properties. An increase in vagal tone may be caused by an increased immune response in efforts to reduce inflammation. In a study by Bower et al. (2001) the vagal outflow was found to be correlated with cytokines such as TNF – a and IL-6 as well as C – reactive protein (CRP). An increase in TNF-a and other cytokines such as IL-1, IL-6, and CRP are predictors of cardiac mortality and dysfunction and also have been found to be increased in patients with CRF (Bower et al., 2001; Fairey et al., 2005; Nian et al., 2004). Aerobic exercise has been documented to reduce the level of cytokines as well as reduce their enduring expression. For example, in a study by Fairey et al., (2005), the research team investigated the effects of exercise on CRP in postmenopausal breast cancer survivors. They found that a 15 weeks exercise intervention with three session a week using 70 – 75% of individual peak oxygen consumption decreased CRP by 1.39 mg/L in comparison to the controlled group where CRP increased by .10mg/L. This increase provided a twofold benefit for patients. One, it reduces the risk of cardiovascular disease and two, it reduces the overall inflammation which in turn reduces sickness behaviour and potentially fatigue.

The effects of aerobic exercise have been found to reduce the risk of many potential etiologies related to CRF such as improved serotonin production and utilization, enhanced neural profiles, and improved immune system function. In addition, aerobic exercise has been found to increase functional capacity in oncology patients. Also, aerobic exercise has been found to reduce symptoms clustered with CRF such as depression and therefore, reductions in depression and even pain and or sleep quality could also mitigate CRF. Although our meta analysis cannot account for changes and

adaptations to the potential biological mechanisms and symptom clusters associated with CRF and the effect of aerobic exercise on these parameters, we found that aerobic exercise can significantly reduce CRF. Further research into the potential underlying mechanisms causing this effect is much needed to improve the efficiency of aerobic exercise prescriptions.

Resistance Training

To our knowledge this is the first meta analysis to investigate the effect of resistance training on CRF. Resistance training regiments ($k = 3$) produced a small effect size which indicates that resistance training resulted in a small decrease in CRF compared to controls. However, this effect size failed to attain statistical significance ($d = 0.17$, $p > 0.05$). Due to the variation in study populations, designs, timing of intervention, and small number of studies, it was not possible to identify differences in effectiveness between various programs. However, results of our study level coding revealed that on average, participants exercised 3 times per week. All weight training interventions use resistance between 60 – 70% of their 1 repetition max (1RM). Repetitions of 8 – 12 and sets of 2 were used in all three studies. Increases in weight either by 5 lbs or 10% 1RM were considered when 12 reps and 2 sets were able to be completed comfortably. Two studies investigated the effects of weight training for 24 weeks, where one study investigated the effects of weight training over 12 weeks. All programs were supervised by exercise physiologists due to the potential risks related to resistance training.

CRF has been found to be a cause of or related to overall reductions in QOL, reduced self esteem, negatively altered body composition and impeded physical

functioning induced by poor musculoskeletal strength and poor neuromuscular functioning (Courneya et al., 2007; Lucia et al., 2003; Segal et al., 2008; Stone & Minton, 2008; Ryan et al., 2007; Wang, 2008). Resistance training in oncology patients has been found to significantly improve self esteem, QOL as well as depression (Courneya et al., 2007). Considering the potential of symptom clusters related to CRF, especially depression, improvements to self esteem and QOL due to resistance training interventions may partially explain the small reduction in CRF observed in our results.

As described previously the severity of CRF may be predicted by reductions in physical functioning. Cancer and cancer treatments have been found to alter body composition and promote the loss of lean muscle tissue and reduce muscle strength and thus, mitigate physical capacity (Al-Majid & McCarth, 2001; Galvao et al., 2006; Lucia et al., 2003; Schmitz et al., 2005). Potential ways in which the observed effect of resistance training on CRF may be explained are by first, the ability of resistance training to improve body composition. For example, Schmitz et al. (2005) found that a resistance training program was able to significantly increase lean muscle mass by .88kg as well as significantly decrease body fat percentage by 1.15% in breast cancer survivors (Schmitz et al., 2005). Second, resistance training has been documented to increase muscular strength and endurance. For example, Galvao et al. (2006) found that a resistance training program designed for patients with prostate cancer significantly increased chest press by 40.5% and leg press by 96.3%. In addition muscular endurance was also improved as measured by a 114.9% improvement in chest press and 167.1% improvement in the leg press (Galvao et al., 2006). Third, physical functioning has also been found to be increased in oncology populations undergoing resistance training

programs. In the same study produced by Galvao et al. (2006), this team observed significant improvements in the 6 meter walk, a 6 meter backwards walk, chair rises, stair climbing, 400 meter walk, and balance (Galvao et al., 2006). These results are also supported by work done by Courneya and colleagues in 2007.

The studies included in the meta analysis of resistance training interventions for CRF did not provide data on changes to potential etiologies. However, possible reasons why resistance training was able to elicit a small reduction in CRF may be due to its ability to reduce the effect of cancer cachexia. One mechanism that contributes to CRF is the progressive wasting of skeletal muscle which occurs as part of cancer cachexia (Al-Majid & McCarthy, 2001). Cancer cachexia is associated with a dysfunctional protein metabolism which leads to the wasting of muscle tissue. Resistance exercise has been found to improve the rate of protein synthesis in muscle tissue and therefore may reduce the net loss of tissue protein due to cancer cachexia (Jurimae et al., 1996).

The effects of resistance exercise training did not reach significance in the present meta analysis. However, this may be due to the lack of studies contributing to standard weighted mean effect size. Although, this effect size did not reach statistical significance the results indicate that resistance training can produce a small reduction in CRF compared to controls. This may be due to the effect of resistance training on improving self esteem, promoting healthier body composition, increasing muscle strength and endurance as well as increasing or maintaining physical function. Improvements to muscular strength may be due to improved neuromuscular function and or an increased rate of protein synthesis reducing the loss of lean tissue due to cancer cachexia. Further

research is needed to study the effects of resistance training on oncology patients with CRF. This exercise type seems to be a promising intervention strategy but further investigation into the effects on potential etiologies of CRF is needed to provide the most effective intervention strategy.

Mixed Exercise Interventions

The standardized weighted mean effect size indicative of mixed interventions suggests that a mixed exercise program ($k = 1$), composed of both resistance and aerobic exercise, has the greatest effect on reducing CRF. Although the effect size is large, the effect size did not meet statistical significance ($d = 1.34$, $p > 0.05$), most likely due to the limited statistical power resulting from a sample size of one. Therefore, this large effect size should be carefully interpreted. Study level features of this lone study investigating the effect of a mixed exercise intervention on CRF include an aerobic and resistance frequency of a 3 exercise session per week, an aerobic intensity of 75% of heart rate max and a resistance training intensity described as light weight. The aerobic exercises were performed for 20 minutes. Resistance exercises began at 10 repetitions and graduated to 15 repetitions as the weights used became comfortably lifted. These repetitions were performed in sets of 2. The exercise intervention lasted for 12 weeks in a supervised setting.

A possible explanation of such a large effect size may be attributed to the accumulation of effects of mixing both aerobic and mixed interventions strategies. Independently, aerobic exercise has been found to improve CRF through its ability to reduce depression, improve sleep quality, enhance aerobic fitness, increase and or

maintain physical capacity, regulate serotonin, improve neural profiles, and improve immune system function resulting in a less abundant production and enduring production of pro inflammatory cytokines (Bower et al., 2001; Courneya et al., 2007; Dimeo et al., 2004; Dwyer & Browning, 2000; Fairey et al., 2005; Nian et al., 2004; Zoppini et al., 2006). In addition, resistance training has been found to decrease CRF through its effects on improving body composition and self esteem, increase muscular strength and physical capacity, as well as, reduce the effects of cancer cachexia (Galvao et al., 2006; Jurimae et al., 1996; Lucia et al., 2003; Schmitz et al., 2005;). It is possible that due to the mixed intervention incorporating both resistance and resistance training styles the beneficial effects of each of these regiments were impressed upon the breast cancer survivors. This would explain a large effect size indicating a large reduction in CRF. However, it may also be possible that the improvements in various variables may act synergistically with each other. For example, improvements in physical functioning are highly related to reductions in CRF. Improved aerobic conditioning attributed to reduced submaximal heart rate, improved pulmonary efficiency, and reduced lactic acid production at sub maximal levels would allow the patient to perform activities of daily living with less physical stress and less fatigue. In addition, resistance training may enhance this effect by providing the patients with increased muscular strength. In combination, both improved aerobic capacity and musculoskeletal strength would result in potentially greater increases in overall physical performance and capacity, which in turn would cause greater reductions in CRF.

In addition to an overall greater physical capacity, a mixed program may provide effects to the immune system that may not be as substantial if the exercise types were not

mixed. Aerobic exercise has been found to reduce the production of cytokines and improve the efficiency of the immune system (Fairey et al., 2005; Malaguarnera et al., 2008). In addition, resistance training has been found to increase the protein synthesis thus resulting in gains in muscle mass and strength (Galvao et al., 2006; Jurimae et al., 1996). Taken together, it is possible that with the reduction of cytokines, which are hypothesized to participate in protein degradation associated with cancer cachexia, and that with the increased protein synthesis as a result of resistance training that greater improvements in body composition, increased lean muscle tissue as well as improved muscular strength and endurance could result. As described previously these improvements are found to be related to reduction in CRF (Courneya et al., 2007; Segal et al., 2008).

A mixed aerobic and resistance training program provides an opportunity to induce changes both individually and synergistically to a wide variety of symptoms and etiologies related to CRF. Therefore, further research into this treatment method should be done to identify the safety and efficacy of a mixed exercise program in a variety of oncology populations undergoing treatment and following treatment.

Comparisons of Exercise Types

Mixed interventions produced greater mean effect sizes compared to aerobic and resistance training interventions. These results suggest that using a mixed exercise intervention may produce greater reduction in CRF compared to aerobic or resistance training programs alone. This may be due to the ability of a mixed intervention to elicit a more comprehensive reduction of symptoms and etiologies related to CRF than just

aerobic or resistance training. However, this result needs to be interpreted carefully since the mixed training mean effect size is composed of a single study. There is a need for more studies to compare the effects of different exercise interventions. Results of these studies would provide the clinician and interprofessional health care teams with valuable information needed to determine the most effective exercise intervention to reduce CRF.

Effects of Exercise on Reducing CRF based on Cancer Characteristics

Rates of CRF differ between cancer populations and as a consequence of different treatment types (Hofman et al., 2007). Therefore, to better understand the effects of exercise on various cancer populations we investigated the standardized weighted mean effect size for studies reporting on CRF in breast cancer (k = 9), prostate cancer (k = 4), AML (k = 1), colorectal (k = 1) and heterogeneous samples (k = 4). We also produced the standard weighted mean effect size for studies reporting on CRF in groups being treated with chemotherapy (k = 5), radiotherapy (k = 3), mixed regiments (k = 3), androgen deprivation therapy (k = 1) and darbepoetin alfa (k = 1) to investigate the effect of exercise on CRF in populations undergoing various treatments. In the following sections we will discuss our results of exercise interventions on different cancer types. We will first discuss the role of exercise on potential etiological mechanisms of CRF related to different cancer types. Second, we will discuss the effects of exercise on the identified cancer type due to the effects of exercise on common treatments used for this oncology population. Where possible we will incorporate and discuss our findings of the effects of exercise on various cancer treatments to help explain our results of exercise on different cancer types.

Effect of Exercise on Acute Myeloid Leukemia

The largest effect size found was produced from a study investigating the effects of a walking intervention on CRF in patients with AML undergoing chemotherapy. Although this effect size suggests that exercise can cause a moderate reduction in CRF ($d = 0.57$, $p > 0.05$), the effect size did not meet statistical significance and it was a result of one study. Therefore careful interpretation of this result is needed. However, AML is a major haematological malignancy in which patients are at high risk of CRF and should be discussed in further detail (Chang et al., 2007; Hofman et al., 2007). A potential way in which the pathology of haematological malignancies such as AML can cause CRF is through its effects on haemoglobin. Anemia can occur in cancer patients, such as those with AML, as a direct result of the cancer or as a result of cancer treatments such as chemotherapy. In regards to direct effects of the malignancy itself, metastases within the bone marrow can destroy and displace stem cells needed to ensure adequate haematopoietic cell production as well as destroy and displace progenitor cells. This consequently inhibits the production of hematopoietic growth factors which are essential for regulating the proliferation, differentiation and survival of haematopoietic cells (Mercadante et al., 2000). The resulting reduction in oxygen transport and tissue hypoxia has been linked to reduced cardiovascular function and overall reductions in functional capacity and QOL (Chang et al., 2008; Dimeo et al., 2003).

The large effect size observed from this study may be explained by the effect of exercise on haemoglobin production. One way in which exercise may enhance haemoglobin concentrations in AML cancer patients could be by stimulating

erythropoiesis (Lucia et al., 2003). For example, Dimeo et al. (1997) showed that an endurance exercise program following chemotherapy is able to increase haemoglobin concentration from 10.1 g/dL at base line to 13.1 g/dL ($p < 0.05$). As a result, patients undergoing the exercise intervention experienced reduced fatigue and improved ability to carry out activities of daily living (Dimeo et al., 1997).

Effects of exercise on Chemotherapy patients: a further look at AML

In addition to an increased risk of anemia in AML patients due to the malignancy itself, this problem may be further exacerbated by the intensive course of chemotherapy used in populations with haematological malignancies. Chemotherapy has been found to cause fatigue in 75 – 90% of cancer populations (Hofman et al., 2007). One way in which chemotherapy may increase CRF in cancer patients, especially AML patients, is due to the impact on chemotherapy drugs on the production of haemoglobin. For example, Nieboer et al. (2005) demonstrated that high dose chemotherapy induced a reduction in haemoglobin content. Also, in the same study a relationship was found between a higher haemoglobin concentration and a reduction in fatigue (Nieboer et al., 2005). The exact mechanisms causing anemia in patients undergoing chemotherapy is not fully understood. However, it is hypothesized that chemotherapy can damage bone marrow and produce renal toxicity which may inhibit the function of erythropoietin, the hormone that stimulates maturation of red blood cells. In addition, a state of anemia present at the time of chemotherapy, which is often the case in AML patients, exacerbates the fatigue even further following therapy (Wang, 2008).

Another potential cause for a high effect size in the study of CRF in AML patients undergoing chemotherapy following an exercise intervention could be explained by the effect of exercise which causes a small but significant reduction in CRF in patients that are undergoing chemotherapy as indicated by our results on the effectiveness of exercise interventions on patients undergoing chemotherapy ($d = 0.13$, $p < 0.05$). In addition to chemotherapy increasing the risk of anemia, chemotherapy can induce toxicity to pulmonary and cardiovascular organs as well as produce neurotoxicity, Cardiotoxicity in conjunction with pulmonary toxicity results in a reduction of oxygenated blood to working muscles due to reduced cardiac output and altered ventilation perfusion ratios (Lucia et al., 2003). This results in a decreased ability to perform physical work which is highly associated with CRF. In addition, chemotherapy drugs may cross blood brain barriers and induce neurotoxicity which may cause fatigue (Wang, 2008). Chemotherapy can also increase in apoptotic and damaged cells results in increased cytokines and inflammation (Wright et al., 2005).

As described in detail in previous sections related to the effects of aerobic exercise on CRF, exercise has been demonstrated to provide cardio protective effects by reducing inflammation, and improving neural tone (Fairey et al., 2005; Hartvig et al., 2006; Malaguarnera et al., 2008; Zoppini et al., 2006). This in return may preserve cardiovascular function and protect patients undergoing chemotherapy from cardiotoxic effects of chemotherapy drugs and therefore reduce CRF. In addition, exercise may improve CRF in patients undergoing chemotherapy by increasing the production of haemoglobin which in turn would improve cardiovascular function, physical capacity and fatigue (Dimeo et al., 1997; Lucia et al., 2003).

Cancer populations with haematological malignancies may experience greater risk of CRF due to the malignancies effect on haemoglobin function and production, as well as invasive chemotherapy treatments. However, as our effect size results suggest exercise can cause a moderate reduction in CRF in AML patients which may be explained by the ability of exercise to cause a small but significant reduction in CRF in patients undergoing chemotherapy. Careful interpretation is required when considering the accuracy of the effect of exercise on CRF in AML patients due the statistic being produced from one study. However, it is therefore suggested that increased research be done on the effects of exercise on CRF in patients with AML and other haematological malignancies.

Effects of Exercise on Breast Cancer

Breast cancer studies provided 9 eligible studies to be analyzed. The standard weighted effect size for the effect of exercise on CRF in breast cancer populations was small but significant (d = 0.29, $p < 0.05$). This suggests that exercise has a significant effect in providing small reductions CRF in breast cancer patients compared to controls. However, this effect size may not provide an accurate estimate of the population mean effect since significant heterogeneity was present. This may be due to heterogeneous exercise prescriptions, patients and survivor samples, and treatment characteristics. Due to the small sample size, further analysis into moderators was not conducted.

The pathogenesis of breast cancer may cause CRF by increasing inflammation and cytokine production, increasing stress, causing weight gain, producing body image concerns, reducing functional capacity, diminishing shoulder mobility as well as reduce

sleep quality (Berger et al., 2007; Courneya et al., 2003; Fairey et al., 2005). An additional potential etiology of CRF highlighted in breast cancer populations that has not been described in this review is the dysfunction of circadian rhythms and reduced sleep quality (Berger et al., 2007). It has been documented that breast cancer patients prior to adjuvant therapy have high levels of fatigue related to sleep maintenance problems and low day time activity (Berger et al., 2007). Potential causes of circadian rhythm dysfunction in breast cancer patients may be due to an irregular expression of serotonin, altered rhythmic excretion of cytokines and altered production of the stress hormone cortisol due to a disabled HPA – axis (Bower et al., 2005; Rich et al., 2005; Ryan et al., 2007).

Exercise may have been able to elicit a small but significant reduction in breast cancer populations compared to controls due to its ability to improve the etiologies excepted to result in altered circadian rhythms. As detailed previously, exercise has been found to improve the response of cytokines and host defence mechanisms as well as regulate the production and uptake of serotonin which have been found to be dysfunctional in breast cancer patients (Greiwe, et al., 2001; Ryan et al., 2007). In addition, exercise may improve the response of cortisol production through enhancing the function of the HPA – axis. For example Kim and colleagues (2008) found that exercise may aid in the recovery of hypoactive HPA axis function which may contribute to altered rhythmic production of cortisol (Kim et al., 2008; Ryan et al., 2007). This is only one way in which exercise may regulate processes that act in part on circadian cycles. One end result of altered circadian rhythms is poor quality of sleep and reduced daily activity. Although the exact mechanisms responsible for the ability of exercise to regulate

circadian rhythms are not fully understood, exercise has been found to improve quality of sleep and improve ability to perform daily activity which is an indicator of improved circadian rhythm (Payne et al., 2008).

Effects of Exercise on Mixed Treatments and Radiotherapy

Breast cancer patients undergo a variety of adjuvant therapies which have been found to induce CRF (Courneya et al., 2002). The combined burden of mixed treatment regiments provide a greater risk of CRF in cancer populations possibly due to the effects of one treatment enduring into secondary adjuvant treatments. In a study done my Milne et al. (2008) the sample of breast cancer survivors examined were completed treatments; however, the majority of the sample underwent mixed therapies and reported very high baseline values of CRF and reduced QOL. One way in which exercise therapies may contribute to the small significant effect size observed in reducing CRF in breast cancer patients is through the effects of exercise on reducing CRF in patients currently or previously completed mixed adjuvant therapy regiments. All of the three studies that produced the standardized weighted mean effect size for the effects of exercise on CRF during or after mixed therapy regiments were on breast cancer patients and survivors. It was found that exercise is able to cause moderate but significant reductions in breast cancer patients that underwent mixed therapies ($d = 0.51$, $p < 0.05$).

Effects of exercise on radiotherapy related CRF

As described previously, exercise has been found to reduce CRF in patients undergoing chemotherapy. In addition, exercise has been found to also reduce CRF in patients undergoing radiotherapy as illustrated by our results (d = 0.37, $p > 0.05$). Although this effect size indicates a moderate effect compared to controls, it was not significant. This may be due to the small number of studies contributing to the effect size. Also, the significance of this effect size should be interpreted carefully due the heterogeneity present with the effect size distribution as declared by the rejected Chi square test. To understand why exercise was able to reduce CRF in breast cancer patients undergoing both types of adjuvant therapies we will first provide potential causes to the moderate reduction in CRF due to exercise during radiotherapy.

The mechanisms that cause radiotherapy to induced CRF are not well understood; however, potential physiological changes and physical symptoms associated with radiotherapy include myelosupression, diarrhea, malnutrition, dehydration, electrolyte disorders, dyspnea, nausea/vomiting, hormonal and immune insufficiencies, changes in weight, as well as a decline in neuromuscular efficiency leading to reduced strength and functional capacity (Jereczek-Fossa et al., 2002). These radiotherapy complications have been correlated with fatigue and fatigue severity and may provide avenues in which exercise may provide effective intervention (Servaes et al., 2002a; Servaes, Verhagen, & Bleijenberg, 2002b).

Exercise may be able to reduce or improve a variety of potential physiological conditions associated with radiotherapy. In addition to improving physical capacity,

improving muscular strength and neuromuscular function; exercise may reduce myelosupression by increasing red blood cells, white blood cells and total blood volume (Dimeo et al., 2004; Malaguarnera et al., 2008; Windsor et al, 2004). Second, exercise has been found to improve the strength of the immune system and reduce the chances of infections (Malaguarnera et al., 2008; Pedersen & Hoffman-Goetz, 2000). Third, in a report by Brown et al. (2003) on cancer patients and nutrition, they state that exercise has been documented to improve appetite and reduce the effects of malnutrition (Brown et al., 2003). Through these adaptations and biological effects of exercise on patients undergoing radiotherapy, CRF in patients and survivors treated with radiotherapy may be reduced. However, more investigation is needed to understand the biological mechanisms causing CRF following radiotherapy.

Effect of exercise on CRF during mixed adjuvant therapies

Taken together, mixed treatments of radiotherapy, chemotherapy, hormonal therapy and biological response treatments can cause detrimental effects to many physiological systems related to the risk of CRF. In addition, mixed treatments may exacerbate pre-existing comorbidities such as anemia, anorexia, mood disturbances, functional disabilities and pain resulting from previous adjuvant therapies increasing the severity of CRF. The effects of exercise on patients during mixed therapy regiments resulted in a medium reduction in CRF and statistically significance effect size ($d = 0.51$, $p < 0.05$). Potential reasons for this beneficial effect of exercise is its ability to improve physical functioning following adjuvant therapy, as well as protect or improve a variety biological adaptations occurring in response to radiation and or cytotoxic drugs.

Effects of Exercise on Prostate Cancer

Included in the meta analysis are 4 studies investigating the effects of exercise on prostate cancer. Cumulatively, the standard weighted mean effect size of 0.27 indicates that exercise for prostate cancer patients can result in small reductions in CRF compared to controls. This effect size did not reach statistical significance and heterogeneity within the effect size distribution is present. Therefore, the result should be interpreted carefully.

Patients with prostate cancer may experience CRF due to the tumour itself; however, a dramatic increase in fatigue is experienced in this population during and following adjuvant therapies compared to pre-adjuvant therapy levels. Two common adjuvant therapies known to induce CRF in prostate cancer patients include Andgrogen deprivation therapy, and radiotherapy. As a result of androgen deprivation therapy in the form of gonadotropin-releasing hormone agonist commonly reported symptoms include; reduced lean muscle and bone mass, increased fat mass, reduced strength, increased risk of fractures, unfavourable lipid profiles as well as depression which has been found to compromise physical functioning, psychological functioning and increased fatigue (Galvao et al., 2006). This form of therapy for patients with prostate cancer has been found to reduce testosterone which is associated with these adverse side effects. In addition, a common treatment for prostate cancer is radiotherapy (Galvao et al., 2006). As mentioned previously, radiotherapy may cause CRF by increasing psychological stress, depression, anemia, pain, sleep disturbances, poor nutrition and reduced functional capacity (Monga et al., 2007; Windsor et al., 2003).

Potential reasons why we observed a small overall reduction of CRF compared to controls due to exercise interventions may be due to the beneficial effects of exercise on radiotherapy related symptoms described previously. Furthermore, small reductions in CRF may arise due to the effect of exercise on improving physical function without promoting testosterone production. For example, Segal et al. (2003) reported that a resistance training program increased total upper body strength and lower body strength without raising serum testosterone levels. Also, fatigue interference on activities of daily living was reduced (Segal et al., 2003). Reduced fatigue and interference with daily living may be explained by improved muscular fitness increasing the ability to perform daily tasks with less effort and fatigue (Monga et al., 2007). Other studies testing the effects of aerobic programs on prostate cancer have concluded that aerobic exercise has been found to increase aerobic fitness, improve body composition, increase self esteem, improve mood and as a result reduce CRF (Windsor et al., 2003).

Prostate cancer is the leading type of cancer in men in North America (Segal et al., 2009). Therefore, more studies should be conducted to investigate the effects of exercise on CRF and other side effects of adjuvant therapies. Considering the potentially potent effects of a mixed exercise regiment in improving aerobic and muscle function and the likely causes of CRF in prostate cancer patients originating from reduced aerobic and musculoskeletal function, more studies should investigate the effects of mixed programs in this cancer population.

Effects of Exercise on Colorectal Cancer

Colorectal cancer is the third most common cancer in the US for both men and women (Courneya et al., 2003). However, only one study was eligible for inclusion in our meta analysis. The effect size of exercise on CRF was found to be very small (d = 0.006, $p > 0.05$). Since this effect size only represents one study, careful interpretation is needed when inferring from these results. In addition, the authors of the study suggested that the poor result of exercise on CRF and other QOL symptoms may be associated with contamination of the control group (Courneya et al., 2003). Although, this study failed to produce sizable effects of exercise on CRF compared to controls in colorectal cancer patients, a study done by Peddle et al. (2009) found that significant improvements in CRF could be attained by meeting public health guidelines for exercise.

In comparison to breast cancer, colorectal cancer patients tend to be older, include similar amounts of men and women and usually present with more advanced disease as well as undergo different surgical and medical therapies (Courneya et al., 2003). Therefore, treatment of colorectal cancer with exercise must adjust to potential confounders that may arise due to these differences. For example, lower intensity exercise prescriptions may be more beneficial and safe due to the advanced age and disease state commonly presented in this cancer population (Courneya et al., 2003). This suggestion is supported by the beneficial effects of regular light exercise as recommended by general public health exercise guidelines (Peddle et al., 2008).

Considering the large rate of patients and survivors of colorectal cancer, there is a need to increase the amount of research of the effects of exercise on common side effects

of the malignancy and treatment modalities such as CRF. Further investigation into the confounders presented as unique to this population should also be investigated. Also, greater reporting on the etiologies causing the fatigue and reduced QOL would help improve the efficacy of exercise treatments.

Effects of Exercise on CRF in Cancer Patients and Survivors

Patients of a variety of different cancers with various treatment regiments rank CRF as the most prevalent side effect of cancer and its treatments (Hofman et al., 2007; Ryan et al., 2007). Therefore, it is of paramount importance to reduce this symptom in order to improve the patient's QOL and symptoms exacerbated by CRF such as depression and pain (Fleishman, 2004). Fifteen studies included in our meta analysis reported on the effects of exercise on CRF in patient populations. The resulting standardized mean weighted effect size indicates that patients undergoing an exercise program can cause statistically significant improvements in CRF compared to controls CRF (d = 0.26, $p<0.001$). Potential reasons for this significant and small effect size found in patients undergoing exercise compared to control groups is that exercise can alleviate and provide protective adaptations that can reduce the risk of CRF or improve already present CRF (Lucia et al., 2003; Mustian et a., 2007). In cancer patients not involved in exercise therapy CRF may be increased due to the multiple side effects such as depression, pain, reduced immune system function, and anemia occurring in response to cancer and its treatment (Stone & Minton et al., 2008; Wang, 2008). This result supports the role of exercise in cancer patients to reduce CRF compared to controls.

Following cancer and adjuvant therapies, CRF is still present in a third of cancer survivors (Hofman et al., 2007). Included in our meta analysis were 4 studies reporting on the effects of exercise on cancer survivors who have completed their treatments. Our results indicate that the effects of exercise can elicit a small reduction in CRF within this sub population. This effect size did not reach significance and was found to be significantly heterogeneous. This means that this mean effect size may not depict an accurate portrayal of the population mean and therefore, should be interpreted carefully. Potential reasons for the heterogeneity observed in this effect size distribution may originate from 2 studies reporting on the breast cancer patients, 1 reporting on colorectal cancer, and 1 reporting on a heterogeneous sample. In addition, 3 of the treatments were aerobic based and 1 was a mix program. Although this effect size was not significant and was produced with heterogeneity in the sampling distribution, CRF was still found to be reduced in survivor populations compared to controls. More studies are needed to investigate the effects of exercise programs on survivor populations shortly after interventions as well as long term follow up. Very little is known about the lasting effects of exercise in cancer survivors (Courneya et al., 2003; Portenoy & Itiri, 1999; van Weert et al., 2008). Due to the lack of studies reporting on the potential mechanism related to enduring CRF following treatment, more studies are also needed to investigate the profile of change in etiologies following cancer treatment. With this understanding best evidence exercise prescriptions could be developed and improve the quality of life of cancer survivors.

Comparisons between Cancer Patients and Survivors

The effect sizes reporting on the effectiveness of exercise interventions did not differ greatly between survivor and patient populations but favours the use of exercise to reduce CRF in survivors in comparison to patients. This result indicates important information regarding the timing of exercise interventions. Since exercise has been found to be effective in both populations exercise should be a recommended treatment both during and after treatments. During treatment, exercise may elevate symptoms and reduce risk factors of CRF such as psychological distress and poor physical functioning that may carry on into survival and exacerbate already present fatigue (Stone & Minton, van Weert et al., 2008; Watson et al., 2004). In addition, exercise, more specifically resistance exercise during treatment, has been found to improve the ability of the cancer patients to complete full treatments and therefore, reduce the risk of the malignancy returning and thus reduce the amount of treatments taken (Courneya et al., 2007). Improved baseline levels of CRF at the beginning of survivorship may also promote smoother integration of the survivor back into society which in turn may reduce stress and depressive symptoms and enduring fatigue while improving self esteem (Curt et al., 2001; Winningham 2001).

Although the effectiveness of exercise based interventions seem not to differ greatly between patients and survivors, it may be important to notice that patients undergoing treatment regiments have lower physical capacity and increased psychological stress and greater risk of infection and fractures and therefore, more rigorous exercise prescriptions might be better timed following treatment when a

reduction of these symptoms, CRF and contraindication have occurred. However, light to moderate exercise while undergoing treatments as our results indicate are significantly effective and should be implemented.

Effects of Exercise on CRF Etiologies

Our meta analysis is the first to attempt to investigate the effects of exercise on CRF etiologies. However, studies testing the effects of exercise in cancer patients and survivors for CRF as an outcome reported very little data on biological etiologies suspected to include CRF. Although cardiovascular and muscular dysfunction have been associated with increased fatigue and could be a potential cause of CRF, data regarding the effects of exercise on endocrine, neural, blood, and immune system variables associated with CRF were rare. Our search strategies resulted in 12 studies providing sufficient data on cardiopulmonary fitness, 6 studies regarding musculoskeletal function and 2 studies reporting on haemoglobin concentration.

Cardiopulmonary Function

The effects of exercise on cardiopulmonary measures in patients and survivors with CRF were found to be moderate but significant ($d = 0.47$, $p < 0.001$). However, Chi square analyses found significant heterogeneity within the effect size distribution compared to the suspected population and therefore, this mean effect size should be carefully considered when interpreting for application. Heterogeneity may be present due to diverse, treatment types and exercise prescriptions.

Cardiopulmonary function in patients with CRF has been found to be diminished and suggested to be a potential cause of CRF (Lucia et al., 2003, Ryan et al., 2007, Wang 2008). However, exercise has been found to improve cardiopulmonary function in patients with CRF (Conn et al., 2006; Cramp & Daniel, 2008; van Weert et al., 2008). For example, Dimeo et al., 2004 found that an aerobic interval exercise program of moderate to high intensity could significantly improve cardiopulmonary function. In addition, a light walking program performed in a hospital setting with patients diagnosied with AML was also found to be significantly effective in improving cardiopulmonary function (Chang et al., 2008). Furthermore, Quist and colleagues investigate the effect of aerobic and resistance training on cardiovascular and muscular strength variables in cancer patients. They found that over a 9 hour per week, 6 week intervention period muscular strength improved 41.3% ($p < 0.001$) and aerobic capacity increased significantly by 14.5% ($p < 0.001$) (Quist et al., 2006). The results from these studies suggest that aerobic and resistance exercise can improve the efficiency of cardiopulmonary systems which in turn may reduce CRF.

Improved cardiopulmonary function in patients with CRF or healthy individuals is a reflection of improved functioning of different bodily tissues such as the lungs, heart, skeletal muscle and blood. (Dimeo et al., 1997, Lucia et al., 2003; Ryan et al., 2007; Wang et al., 2008). First, cancer and cancer related treatments can induce a variety of insults to pulmonary function and geometry causing a reduction in overall pulmonary efficiency (Wang, 2008). In a study by Schneider et al. (2007), the team investigated the effects of an individual exercise prescription over six months on cardiopulmonary function and fatigue in breast cancer patients during and after treatment. The team found

that aerobic exercise for 6 months improved FVC by 2.8%, FEV1 increased by 4.0% and overall maximal oxygen consumption increased by 15.1% (Schneider et al., 2007). Second, it has been found that improved physical functioning through regular exercise can protect the myocardium against toxic anthracyclines and myeloablative therapies (Lucia et al., 2003). For example, Chicco et al. (2006) found that exercise was associated with an increase in eNOS, myocardial heat shock protein content, and prevention of myocardial lipid peroxidation (Chicco et al., 2006). These results suggest that exercise may protect myocardial function by increasing anti oxidant and anti inflammatory activity. Improved lung and heart function in cancer patients may contribute to improved cardiovascular function and CRF. However, improvements to musculoskeletal strength and haemoglobin production may also contribute to improved cardiopulmonary function, overall functional capacity and reduced CRF.

Musculoskeletal Strength

An additional component required to improve cardiovascular function is improved musculoskeletal strength; however, this variable in its own right has been found to be hindered causing increased effort to carry on many activities of daily living, reducing self esteem and promoting unhealthy body composition (Courneya et al., 2007; Lucia et al., 2003; Segal et al., 2008; Stone & Minton, 2008; Ryan et al., 2007; Wang, 2008). Exercise programs in patients with CRF were found to cause small improvements to musculoskeletal strength ($d = 0.27$, $p > 0.05$). While this effect size indicates a positive reduction in CRF, it was not significant.

Patients with cancer related fatigue commonly are associated with high rates of muscle atrophy or muscle catabolism which in turn reduces proportion of muscle fibers both oxidative and glycolytic which would reduce overall strength and force production in a variety of situations. Increased ratios of protein degradation over protein synthesis can occur from the increased bed rest and reduced physical activity, by cancer induced processes (cytokines), or by cancer related treatments. Regardless of the cause of muscle wasting, the deleterious results can reduce overall physical capacity and cause fatigue and diminished QOL. Resistance as well as aerobic exercises have been documented to improve musculoskeletal dysfunction and reduce muscle wasting due to malnutrition and cachexia (Al-Majid & McCathy, 2001). One way in which exercise makes this possible it through increasing the rate of protein synthesis for example, the rate of protein synthesis in the biceps brachia muscle in human subjects increased by 50% to 109% in four hours and 24 hours respectively following a single bout of resistance exercise compared to non exercised controls (Chen et al., 2008). In addition to resistance exercise, endurance exercises can also induce increases in protein synthesis. For example, Deuster and colleagues (1985), studies the effects of endurance training modification of cachexia in rats with malignant tumours. They found that voluntary endurance training for 4 weeks resulted in a 15% increase in muscle protein synthesis and increased the muscle body weight ratio by 10% (Deuster, Morrison, & Ahrens, 1985). Muscle wasting can lead to substantial weakness and fatigue in cancer patients (Al-Majid & McCathy, 2001). Exercise intervention incorporating both resistance and endurance exercise modalities would be beneficial to the overall functional abilities of cancer patients and improve metabolic efficiency by preserving and strengthening muscle fibers

which may be why we observed an improvement of musculoskeletal strength in patients with CRF.

Hemoglobin Concentration

In order for the cardiopulmonary system to be effective and for oxidative muscle fibers to produce movement, sufficiently oxygenated blood is a requirement. Anemia is a common characteristic in cancer patients and is a potential etiology of CRF. Unfortunately, considering the well established presence of anemia in cancer patients and the abundance of research done on the role of exercise in anemic populations, only two studies reported sufficient data on haemoglobin concentration as an effect of exercise in patients with CRF. The standard weighted mean effect size from these two studies is very high (d = 1.79, $p > 0.05$) and due to the significant heterogeneity found in a Chi square analysis may not be an accurate indicator of the population being studied, therefore, careful interpretation of this finding in necessary. However, anemia in patients with haematological malignancies and patients and survivors who have received adjuvant radio or chemotherapy commonly report anemia and therefore, treatment for anemia in cancer patients in much needed.

Improving haemoglobin levels in patients with cancer or undergoing adjuvant therapies has a beneficial overall effect on QOL and fatigue. In regards to direct effects of the malignancy itself, metastases within the bone marrow can inhibit the production of hematopoietic growth factors which are essential for regulating the proliferation, differentiation and survival of haematopoietic cells (Mercadante et al., 2000). In addition, solid tumours can invade bone marrow which reduces available bone marrow

space and creates a fibrotic reaction which disrupts the marrow environment and inhibits its normal functions (Mercadante et al., 2000). Other causes of cancer induced anemia may result from haemolysis, renal, hepatic or endocrine disorders and nutritional deficiencies. Radiotherapy has been found to increase anemia from pre-existing levels. Stem cells have a poor capacity to repair radiation damage which may be a reason for the increase in anaemia in patients undergoing radiation treatment (Mercadante et al., 2000). In addition to radiation therapy, the incidence of chemotherapy related anemia has been found to be up to 100% in some cases (Varlotto et al., 2005). Drug induced anemia caused by chemotherapy may be due to stem cell death, blockage or delayed haematopoietic factors, oxidant damage to mature haematopoietic cells, long term myelodyplasia or immune – mediated haematopoietic cell destruction (Mercadante et al., 2000). Regardless of the mechanism behind cancer induced anemia, anemia has a powerful influence on overall QOL and fatigue in cancer patients and can be treated.

Our results illustrate that exercise is a powerful treatment option for anemia in cancer patients and survivors which has also been found by many authors (Dimeo et al., 1997; Lucia et al., 2003; Windsor et al., 2004; Courneya et al., 2007). The large effect size may be attributed to a variety of factors. First, endurance training is found to stimulate erythropoiesis with accompanied increases in oxygen transport capacity of the blood (Lucia et al., 2003). For example Dimeo et al., (1997) showed that an endurance exercise program following chemotherapy is able to increase haemoglobin concentration from 10.1 g/dL at base line to 13.1 g/dL ($p < 0.05$). This is a significant finding since it has been found that improvements in overall QOL can occur with increases in 1 g/dl of haemoglobin from 10 – 13 g/dl (Cleeland et al., 1999). Furthermore, in 2003, Dimeo and

colleagues investigated the use of an aerobic program on anemic cancer patients undergoing chemotherapy and found that although haemoglobin concentration decreased, the reduction of haemoglobin was lower compared to controls. Therefore, it may be concluded that an exercise program can reduce the risk of anemia during adjuvant therapy.

In addition to the ability of exercise to preserve and improve haemoglobin concentration, exercise may also increase the rate of haemoglobin production (Courneya et al., 2007). This is an important effect of exercise. If exercise can increase the rate of haemoglobin production this could reduce the total number of adjuvant treatments such as Darbepoetin Alpha which also reduces symptoms of anemia quicker and lowers medication costs. The mechanisms for this response are not clear but Courneya et al. (2008) suggest that it may be due to the effects of exercise on growth hormone, insulin like growth factor, tissue oxygenation, arterial hypoxemia, blood volume expansion and reduced inflammation.

CRF is highly related to reduced QOL and physical functioning. Two predictors of overall QOL and physical capacity are cardiopulmonary and musculoskeletal fitness. Improved cardiopulmonary and musculoskeletal functioning is a reflection improved tissue function originating at the level of the lung, heart, muscle and blood. In regards to the blood, appropriate concentrations of haemoglobin are required to ensure sufficient oxygenation to working tissue to allow for optimal physical functioning. Cancer and or its treatments can reduce functioning at the cellular level in variables such as haemoglobin and reduce overall functioning through impaired cardiopulmonary and musculoskeletal function. One potential treatment to increase haemoglobin

concentrations as well as overall physical functioning is physical exercise. Our study supports the use of exercise to improve these potential mechanisms of CRF. However, further research is much needed into the effects of different exercise on CRF etiologies to provide the most effective exercise intervention.

CHAPTER 6

APPLICATIONS AND CONCLUSIONS

Implications for Practice

The most common treatment for CRF is nothing (40%) and rest (37%). These two recommendations may further exacerbate CRF and reduce the overall QOL of cancer patients and survivors. The resulting meta analysis provide significant support for the use of exercise to reduce CRF in a wide range of different cancer populations, during a diverse set of treatments as well as during an active malignancy and into survivorship stages. Therefore exercise should be a recommended component in the management strategies of CRF and potentially, other comorbidities related to CRF. In addition, specific exercise treatments should be aimed at the presented pathologies suspected to be driving CRF and tailored to the individual and potential contraindications associated with the cancer type. The following section will describe the general guidelines for an exercise prescription for aerobic resistance training and mixed styles based on the data collected from the present study.

Aerobic exercise was found to cause significant reduction in CRF compared to controls. The average exercise prescription used a moderate to high intensity aerobic prescription, generally between 50 – 80% maximal heart rate, which was commonly tested using maximal tests of aerobic capacity such as the Balke Ware and the Bruce or Modified Bruce Protocol. Exercise session of an aerobic nature took place on average, 4 days a week and commonly lasted up to 35 minutes a session. However, studies with our meta analysis have used shorter interval style training for up to 15 minutes with beneficial results as well as longer less intense aerobic sessions lasting up to 60 minutes with beneficial results. On average, 11 weeks was the duration of the exercise prescription. However, adapting an exercise routine into the patient's lifestyle would be optimal for continued benefits and reduced risk of further illness. To ensure continued adaptations, progression of time on task was generally conducted with increments of 5 minutes. The majority of aerobic sessions were performed in a supervised setting; however, at home interventions were effective and may be of benefit for patients with difficulty traveling.

Considering the effects of resistance training on physical capacity, muscle degeneration, and poor body composition, this style of training should be further investigated in populations with CRF. Results of our study level coding revealed that on average, participants exercised 3 times per week. All weight training interventions used resistance between 60 – 70% of their 1 repetition max (1RM). Repetitions of 8 – 12 and 2 sets were used in all three studies. Increases in weight either by 5 lbs or 10% 1RM were considered when 12 reps and 2 sets were able to be completed comfortably. Two studies investigated the effects of weight training for 24 weeks, where one study

investigated the effects of weight training over 12 weeks. Due to the potential danger associated with resistance training, all sessions were supervised by exercise physiologists.

Unfortunately only one mixed program was included into the meta analysis. However, this program produced very high reductions in CRF. Further studies must be done to test the reliability of this finding. However, the features of this lone study include an aerobic and resistance exercise session frequency of 3 exercise sessions per week, a aerobic intensity of 75% of heart rate max and a resistance training intensity described as light weight. The aerobic exercises were performed for 20 minutes. Resistance exercises began at 10 repetitions and graduated to 15 repetitions as the weights became comfortable. These repetitions were performed in sets of 2. The exercise intervention lasted for 12 weeks in a supervised setting.

In summary, exercise interventions have been found to reduce CRF. Aerobic, resistance and mixed styles of training seem to be effective; however, of the three methods mixed training was found to result in the largest reduction in CRF. In association with exercise, contributions from a wide variety of health care fields such as psychosocial therapy and registered dieticians may enhance the overall reduction of cancer and treatment related side effects such as CRF.

Research Implications

Although the results of the meta analysis are promising, they have been based on a small number of studies of which generally display significant heterogeneity between results. A primary goal of the meta analysis is to develop the premise for future research

in the respective field of investigation. Based on our findings, the following recommendations to improve the knowledge and application of exercise for CRF have been made. First, a large amount of heterogeneity found between effect sizes may be due to the diverse set of exercise interventions being used as treatment. Therefore, methodologically rigorous studies are called for with designs developed to specifically test the different effects and compare the results of aerobic, resistance and mixed exercise methods. Second, comparisons need to be made between the effectiveness of exercise between different cancer types. Third, comparisons between the use of exercise interventions during a variety of common therapies as well as between patients and survivor populations is needed to further understand the most effective timing of exercise interventions. Fourth, although exercise interventions has been found to be effective little is known about the enduring effects of exercise in cancer populations and the resulting changes to fatigue. Fifth, to provide the most effective treatment greater understanding into the etiologies of CRF is strongly needed. With a greater understanding of the etiologies of CRF exercise interventions may be tailored to effectively target specific contributing mechanisms. In addition, better pharmaceutical and psychological interventions could also be developed to provide the patient with the best, holistic treatment strategy.

Suggested improvements to study features include first, greater detail in to the specific exercise prescriptions used in terms of frequency, intensity, time, type, duration, and progressive strategies employed. Second a standardized assessment tool for the quantifying changes in CRF would improve the ability to make general conclusions about the finding across many studies. In addition with greater knowledge of CRF etiologies

may benefit the assessment of CRF by producing objective measures for diagnosis and change assessments. Third, a major limitation of the meta analysis is its small sample sizes. These small sample sizes reflect a lack of sufficient data to calculate effect size statistics. Therefore, greater statistical detail of the results, whether significant or not, should be included. Fourth, more studies with larger sample sizes and rigorous methodological designs would improve the reliability and validity of the results in within this developing field of study.

Conclusion

Exercise prescriptions have been used as a central rehabilitative and preventive component for a variety of condition and disease. The purpose of this study was to investigate the efficacy of exercise based interventions for the treatment of CRF. Although the results are limited by small sample sizes and heterogeneity within the effect size distribution our results indicate that exercise can significantly reduce CRF. Furthermore, exercise was found to manage CRF in a variety of different cancer populations and while undergoing different treatment stages and during active malignancy stages and into remission. In addition, aerobic, resistance and mixed exercise prescriptions were found to promote the mitigation of CRF. Exercise may be able to manage fatigue by improving cardiopulmonary function, musculoskeletal strength and hemoglobin production or protection. In conclusion our results indicate that exercise may provide important contributions to the reduction of CRF.

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Appendix A: Inclusion Manual and Form

STUDY ELIGIBILITY CRITERIA MANUAL

Intervention Characteristics: Eligible studies must involve the use of an exercise intervention program designed to improve cardiovascular and or muscle fitness with intention to reduce or treat cancer related fatigue as one of the outcome measures. Eligible studies must meet the definition of exercise as physical body movement that includes contraction of skeletal muscle, causing a substantial increase in energy expenditure greater then basal levels (Conn, Hafdahl, Porock, McDaniel, & Neilson, 2006). The study will be included if the exercise intervention is center based or unsupervised at home. The nature of the exercise activities must either be predominantly aerobic, anaerobic, resistance training based, or any combination of the three for inclusion in the meta analysis. Studies that employ additional interventions such as diet, social support, and psychological counselling will be excluded if the effects of such intervention cannot be disentangled from the effects of the exercise program. Studies designed to investigate the effects of movement therapy and or flexibility exercises to only improve range of motion will be excluded.

Research Respondents: Eligible studies must include subjects over the age of 18 who have been diagnosed with cancer concurrently or prior to the current research study. Eligible studies include subjects treated for cancer prior or concurrently at the time of the study. Studies including a heterogeneous or homogeneous sample of cancer types, cancer stages, treatment types and treatment stage will be eligible for inclusion.

Key Variables: Studies eligible for inclusion must include a quantitative self report assessment of cancer related fatigue as one of the outcome variables. Eligible studies must meet the definition of cancer related fatigue as stated by the National Comprehensive Cancer Network thus being "a persistent sense of tiredness that can occur with cancer or cancer treatment that interferes with usual functioning" (de Nijs, Ros, & Grijpdonck, 2008). Only studies reporting sufficient statistical information from which effect size statistics can computed are eligible.

Research Methods: Small sample studies will be eligible if total number of subjects is greater than 5. Eligible studies must use single group pre – post, quasi-experimental or experimental design. Studies without control groups will be eligible if the study contains the pre – post data needed to produce effect size statistics. Studies that include two treatment groups with no control group will be eligible and included in the meta analysis as two independent single group pre – post design studies. Studies with a true control group must use "treatment as usually", placebo, waitlist, or no treatment conditions. A treatment versus treatment comparison is eligible if one treatment is intended as a control for the other. Studies eligible for meta analysis must use appropriate statistical analysis based on the study design, the nature of the groups and the number of subjects.

Cultural and Linguistic Range: Studies must be reported in English. Studies can be conducted in any country or region.

Time Frame: Only studies since 1980, inclusively, are eligible.

Publication Type: Published and unpublished journal article, abstracts, theses and dissertations are eligible for inclusion

Study Inclusion Criteria Form

Bibliographic Information:

Study ID _____.

Inclusion Criteria Theme	Criteria #	Criteria Description	Yes	No	Unsure
Intervention Characteristics	1	Used an exercise intervention designed to increase flexibility, resistance and or endurance exercise			
	2	Intervention intended to reduce or treat CRF as one of the outcomes			
	3	Exercises meet predetermined definition			
	4	Mode of exercise is either aerobic, anaerobic, resistance training or a combination or the three			
Research Respondents	5	Subjects 18 years old or older			
	6	Currently or previously diagnosed with cancer			
	7	Subjects treated for cancer currently or prior to the current research			
Key Variables	8	Fatigue measured quantitatively			
	9	CRF meets definition			
	10	Sufficient statistical data present to produce Effect Size statistics			
Research Methods	11	Meets Study Design Criteria (pre-experimental, quasi-experimental, or experimental)			
	12	Treatment of control groups meet criteria			
	13	Appropriate statistical procedures applied			
Cultural and Linguistic Range	14	Reported in English			
Time Frame	15	Study Reported between 1980-2008			
Publication Type	16	Journal article, Theses, Dissertations			

Appendix B: Study and Effects Size Coding Forms

Study Level Coding Form

1) Study Characteristics/Descriptors

1) Bibliography

2) Study ID

3) Publication Form
- i)journal
- ii) Dissertation

4) Country of Publication

5) Year of Publication

2) Methodological Features

1) Study Design
- i) Experimental
- ii) Quasi - experimental
- iv) Cross - over

3) Nature of Control Group
- i) Care as Usual
- ii) Placebo
- iii) Treatment With Held
- iv)Phone calls

5) CRF Assessment Instrument Used

7) Blinding of Researcher
- i) Yes
- ii) No
- iii)Unsure

2) Participants Assignment to Conditions

i) Random Allocation
ii) Non Random
1) Describe
iii) Other
1) Describe

4) CRF Inclusion Threshold
i) Yes
1) Method used
ii) No

6) Timing of Data Collection
i) Pre Intervention
ii) Post Intervention

8) Role of Experimenter in Treatment
i) Independent
ii) Provider
iii)Unsure

3) Participant Characteristics	n= ***Controls***	n= ***Treatment1***	n= ***Treatment 2***
1) Gender			
i) Male			
ii)Female			
2) Age			
i) Mean Age Female			
ii) Mean Age Male			
iii) Total Sample Mean Age			
3) Oncology Characteristics			
i) Homogeneous Sample			
a) Site			
ii) Heterogeneous Sample			
a) Site/#			
a) Site/#			
a) Site/#			
a) Site/#			
a) Site/#			
iii) Stage of Cancer			
a) Stage 0			
b) Stage I			
c) Stage II			
d) Stage III			
e) Stage IV			
f) Recovery			

g) Remission
h)
Unsure

4) Oncology Treatment Regime Characteristics
i) Previously Treated
a) Radio
b)Chemo
c)Bio. Res.
d) Horm.
e) Stem Cell
f) Surgical

a1) Length of Treatment

ii)Months since treatment
iii) Concurrently Treated
a) Radio
b)Chemo
c)Bio. Res.
d) Horm.
a1) Length into Treatment wks wks

4i) Lymphoedema
4ii) Menopausal status

5) Diagnosed with CRF
i) Yes
ii) No
6) Instrument used to Diagnosis CRF
7) Years with Cancer Related Fatigue

4) Intervention Characteristics (For Treatment Group)
1) Method of
Delivery
i) Supervised
ii) Unsupervised
a) Fitness Center
b) Home Based

3) Fitness Testing Before Intervention
i) Yes
a) Maximal
ai) Protocol
b) Submaximal
bi) Protocol
ii) No

7) Exercise Intensity Based On
i) % of Aquired Max HR
a) Protocol

ii) % of Estimated Max HR
a) Protocol
iii) % of VO2 Max
a) Protocol
iv) % of VO2 Estimate
a) Protocol
v) Borge Scale
a) Protocol
vi) % METS
a) Protocol
vii) % 1RM
a) Protocol

2) Exercise Mode
i) Aerobic
ii) Resistance
iii) Mixed
iv) Other

4) Total # of Weeks

5) Sessions / Week

6) Individualized Exercise Prescription
i) Yes
ii) No

8) Intensity RX

Aerobic	Resistance

9) Total Duration of Exercise Session
i) Aerobic Component
ii) Resistance Component
iii) Other

10) Progression used
i) Describe
ii) None
iii)
Unsure
a) Describe

5)
Anemia
i) Hemoglobin

ii) Other

a) Describe

7) Immune system

i) TNF – a

ii) IL – 1

iii) IL – 6

iv) CRP

v) Other

a) Describe

9) Cardiovascular/Pulmonary Function

i) Construct/Instrument

2) HPA – axis

i) Cortisol

ii) Adrenal size

iii) ACTH

iv) bi-product/derivative

4) Vagal Activiation

i) HRV

a) HF

b) LF:HF

6) Muscle/ATP Dysfunction

8) Musculoskeletal Strength

7) Cancer Related Fatigue Assessment

i) Assessment Instrument used for Base Line

ii) Assessment Instrument used for Final Trial

8) Adverse Events

a) Occurred ☐
i) Explain ☐
b) none ☐
d) unsure ☐

Effect Size Coding Form

Effect Size Level Coding Form

1) Study ID

2) Variables Investigated for Effect Size

1) Cancer Related fatigue
2) Aerobic capacity
3) Musculoskeletal strength
4) Phyiscal Functioning
5) Serotonin
6) Cortisol
7) Circadian Rhythm
8) Vagal Afferents
9) Muscle Metabolism
10) Anemia
11) Cytokines

3) Effect Size Type

1) Two group
ii) Group Contrast

3) Three or More Groups
ii) Group Contrast

Data

4) Page Number Effect Size Data is Found

5) Type of Data Effects Size Based On

1) Means and Standard Deviation
2) *t - value*
3) *F* - value
4) Chi - Square (df = 1)
5) Other

Group Contrast Design

CRF

6) Sample Sizes (n)

EG n_1	EG n_2	EG n_3	CG n_1

Total (N) 0

7) Pre Intervention Means

XG_1	XG_2	XG_3	XCG_1

8) Post Intervention Means

XG_1	XG_2	XG_3	XCG_1

9) Standard Deviations

SDG_1	SDG_2	SDG_3	$SDCG_1$

10) Pooled Variance

Sp =

11) Uncorrected ES

g=

Effect size Values

1) Corrected Standardized Mean Difference	ES^1sm =	
2) Standard Error	SEsm =	
3) Inverse Variance Weight	wsm =	

Appendix C: Effect Size Statistics

Coding the Effect Size Data

- Determine the appropriate effect size based on study design
- Pre – Post Design Effect Size Computation
  - Standardized Mean Gain Standard Error Inverse Variance Weight

$$ESsg = \frac{\bar{X}_{t2} - \bar{X}_{t1}}{Sp} = \frac{\bar{G}}{Sg / \sqrt{2(1-r)}} \quad SEsg = \sqrt{\frac{2(1-r)}{n} + \frac{ES^2_{sg}}{2n}} \quad \omega_{sg} = \frac{1}{SE^2_{sg}} = \frac{2n}{4(1-r) + ES^2_{sg}}$$

- Group Contrast Effect Size Computation
  - Standardized Mean Difference Standard Error

$$ES_{sm} = \frac{\bar{X}_{G1} - \bar{X}_{G2}}{S_p} \quad ES^i_{sm} = \left[1 - \frac{3}{4N-9}\right] ES_{sm} \quad SE_{sm} = \sqrt{\frac{n_{G1} + n_{G2}}{n_{G1} n_{G2}} + \frac{(ES^i_{sm})}{2(n_{G1} + n_{G2})}}$$

  - Inverse Variance Weight

$$\omega_{sm} = \frac{1}{SE^2_{sm}} = \frac{2n_{G1}n_{G2}(n_{G1} + n_{G2})}{2(n_{G1} + n_{G2})^2 + n_{G1}n_{G2}(ES^i_{sm})^2}$$

Standardized Mean Effect Size (*d*)

$$d = \frac{\sum (N_i - ES_i)}{\sum N_i}$$

Appendix D: SAS Outputs

OVERALL EFFECT OF EXERCISIE ON CRF

CRF_D.lst

```
The SAS System                              14:07 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance          Std Dev          Minimum          Maximum            Range
-------------------------------------------------------------------------------------------
--
0.2660365       0.0792992       0.2816012       0.0200000       1.4400000       1.4200000
-------------------------------------------------------------------------------------------
--
The SAS System                              14:07 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum          Maximum            Range
-----------------------------------------------------------------------------
106.6315789         2026.00    19      21.0000000     242.0000000     221.0000000
-----------------------------------------------------------------------------
The SAS System                              14:07 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.26413     0.040725     0.20180     0.038575     48.6443     -0.13141      0.65966
39.0590
```

CRF_EXTYPE_mD.lst (AER)

```
The SAS System                              14:22 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance          Std Dev          Minimum          Maximum            Range
-------------------------------------------------------------------------------------------
--
0.2565679       0.0600188       0.2449874       0.0200000       1.4400000       1.4200000
-------------------------------------------------------------------------------------------
--
The SAS System                              14:22 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum          Maximum            Range
-----------------------------------------------------------------------------
96.7333333          1451.00    15      21.0000000     242.0000000     221.0000000
-----------------------------------------------------------------------------
The SAS System                              14:22 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE      L95_CONF     U95_CONF
CHI_SQ

1      0.25453     0.017438     0.13205     0.042581     70.9454     -.004294207      0.51336
21.1430
```

CRF_EXTYPE_mD.lst (RES)

```
The SAS System                              14:28 Monday, March 2, 2009   1

The MEANS Procedure
```

```
Analysis Variable : D

Mean        Variance          Std Dev         Minimum         Maximum           Range
-------------------------------------------------------------------------------------
--
0.1743822       0.0064628       0.0803918       0.1300000       0.3200000       0.1900000
-------------------------------------------------------------------------------------
--
The SAS System                              14:28 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum         Maximum           Range
-----------------------------------------------------------------------------
172.6666667     518.0000000     3     121.0000000     242.0000000     121.0000000
-----------------------------------------------------------------------------
The SAS System                              14:28 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.17361          0            0        0.023528     364.053      0.17361      0.17361
0.82405
```

CRF_EXTYPE_mD.lst (MIX)

```
The SAS System                              14:33 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance          Std Dev         Minimum         Maximum           Range
-------------------------------------------------------------------------------------
--
1.3400000               0               0       1.3400000       1.3400000               0
-------------------------------------------------------------------------------------
--
The SAS System                              14:33 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum         Maximum           Range
-----------------------------------------------------------------------------
57.0000000      57.0000000     1      57.0000000      57.0000000              0
-----------------------------------------------------------------------------
The SAS System                              14:33 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1     1.32164         0           0        0.089109         .        1.32164      1.32164         0
```

CANCER TYPE MODERATOR ANALYSIS ON CRF
RESULTS of CANCER LOCATION MODERATORS ON CRF
LOC-mD.lst (BRC)

```
The SAS System                              14:44 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance          Std Dev         Minimum         Maximum           Range
-------------------------------------------------------------------------------------
--
```

```
0.2870054       0.0884438       0.2973950       0.0600000       1.3400000       1.2800000
-------------------------------------------------------------------------------------------
--
The SAS System                              14:44 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum          Maximum           Range
-------------------------------------------------------------------------------
143.2222222          1289.00     9       24.0000000      242.0000000      218.0000000
-------------------------------------------------------------------------------
The SAS System                              14:44 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.28548     0.059825     0.24459     0.028619     32.3580     -0.19392      0.76488
27.8138
```

LOC_mD.sas (HET)

```
The SAS System                              14:50 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance          Std Dev          Minimum          Maximum            Range
-------------------------------------------------------------------------------------------
--
0.1665686       0.0282872       0.1681881       0.0200000       0.6100000       0.5900000
-------------------------------------------------------------------------------------------
--

The SAS System                              14:50 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum          Maximum           Range
-------------------------------------------------------------------------------
51.0000000      204.0000000     4       21.0000000       69.0000000       48.0000000
-------------------------------------------------------------------------------
The SAS System                              14:50 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.16401          0            0        0.081983     289.822      0.16401      0.16401
1.38016
```

LOC_mD.lst (AML)

```
The SAS System                              14:59 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance          Std Dev          Minimum          Maximum            Range
-------------------------------------------------------------------------------------------
--
0.5700000                0                0       0.5700000       0.5700000                0
-------------------------------------------------------------------------------------------
--
The SAS System                              14:59 Monday, March 2, 2009   2

The MEANS Procedure
```

Analysis Variable : N SAMPLE SIZE

Mean	Sum	N	Minimum	Maximum	Range
22.0000000	22.0000000	1	22.0000000	22.0000000	0

The SAS System 14:59 Monday, March 2, 2009 3

Obs	SWMD_C	VAR_DLTA	SD_DLTA	VAR_E	PVA_SE	L95_CONF	U95_CONF	CHI_SQ
1	0.54835	0	0	0.20912	.	0.54835	0.54835	0

LOC_mD.sas (PRC)

The SAS System 15:01 Monday, March 2, 2009 1

The MEANS Procedure

Analysis Variable : D

Mean	Variance	Std Dev	Minimum	Maximum	Range
0.2797608	0.0771320	0.2777265	0.1300000	1.4400000	1.3100000

The SAS System 15:01 Monday, March 2, 2009 2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean	Sum	N	Minimum	Maximum	Range
104.5000000	418.0000000	4	21.0000000	155.0000000	134.0000000

The SAS System 15:01 Monday, March 2, 2009 3

Obs	SWMD_C	VAR_DLTA	SD_DLTA	VAR_E	PVA_SE	L95_CONF	U95_CONF	CHI_SQ
1	0.27771	0.037718	0.19421	0.039414	51.0989	-0.10295	0.65836	7.82796

LOC_mD.sas (CRC)

The SAS System 15:03 Monday, March 2, 2009 1

The MEANS Procedure

Analysis Variable : D

Mean	Variance	Std Dev	Minimum	Maximum	Range
0.0600000	0	0	0.0600000	0.0600000	0

The SAS System 15:03 Monday, March 2, 2009 2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean	Sum	N	Minimum	Maximum	Range
93.0000000	93.0000000	1	93.0000000	93.0000000	0

The SAS System 15:03 Monday, March 2, 2009 3

```
Obs      SWMD_C      VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.059504          0           0         0.043986        .       0.059504     0.059504
0
```

CANCER TREATMENT MODERATOR ANALYSIS ON CRF
TRT_mD.lst

RESULTS OF CANCER TREATMENT MODERATORS ON CRF
TRT_mD.lst (PST)

```
The SAS System                              15:06 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean         Variance          Std Dev          Minimum          Maximum            Range
-------------------------------------------------------------------------------------------
--
0.2889427       0.1734253       0.4164437       0.0600000       1.3400000       1.2800000
-------------------------------------------------------------------------------------------
--
The SAS System                              15:06 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean              Sum     N          Minimum          Maximum            Range
-----------------------------------------------------------------------------
75.6666667     454.0000000     6       21.0000000      190.0000000      169.0000000
-----------------------------------------------------------------------------
The SAS System                              15:06 Monday, March 2, 2009   3

Obs      SWMD_C      VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.28599       0.11854     0.34430      0.054885     31.6478     -0.38883      0.96081
18.9587
```

TRT_mD.lst (CHE)

```
The SAS System                              15:10 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean         Variance          Std Dev          Minimum          Maximum            Range
-------------------------------------------------------------------------------------------
--
0.1290608       0.0082450       0.0908018       0.0200000       0.5700000       0.5500000
-------------------------------------------------------------------------------------------
--
The SAS System                              15:10 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean              Sum     N          Minimum          Maximum            Range
-----------------------------------------------------------------------------
144.8000000     724.0000000     5       22.0000000      242.0000000      220.0000000
-----------------------------------------------------------------------------
The SAS System                              15:10 Monday, March 2, 2009   3

Obs      SWMD_C      VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.12838          0           0         0.028072     340.477      0.12838      0.12838
1.46853
```

TRT_mD.lst (RAD)

```
The SAS System                              15:11 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance         Std Dev         Minimum         Maximum          Range
-------------------------------------------------------------------------------------
--
0.3680228       0.1015816       0.3187188       0.2300000       1.4400000       1.2100000
-------------------------------------------------------------------------------------
--
The SAS System                              15:11 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum         Maximum          Range
-----------------------------------------------------------------------------
87.6666667     263.0000000     3       21.0000000      121.0000000     100.0000000
-----------------------------------------------------------------------------
The SAS System                              15:11 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE      L95_CONF     U95_CONF
CHI_SQ

1      0.36479     0.054086     0.23256     0.047496     46.7564     -0.091033      0.82062
6.41623
```

TRT_mD.lst (CRT)

```
The SAS System                              15:13 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance         Std Dev         Minimum         Maximum          Range
-------------------------------------------------------------------------------------
--
0.5118133       0.0150538       0.1226938       0.3800000       0.6300000       0.2500000
-------------------------------------------------------------------------------------
--
The SAS System                              15:13 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum         Maximum          Range
-----------------------------------------------------------------------------
125.0000000     375.0000000     3       82.0000000      174.0000000      92.0000000
-----------------------------------------------------------------------------
The SAS System                              15:13 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE      L95_CONF     U95_CONF
CHI_SQ

1      0.50869          0            0        0.033590     223.131      0.50869      0.50869
1.34450
```

TRT_mD.lst (DPA)

```
The SAS System                              15:14 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean         Variance          Std Dev          Minimum          Maximum            Range
-------------------------------------------------------------------------------------------
--
0.1000000                0                0        0.1000000        0.1000000                0
-------------------------------------------------------------------------------------------
--
The SAS System                              15:14 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean              Sum     N          Minimum          Maximum            Range
-----------------------------------------------------------------------------
55.0000000       55.0000000    1       55.0000000       55.0000000                0
-----------------------------------------------------------------------------
The SAS System                              15:14 Monday, March 2, 2009   3

Obs       SWMD_C       VAR_DLTA      SD_DLTA        VAR_E       PVA_SE      L95_CONF      U95_CONF
CHI_SQ

1       0.098578           0             0          0.075619         .         0.098578      0.098578
0
```

TRT_mD.lst (ADP)

```
The SAS System                              15:16 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean         Variance          Std Dev          Minimum          Maximum            Range
-------------------------------------------------------------------------------------------
--
0.1300000                0                0        0.1300000        0.1300000                0
-------------------------------------------------------------------------------------------
--
The SAS System                              15:16 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean              Sum     N          Minimum          Maximum            Range
-----------------------------------------------------------------------------
155.0000000      155.0000000    1      155.0000000      155.0000000               0
-----------------------------------------------------------------------------
The SAS System                              15:16 Monday, March 2, 2009   3

Obs       SWMD_C       VAR_DLTA      SD_DLTA        VAR_E       PVA_SE      L95_CONF      U95_CONF
CHI_SQ

1       0.12936            0             0          0.026201         .         0.12936       0.12936         0
```

CANCER STATUS MODERATOR ANALYSIS ON CRF
ST_mD.sas

RESULTS OF CANCER TREATMENT MODERATORS ON CRF
ST_mD.lst (ACT)

```
The SAS System                              15:21 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance         Std Dev         Minimum         Maximum          Range
-------------------------------------------------------------------------------------
--
0.2576697       0.0491242       0.2216398       0.0200000       1.4400000       1.4200000
-------------------------------------------------------------------------------------
--
The SAS System                              15:21 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum         Maximum          Range
-----------------------------------------------------------------------------
111.0000000          1665.00    15       21.0000000      242.0000000      221.0000000
-----------------------------------------------------------------------------
The SAS System                              15:21 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.25589     0.012116     0.11007     0.037008     75.3356     0.040148      0.47164
19.9109
```

ST_MD.lst (SRV)

```
The SAS System                              15:24 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance         Std Dev         Minimum         Maximum          Range
-------------------------------------------------------------------------------------
--
0.3046260       0.2166603       0.4654678       0.0600000       1.3400000       1.2800000
-------------------------------------------------------------------------------------
--
The SAS System                              15:24 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N          Minimum         Maximum          Range
-----------------------------------------------------------------------------
90.2500000      361.0000000     4       21.0000000      190.0000000      169.0000000
-----------------------------------------------------------------------------
The SAS System                              15:24 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      0.30203      0.17080     0.41328     0.045863     21.1682     -0.50799      1.11205
18.8962
```

EFFECTS OF EXERCISE ON HEMOGLOBIN CONCERNTRATION IN PATIENTS WITH CRF
HEM_D.sas

RESULTS OF EXERCISE ON HEMOGLOBIN CONCENTRATION IN PATIENTS WITH CRF
HEM_D.lst

```
The SAS System                              15:29 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance         Std Dev         Minimum         Maximum           Range
-------------------------------------------------------------------------------------
--
1.7912500       1.6143359       1.2705652       0.4100000       2.9600000       2.5500000
-------------------------------------------------------------------------------------
--
The SAS System                              15:29 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N         Minimum         Maximum           Range
-----------------------------------------------------------------------------
60.0000000     120.0000000     2      55.0000000      65.0000000      10.0000000
-----------------------------------------------------------------------------
The SAS System                              15:29 Monday, March 2, 2009   3

Obs      SWMD_C     VAR_DLTA     SD_DLTA       VAR_E       PVA_SE     L95_CONF     U95_CONF
CHI_SQ

1      1.76799      1.51765     1.23193     0.096682     5.98897     -0.64660      4.18257
33.3947
```

EFFECTS OF EXERCISE ON CARDIOPULMONARY FUNCTION IN PATIENTS WITH CRF
CPF_D.sas

RESULTS OF EXERCISE ON CARDIOPULMONARY FUNCTION IN PATIENTS WITH CRF
CPF_D.lst

```
The SAS System                              15:33 Monday, March 2, 2009   1

The MEANS Procedure

Analysis Variable : D

Mean        Variance         Std Dev         Minimum         Maximum           Range
-------------------------------------------------------------------------------------
--
0.4195920       0.0672256       0.2592790       0.0300000       0.9200000       0.8900000
-------------------------------------------------------------------------------------
--
The SAS System                              15:33 Monday, March 2, 2009   2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean             Sum     N         Minimum         Maximum           Range
```

108.2500000	1299.00	12	21.0000000	242.0000000	221.0000000	

The SAS System 15:33 Monday, March 2, 2009 3

Obs	SWMD_C	VAR_DLTA	SD_DLTA	VAR_E	PVA_SE	L95_CONF	U95_CONF	CHI_SQ
1	0.41662	0.028743	0.16954	0.038482	57.2435	0.084328	0.74892	20.9631

EFFECTS OF EXERCISE ON MUSCULOSKELETAL FUNCTION IN PATIENTS WITH CRF
MSF_D.sas

RESULTS OF EXERCISE ON MUSCULOSKELETAL FUNCTION IN PATIENTS WITH CRF
MSF_D.lst
The SAS System 15:36 Monday, March 2, 2009 1

The MEANS Procedure

Analysis Variable : D

Mean	Variance	Std Dev	Minimum	Maximum	Range
0.2745274	0.0458641	0.2141590	0	0.6300000	0.6300000

The SAS System 15:36 Monday, March 2, 2009 2

The MEANS Procedure

Analysis Variable : N SAMPLE SIZE

Mean	Sum	N	Minimum	Maximum	Range
134.0000000	804.0000000	6	21.0000000	242.0000000	221.0000000

The SAS System 15:36 Monday, March 2, 2009 3

Obs	SWMD_C	VAR_DLTA	SD_DLTA	VAR_E	PVA_SE	L95_CONF	U95_CONF	CHI_SQ
1	0.27296	0.015272	0.12358	0.030592	66.7014	0.030747	0.51518	8.99531

Appendix E: Study Characteristics

Authors	Participants	Cancer Characteristics	Exercise Intervention	Outcomes of Interest	Assessment	Results (Between Groups)	Effect Size
Milne et al., 2007	N=57 EGn=28 CGn=29	Breast Cancer Stage I - II Survivors Post Treatment	F: 3x/wk I: 75% MaxHR T:50mins T:Mixed Duration: 12 wks Setting: Supervised	Fatigue CP Function MS Function	SCFS API Resistance used	Sig. decrease in fatigue Sig. increase in Physical fitness	Fatigue 1.34 CP Function 0.03 MS Function 0.64
Dimeo et al., 1999	N=59 Active Solid Tumour or Lymphomas	Solid Tumours or Lymphomas Patients Chemotherapy	F: 7x/wk I: 50% HRR T: 30min T: Aerobic Intervals Duration: Admission to discharge Setting: Supervised	Fatigue	POMS	No Sig. difference in fatigue	Fatigue 0.02
Chang et al., 2008	N=22 EGn=11 CGn=11	Acute Myelogenous Leukemia Patients Chemotherapy	F: 5x.wk I: 30bpm>resting HR T: 12min T: Aerobic Duration :3 wks Setting: Supervised	Fatigue, CP Function	BFI 12min walk test	Sig. decrease in fatigue Sig . increase In CP function	Fatigue 0.57 CP Function 0.63
Courneya et al., 2008	N=55 EGn=26 CGn=29	Anemic nonmyelid (heterogeneous) Patients Darbepoetin Alpha	F: 3x/wk I: 60-100% exercise capacity T: ? T: Aerobic Duration: 12 wks Setting: Supervised	Fatigue CP Function Hemoglobin	FACT-An Watts Hb (g/l)	No Sig. difference in fatigue Sig. increase in VO2max Sig. decrease In Hb (g/l)	Fatigue 0.1 CP function 0.53 Hb(g/l) 0.41

Courneya et al., 2007	N=159 EGn(Aer)= 58 EGn(Res)=16 CGn=85	Breast Cancer Stage I-III Patients Chemotherapy	F: 3x/wk I: 60-80% VO2max (aer) 60-70% 1RM (res) T: 60min T: Aerobic or Resistance Duration: 6 wks Setting: Supervised	Fatigue	FACT-An	No Sig. difference in fatigue, trends favour reductions in fatigue in both exercise groups	Fatigue EG1= 0.06

Authors	Participants	Cancer Characteristics	Exercise Intervention	Outcomes of Interest	Assessment	Results (Between Groups)	Effect Size
Monga et al., 2007	N=21 EGn=11 CGn=10	Prostate Cancer Patients Radiotherapy	F: 3x/wk I: 65% Max HR T: 50min T: Aerobic Duration: 8wks Setting: Supervised	Fatigue MS Function	PFS Revised Sit and Stand	Sig. decrease in fatigue Sig. Increase in MS function	Fatigue 1.44 MS Function 0.0
Segal et al., 2008	N=121 EG1n=40 EG2n=40 CGn=41	Prostate Cancer Stage I-IV Patients Radiotherapy	F: 3x/wk I: 50-75% VO2max(Aer) 60-70% 1RM(Res) T: 45min T: Aerobic or Resistance Duration: 24wks Setting: Supervised	Fatigue CP Function MS Function	FACT-F VO2max 1RM	No Sig. difference in fatigue. Sig. Increase in CP function in both EGs Sig. increase in MS function in both EGs	Fatigue EG1= 0.23 EG2= 0.34 CP Function EG1= 0.35 EG2= 0.25 MS Function EG1= 0.16 EG2= 0.63

Courneya et al., 2007	N=242 EG1n=82 EG2n=78 CGn=82	Breast Cancer Stage I-III Patients Chemotherapy	F: 3x/wk I: 60-80% VO2max(Aer) 60-70% 1RM(Res) T: 45 min T: Aerobic or Resistance Duration: 24wks Setting: Supervised	Fatigue CP Function MS Function	FACT-An VO2max 1RM	No Sig. difference in fatigue Sig. increase in CP function in EG1 Sig. increase In MS function in EG2	Fatigue EG1= 0.16 EG2= 0.13 CP Function EG1= 0.34 EG2= 0.12 MS Function EG1= 0.08 EG2= 0.43
Mutrie et al., 2007	N=174 EG1n=82 CGn=92	Breast Cancer Stage 0-III Patients Radiotherapy & Chemotherapy	F:3x/wk I: 50-75% HR T: 45min T: Aerobic Duration: 12wks Setting: Supervised	Fatigue CP Function	FACT-F 12min walk test	No Sig difference in fatigue Sig. increase in CP function	Fatigue 0.38 CP Function 0.80

Authors	Participants	Cancer Characteristics	Exercise Intervention	Outcomes of Interest	Assessment	Results (Between Groups)	Effect Size
Pinot et al., 2003	N=24 EGn= 12 CGn= 12	Breast Cancer Stage 0-II Patients Post Treatment	F: 3x/wk I: 60-70% HRmax T: 50min T: Aerobic Duration: 12wks Setting: Supervised	Fatigue	POMS	No Sig. difference in fatigue	Fatigue 0.28
Burnham et al., 2002	N=21 EGn=14 CGn= 7	Heterogeneous Survivors Post Treatment	F: 3x/wk I: 25-60% HRR T: 32min T: Aerobic Duration: 10wks Setting: Supervised	Fatigue CP Function	LASA VO2max	No Sig. difference in fatigue Sig. increase in CP function	Fatigue 0.61 CP Function 0.64

Dimeo et al., 2004	N=69 EGn=34 CGn=35	Heterogeneous Stage I-IV Patients Post Treatment	F: 5x/wk I: 80%HRmax T: 30min T:Aerobic Intervals Duration: ? Setting: Supervised	Fatigue CP Function	EORTC-QOL30 VO2max	No Sig. difference in fatigue Sig. Increase in CP Function	Fatigue 0.21 CP Function 0.92
Courneya et al., 2003	N=93 EGn=62 CGn= 31	Colorectal Survivors Post Treatment	F: 3-5x/wk I: 65-75% HRmax T: 20-30min T: Aerobic Duration: 16wks Setting: Unsupervised Home based	Fatigue CP Function	FACT-C Balke Ware	No Sig. difference in fatigue Sig. increase in CP function	Fatigue 0.06 CP Function 0.47
Segal et al., 2003	N=155 EGn=82 CGn=73	Prostate Cancer Patients Androgen Deprivation	F: 3x/wk I: 60-70% 1RM T: Completion of sets T: Resistance Duration: 12 wks Setting: Supervised	Fatigue	FACT-F	Sig. decrease in fatigue Sig. Increase in MS function	Fatigue 0.13

Authors	Participants	Cancer Characteristics	Exercise Intervention	Outcomes of Interest	Assessment	Results (Between Groups)	Effect Size
Windsor et al., 2004	N=65 EGn=32 CGn=33	Prostate Cancer Patients Radiotherapy	F: 3x/wk I: 60-70% T: 30min T: Aerobic Duration: 4wks Setting: Unsupervised home based	Fatigue Hb (g/l)	BFI Serum Hb	No Sig. difference in fatigue No Sig. difference in Hb	Hb 2.96
Pinto et al., 2005	N=82 EGn=39 CGn=42	Breast Cancer Stage 0-II Patients Chemotherapy Radiotherapy Hormonal Therapy	F: 5x/wk I: 55-65% T: 30min T: Aerobic Duration: 12wks Setting: Unsupervised home based	Fatigue CP Function	POMS 1 mile walk	Sig. decrease in fatigue Sig. increase in CP function	Fatigue 0.62 CP Function 0.69

Vallance et al., 2007	N=190 EGn=94 CGn=96	Breast Cancer Stage I-III Survivors Post Treatment	F: 89min/wk I: self paced T: Cumulative 89min/wk T: Aerobic Duration: 12wks Setting: Unsupervised	Fatigue	FS	No Sig difference in fatigue	Fatigue 0.08
Mock et al., 2005	N=119 EGn=60 CGn=59	Breast Cancer Stage 0-III Patients Radiotherapy Chemotherapy	F: 5-6x/wk I: 50-70% T: 15-30min T: Aerobic Duration: 6wks Setting: Unsupervised	Fatigue	PFS	Sig. decrease in fatigue	Fatigue 0.63