Neuromuscular Mechanisms Contributing to Self-Reported Post-Treatment Cancer Fatigue and the Effects of Resistance Training

by

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CERTIFICATE OF AUTHORSHIP

I, Danielle Girard,

“I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma at Charles Sturt University or any other educational institution, except where due acknowledgment is made in the thesis Neuromuscular Mechanisms Contributing to Self-Reported Post-Treatment Cancer Fatigue and the Effects of Resistance Training. Any contribution made to the research by colleagues with whom I have worked at Charles Sturt University or elsewhere during my candidature is fully acknowledged. I agree that this thesis be accessible for the purpose of study and research in accordance with the normal conditions established by the Executive Director, Library Services or nominee, for the care, loan and reproduction of theses, subject to confidentiality provisions as approved by the University.”

Signature Date 23/3/16
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Jessica, who is a truly amazing person and cherished friend. Finally, to my dearest Kieron, thank you for making me smile and reminding me that it will all be worth it in the long run. To my friends and work colleagues at home for their understanding, and for their frequent offer of assistance and support over the last few years.
ETHICS APPROVAL

Human Research Ethics approval was obtained from the Charles Sturt University Human Research Ethics Committee, Approval No. 2011/173. A copy of the approval letter can be found in the Appendices of this thesis.
Cancer fatigue is reported as the most frequent symptom experienced by disease-free, post-treatment cancer patients and is perceived to be more severe than both pain and nausea. The significance of cancer fatigue is that it interferes with usual functioning, limiting the ability to carrying out essential activities of daily living and reduces quality of life. Despite this, the underlying pathophysiological mechanisms involved remain largely unknown. This is probably because the development of cancer fatigue likely represents a complex interaction between various disease and treatment factors and patient susceptibility. As such, limited understanding of the mechanisms involved in cancer fatigue impairs our ability to develop objective diagnostic criteria and successful mechanistic-driven interventions for this symptom. One approach to enhance our understanding of the pathophysiological mechanisms associated with cancer fatigue is to examine the manifestations of this symptom using exercise-induced fatigue models. The benefit of this approach is that manifestations of cancer fatigue symptoms could be objectively examined using reliable assessment methodologies widely adopted in neuromuscular research. However, few studies have used an exercise-induced fatigue models to investigate cancer fatigue. As such, the principal aim of this PhD thesis is compare the central contributions to exercise-induced fatigue associated with a sustained maximal voluntary isometric contraction of the elbow flexors between disease-free cancer survivors with persistent fatigue symptoms and healthy participants. In addition, physical activity, such as resistance training has demonstrated some success as an intervention for
reducing patient reported severity of cancer fatigue. However, the
neuromuscular and physical capacity adaptations associated with
improvements in reported fatigue symptoms within this clinical population
are unknown. Therefore, a secondary purpose of this PhD thesis is to
investigate the neuromuscular and physical capacity adaptations that occur
following a 12-week progressive resistance training program.

The PhD studies outlined in this thesis have intended to address the
gap within the literature by investigating the neuromuscular and physical
capacity adaptations associated with the performance of a 2min sustained,
maximal voluntary isometric contraction of the right elbow flexors and the
systemic inflammation, self-reported fatigue, sleep quality, depressive
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LIST OF ABBREVIATIONS

1RM: one repetition maximum
API: aerobic power index
BB: biceps brachii
BCa: breast cancer
BDI-II: beck depression inventory
BFI: brief fatigue inventory
BR: brachioradialis;
Ca: cancer
CAR: central activation ratio
CNS: central nervous system
CON: control group
CFS: chronic fatigue syndrome
CMAP: compound muscle action potential
CRF: cancer-related fatigue
CRP: c-reactive protein
CNS: central nervous system
DXA: dual energy x-ray absorptiometry
EORTC-F: european organisation for research and treatment of cancer quality of life questionnaire - fatigue subscale
EMG: electromyography
EMG_{rms}: root mean squared electromyogram
ERT: estimated resting twitch
GLU: glucose
Hb: haemoglobin
HEx: exercise comparison group
HPA: hypothalamic pituitary axis
HR: heart rate
HRQOL: health-related quality of life
HW: healthy women
IL: interleukin
M1: primary motor cortex
MEP: motor evoked potential

M_{max}: maximum compound muscle action potential

MVC: maximal voluntary contraction

MVF: maximal voluntary force

MVT: maximal voluntary torque

NM: Neuromuscular

NRS-101: 101-point numerical pain intensity rating scale

PCF: post cancer fatigue

PNS: peripheral nerve stimulation

PPO: peak power output

PSQI: Pittsburgh Sleep Quality Index

PTCa: post treatment cancer survivors

RALM: right upper arm non-osseous lean tissue mass

RMS: root mean square

RPE: rating of perceived exertion

RPFS: revised piper fatigue scale

RT: resting twitch

SIT: superimposed twitch

SP: silent period

TB: triceps brachii

TBFM: total body fat mass

TBLM: total body non-osseous lean tissue mass

TNF-α: tumour necrosis factor-alpha

TMS: transcranial magnetic stimulation

VA: voluntary activation

VAS-F: visual analogue scale

VO_{2\max}: maximal oxygen consumption

VO_{2\ peak}: peak oxygen consumption

VO^2: volume of oxygen consumption

Qol: quality of life
1 INTRODUCTION

1.1 Cancer Incidence, Survival, and Side-Effects

Cancer represents a major public health concern contributing to approximately 19% of the total burden of disease in Australia in the year 2012 (Australian Institute of Health and Welfare & Australasian Association of Cancer Registries (AIWH & AACR, 2008; AIHW, 2014, 2010; Hayes et al. 2009). In Australia, breast cancer is the third most commonly diagnosed cancer in women (AIHW, 2012c). In 2008, 28% of all cancers reported in females were breast cancer, with females in the 40-69 year old age bracket representing 69% of the total reported diagnose (AIHW, 2012c). A woman’s chance a breast cancer diagnosis before the age of 85 in the year 2012 was 1 in 8 (AIHW, 2012c). The total incidence of breast cancer in Australian women in 2011 was 14,465 new cases. Between 1982 and 2008 the number of new cases doubled from 5,310 to 13,567 cases (AIHW, 2012c), due mostly to the introduction of the national breast cancer screening program (AIHW, 2012c). Relative 5 year survival rates have increased from 79 -89% between the 1982 and 1987 and the 2006 and 2010 periods due largely to screening, earlier diagnosis and improved treatments (AIHW, 2012c). It is predicted that the number of new cases in 2020 will rise to 17,210 due to current trends in population ageing in Australia (Australia, 2012c).
Although declines in mortality and increases in survival rates for many cancers have been made in recent years, largely due to early detection and improved treatment regimens (AIHW, 2012a), more Australian women are living beyond the initial cancer diagnosis and treatment period. This sub-population of women who have completed primary cancer related treatments (surgery, chemotherapy, radiotherapy), and may be managing cancer through pharmacology aimed at preventing recurrence (e.g. tamoxifen) are commonly referred to within the literature as post-treatment cancer survivors (Beckjord et. al., 2014). Evidence suggests that post-treatment cancer survivors frequently experience significant morbidity and adverse side-effects associated with cancer and/or its treatment long after the cessation of treatment (Beckjord et. al., 2014). The most commonly frequently reported side-effects experienced by post-treatment cancer survivors include fatigue (Ryan et al., 2007a; Berger et. al., 2010; Ng, 2010; Schmidt et. al., 2012), pain (Chapman, 2011), sleep problems (Humpel & Iverson, 2010), depression (Reich et. al., 2008), lymphedema (Schmitz et. al., 2015) and nausea (Bower, 2007). Such enduring physical symptoms greatly undermine survivor’s health related quality of life (HRQOL) (Peoples et. al., 2013) impacting on both the social and economic wellbeing of the individual and their significant others (e.g. family, friends and caregivers) (Beckjord et. al., 2014; Schmitz et. al., 2015). Due to the increase in cancer survival rates, a larger number of cancer survivors are living with the long-term consequences associated with cancer and/or its treatment. Thus it is critical that the scientific community expands current understandings of the post-treatment side-effects in cancer survivors as the
focus for clinical practice in this population is frequently related to managing ongoing symptoms.

1.2 Cancer-Related Fatigue

Of the aforementioned adverse and enduring side-effects, fatigue is reported as the most persistent and debilitating by post-treatment cancer survivors (Wang et. al., 2014) which often continue for several years following treatment cessation (Bower et. al., 2006a; Prue et. al., 2006; Berger et. al., 2015a). Research evidence suggested that between 25 – 99 percent of cancer patients will report fatigue during the initial treatment period (Servaes et. al., 2002a; Lawrence et. al., 2004), although dependent on the sample group, type of treatment, and method of assessment (Bower & Lamkin, 2013). Furthermore, studies examining breast cancer survivors consistently report between 40-60% of persons will continue to experience persistent fatigue symptoms for up to 10 years following the cessation of curative treatment (Andrykowski et. al., 1998; Servaes et. al., 2002c; Bower et. al., 2006a; Meeske et. al., 2007).

The term cancer-related fatigue (CRF) is used to describe the fatigue associated with cancer or its treatment (Piper & Cell, 2010). For the purposes of this thesis persistent cancer fatigue is defined as a symptom experienced by post-treatment cancer survivors who have ceased receiving cancer related treatments for a minimum period of 6 months, which is characterised as being a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion that is not proportional to recent activity that interferes with usual functioning (NCCN, 2010) and cannot be primarily explained by other comorbid physiological (e.g.}
anemia) or psychiatric disorders (e.g. clinical depression) (Cella et al., 1998). To date no specific confirmatory laboratory or clinical tests are known for the diagnosis of CRF and no consistent abnormalities in muscle histology or biochemistry have been found (Berger et al., 2015b). Diagnosis is typically made by the process of exclusion and the presence of a constellation of clinical symptoms as stated in the *International Classification of Diseases 10th Revision-Clinical Modification* (Table 1.1) (Cella et al., 2001).

Compared to other cancer related physical symptoms persistent fatigue is reported as being the most prevalent and severe symptom experienced by post treatment cancer survivors (Ryan et al., 2007; Berger et al., 2010; Ng, 2010). As such persistent post-treatment fatigue substantially interferes with cancer survivor’s capacity to resume and perform normal activities of daily living and functioning and reduces their overall health related quality of life (Curt et al., 2000; Wu & McSweeney, 2007; Díaz et al., 2008; van den Beuken-van Everdingen et al., 2009; Peoples et al., 2013) and has long term implications for the individual, their family, careers and society (Beckjord et al., 2014). Researchers suggest that fatigue may also be a predictor of shorter survival and increased mortality rates (Groenvold et al., 2007; Weis & Horneber, 2015). As such, clinicians and health care providers are increasingly recognising that persistent fatigue in the post-treatment period is a significant health problem that warrants intervention.
**Table 1.1: ICD-10 diagnostic criteria for cancer-related fatigue**

(Cella et. al., 2001).

<table>
<thead>
<tr>
<th>The following symptoms have been present every day or nearly every day during the same 2-week period in the past month:</th>
</tr>
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<tbody>
<tr>
<td>Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level</td>
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<tr>
<th>Plus five (or more) of the following:</th>
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<tbody>
<tr>
<td>Complaints of generalised weakness or limb heaviness</td>
</tr>
<tr>
<td>Diminished concentration or attention</td>
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<tr>
<td>Decreased motivation or interest in engaging in usual activities</td>
</tr>
<tr>
<td>Insomnia or hyper-insomnia</td>
</tr>
<tr>
<td>Experience of sleep as unrefreshing or non-restorative</td>
</tr>
<tr>
<td>Perceived need to struggle to overcome inactivity</td>
</tr>
<tr>
<td>Marked emotional reactivity (e.g. sadness, frustration, or irritability) to feeling fatigued</td>
</tr>
<tr>
<td>Difficulty completing daily tasks attributed to feeling fatigued</td>
</tr>
<tr>
<td>Perceived problems with short-term memory</td>
</tr>
<tr>
<td>Post-exceptional malaise lasting several hours</td>
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**Other:**

<table>
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<tr>
<th>The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning</th>
</tr>
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<tbody>
<tr>
<td>Evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer-related therapy</td>
</tr>
<tr>
<td>The symptoms are not primarily a consequence of co-morbid psychiatric disorders such as major depression, somatisation disorder, somatoform disorder, or delirium.</td>
</tr>
</tbody>
</table>
Despite the clinical significance of cancer fatigue, the underlying pathophysiological mechanisms are poorly understood (Carroll et al., 2007; Berger et al., 2015b; Wang & Woodruff, 2015). However, it appears the etiology of cancer-related fatigue is complex and thought to involve the interaction of many factors due to dysregulation of several interrelated physiological, biochemical, and psychological systems (Gutstein, 2001; Mock, 2003; Ryan et al., 2007; Carroll, 2007; Ng, 2006) as demonstrated through the presence of multiple cancer fatigue correlates, including anaemia, cachexia, stress, sleep, anxiety, and depression (Cella et al., 1998). Further evidence of the complexity of the pathophysiology of cancer fatigue is the lack of reliable biomarkers indicating the presence of fatigue and that not all cancer patients or survivors develop fatigue symptoms (Mendoza et al., 1999; Lawrence et al., 2004; Hickok et al., 2005), which suggests the dysregulation of physiological systems due to various disease and treatment factors interact with patient susceptibility (Wang, 2008). The limitations in our current understanding of the mechanisms involved in cancer fatigue significantly impairs our ability to develop objective diagnostic criteria and mechanistic-driven interventions for this symptom (Wang, 2008). Therefore, research examining the pathophysiological mechanisms associated with cancer fatigue is a priority.

1.3 Research Approach

One approach to enhance our understanding of the pathophysiological mechanisms associated with cancer fatigue is to examine the manifestations of this symptom from a known perspective such as exercise-induced neuromuscular fatigue. Neuromuscular fatigue is defined
as an exercise-induced reduction in the ability to exert voluntary torque or power regardless of whether or not the task can be maintained despite maintained or increased perception of effort (Gandevia, 2001). The development of neuromuscular fatigue is broadly classified as either central and/or peripheral in origin. Central fatigue results from the inability of the nervous system to adequately drive motoneurons and may originate in any region of the motor pathway proximal to the neuromuscular junction (Boyas & Guével, 2011). Peripheral fatigue is associated with decline in the force-generating capacity of motor units due to changes at, or distal to, the neuromuscular junction (Gandevia, 2001). Studies examining contributions to exercise-induced neuromuscular fatigue have been successfully performed in other pathologies, such as chronic fatigue syndrome (CFS) (Samii et. al., 1996; Schillings et. al., 2004; Siemionow et. al., 2004; Chen et. al., 2008), Multiple Sclerosis (Steens et. al., 2012), Parkinson’s disease and fibromyalgia (Gur & Oktayoglu, 2008), and have provided new insights into the pathophysiological mechanisms involved.

Support for this approach comes from a proposed model of cancer-related fatigue offered by Ng et. al. (2007) in which the neuromuscular system is implicated as a possible contributor to the genesis of fatigue symptoms (Figure 1.1). This model suggests that cancer and/or related therapies may affect immune function (via pro-inflammatory cytokines) thereby influencing the functioning of the central nervous system (CNS), via the hypothalamic pituitary axis (HPA), leading to fatigue symptoms that are expressed through impaired neuromuscular function resulting in reduced exercise performance and/or increased sense of effort, which may result in decreased physical activity levels and a reduction in quality of life (Qol).
Figure 1.1: Proposed model for impaired neuromuscular function in the development of cancer-related fatigue (CRF) resulting in physical inactivity and a decline in quality of life (Qol).
Evidence to support this model comes from studies reporting elevated markers of peripheral systemic inflammation, such as interleukin (IL)-1, IL-6, C-reactive protein (CRP), and tumour necrosis factor-alpha (TNF)-α, in post-treatment cancer survivors with fatigue (Bower et. al., 2002; Alexander et. al., 2009). A bi-directional, immune-to-brain communication pathway is known to exist between the central nervous system (CNS) and the peripheral systemic system (Dantzer et. al., 2014). As such, it is proposed that peripherally released cytokines may affect central neurotransmission indirectly by modulating the bioavailability of amino acid precursors of neurotransmitters (Dantzer et. al., 2014) whereby continued activation of the immune system may lead to persistent fatigue symptoms (Dantzer et. al., 2014).

Several reports suggest that neuromuscular function may be impaired in response to exercise-induced fatigue in cancer patients (Bruera, et al., 1988; Monga et. al., 1997; Yavuzsen et. al., 2009); however, available data are limited and few studies focus exclusively on the post-treatment period. Previous studies investigating neuromuscular function in cancer patients with persistent fatigue symptoms have failed to demonstrate consistent findings. Some neurophysiological studies have indicated the involvement of central mechanisms (Yavuzsen et. al., 2009; Kisiel-Sajewicz et. al., 2012; Kisiel-Sajewicz et. al., 2013; Cai et. al., 2014), where others have observed no difference in central motor function in cancer patient with fatigue compared to healthy participants (Neil et. al., 2013; Prinsen et. al., 2015). Thus, the presence altered central and/or peripheral contributions to exercise-induced neuromuscular fatigue in persons with cancer remains unclear.
1.4 Exercise Interventions

Exercise appears to be one of only a few interventions that have demonstrated some efficacy in reducing cancer fatigue symptoms (McNeely & Courneya, 2010b; Puetz & Herring, 2012; Denlinger et. al., 2014). To date, the majority of research examining exercise as an intervention for cancer fatigue has utilized aerobic-based programs (Battaglini et. al., 2006; Culos-Reed et. al., 2007) and/or the effects of combined aerobic and resistance training activities (Schmitz et. al., 2010; Cramp & Byron-Daniel, 2012; Berger et. al., 2015a); while few studies have been conducted investigating resistance training as an independent intervention for fatigue outcomes (Battaglini et. al., 2006) there are no available data on the extent of neuromuscular adaptation associated with resistance training in cancer survivors with persistent fatigue symptoms. This is surprising given the possible involvement of the neuromuscular system in the development of cancer-related fatigue and the fact that resistance training is the most effective exercise stimulus to enhance neuromuscular function. As such, additional research in these areas is warranted.

1.5 Research Aims

From reviewing the current literature on there appears to be a number of areas requiring further investigation. The respective studies within the present thesis will attempt to address the following aims.

Study 1: Persistent fatigue, systemic inflammation, neuromuscular function and the association between variables in cancer survivors and healthy women.
Research Aim: To compare perceived fatigue, levels of circulating pro-inflammatory cytokines, aerobic exercise capacity, and neuromuscular function between disease-free, post primary treatment cancer survivors and healthy persons and examine the associations between variables.

**Study 2: Central Manifestations Associated With A Sustained Maximal Voluntary Contraction Between Cancer Survivors with Fatigue Symptoms and Healthy Women**

Research Aim: To compare the central contributions to exercise-induced fatigue associated with a sustained maximal voluntary isometric contraction of the elbow flexors between disease-free cancer survivors with persistent fatigue symptoms and healthy participants.

**Study 3: Effects of Short-Term Resistance Training On Muscular Strength and Central Adaptations In Cancer Survivors With Fatigue Symptoms And Healthy Women**

Research Aim: To compare the effects of 12-week of resistance training on muscle mass, muscular strength and neuromuscular performance between cancer survivors with persistent fatigue symptoms and healthy women.

**Study 4: Effects of Short-Term Resistance Training On Fatigue Symptoms And Neuromuscular Manifestations Associated With A Sustained Maximal Voluntary Contraction In Cancer Survivors And Healthy Women**
Research Aim: To compare the effects of 12 weeks of resistance training on persistent fatigue symptoms and neuromuscular manifestations associated with an exercise-induced fatigue task before and after training between cancer survivors and healthy women.

1.6 Significance of the Thesis

The pathophysiology of cancer fatigue has not yet been adequately elucidated and no physiological markers have been established. Frequently reported comorbidities of cancer fatigue included sleep disturbances and depressive symptoms, which lead to significant impairments in the health-related quality of life of cancer survivors. Current understanding indicates that inflammatory processes may contribute to alterations in central processing thereby causing behavioural changes leading to persistent fatigue symptoms. This proposed model of cancer-related fatigue suggests the possibility of impaired central processes underlying, at least in part some of, the mechanisms involved in cancer fatigue. Knowledge regarding the neuromuscular mechanisms associated with cancer fatigue may assist in furthering current knowledge of the involvement of central processing in the manifestations of fatigue symptoms in cancer survivors. By examining the manifestations of this symptom using a neuromuscular exercise-induced fatigue model the expression of fatigue can be objectively examined using reliable assessment methodologies widely adopted in neuromuscular research. Thus, the findings from this thesis may provide new insights into the factors contributing to persistent fatigue symptoms in cancer survivors, including evidence to support the complex model of cancer-related fatigue.
and the possible involvement of the neuromuscular system via altered functioning of central processes.

Exercise, including resistance based training has demonstrated some efficacy in reducing self-report symptoms of fatigue in the cancer fatigue population. Currently limited literature and recommendations pertaining to resistance training within the disease-free, post-treatment cancer survivors exists. Understanding the effects of resistance training programs on fatigue symptoms may assist in the development of evidence-based exercise interventions that assist with managing ongoing symptoms and improve physical function and overall quality of life. As such, it is anticipated that the research findings from this thesis may strengthen existing literature regarding the effect of resistance training exercise as a stand-alone intervention in ameliorating fatigue symptoms in post-treatment cancer survivors, thereby providing practical recommendations that can be implemented by exercise professionals to enhance client health outcomes.

1.7 Limitations

Despite the significance of this thesis, there are several limitations with respect to studies performed that should be disclosed.

- The comparative, cross-sectional design of the study constrains the generalisability of most of the study findings. Therefore, cause and effect relationships cannot be elucidated based on the current research findings.
• Due to the specific participant sample being investigated any results from this study should be transferred to other cancer and/or fatigued participants with caution.

• The sample population was limited and consisted of a convenience sample; therefore participants were not randomly selected.

• The participant groups were not age-matched. Although the cancer survivors were older than the healthy women, both groups were well matched for physical characteristic including height, Mass, BMI, TBLM, TBFM, RALM, API, VO_{2peak}. Ageing is a complex and multidimensional process with age-associated declines in physical function attributed to characteristics beyond chronological age. Based on current understandings of the rate of age-related loss in muscle mass and motor unit recruitment, the 7 year age difference between groups is unlikely to result in major differences in physical performance and/or neuromuscular function.

• The cancer participants within this study were a heterogeneous sample of disease-free survivors who differed in cancer type (breast and ovarian cancers), stage at diagnosis, time since diagnosis, treatments received, and duration of treatment, among other things. As both breast and ovarian cancer are hormonally drive, they may share a common underlying pathology. Evidence indicates that cancer fatigue is not isolated to one particular cancer type and the mechanisms of such are viewed as being comparable amongst different cancers due to similar treatment/s. Therefore, the data presented is limited to providing general descriptive information as it
related to fatigue and neuromuscular adaptations to resistance training.

- Cancer fatigue, for the purposes of this thesis, was defined as a symptom experienced by post-treatment cancer survivors that could not be primarily explained by other comorbid physiological (e.g. anemia) or psychiatric disorders (e.g. clinical depression) (Cella et al., 1998).

- The exclusion/inclusion criteria was based on limiting other common clinical symptoms and conditions (e.g. sleep, depression, anaemia etc.) that can independently cause fatigue thereby potentially influencing the research findings. The aim was to recruit as close to a homogenous group as possible so that the variables under investigation could be appropriately compared between the groups.

- Participants were required to complete several self-report questionnaires related to fatigue severity, depression symptoms, sleep quality and pain as well as report ratings of perceived exertion. All efforts were made to ensure compliance with the study objectives; however, the validity of such self-reported data may be questionable.

- During each testing session, it is possible that participant positioning on the testing apparatus and/or placement locations of the TMS coil and EMG electrodes, for example, used for testing placement may have altered slightly between tests despite the efforts used for standardisation.

- Study findings are restricted to the specific task condition including joint angle, contraction and movement velocity, muscle group and
extrapolation of these observations to other movements and muscles will not be inferred.
2 REVIEW OF THE LITERATURE

2.1 Overview

This literature review aims to provide a detailed background context to support the studies presented in this thesis. Firstly, cancer fatigue is discussed where it is defined according to clinical diagnostic criteria and discusses our current understanding regarding the pathophysiological mechanisms involved. Issues associated with the assessment of cancer fatigue and an evaluation of the primary self-report tools used in the literature to quantify fatigue symptoms is presented. The concept of neuromuscular fatigue is then addressed and the two broad classifications used to describe fatigue processes are explained along with the primary factors influencing the task dependency of fatigue. This review concludes by reviewing the available literature examining neuromuscular fatigue within cancer setting and the effects of resistance training.

2.2 Background

Cancer is a major cause of illness in Australia which has a significant social and economic impact on individuals, families and the community (AIHW, 2014). In 2014, it was estimated that 123,920 people would be diagnosed with cancer and 45,780 people would die from cancer in Australia (AIHW, 2014). A recent report regarding the global burden of disease studies indicates that cancer contributed to between 16% and 19% of the total disease burden in Australia (Horton, 2012). Improvements in the screening and treatment of cancers has created a large and growing
population of survivors, estimated to be over 300,000 in Australia (Eakin et al., 2007). Cancer survivorship is recognised as beginning at diagnosis and continuing long after treatment ends. Over 130,000 Australian women are reported as being survivors of breast cancer, with improvements in five-year survival rates increasing from 72% 20 years ago to current rates of 89% (AIHW, 2012).

Cancer survivors frequently undertake extensive treatment regimens that is associated with long term sequelae subsequent to cancer and its treatment that may chronically impair the health status and quality of life (Qol) of cancer survivors. Common acute treatments for breast cancer specifically include surgery, chemotherapy and radiotherapy are the most common acute treatments (Jiwa et. al., 2014). Hormone therapy, such as Tamoxifen or aromatase inhibitors are often continued for periods of up to five years, which are used to prevent reoccurrence in breast cancer survivors (Patidar et. al., 2013). Although these forms of treatments have been successful in the treatment of breast cancer, many of the side-effects are known to contribute to a decline in normal functioning of many physiological systems of the cancer survivor (Battaglini et. al., 2006). Frequently reported side-effects includes fatigue, pain, and sleep problems (Beckjord et. al., 2014). However, current understandings and availability of effective treatments for these the long-term health consequences associated with cancer and or its treatment is incomplete. Moreover, such side-effects can lead to decreased physical activity, and a reduction in quality of life. As such improving current knowledge regarding the long term, health related side-effects experienced by post-treatment cancer survivors and the underlying mechanisms is essential in being able to develop effective
management strategies aimed at improving health-related quality of life (HRQOL). Promoting the health and wellness of cancer survivors is essential to improving current and future population health in Australia.

Cancer, in addition to several other health conditions that contribute greatly to Australia’s current burden on health (e.g. arthritis and musculoskeletal disease, asthma, cardiovascular health and stroke, diabetes mellitus, injury prevention and control, mental health, obesity and dementia) represent a key area of national research priority by the National Health and Medical Research Council, National Health Council in Australia (NHMRC, 2015). The current precedence for research into the cancer survivorship population includes the development of tools and instruments for use in survivorship research; effective care models and interventions; investigations of the long-term effects of cancer diagnosis and treatment on patients, their families and caregivers (Girgis & Butow, 2009). Hence, investigations in the area of improving the overall health of cancer survivors is of importance.

### 2.3 Definition of Cancer Fatigue

The term fatigue can be defined in a number of ways, referencing not only to a physiological or pathological state in which muscles perform below their expected maximum, but to a symptom reported by subjects in whom there may be no obvious defect in muscle performance. In the oncology setting fatigue has been defined by the National Comprehensive Cancer Network (NCCN, 2010) as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion that is not
proportional to recent activity or relieved by rest that interferes with usual functioning. Fatigue is a notable clinical problem in cancer survivors. It may appear as a symptom prior to cancer diagnosis, become evident during the treatment (Smets et. al., 1993), or long after the cessation of treatment (Prue et. al., 2006). For long term cancer survivors, fatigue is the most common and interfering symptom (Bower et. al., 2002; Anderson et. al., 2003). In a longitudinal study involving 763 breast cancer survivors, 34% reported being fatigued 5-10 years after diagnosis, with 35% reporting fatigue 1-5 years after diagnosis. At total of 21% of the participants were fatigued at both time points, indicating that persistent fatigue is experienced by a significant proportion of cancer survivors (Bower et. al., 2006). Cancer fatigue is clinically significant as it interferes with overall quality of life, mood states, sleep-wake cycle, and personal relationships (Bower et. al., 2002; Lawrence et. al., 2004; Collado-Hidalgo et. al., 2006). Prospective studies have also demonstrated a strong association between the manifestations of cancer fatigue and shorter survival (Groenvold et. al., 2007).

### 2.4 Pathophysiology of Cancer Fatigue

The specific mechanisms that precipitate or sustain the cancer fatigue phenomenon are not known (Portenoy & Itri, 1999). It has been suggested that the cancer fatigue is related to both tumour and treatment related variables (Dimeo, 2001). However, neither disease nor treatment type have demonstrated reliable associations with fatigue in cancer survivors (Fagundes, 2011). A recent meta-analysis reports that the severity
of fatigue appears to be unrelated to the type of cancer, cancer stage at
diagnosis, size of original tumour, number of nodes involved, presence and
site of metastases (Servaes et. al., 2001). Additionally, cancer fatigue does
not appear to be related to the type or extent of cancer treatment (including
chemotherapy regime, dose, and cycles, and type of radiation), length of
treatment. Moreover, time since treatment completion is not consistently
related to the presence or severity of fatigue among survivors (Morrow et.
al., 2002; Prue et. al., 2006).

Due to the lack of consensus and the wide range of possible
variables that may contribute to cancer fatigue, it has been proposed that
cancer fatigue maybe a final common pathway which is influenced by
several predisposing and etiologic factors (Portenoy & Itri, 1999). Evidence
to support this come from numerous reports demonstrating that cancer
fatigue is not an isolated symptom; rather it co-exists with other co-morbid
conditions (Ryan et. al., 2007a). Common physiological correlates of cancer
fatigue include anemia, cachexia, altered sleep patterns, poor nutritional
status, and psychological health, such as depression and anxiety (Gutstein,
2001; Mock, 2003; Ryan, et al., 2007). Therefore, cancer fatigue is likely to
manifest due the dysregulation of several interrelated physiological,
biochemical, and psychological systems (Ryan, et al., 2007). Unfortunately
at present, research into cancer fatigue has not progressed to a point where
researcher understand why several symptoms may co-exist, how these
factors interact and/or the underlying processes which cause symptoms to
cluster together (Ryan, et al., 2007). Several theoretical models of cancer
fatigue have been developed; however, due to the complex nature of this
phenomenon, no model currently provides adequate perspective to examine the construct of cancer fatigue.

Frequently proposed physiological mechanisms underlying cancer fatigue have included increased levels of pro-inflammatory markers, altered serotonin metabolism, hypothalamic-pituitary-adrenal axis disruption and vagal afferent nerve activation, and circadian rhythm de-synchronisation (NCCN, 2010). Recently an increasing number of studies have reported evidence suggesting that pro-inflammatory cytokines are possible contributors to the manifestations of fatigue in susceptible individuals (Bower et. al., 2002; Shor, 2003; Alexander et. al., 2009; Wyller et. al., 2009; Minton et. al., 2015). Both the cancer itself and the range of treatment modalities (chemotherapy, radiation, surgery etc) used to treat and manage cancer can trigger an inflammatory response (Navigante et. al., 2013; Minton et. al., 2015). Strong associations between increased fatigue symptoms and inflammatory cytokines such as interleukin IL-1, IL-6, C-reactive protein (CRP), and tumour necrosis factor-alpha (TNF)-α have been demonstrated in a number of studies (Bower et. al., 2002; Morrow et. al., 2002; Alexander et. al., 2009). Higher proinflammatory cytokine levels including TNFα, and IL-6 were reported in breast cancer survivors experiencing fatigue as compared to non-fatigued survivors (Morrow et. al., 2002). Most of the evidence linking inflammation and fatigue in cancer survivors has been collected in breast cancer survivors; however immune activation has been implicated in fatigue among other groups as well. Higher blood CRP levels were found in fatigued post treatment testicular cancer survivors (median of 11 years post-treatment) (Orre et. al., 2011). Moreover, decreases in plasma IL-6 concentration have been observed in
ovarian cancer survivors who experienced improvements in fatigue symptoms in the year following treatment (Schrepf et. al., 2013). However it is important to state that correlation does not mean causation. A variety of proinflammatory cytokines and markers of increased cytokine activity, across a diverse range of cancer types and during different treatment and survivorship periods have been reported (LaVoy et. al., 2016). However, at present a specific biomarker of cancer fatigue has yet to be established. The lack of a cancer fatigue biomarker greatly limits diagnosis and clinical management.

Research evidence suggests that a bi-directional, immune-to-brain communication pathway exists between the central nervous system (CNS) and peripheral systemic systems (Dantzer et. al., 2014). Both animal and healthy human based studies have found that pro-inflammatory cytokines can signal the central nervous system to generate symptoms of fatigue and other behavioural changes (Dantzer et. al., 2014). It has been postulated that peripherally released cytokines affects central neurotransmission, indirectly by modulating the bioavailability of amino acid precursors of neurotransmitters (Dantzer et. al., 2014). Cytokine may act on the CNS via the activation of sensory nerves (Dantzer et. al., 2012). Continued activation of the immune system may lead to behavioural changes including persistent fatigue symptoms (Dantzer et. al., 2014). Specifically, peripheral cytokines prompt the production and release of inflammatory mediators, including prostaglandins and cytokines by endothelial cells, and macrophages and microglia in the central nervous system. These inflammatory mediators are thought to be capable of altering astrocyte, oligodendrocyte, and endothelial cell functions thereby influencing neurons (Dantzer et. al., 2014). Based on
this evidence prolonged systemic inflammation and cytokine dysregulation associated with cancer and its treatment has been considered as a possible precipitant leading to alterations in central processes; which may contribute to disruption in sensory perception causing ongoing perception of fatigue symptoms and the development of central fatigue. To date, there is limited understanding of the neural processes that may mediate effects of peripheral inflammation on behavioural outcomes, including fatigue in cancer survivors.

Other factors suggested to be associated with cancer fatigue include losses in muscle mass and physical deconditioning (LaVoy et al., 2016). It has been proposed that reduced muscle mass and decreased strength capacity may contribute to cancer fatigue (Al-Majid & McCarthy, 2001). However, evidence supporting this theory is equivocal as authors have observed that muscle weakness remains evident in this population even after correction for muscle mass and/or size (Bruera, Brenneis, Michaud, Jackson, & MacDonald, 1988). Similarly, it has been suggested that reduced physical activity levels and consequential muscle disuse may be one potential mechanism contributing to fatigue. Cancer patients are frequently advised to rest and reduced their daily physical activity levels (Dimeo, 2001). Unfortunately prolonged rest and inactivity can lead to reduced neuromuscular functioning, which may contribute to perpetuating the symptom of fatigue. Several recent meta-analyses indicate that exercise is one of a few valuable interventions for reducing cancer fatigue (Schmitz et al., 2005b; Kangas et al., 2008; Minton & Stone, 2008). Such findings provide strong evidence that the pathophysiology associated with cancer fatigue may manifest through neuromuscular mechanisms.
In contrast to the view that cancer fatigue represents systemic dysfunction, it has been suggested that the fatigue response in cancer patients may be a protective mechanism that acts to prevent overexertion, which could lead to enduring tissue injury and/or to promote tissue regeneration (Ryan, et al., 2007). Therefore, cancer fatigue may have a function as a warning sign similar to pain, which functions to drive the individual to seek a refuge where they can rest and repair (Armes et. al., 2004).

Several hypotheses have been proposed to explain the development of fatigue symptoms with cancer and/or its treatment. However, these hypotheses have largely been developed based on observed associations between variables that have led to mechanisms being proposed that are yet to be fully established (Ryan et. al., 2007; Wang, 2008; Bower, 2014). More research is needed to identify cause-effect relationships and the primary mechanisms involved.

2.5 Assessment of Cancer Fatigue

At present, no valid biological objective measure of cancer fatigue is available. As such, the assessment of cancer fatigue involves the use of self-report instruments (Stone et. al., 2000). Self-report instruments are used frequently within health-related research. This type of instrumentation is often employed when variables of interest are difficult or impossible to directly observe. This methodology involves the individual self-rating their subjective interpretation of the phenomenon in question, typically involving the completion of a questionnaire. Accordingly, due to the subjective
methodology, self-report measurements are confounded by limitations. Several factors that may affect the validity of self-reported measures include method variance, situation variance, natural variability within a given method and situation, and rater variance (Howard, 1994). However, others have indicated that when used properly self-report instruments can be reliable, valid and sensitive in assessing subjective patient experiences (Gift, 1989).

Several validated self-report tools have been devised to evaluate the presence of fatigue symptoms in patient populations; however, currently no gold-standard self-report instrument exists (Bruera & Neil MacDonald, 1988; Prue et. al., 2006; Shen et. al., 2006). Several questionnaire have been constructed to measure overall fatigue levels using a single score system (Dittner et. al., 2004). These single item instruments are collectively referred to as uni-dimensional scales, which typically use visual analogue and likert-type scales (Jacobsen, 2004). These scales are easy to administer, interpret and some report good level of internal consistency and test–retest reliability (Jacobsen, 2004). However, fatigue is a complex phenomenon that involves several distinct features, including severity, persistence, duration, impact and interference on usual functioning, and variability (Portenoy & Itri, 1999). Therefore, it has been suggested that uni-dimensional instruments are deficient in that they consider fatigue as a single entity without consideration of these additional co-existing features. Moreover, fatigue has been described as being multidimensional with several modes of expression including physical, cognitive and psychological components (Smets et. al., 1993; Hwang et. al., 2003). Therefore, some authors have recommended the use of multi-dimensional questionnaires,
which consider more than a single fatigue dimension in the assessment (Portenoy & Itri, 1999). Multidimensional scales are typically longer but captures multiple characteristics and manifestations of fatigue and its impact on function, providing a more a detailed qualitative and quantitative assessment of fatigue than the measurement of severity alone. This can make them useful for comparing profiles across conditions for descriptive research or in seeking to identify mechanisms underlying specific aspects of fatigue (Dittner et. al., 2004).

Several self-report instruments have been used more frequently in the literature to assess fatigue in cancer patients. These include the Brief Fatigue Inventory (BFI), the revised Piper Fatigue Severity Scale, and the Visual Analogue Scale.

### 2.5.1 Brief Fatigue Inventory

The Brief Fatigue Inventory (BFI) consists of a nine item questionnaire, which measures both severity and impact of fatigue (Mendoza et al., 1999). A single item of the instrument assesses fatigue at the present time and the other 8 items assess fatigue during the last 24 hrs. The questions consist of self-report descriptions which range from experiencing no fatigue to fatigue as bad as you can imagine. Each item is responded to by subjects using a 0-10 numeric scale, and a global BFI score is calculated as the mean of the nine questions (Chang et. al., 2007). A benefit of this scale is that it identifies cut off points to discriminate different levels of fatigue severity and is reported as a reliable instrument (Shen et. al., 2006). A score of 1–3 mild fatigue, 4–6 for moderate, and 7–10 for “severe” fatigue (Mendoza et. al., 1999). Moreover, the BFI enable a
fast assessment of fatigue severity which has been used previously within clinical screening and trials. The BFI has been demonstrated as being significantly correlated with the Profile of Mood States (POMS) Fatigue subscale ($r=0.84$, $P<0.001$) and the Functional Assessment of Cancer Therapy (FACT) ($r=-0.88$, $P<0.001$). This suggests that the BFI has a reasonable level of validity (Shen et al., 2006). The BFI has been previously used in CRF investigations (Wang et al., 2001).

### 2.5.2 Revised Piper Fatigue Scale

Originally developed to measure fatigue in cancer patients, the Piper Fatigue Scale Survey (PFSS) provides a quick and accurate assessment of current level of fatigue. In 1998, the Revised PFS (RPFS) was developed and validated in a sample of women recovering from breast cancer (Piper et al., 1998). The Piper Fatigue scale consist of a multidimensional questionnaire with four major dimensions including sensory, affective meaning, cognitive/mood and behavioural/severity. The response format consists of asking subjects to provide a rating of between 0-10. The internal consistency of the scale is high with concurrent validity with the fatigue questionnaire (FQ) ($r=.80$) and good test–retest reliability results ($r=.98$). Moreover, a recent study also observed good psychometric properties in a population of postpoliomyelitis patients.

### 2.5.3 Visual Analogue Scale

In contrast to the BFI and PFSS, a Visual Analogue Scale (VAS) is a measuring instrument that attempts to assess characteristics such as fatigue that is thought to occur along a continuum. Unlike the BFI and PFSS, which
both use a 0-10 rating scale, the VAS consists of a horizontal line, 100mm in length, anchored by word descriptors including ‘No fatigue’ and ‘Very severe fatigue’ at each end of the line (continuum). Subjects are asked to place a mark on the line at the point that they feel best represents their perception of their current fatigue state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the subject marks (Wewers & Lowe, 1990).

2.5.4 European Organisation for Research and Treatment of Cancer quality of life questionnaire: Fatigue Subscale

The QLQ-C30 is a multi-dimensional assessment tool as it includes a range of items covering physical, emotional and social health issues. The fatigue subscale of European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-F) is also recommended for assessing fatigue associated with cancer (Seyidova-Khoshknabi et al., 2010) and consists of three questions examining the physical domain over the past week; “Did you need to rest?”, “Have you felt weak?”, and “Were you tired?”. Each item scored out of 4, whereby a raw score, calculated as the mean score of the three (3) questions, was linearly transformed \( \left[ \frac{\text{mean score} - 1}{\text{range}} \times 100 \right] \) so that the overall fatigue was scored between 0 - 100; a higher score indicating greater fatigue (Holzner et al., 2001; Knobel et al., 2003). The ECORT-F measures symptom intensity during past week. The items shows a high correlation between fatigue and physical function. There is sufficient evidence to support its reliability and validity (Aaronson et al., 1993; Fayers et al., 2001).
Thresholds to define clinically relevant fatigue levels have been suggested for the ECORT-F although approaches vary across studies (Yarbro et. al., 2013). A previous study used a cut off score of 20 for establishing clinical fatigue in cancer patients using this instrument (Snyder et. al., 2010). Another approach is based on the response, thereby classifying individuals as having a clinically important fatigue if they respond with at least “a little” for any given item assessed on the 4 point response scale (i.e. “not at all,” “a little,” “quite a bit,” and “very much”) (Giesinger et. al., 2016).

2.5.5 A Practical Approach to Measuring Cancer Fatigue

A wide range of self-report tool are currently available for measuring cancer-related fatigue (Seyidova-Khoshknabi et. al., 2011). The large number of available tools is due somewhat to the disparities in the way that cancer fatigue is conceptualised by both researchers and clinicians (Jean-Pierre et. al., 2007). At present, there is a lack of agreement regarding the optimal tool to use (Koornstra et. al., 2014; Wang & Woodruff, 2015), and little standardisation between research investigations (Ahlberg et. al., 2003). Consequently, the selection process for isolating one criterion tool for measuring cancer fatigue using a self-report tool remains challenging.

While existing instruments may demonstrate satisfactory psychometric properties, the etiology of cancer related fatigue is not discrete rather it is multi-dimensional and may manifest itself in several domains (e.g. mood, cognition, and physical symptoms). Ideally the tool selected should be sensitive to the full range of fatigue related presentations (Dittner
et. al., 2004). Presently, no one questionnaire is currently capable of capturing simultaneously all of the aspects and/or dimensions (Morrow et. al., 2005; Prue et. al., 2006; Bardwell & Ancoli-Israel, 2008; Strasser et. al., 2009). Some tools measure phenomenology, others quantify fatigue severity or impact, while many assess a combination of all these fatigue related characteristics (Dittner et. al., 2004). As such, the use of a single instrument could lead to the possibility of inadequately capturing important, holistic details regarding this phenomenon (Strasser et. al., 2009). From a practical point of view, it has been suggested that the measurement and monitoring of cancer fatigue may require the use of several instruments concurrently (Schwartz, 2002; Morrow et. al., 2005).

### 2.6 Motor Pathway

Voluntary movements are initiated and controlled through the interaction between the nervous system and muscular system. The motor pathway originates in the precentral gyrus, located in the cerebral cortex, and descends through the spinal cord where it synapses with alpha motoneurons located within the ventral horn (Enoka, 2008). The major descending motor pathway is known as the corticospinal tract, which transmits the action potentials necessary for exciting alpha-motoneurons, which activate skeletal muscle. This pathway involves a monosynaptic connection between the motor cortex and the alpha motoneuron. The alpha-motoneuron is considered to be the final common pathway for transmitting neural information from a variety of sources to the skeletal muscles, thereby controlling the contraction of skeletal muscles (Enoka, 2008). For a muscle
contraction to occur successfully the action potential must propagate along
the motor axon and then propagate from the nerve to the muscle.

2.7 Neuromuscular Fatigue

For the purpose the thesis neuromuscular fatigue is defined is an
exercise-induced reduction in the ability to exert voluntary torque or power
regardless of whether or not the task can be maintained despite maintained
or increased perception of effort (Gandevia, 2001). Neuromuscular fatigue
may develop as a result of impaired function at one or more sites anywhere
along the motor pathway. In order to more clearly distinguish between sites
along the motor pathway contributing to the development of neuromuscular
fatigue and to distinguish between the physiological mechanisms involved,
neuromuscular fatigue may be classified as being peripheral and/or central
in origin (Kisiel-Sajewicz et. al., 2012) (Figure 2.1).

2.7.1 Peripheral Fatigue

Peripheral fatigue is characterised by impairments in specific areas
within the motor pathway distal to the central nervous system; specifically
the neuromuscular junction or within the muscle fibres (Gandevia, 2001)
when the neural drive to the muscle has increased or remains unchanged
(Davis & Bailey, 1997; Enoka, 2008). Peripheral fatigue occurs when there
is a decrease in the force generating ability of a muscle as a result of
impairments in neuromuscular transmission, signal propagation along the
sarcolemma, cross-bridge formation, or excitation contraction coupling.
Thus, the capacity for forceful muscle contraction is reduced. Peripheral
fatigue has been suggested to be related to the interaction among several
Figure 2.1: Schematic illustration of potential sites of fatigue (Kisiel-Sajewicz et. al., 2012).
factors, including the availability of blood flow, tissue oxygen saturation, delivery and availability of necessary substrates for muscle metabolism, the accumulation of metabolites such as lactate, hydrogen ions, ammonia (Kayser, 2003), in addition to changes in the release and binding of calcium ions (Allen et. al., 1995; Davis & Bailey, 1997).

2.7.2 Central Fatigue

In contrast to peripheral fatigue, central fatigue occurs at spinal or supraspinal locations and is best demonstrated by a progressive failure to voluntarily drive alpha-motoneurons causing a decline in motor unit recruitment and/or firing frequency (Gandevia, 2001; Ryan, et al., 2007a). The physiological basis of central fatigue remains unclear. Central fatigue can originate in any of the sites involved in the production of movement located above the neuromuscular junction. Potential factors include a reduction in cortical drive, corticospinal excitability and alpha-motoneuron excitability (Lepers et. al., 2002), as well as reflex inhibition and disfacilitation, Renshaw cell inhibition (Schillings, Hoefsloot, Stegeman, & Zwarts, 2003, 2003) and possible depletion of neurotransmitters at central synapses (Taylor, Butler, & Gandevia, 2000a).

2.7.2.1 Alpha-Motoneuron

Alpha motor-neuron activity is influenced by synaptic input from the descending tracts, afferent pathways, and by the intrinsic neuron properties. Additionally, the inter-neuronal circuitry within the spinal cord is involved in reorganising and transmitting signals to the motor-neurons. Moreover, fatigue-sensitive afferent input from skeletal muscles, such as 1a afferents as
well as group III and IV afferents, can have a direct influence on alpha-
мотонейрон excitability and increase motor activity (Gandevia, Allen,
Butler, & Taylor, 1996).

2.7.2.2 Motor Unit Recruitment and Firing Frequency

The neural control of muscle force is regulated through varying the
level of motor unit activity during contraction. Motor unit recruitment refers
to the total number and type of motor units activated during contraction.
Motor units are recruited according to the size principle (Latash, 2008).
Smaller motor units have a small motoneuron and a low threshold for
activation. These motor units are recruited first. As more force is required to
continue performing a contraction, progressively larger motor units are
recruited. This is functionally significant. During activities that require low
force production the ability to recruit only a few muscle fibres enables fine
motor control. As more force is required each newly recruited motor unit
contributes to the overall force produced.

Muscle force may also be controlled through regulating the
frequency at which each motor unit is signalled to fire (Barnes, 1980). The
firing of motor units is regulated independently by its matched alpha-
motoneuron. Within a given motor unit there is a range of possible firing
frequencies at which it may discharge. Slow units operate at a lower
frequency range than faster units. Within that range, the force generated by
a motor unit increases with increasing firing frequency. If an action
potential reaches a muscle fibre before it has completely relaxed from a
previous impulse, then force summation will occur. By this method, firing
frequency affects muscular force generated by each motor unit. Motor unit
recruitment is regulated by required force. In the unfatigued muscle, a
sufficient number of motor units will be recruited to supply the desired force. Initially desired force may be accomplished with little or no involvement of fast motor units. However, as slow units become fatigued and fail to produce force, fast units will be recruited as the brain attempts to maintain desired force production by recruiting more motor units. Consequently, the same force production in fatigued muscle will require a greater number of motor units. This additional recruitment brings in fast, fatigable motor units.

2.7.2.3 Other Potential Factors Influencing Central Fatigue

Altered motivation and/or sensory-perception may also contribute to the development central fatigue (Davis & Bailey, 1997; Meeusen, Watson, Hasegawa, Roelands, & Piacentini, 2006). A proposed mechanism of central fatigue related to motivation involves the serotonergic pathways (Meeusen, et al., 2006). It has been suggested that the ratio between certain brain neurotransmitters, specifically serotonin and dopamine, may influence the level of central activation, thereby influencing the ability to perform sustained motor output (Van Houdenhove et. al., 2007). It has been suggested that an increase in the central ratio of serotonin to dopamine is associated with the sensation of tiredness and decreased motivation, which is observed to accelerate the onset of fatigue. In contrast, a low ratio favours improved performance with a notable increase in motivation and arousal. Moreover, the serotonergic system has been reported to be an important modulator of mood, emotions, sleep and appetite (Meeusen, et al., 2006). Research examining persons with chronic fatigue syndrome has demonstrated an increase in brain 5-hydroxytryptamine (5-HT) function,
increase numbers and more sensitive 5-HT receptors, and decreased 5-HT receptor affinity with a higher perception of effort.

It has been proposed that altered sensory-perception, which is defined as a state in which an individual experiences a change in the amount or patterning of afferent stimuli accompanied by a diminished, exaggerated or impaired response to a given stimulus, may be associated with central fatigue (Gibson et al., 1993; Van Houdenhove et al., 2007). It has been theorised that the sensory thresholds associated with the sensation of fatigue may become reduced; thus, the persistence of fatigue symptoms may become a learned response to stimuli that is no longer present. That is to say, the sensation threshold to fatigue may be reset. Therefore, it is possible that an exacerbated perception of effort or sensory feedback during activity may lead to a decline in central motor output (Gibson et al., 1993; Van Houdenhove et al., 2007).

2.8 Task Dependency of Neuromuscular Fatigue

Previous research has established that the manifestations of neuromuscular fatigue are specific to the conditions under which the exercise task is performed (Alexander, et al., Clark et al., 2005; 2010). This concept is known as the principle of ‘task dependency’ (Enoka, 1995; Allman & Rice, 2002). Task conditions which influence the progression of neuromuscular fatigue include, but are not limited to, contraction intensity, muscle action, and the muscle group examined (Clark et al., 2005; Alexander et al., 2010). Other task-related factors that may also influence
the manifestation of neuromuscular fatigue include whether or not the task is externally or internally regulated.

2.8.1 Contraction Intensity

The development of neuromuscular fatigue across contractions of various intensities has been primarily characterised using isometric actions (Latash, 2008). Broadly, the decline in force output associated with maximal intensity isometric contractions has been reported as being attributed mostly to sites within the motor pathway located distal to the neuromuscular junction (Gandevia, 1998; Westerblad et. al., 1998; Semmler et. al., 1999). However, evidence of supraspinal factors have also been reported during maximal intensity isometric tasks (Taylor & Gandevia, 2008). In contrast, mechanisms associated with sustained, low intensity isometric contractions have been more difficult to delineate (Semmler et. al., 1999). It has been proposed that several mechanisms concurrently contribute to neuromuscular fatigue during submaximal tasks (Semmler et. al., 1999). These mechanisms may include sites within the motor pathway that are located distal to the neuromuscular junction demonstrated through impaired excitation-contraction coupling, in addition to supraspinal areas demonstrated through declines in cortical output and increased inhibition due to sensory feedback (Garland, 1991; Fuglevand et. al., 1993; Semmler et. al., 1999).

2.8.1.1 Maximal Isometric Contractions

Previous investigations have delineated that during sustained maximal isometric contraction (MVC), force output is greatest at the
beginning of muscular contraction, followed by a progressive reduction in force as the task continues (Gandevia, et al, 1996). The motor unit recruitment pattern observed during a maximal isometric contraction as measured by EMG (signal amplitude and frequency) is characterised by higher motor unit activity (greater EMG signal) at the beginning of contraction subsequent to a reduction in motor unit activity (smaller EMG signal) as the task continues (Gandevia, et al, 1996). The progressive reduction in EMG activity during maximal sustained contractions is thought to be associated with a gradual decline in motor unit excitation firing rates (Taylor & Gandevia, 1997; St Clair, Lambert, & Noakes, 2001; Taylor & Gandevia, 2008).

One major theory related to the slowing of motor unit firing rates is the ‘muscle wisdom’ hypothesis. It has been suggested that as a muscle fibre fatigues, the duration of action potentials (efferent signal) to the fibre increases, resulting in a muscle fibre that cannot respond appropriately to the high frequency signal. In response, an afferent signal is returned to the motoneuron indicating that the fibre is impaired and cannot contract. This feedback results in a decrease in firing frequency to match the capabilities of the muscle fibre membrane to contract. Thus the motor system lowers the firing frequency of action potentials to match the muscle capabilities. However, evidence indicates that this phenomenon is not evident under all circumstances (Taylor & Gandevia, 2008). Instead Taylor et al. (2008), suggests that the slowing of motoneuron firing may be related to a decrease in excitatory input, an increase in inhibitory input, and/or a decrease in responsiveness of the motoneurons through a change in their intrinsic properties.
2.8.1.2 Submaximal Isometric Contractions

A submaximal task can be defined as an activity that requires a predetermined target force that is less than maximal output to be maintained over an extended period of time. Accordingly, only a small number of motor units are recruited at the beginning of the submaximal contraction (Vøllestad, 1997). In contrast to the characteristic recruitment strategies regulating force production during a maximal isometric task, in order to continue maintaining the required submaximal force output the subject is able to voluntarily increase output from the motor cortex thereby activating previously inactive motor units and/or increase the discharge rate of those motor units already recruited (Enoka, 2008; Taylor & Gandevia, 2008). This strategy enables the subject to counteract the progressive reduction in muscle force that occurs during the development of fatigue in those active motor units (St Clair Gibson et. al., 2001).

However, it is important to note that no clear motor unit recruitment patterns have been consistently reported during submaximal isometric contractions throughout the literature (De Ruiter et. al., 2005). Studies have reported that EMG activity either increases, decreases or remains constant during various phases of sub-maximal contractions. Several studies have reported a progressive increase in the amplitude of the EMG signal during a sustained isometric contraction performed at a sub-maximal intensity (Fuglevand et. al., 1993; Vollestad, 1997; Semmler et. al., 1999). In contrast, other studies have reported that EMG activity during submaximal knee extension tasks decreases (Garland et. al., 1997) or alternatively remains constant (Ruiter et. al., 2004). It has been suggested that firing rates have been observed to decrease or remain the same during moderate to
strong contractions, yet in contrast during weaker contractions firing rates appear to increase (Taylor & Gandevia, 2008). These discrepancies may be attributed to differences in the specific task conditions, including fatigue protocol and muscle group being investigated, highlighting the importance of the task dependent nature of fatigue (Taylor & Gandevia, 2008). Additionally, inconsistencies reported between studies may relate to difference in factors associated with the regional supply of blood flow, and metabolic factors.

2.8.1.3 Regional Blood Flow

Blood flow has long been investigated for it potential role in the development and progression of neuromuscular fatigue (Sjøgaard et. al., 1988) and is a likely factor contributing to differences in the manifestations of neuromuscular fatigue between sustained maximal and submaximal isometric tasks. Adequate blood flow is essential for the delivery of oxygen, supply of necessary metabolic substrates, removal of metabolic by-products, and to assist in dissipating heat generated during contraction within the active muscles (Enoka, 2008). Previous studies have reported that during muscle contraction intramuscular pressure increases, which can lead to compression of local blood vessels and reduced or occluded blood flow (Crenshaw et. al., 1997). This is important as significant reductions in blood flow can contribute to greater reliance on anaerobic metabolism for energy production (Clark et. al., 2005). The degree of blood vessel compression depends largely upon muscle action, contraction intensity, duration of sustained contraction, and the involved muscles (Crenshaw et. al., 1997; Clark et. al., 2005). It appears that blood flow is directly and positively associated with force production during contraction (Zwarts & Arendt-
Nielsen, 1988; Crenshaw et. al., 1997). In addition, it has also been suggested that difference in muscle mass and strength between subjects may also have a role in the degree of blood flow occluded (Clark et. al., 2005).

With regard to the knee extensors, De Ruiter (2007) observed using near infrared spectrometry that maximal de-oxygenation during an isometric knee extension task occurred at contraction intensities greater than 35% MVC for rectus femoris and 25% MVC for both the vastus medialis and vastus lateralis muscles. Furthermore, Zwarts et al., (1988) observed that blood flow remained adequate up to 30% MVC during sustained isometric contractions. These findings indicate that blood flow to the knee extensors is significantly impaired during sustained isometric contractions at intensities greater than 25% MVC. This is important as it has been suggested that feedback mechanisms associated with afferent pathways are sensitive to blood flow occlusion and are likely to influence the mechanisms contributing to neuromuscular fatigue (Enoka, 2008), which may partially account for explaining differences in the development and manifestations of neuromuscular fatigue observed between the maximal and submaximal isometric tasks.

Much of what is currently known about the neuromuscular mechanisms of exercise induced fatigue comes from data obtained from studies of the knee extensors. Studies pertaining to other muscle groups is limited and further investigations are required to determine whether the findings from the knee extensors translate to other muscle groups, such as the elbow flexors.
2.8.1.4 Perception of Effort

Another important issue to consider comparing the manifestations to neuromuscular fatigue between maximal and submaximal contractions relates to differences between tasks in the perceived effort during activity performance (Clark et. al., 2005). In a study by Gerdle et al., (1997) the perception of effort was higher during a voluntary contraction performed at 25% of maximal voluntary contraction (MVC) as compared to 70% MVC during a leg extension task (Gerdle et. al., 1997). Other authors have reported that subjects rating of perceived effort increase disproportionately to the target force and EMG during low intensity sub-maximal efforts relative to their maximal, thus it has been said that a mismatch between perceived effort and motor output occurs during sub-maximal efforts (Taylor & Gandevia, 2008).

Several scales have been developed to quantify exertion; a commonly used scale within neuromuscular fatigue research is the modified Borg 10-point categorical-ratio rating of perceived exertion (RPE) scale (Borg, 1982). This self-report scale offers a valid and reliable instrument for evaluating whole body exertion during exercise. The, Borg category-ratio scale will be used to quantify perceived overall level of exertion during specific time points throughout each session. The 10-point scale was selected as opposed to Borg’s 15-point scale, as it has been suggested to more closely parallel the exponential increase in many of the parameters associated with peripheral exertion, for example heart rate. Additionally, the Borg CR10 scale has been used in an earlier investigation of NM fatigue in chronic fatigue syndrome (CFS) patients (Lloyd et. al., 1991).
2.8.1.5 Task Loading

Traditional models for studying neuromuscular fatigue have used constant-load tasks, such as sustained maximal or submaximal tasks. During these activities motor output during performance is externally paced according to the demands of the task and often must continue for an unspecified period of time, such as until voluntary exhaustion or task failure. The use of such activities in the investigation of neuromuscular fatigue have recently been criticised as they do not permit normal behavioural changes to occur in response to both feedback information from peripheral receptors and feedforward (anticipatory) mechanisms which regulate performance (Lander et. al., 2009). Accordingly, variable load tasks that permit the subject to internally regulate and self-select the exercise work rate at which they perform the given activity are now being used as an alternative model to examine the mechanism contributing to neuromuscular fatigue (Tucker & Noakes, 2009).

In a recent study Lander et al., (2009) investigated the influence of self-pacing versus constant effort pacing upon physiological load. Nine, well trained (n=9) subjects performed a total of three rowing ergometry tasks: task one, a self-paced 5000 meter task performed at a constant RPE of 15; task two, a sub-maximal 5000 meter task performed at a matched intensity (equivalent to the mean power output performed in task one; PO) constant effort task; task three, a maximal time-trail which was largely incorporated to mask the purpose of the study and to aid randomisation of the task testing order. An interesting finding of the study was that enforced constant load exercise presented a greater physiological change compared to the matched self-paced task. The author concluded that the ability to
dynamically self-pace effort through manipulating power output during exercise is an important behavioural response to homeostatic challenges (Lander et. al., 2009).

2.8.2 Assessment of Neuromuscular Fatigue

The development and manifestations of neuromuscular fatigue may be evaluated through a number of voluntary and/or evoked assessments that objectively assess the responsiveness and excitability of sites throughout the motor pathway.

2.8.2.1 Voluntary Measurements

Voluntary neuromuscular measurements refer to those tasks that involve volitional performance only. Such tasks provide an all global indication of the functionally of the entire motor pathway and cannot be used to identify specific sites responsible for reduced performance associated with neuromuscular fatigue. The most common measures of voluntary neuromuscular performance include maximal voluntary torque and motor unit activity.

2.8.2.1.1 Maximal Voluntary Torque

Maximal voluntary torque (MVT) refers to the maximum amount of torque that a muscle group can produce during the performance of a single, maximal effort voluntary contraction. MVT often is measured to assess volitional torque-generating capacity (Cairns et. al., 2005). As such, MVT
is frequently used in neuromuscular fatigue research to quantify the magnitude of exercise-induced fatigue.

### 2.8.2.1.2 Motor Unit Activity

Motor unit activity during voluntary contractions can be assessed using surface electromyography, which records summated motor unit action potentials. Surface EMG signals provide an indication of the pattern of motor unit activity during contraction and can be assessed for amplitude and frequency characteristics. Surface EMG amplitude is influenced by both motor unit recruitment and firing frequency and is used to assess the quantity of motor unit activity (Kamen & Caldwell, 1996). As such, EMG amplitude is used in neuromuscular fatigue research to provide evidence for changes in the quantity of neural input received by the muscle during contraction. EMG frequency is influenced by the motor unit action potential waveform characteristics and may be used, although cautiously, to provide information on muscle fibre conduction velocity (Kamen & Caldwell, 1996). Because muscle fibre conduction velocities differ between muscle fiber types, EMG signal frequency is used in neuromuscular fatigue research to provide evidence of a change in the types of motor units recruited during contraction.

### 2.8.3 Evoked Measurements

Evoked neuromuscular measurements refer to those tasks that involve the delivery of an electrical stimulus to the corticospinal tract or peripheral nerve or electromagnetic stimulus to the motor cortex during voluntary contraction or at rest. By using both peripheral nerve stimulation
and transcranial magnetic stimulation (TMS) techniques during voluntary contraction it is possible to gain a more detailed understanding of the central mechanisms contributing to exercise-induced fatigue as both spinal and supraspinal excitability can be identified (Cairns et. al., 2005). In contrast, by stimulating the peripheral nerve or motor cortex with the muscle at complete rest allows for assessment of intrinsic muscle function without the influence of neural input, which permits detailed assessment of the peripheral mechanisms contributing to exercise-induced fatigue to be performed.

2.8.3.1 Level of Voluntary Muscle Activation

The level of voluntary muscle activation is a measure used to objectively assess the extent of alpha-motoneuron excitation or completeness of neural drive to the muscle during a voluntary contraction (Shield & Zhou, 2004). The interpolated twitch technique is one method for performing this assessment (Herbert & Gandevia, 1999). This technique is performed by delivery a supramaximal electrical stimulus to the innervating peripheral nerve of the active muscle group whilst the subject performs and maintains a voluntary contraction. Immediately following this, a second stimulus is applied while the muscle is completely relaxed. The additional torque produced following stimulus delivery during the voluntary contraction (interpolated twitch amplitude) is then compared to the evoked twitch torque produced following stimulus delivery with the muscle at rest (control twitch amplitude) using the following equation: Level of Voluntary Muscle Activation (%) = \[1 – (\text{Interpolated Twitch Amplitude} / \text{Control Twitch Amplitude}) \times 100\]; where a value of 100% reflects maximal alpha-motoneuron excitation or level of neural drive to the muscle during
contraction. In neuromuscular fatigue research, the level of voluntary muscle activation is used to quantify the capacity of spinal and/or supraspinal sites to elicit muscle force during contraction (Taylor et al., 2006).

2.8.3.2 Level of Corticomotor Excitability

The level of corticomotor excitability is a measure used to objectively assess the extent of excitation of neurons within the corticomotor pathway during voluntary contraction. The technique used is similar to that for assessing the level of voluntary muscle activation where stimuli are delivered during contraction and at rest with the exception that TMS is used to induce weak electric currents in the cerebral motor cortex, which activates fast-conducting pyramidal motor neurons. Both mechanical (twitch) and electrical (motor evoked potential; MEP) responses at the target muscle following stimulation can be recorded and response amplitude determined. The level of motor cortex excitability during contraction can be calculated using either the twitch or MEP response using the following equation: Level of Corticomotor Excitability (%) = [1 – (Active Response Amplitude / Control Response Amplitude) x 100]; where a value of 100% reflects maximal excitation during contraction. The amplitude of the response to stimulation is influenced by neuronal excitability at the level of the motor cortex and at the level of the motoneuron pool. As such, this technique is used in neuromuscular fatigue research to quantify the output from the central motor pathways.

Corticospinal excitability has been assessed extensively in upper limb muscles without complication (Sacco et al., 1999; Taylor et al., 2000b). However, obtaining a MEP under resting conditions from lower
limb muscles, such the knee extensors, is problematic as some level of facilitation is necessary to elicit a response (Kalmar & Cafarelli, 2006). To overcome this issue, studies examining corticospinal excitability that involve the knee extensors obtain a resting MEP by delivering the stimulus to the motor cortex while the subject maintains a very low level contraction (3% MVC).

2.8.3.3 MEP Silent period

A characteristic delay occurs between the delivery of the TMS pulse and the MEP response as viewed with EMG. This delay is due to time needed for the afferent signal from the motor cortex to propagate to the muscle fibre (Clark, Issac, Lane, Damron, & Hoffman, 2008). This period of delay is known as the cortical silent period (SP). Studies in healthy population show that immediately following TMS stimulation, elicited during the performance of a voluntary isometric contraction, that a delay of approximately 200ms occur before the EMG signal returns (Taylor & Gandevia, 2001). Studies have suggested that the initial portion of the SP is due mostly to spinal mechanisms, while the later portion reflects reduced motor cortex excitability (Chen, Lozano, & Ashby, 1999). Interestingly, this delay appears to lengthen during a sustained maximal and sub-maximal contractions (Taylor & Gandevia, 2001). The mechanisms responsible are not well understood. It has been suggested that the change in the central motor conduction time SP can be used to infer inhibitory mechanisms (Clark, et al., 2008).
2.8.3.4 MEP Post-Exercise Facilitation and Depression

Within seconds following a fatiguing contraction, short-lasting facilitation of the MEP occurs, which last up to 4 minutes. This phenomenon appears to be independent of the intensity of contraction (Samii et al., 1996). This initial response is followed by a longer lasting depression of MEP that may persist for up to 30 minutes or more (Brasil-Neto et. al., 1994; Zanette et. al., 1995; Liepert, Kotterba, Tegenthoff, & Malin, 1996). In contrast to post-facilitation, the post-depression period is prolonged with increasing intensity and duration of contraction (Samii, Wassermann, & Hallett, 1997). Both post-exercise facilitation and depression are thought to reflect changes at the cortical level (Taylor & Gandevia, 2001).

2.8.3.5 Resting Evoked Twitch Contractile Properties

The mechanical response of a resting muscle following the delivery of a supramaximal electrical stimulus to the peripheral nerve is referred to as a resting evoked twitch contraction. The amplitude and temporal characteristics of the evoked twitch contraction are influence by many factors, including muscle size, muscle fibre-type proportions, muscle calcium kinetics, and efficiency of excitation-contraction coupling (Fitts, 2003). In neuromuscular fatigue research, evoked twitch contractions are used to quantify to the intrinsic function of the peripheral contractile apparatus.
2.8.3.6 Compound Muscle Action Potential

A compound muscle action potential (CMAP) is the electrical response of a resting muscle recorded using surface EMG following supramaximal electrical stimulation of a peripheral nerve. The CMAP provides an indication of muscle membrane excitability and is largely influenced by sodium-potassium pump activity (Allman & Rice, 2002). Generally, the CMAP is quantified as the negative peak to positive peak amplitude. In neuromuscular fatigue research, the CMAP is used to evaluate neuromuscular propagation and provide an indication of the quantity of muscle available for recruitment during contraction (Palmieri et. al., 2004).

2.9 Neuromuscular Mechanisms In Exercise-Induced Fatigue In Cancer

Studies examining neuromuscular mechanisms contributing to exercise-induced fatigue in cancer patients receiving treatment are limited and results are conflicting (Bruera, et al., 1988; Yavuzsen et. al., 2009; Alt et. al., 2011). A synopsis of this research is provided below and are presented in Table 2.1.

Bruera et al. (1988) examined 61 stage VI breast cancer patients and 20 healthy controls matched for nutritional status, lean body mass, and ultrasonographic measurement of the triceps brachialis, sternomastoid, and adductor pollicis. Data collection was performed a minimum of 2 weeks after the cessation of treatment in the cancer patients. Testing involved the assessment of maximal voluntary isometric force of the adductor pollicis
Table 2.1: Summary of experimental studies investigating mechanisms associated with cancer and cancer related fatigue.

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Methods</th>
<th>Key Findings</th>
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<tr>
<td>Bruera et. al. (1988)</td>
<td>61 Advanced BCa (metastatic disease) currently receiving treatment for advanced stage BCa (not specifically fatigued) and 20 healthy age-gender matched</td>
<td>Neurophysiology of adductor pollicis was assessed during isometric voluntary contraction and electrical stimulation of the ulnar nerve in BCa compared to healthy controls. Maximal strength was measured before and after supramaximal peripheral stimulation of ulna nerve. A 30 sec supramaximal peripheral stimulation of ulna nerve was performed using electrical stimulation. Muscle mass was assessed by ultrasound adductor pollicis. No indices of fatigue symptoms were measured.</td>
<td>Fatigue expressed as a percentage of initial strength and relaxation velocity after 30 sec of stimulation was ↓ in BCa. ↔ muscle mass between groups. Normal muscle electrophysiology found in BCa.</td>
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<tr>
<td>Monga et. al. (1997)</td>
<td>13 PCa pre-radiotherapy (not specifically fatigued)</td>
<td>Neuromuscular fatigue of tibialis anterior was assessed pre immediately post 8 weeks 5-6 weeks post treatment. A MVC of the tibialis anterior was assessed pre and post a sustained isometric contraction performed at 80% MVC for 60sec. Neuromuscular efficiency (NME) calculated as force (N)/IEMG (mV) was measured. No indices of fatigue symptoms were measured.</td>
<td>Evidence of a transient ↓ in NME suggesting ↓activation from the central nervous system which recovered 5-6 weeks following radiotherapy</td>
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<td>Dimeo et. al. (1997)</td>
<td>72 mixed cancer (48 women and 30 men) with active disease status who are candidates for chemotherapy and stem cell transplantation treatment (not specifically fatigued).</td>
<td>A maximal treadmill performance measuring maximal VO₂ (ml/kg/min) and maximal workload (km/h). Several questionnaires including the Profile of Mood States (POMS) and the Symptom Checklist-90-Revised (SCL-90-R). Fatigue symptoms were measured using the fatigue scale of the POMS.</td>
<td>Cancer fatigue was independent of physical performance; however may be related to mood disturbance</td>
</tr>
<tr>
<td>Stone et. al. (1999)</td>
<td>95 Ca patients (Ca type not specified; not specifically fatigued) and 98 Controls (age and sex-matched volunteers without cancer)</td>
<td>Maximal strength was assessed using handgrip dynamometer. Muscle fatigability was determined by subjects squeezing the investigator’s fingers tightly for 10 s and recording a MVC on the dynamometer. This process was repeated 18 times over a 6-min period. The speed of MVC handgrip muscle recovery at 1, 5 and 10mins post fatigue task was assessed. Fatigue symptoms were measured using the fatigue severity Scale (FFS). HRQOL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life.</td>
<td>↓ Voluntary muscle strength in cancer compared to controls pre and 6min grip fatigue; however ↔ at 10min grip task recovery. No relationship between muscle strength measures and subjective fatigue; suggesting that the experienced fatigue was not caused primarily by muscular weakness.</td>
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Questionnaire (EORTC-QOL 30) and Visual Analogue Scales were used to assess tiredness, weakness, ability to concentrate.

<table>
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<tr>
<th>Study</th>
<th>Participants</th>
<th>Procedure</th>
<th>Results</th>
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<tr>
<td>Ng et. al. (2008)</td>
<td>BCa during chemotherapy</td>
<td>Participants performed a 40% maximal voluntary isometric contraction involving the biceps brachii (elbow angle = 90 degrees. Time to task failure (ET) was measured and muscle fatigue was indicated by the ratio of post-exercise MVC, obtained 35 sec after the task, compared to the pre-task MVC. Transcranial magnetic stimulation (TMS) was used to investigate whether or not changes in cortical excitability corresponded with any changes in fatigue symptoms, endurance or muscle fatigue after treatments 2 and 6. Fatigue Impact Scale (FIS) used to assess fatigue symptoms.</td>
<td>ET ↓ from early to end treatment. Strength remained ↔. Fatigue symptoms ↑ from early treatment by the end of treatment. Depression ↑ throughout treatment (although at subclinical levels. Muscle fatigue ↑ (i.e., greater loss of force) throughout therapy (post-ex/pre-ex MVC (%). TMS measures including MEP amplitudes, and silent periods were ↔. Strength was preserved, muscle endurance is ↓ and muscle ↑ during chemotherapy in breast cancer survivors.</td>
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<tr>
<td>Yavuzsen et. al. (2009)</td>
<td>16 palliative care patients with cancer fatigue who were off treatment for min 4 weeks and 16 healthy controls.</td>
<td>Max elbow flexion was measured per-post associated with a sustained submaximal biceps brachii MVC at 30% of MVC performed until exhaustion. Electrical stimulation was applied at 30 sec intervals during the task. Peak evoked twitch force, and Mmax were assessed. Fatigue symptoms were assessed using the BFI.</td>
<td>Shorter endurance time was observed in the cancer fatigue group. ↔ change in Mmax pre-post task. The ratio of twitch force to voluntary force was significantly greater in the cancer patient group indicating a failure in the ability to voluntarily recruit skeletal muscle to maintain the contraction. The cancer fatigue had a 15% ↓ in twitch force compared to a 37% ↓ in the control following the sustained task. Indicating &gt; central fatigue and impaired neuromuscular junction conduction in the cancer fatigue group compared to the control group.</td>
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<tr>
<td>Study</td>
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<td>Task Description</td>
<td>Findings</td>
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<td>Alt et al. (2011)</td>
<td>13 PCa with fatigue undertaking 6 weeks of radiotherapy and 12 healthy controls.</td>
<td>A sustained intermittent, submaximal isometric endurance task involving the dorsiflexors was performed at 40% MVC using a 75% duty cycle (6 seconds on, 2 seconds off) until task failure. Indices measured included: MVC which was used to indicate and determine target force; voluntary activation (CAR); contractile properties, resting evoked twitch contractions, maximal mwave (Mmax) and endurance time using. Task failure was defined as when two consecutive contractions were less than target or 4 sec of the 6 sec contraction. The piper fatigue Scale (PFS) was used to assessed fatigue symptoms.</td>
<td>Cancer fatigue group demonstrated a 30% ↓ in endurance time after 6 weeks radiotherapy while the healthy controls experienced a significant ↑ in endurance time following 6 weeks. No significant changes were observed for CAR, Mmax, or peak evoked twitch torque in either group following the fatigue task before or after the treatment period. The ↑ neuromuscular fatigue in the cancer group after the treatment period was not ascribed to a greater contribution from central and/or peripheral mechanisms. The increased rate of neuromuscular fatigue observed in the cancer groups after the treatment period may be related to impaired metabolic events such decreased muscle oxidative capacity.</td>
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<td>Kisiel-Sajewicz et al. (2012)</td>
<td>10 mixed cancer types with fatigue participants who were post-operative min 4 weeks who had not received any treatment in previous 4 weeks and 12 healthy gender matched women.</td>
<td>A sustained 30% MVC elbow flexion was performed until exhaustion. Pre and post PNS Measures included twitch force (TF), time to peak twitch force development and half relaxation time. Fatigue symptoms were assessed using the BFI.</td>
<td>The cancer fatigue group reached tasks exhaustion earlier than controls. No significant changes in contractile function in cancer fatigue group; however significant changes were observed in control group. The cancer fatigue group perceived fatigue earlier with minimal muscular fatigue suggesting that central factors were more significant than peripheral in limiting motor function and performance.</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Task Description</td>
<td>Findings</td>
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<tr>
<td>Kisiel-Sajewicz et al. (2013)</td>
<td>12 advanced cancer, from mixed types with fatigue who were a min of 4 weeks post-operative and 12 age-gender matched healthy controls.</td>
<td>A sustained 30% MVC elbow flexion task performed until exhaustion was performed. Mean power frequency of EMG signals of BB, BR and TB were measured. Fatigue symptoms were assessed using the BFI.</td>
<td>Physical fatigue was perceived earlier in the cancer fatigue group compared to the healthy group. Less myoelectrical manifestations of fatigue were observed in cancer fatigue compared to control. Indicating that the CNS may limit motor performance in cancer fatigue.</td>
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<tr>
<td>Neil et. al. (2013)</td>
<td>16 BCa (Stage I-IIIA) who had completed radiation therapy and/or chemotherapy for ≥ 3 months but &lt; 5 years with fatigue and 11 BCa with no fatigue.</td>
<td>A 30% MVC of the right quadriceps was performed until volitional exhaustion. TF using electrical stimulation was used to calculate voluntary activation. Fatigue symptoms were assessed using the FACT-F.</td>
<td>No significant difference in neuromuscular indices were observed between groups following the fatiguing protocol.</td>
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<tr>
<td>Cai et. al. (2014)</td>
<td>10 palliative care patients with fatigue who were off treatment for min 4 weeks and 14 age matched health controls.</td>
<td>Intermittent elbow flexion motor task at 40% MVC were performed until self-perceived exhaustion. Indices included TF, using peripheral electrical stimulation. The number and total duration of all trails were recorded. Fatigue symptoms were assessed using BFI.</td>
<td>A significantly ↓ numbers of trials and ↓ duration was observed in the cancer fatigue group compared to controls. TF ratio was higher in cancer fatigue compared to controls indicating less peripheral fatigue at time of perceived exhaustion. Under submaximal sustained task conditions the cancer fatigue group experienced &gt; central compared to peripheral fatigue compared to controls. Central factors appear to limit prolonged motor performance in cancer fatigue.</td>
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<tr>
<td>Platt et. al. (2014)</td>
<td>7 early stage cancer and fatigue (3 female; 3 male) and 4 control (2 female; 2 male).</td>
<td>A 30% MVC task using handgrip dynamometry was performed until task failure. Fatigue symptoms were assessed using the BFI and FACIT-F</td>
<td>Cancer and fatigue group experienced greater perception of fatigue and lower force output than controls suggesting the centrally based mechanisms may be involved in the manifestations of fatigue; however due to the small sample size this</td>
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<td>Prinsen et. al. (2015)</td>
<td>20 cancer survivors with fatigue and 20 cancer survivors without fatigue who had completed curative treatment a minimum of 1 year prior to study with no evidence of active disease.</td>
<td>Participants performed a 2 minute sustained maximal voluntary contraction involving the elbow flexors task. EMG was recorded from the biceps brachii and muscle fibre conduction velocity (MFCV) was used as an indicator of peripheral fatigue. Peripheral electrical stimulation was used to calculate central activation ratio before, during and after the performance of where by CAF was calculated. Fatigue was assessed using the Check-list Individual Strength (CIS-Fatigue)</td>
<td>No significant differences in central or peripheral fatigue were reported between the fatigued and non-fatigued cancer survivors. The findings provided no evidence of impaired neuromuscular function in cancer fatigue compared to non-fatigued cancer survivors.</td>
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Profile of Mood States (POMS); Symptom Checklist-90-Revised (SCL-90-R); Fatigue Impact Scale (FIS); Fatigue severity Scale (FFS); The European Organisation for Research and Treatment of Cancer Quality of Life (EORTC); Visual Analogue Scales (VAS); Brief Fatigue Inventory (BFI); Functional Assessment of Cancer Therapy (FACT-F); Twitch force (TF); Maximal Voluntary contraction (MVC); Endurance time (ET); Central activation ratio (CAR); Voluntary activation (VA); Maximal Mwave (Mmax); Transcranial magnetic stimulation (TMS); Motor Evoked Potential (MEP); Breast Cancer (BCa); Prostate Cancer (PCa); Cancer (Ca).
before and after supramaximal stimulation of the ulna nerve for 30 seconds duration at a rate of 50Hz. No significant difference in maximal voluntary isometric force was observed between groups before stimulation. However, after stimulation maximal voluntary isometric force was statistically lower in breast cancer patients. Furthermore, it was also reported that the fatigue index associated with stimulation determined as the decrement in muscle force between the initial and final periods of stimulation was significantly higher in the breast cancer patients. These findings provide evidence for a greater contribution from peripherally mediated mechanisms to the development of neuromuscular fatigue in the breast cancer patients compared with the healthy matched subjects.

Yavuzsen et al. (2009) compared the contributions of central and peripheral factors to exercise-induced neuromuscular fatigue between 16 advanced cancer patients with various solid tumors referred to palliative care and 16 healthy controls. Cancer patients received heterogeneous cancer treatments, including chemotherapy, radiotherapy or combined therapies. Subjects were excluded if they were currently depressed, receiving antidepressants or had a haemoglobin level of < 10g/dL. All subjects were assessed for fatigue using the Brief Fatigue Index questionnaire prior to exercise where fatigue scores were higher for the cancer group. For testing, subjects performed a sustained submaximal isometric contraction of the biceps brachii at 30% MVT. Neuromuscular assessments were performed before and after the sustained contraction included MVT, peak evoked twitch force, and CMAP. Electrical stimulation was also applied to the peripheral nerve at regular intervals throughout the contraction. It was
observed that the time to fatigue was significantly shorter for the cancer group compared to control while the relative losses in MVT and peak evoke twitch force after exercise was lower in the cancer patients compared with controls. Furthermore, the superimposed twitch response near the point of voluntary exhaustion was greater in the cancer group. Moreover, no changes in CMAP amplitude after exercise were observed. These data provide evidence that reduced sustained physical performance in the cancer patients was due to greater contributions from central fatigue mechanisms.

More recently, Alt et al. (2011) published a systematic comparison of neuromuscular fatigue between 13 prostate cancer patients with cancer related fatigue who were undertaking 6 weeks of radiotherapy and 12 healthy matched persons. Before testing, subjects completed a series of self-report questionnaires, including the Centre for Epidemiology Studies Depression Sub-scale, and the Epworth Sleepiness Scale to evaluate sleep hygiene, and were assessed for haemoglobin levels (Hb). Physical activity levels were also measured using accelerometers that were worn for a 7-day period before and after the study. Neuromuscular function was evaluated using a sustained intermittent, submaximal isometric endurance task involving the dorsiflexors at 40% MVC using a 75% duty cycle (6 seconds on, 2 seconds off). The central activation ratio (CAR), resting evoked twitch contractions, and CMAP were assessed before and after the treatment period. No differences between groups were observed in depression, sleepiness, Hb, physical activity levels, or MVT before the fatigue task in either test session. However, despite this, the cancer patients demonstrated a 30% reduction in endurance time after treatment while the healthy controls experienced a significant increase in endurance time. No significant changes
were observed for CAR, CMAP, or peak evoked twitch torque in either group following the fatigue task before or after the treatment period. Based on these findings the increased neuromuscular fatigue in the cancer group after the treatment period cannot be ascribed to a greater contribution from central and/or peripheral mechanisms. The authors suggested that the increased rate of neuromuscular fatigue observed in the cancer groups after the treatment period may be related to impaired metabolic events distal to the sarcolemma, such as decreased muscle oxidative capacity.

A cross sectional study involving 10 mixed gender cancer fatigue (7 women) and 12 healthy gender matched (9 women) participants reported evidence of impaired motor output in the cancer fatigue compared to healthy persons (Kisiel-Sajewicz et. al., 2012). The cancer participants consisted of advanced stage patients who had received no treatment in the previous 4 weeks and were a minimum of 4 week post-operative. Fatigued was assessed using the BFI. Indices of muscle contractile function were assessed during a sustained, submaximal 30% MVC elbow flexion task performed until exhaustion. Pre and post neuromotor measures including twitch force, time to peak twitch force development and half relaxation time were assessed using EMG and peripheral electrical stimulation. The cancer fatigued group reached task exhaustion earlier than the healthy group. However, no evidence of significant changes in contractile function were observed during task performance in the cancer fatigue group; however significant changes in contractile function were reported in the healthy group. In addition the cancer fatigued group perceived fatigue earlier despite less evidence of the development of muscular fatigue compared to the healthy group. This indicated that central factors may have been more
significant than peripheral factors in contributing to the sensation of fatigue in the cancer fatigue participants which limited motor output and performance.

A cross sectional study involving 12 cancer fatigued participants with advanced cancer from a heterogeneous sample of cancer diagnoses and 12 age-gender matched healthy controls found evidence of reduced myoelectrical manifestations of fatigue as indicated by EMG amplitude and MPF of EMG signals in the cancer fatigued compared to control group (Kisiel-Sajewicz et. al., 2013). Fatigue was measured using BFI. Cancer participants had received no treatment in the previous 4 weeks and were a minimum of 4 week post-operative. A sustained 30% MVC elbow flexion task was performed until exhaustion. Output measures included mean power frequency of EMG signals recorded from the biceps brachii (BB), brachioradialis (BR) and triceps brachii (TB). Physical fatigue was perceived earlier in the cancer fatigue group than the healthy group. This finding suggests that the CNS may limit motor performance during a submaximal elbow flexion task.

A recent cross-sectional study reported that cancer and fatigue participants have greater central compared to peripheral fatigue under submaximal sustained exercise tasks (Cai et. al., 2014). Participants included 10 palliative care cancer and fatigue participants and 14 healthy controls. The BFI was used to measure fatigue. Participants performed an intermittent elbow flexion task at 40% MVC, performed until self-perceived exhaustion. Peripheral electrical stimulation was used to measure twitch force (TF) production. A significantly smaller numbers of trials and shorter total duration of the task performance was observed in the cancer and
fatigue group compared to controls. TF ratio (pre to post task) was higher in cancer and fatigue participants compared to controls indicating less peripheral fatigue at the time of perceived exhaustion. The cancer and fatigue participants appeared to experience greater central compared to peripheral fatigue under submaximal sustained task conditions compared to controls indicating the central factors appear to limit prolonged motor performance in cancer and fatigue participants.

A recent pilot study Platt et. al. (2014) reported impaired muscle function at task failure in a small group of mixed gender, early stage cancer and fatigue participants (n=7) compared to 4 controls participants. Fatigue was assessed using the BFI and FACT-F questionnaires. Participants performed a 30% maximal handgrip task until failure during which the cancer fatigue group experienced greater perception of fatigue and lower force output compared to controls suggesting that centrally based mechanisms may be involved in the manifestations of fatigue; however due to the small sample size this finding needs to be conformed in a larger study sample. In contrast no significant difference in neuromuscular indices were reported following a fatiguing protocol in fatigued compared to non-fatigued breast cancer survivors in a cross-sectional investigation Neil et. al. (2013). 16 fatigue breast cancer participants (Stage I-IIIa) who had completed radiation therapy and/or chemotherapy for ≥ 3 months but < 5 years and 11 non fatigued breast cancer survivors were included. Participants performed a sustained sub maximal contraction (30% MVC) involving the right quadriceps on an isokinetic dynamometer performed until volitional exhaustion. Measures included self-reported fatigue using Functional Assessment of Cancer Therapy: Fatigue (FACT-F), maximal
voluntary force and twitch force using peripheral nerve stimulation of the right quadriceps voluntary activation.

Similarly in a longitudinal randomised control trial (RCT) involving a 6 month cognitive behavioural therapy intervention (Prinsen et. al., 2015) involving twenty fatigued cancer survivors and twenty non-fatigued controls reported no evidence of impaired neuromuscular function in cancer fatigue compared to non-fatigued cancer survivors. All participants had completed curative treatment for a minimum of 1 year prior to the study with no evidence of active disease and were from a mixed cancer diagnoses cohort. Fatigue was measured using the Check-list Individual Strength (CIS-Fatigue) questionnaire. Participants performed a 2 minute sustained maximal voluntary contraction involving the elbow flexors task. EMG was recorded from the biceps brachii and muscle fibre conduction velocity (MFCV) was used as an indicator of peripheral fatigue. Peripheral electrical stimulation was used to calculate central activation ratio before, during and after the performance of where by central activation ratio (CAF) was calculated. No significant differences in central or peripheral fatigue were reported between the fatigued and non-fatigued cancer survivors. The findings provides no evidence of impaired neuromuscular function in cancer fatigue compared to non-fatigued cancer survivors.

Other evidence suggestive of centrally based neural changes includes difference in electroencephalography frequency power dynamics in cancer survivors reporting persistent fatigue during a sustained elbow flexion task compared to non-fatigued healthy persons (Khoshknabi, 2006; Platt et. al., 2014). Moreover, distinct patterns of resting brain connectivity, measured by functional connectivity magnetic resonance imaging, were
found in fatigued compared to non-fatigued breast cancer survivors (Hampson et. al., 2015). Based on these findings current understanding of the involvement of the neural pathways in persistent fatigue in cancer survivors is equivocal.

Functional brain imaging studies have observed alterations in persons with cancer fatigue compared to healthy controls. In a 2008 case study report, a 58 year old female with multiple lung metastases and severe cancer fatigue was observed as having altered pattern of electroencephalogram (EEG) signals compared to healthy controls during a 30% MVC contraction of the elbow flexors performed until exhaustion (Khoshknabi & Davis, 2008). Other neuromotor measures including EMG of the brachioradialis were obtained. Reduced EEG-EMG coherence, an indicator of functional corticocomotor coupling was reported during the second half of the sustained contraction when compared to controls. The patient undertook an 8 month methylphenidate trial, commonly prescribed to stimulate the sympathetic and central nervous systems in persons with attention deficit disorders. Pre to post changes demonstrated improvements in EEG-EMG signalling, suggesting that cortical factors are involved in cancer fatigue.

Hampson et. al. (2015) assessed functional brain connectivity in 15 breast cancer with post cancer fatigue and compared the results to 8 non-fatigued breast cancer survivors using resting FMRI imagining. Cancer survivors were, at minimum, 12 weeks post-treatment. Significant differences in intrinsic default mode network (DMN) connectivity to the superior frontal gyrus (SFC) was observed in cancer fatigue participants.
compared to non-fatigued controls, indicating the presence of abnormalities in areas of the brain associated with memory and cognition.

In a 12 month RCT involving cognitive behaviourial therapy, Prinsen et. al. (2015) measured brain volume and metabolic tissue concentrations in 20 participants with CRF compared to 20 cancer patients without fatigue using FMRI and MRS techniques. Both groups consisted of 10 female and 10 males with mixed cancer types included. The RCT lasting 12 months. No difference in subcortical brain volumes, global brain volumes, hippocampus metabolic tissues concentrations and/or metabolic signal ratio in the occipital cortex were observed between groups.

Based on this evidence it is clear that results regarding evidence of the neuromuscular mechanisms contributing to exercise-induced fatigue in cancer survivors with fatigue in equivocal. It appears that greater central compared to peripheral fatigue have been reported in this population compared to healthy persons and/or non-fatigued cancer survivors (Yavuzsen et. al., 2009; Kisiel-Sajewicz et. al., 2012; Kisiel-Sajewicz et. al., 2013; Cai et. al., 2014; Platt et. al., 2014). Although other authors have failed to confirm reports of central based mechanisms within this setting (Prinsen et. al., 2012; Neil et. al., 2013). Differences within and between studies in patient cancer types and phase of treatment may be important as a number of studies indicate that self-reported cancer fatigue correlates with cancer type, stage of disease, and treatment regime (Smets et al., 1998; Hann et. al., 1999; Holzner et. al., 2002; Hwang et. al., 2003). Thus, differences in the neuromuscular mechanisms contributing to exercise-induced fatigue in the studies previously reviewed may reflect this. However, disease-free breast cancer survivors may be a more robust
population to examine as a large cross-sectional investigation failed to observe a significant relationship between cancer fatigue severity and the type of surgery, type of adjuvant therapy, length of treatment, or time since treatment (Servaes et. al., 2002). At present few studies have been undertaken examining the neuromuscular basis of fatigue in cancer survivors and the currently published reports are contradictory. Given the complex nature of fatigue, with its many physiologic and behavioural risk factors and correlates the simultaneous evaluation of neural, endocrine, and immune biomarkers, using non-invasive methodologies, may assist in providing the evidence required for more conclusive findings. This greater understanding may help inform the design of more effective therapeutic interventions such as exercise and cognitive behavioural therapy for these patients.

2.10 Effects of Resistance Training As An Intervention for Reducing Cancer Fatigue

A growing body of research indicates regular physical exercise to be a safe and beneficial non-pharmacological intervention for ameliorating cancer fatigue in BCa survivors (Watson & Mock, 2004; Jones & Demark-Wahnefried, 2006; Schneider et. al., 2007). Currently, the mechanisms by which exercise exerts a positive benefit on symptoms of cancer fatigue remains unknown (Ardies, 2002; Al-Majid & Gray, 2009). Most studies examining the role of resistance training have focused on examining muscular fitness including strength and improvements in HRQOL
parameters. Due to the involvement of the neuromuscular system in the production of movement it is possible that alterations in fatigue symptoms may be somewhat related to changes in neuromuscular functioning. Currently, the neuromuscular adaptations to resistance training in cancer survivors is unknown.

To date, the majority of research examining exercise as an intervention for cancer fatigue has utilized aerobic-based programs (Battaglini et al., 2006; Culos-Reed et al., 2007) and/or the effects of combined aerobic and resistance training activities (Cramp & Byron-Daniel, 2012). Few studies have been conducted investigating resistance training as an independent intervention (Battaglini et al., 2006). A recent Cochrane systematic review of exercise and cancer-related fatigue concluded that aerobic exercise significantly reduces cancer-related fatigue. However resistance training was not significantly associated with improvements in fatigue (Cramp & Byron-Daniel, 2012). These discrepancies between aerobic and resistance training are largely influenced by the lack of studies using resistance training as an intervention (6 studies) compared to a larger number of aerobic-based training modalities (29 studies). The authors advocate that further research into other exercise modalities including resistance training should be undertaken (Cramp & Byron-Daniel, 2012).

In contrast to these findings, a recent meta-analysis investigating the efficacy of exercise as an intervention to reduce cancer fatigue among cancer survivors reported that moderate resistance exercise reduces cancer fatigue in breast and prostate cancer survivors and cancer survivors of older age (Brown et al., 2011). Moreover, the authors reported that cancer survivors engaging in moderate-intensity resistance exercise modulated
cancer levels more than those engaging in low-intensity resistance exercise or low to moderate intensity, aerobic exercise. Resistance training intensity may be an important training consideration for promoting positive change in fatigue symptoms in cancer survivors.

Thus, exercise as an adjuvant therapy for cancer treatment related symptoms such as fatigue is become recognised as a promising intervention (Watson & Mock, 2004). Although strong evidence supports the benefit of exercise for fatigue symptoms exists, exercise is not commonly incorporated into clinical practise (McNeely & Courneya, 2010). This may in part be related to the lack of conclusive evidence regarding the appropriate prescription of exercise, as previous studies have included a wide variety of exercise prescriptions. Variables include number and duration of intervention sessions, type, intensity, and length of exercise, study design and supervision of exercise (Ferrer et al., 2010). Thus, evidence is not sufficient to demonstrate the best type or intensity of exercise for reducing the symptom of fatigue (Cramp & Daniel, 2008). Therefore, in order to advance the existing exercise-based exercise literature additional research investigating the role of resistance training programs in improving fatigue symptoms in post-treatment survivors is necessary.

2.11 The Health Benefits of Progressive Resistance Training

Progressive resistance training is a well-established, safe and beneficial exercise modality for individuals of all ages and fitness levels, including those afflicted with severe chronic illnesses (Cheema et al.,
The neuromuscular benefits of resistance exercise in healthy adults and in ageing populations have been previously documented. Specifically, resistance exercise has been demonstrated to induce neural learning and muscle adaptation that results in improved muscle activation following resistance training (de Lateur 1994). Other benefits of resistance based exercise include increase in muscle mass, endurance, bone mineral density and body composition (Al-Majid & McCarthy, 2001). Moreover, resistance training may prove to be an effective alternative to improving bone mineral density in postmenopausal breast cancer survivors with estrogen-dependent tumours who are at greater risk for osteoporosis but are unable to take hormone replacement therapy (Cheema et. al., 2008). Previous investigations of resistance training in cancer survivors has shown strong evidence of improvements in upper body muscular strength and endurance, range of motion (Schmitz et. al., 2005a; Cheema & Gaul, 2006; Ohira et. al., 2006), reductions in exacerbations and symptoms of lymphedema (Schmitz et. al., 2009), improvements in self-esteem (Musanti, 2012), bone mineral density (Winters-Stone et. al., 2011), and body composition. As such, cancer patients and survivors should be encouraged to participate in resistance training to achieve multiple health benefits to ameliorate the effects of cancer and/or its treatment.

2.12 Resistance Training in the Cancer Survivor Population

In reviewing the exercise-based literature it is evident that significant clinical heterogeneity exists between studies in regards to the type of cancer,
mode, and intensity of exercise and the timing of the exercise intervention (Ferrer et. al., 2010; McNeely & Courneya, 2010). The majority of studies have largely involved breast cancer patients (Watson & Mock, 2004). However, the positive results reported throughout the literature do not appear to be related to cancer type or treatment. Additionally, most previous studies have not specifically examined changes in fatigue in individuals reporting severe fatigue levels. Rather the literature reporting reductions in fatigue severity in cancer patients have stemmed from studies investigating other primary outcomes of interest including psychological health, physical functioning and quality of life with fatigue as a secondary beneficial finding (Schmitz et. al., 2005b). Many studies have recruited subjects without significant expression of fatigue symptoms, instead taking an all in approach to recruitment. Therefore the result may underestimate the findings reported for a specific outcome (Speck et. al., 2010). Moreover, studies investigating the benefits of physical activity and exercise on fatigue symptoms during the post-treatment period are greatly lacking.

The exercise interventions have varied considerably from brief instructions for subjects to increase current exercise levels performed at home to highly structured, supervised exercise sessions on sophisticated fitness equipment (Conn et. al., 2006). Furthermore, previous study designs have varied from single-group pilot studies with fewer than ten subjects to randomized controlled trials (Conn et. al., 2006). Overall, studies have indicated that several improved health benefits and outcomes can be gained from physical activity both during and post-treatment (Speck et. al., 2010). Despite evidence showing that exercise based interventions improve QOL in cancer survivors the optimal exercise prescription with regard to resistance
training for this population has yet to be determined (Schmitz et. al., 2005a; McNeely et. al., 2006). Hence, there is a need for more specific resistance training guidelines on exercise prescription for fatigued cancer survivors.

2.12.1 Effect of Resistance Training on Health Related Quality of Life

Studies investigating the benefits and role of resistance training in cancer survivors have focused mostly on the improvements in muscular strength and HRQOL parameters. Schneider et. al. (2007a) investigated the effects of a 6 month resistance training exercise program either during or after cancer treatment to determine the effects on upper-body and lower-body muscular fitness, flexibility, depression and quality of life in one hundred and thirty-five breast and prostate cancer survivors. The exercise intervention included 60 minutes of resistance based exercise performed 2–3 days per week. Cancer survivors showed significant improvements in upper-body muscular endurance, lower-body muscular endurance, core muscle endurance and flexibility (P = 0.006). Additional improvements in depression and total quality of life were evident (P = 0.013).

A large randomised control study designed to determine the effects of supervised resistance exercise training on muscular fitness and HRQOL in prostate cancer survivors being treated with androgen deprivation therapy was recently published by Segal et al. (2009). One hundred and fifty five subjects were randomly assigned to an exercise (N = 82) or control (N = 73) group. The exercise group performed nine resistance exercises, three times per week at 60–70% of one repetition maximum for a 12-wk period. The control group did not participate in exercise. Outcomes were assessed at
baseline and post intervention. The primary outcomes were fatigue and QOL assessed by the Functional Assessment of Cancer Therapy-Fatigue survey. Secondary outcomes were upper-body and lower-body muscular fitness assessed by standard load tests for the chest press and leg press. Statistically significant differences in change scores favouring the exercise group for fatigue, HRQOL, and upper-body and lower-body muscular fitness were reported.

Schmitz and colleagues (2005a), examined the effects of resistance training on body composition, health related quality of life, and hormonal risk factors for cancer recurrence in breast cancer survivors in a randomized, controlled intervention trial. The effects of a 12-month resistance training program (complete-body, 9 exercises, 1–3 sets × 8–10 repetitions, 2 days per week) were studied in 85 recent breast cancer survivors (4–36 months post adjunct therapy). Participants were randomized into immediate (n =42, trained from 0 to 12 months) and delayed (n =43, trained from 7 to 12 months) treatment groups. Anthropometric measurements, nutrient intake, physical activity, biomarkers, and maximal strength were measured at baseline, 6 and 12 months. Resistance exercise resulted in significant increases in fat-free mass and 1-RM strength in both groups, as well as reductions in fat mass.

2.12.2 Effect of Resistance Training on Muscular Strength

In a randomised control study, Segal and colleagues (2009), reported an increase in muscular strength in response to 24 weeks of resistance training in a group of cancer survivors. 41 men with prostate cancer
undergoing androgen deprivation therapy (ADT) undertook resistance training sessions 3 days a week. Ten different exercises (leg extension, leg curl, seated chest fly, latissimus pulldown, overhead press, triceps extension, biceps curls, calf raises, low back extension, and modified curl-ups) were performed at an intensity of between 60-70% of estimated 1RM for a total of two sets of eight to twelve repetitions. An improvement in upper and lower body muscular strength of 22% and 24%, respectively were observed in the resistance trained group compared with a group of prostate cancer (PCa) undertaking usual care.

Increased muscular strength was observed in a randomised controlled study investigating breast cancer survivors undertaking chemotherapy. 83 cancer survivors performed nine different exercises (leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, biceps curls, and modified curl-ups, 3 times a week at an intensity of 60% to 70% of their estimated 1RM for two set of eight to twelve repetitions. Muscular strength was assessed using an 8RM protocol for both bench press and leg extension. Following resistance training muscular strength increased by 25% to 35% for the bench press and leg extension respectively (Courneya et. al., 2007). Limitation of the study include a variable training period according to the individual’s length of treatment, with a median length of between 17 ± 4 weeks.

These findings provide evidence that cancer survivors can successfully undertake resistance exercise at a sufficient intensity to stimulate physiologic adaptations in muscular strength.
2.12.3 Upper Body Resistance Training and Lymphedema

The performance of upper body exercise following breast cancer treatment has been an area of controversy within the exercise and breast cancer literature due to concerns regarding the occurrence of lymphedema, a condition characterized by localized fluid retention and tissue swelling caused by a compromised lymphatic system. The medical community has considered vigorous upper body exercise contraindicated in this cohort as it might induce or exacerbate upper extremity lymphedema. However, no empirical evidence exists to substantiate this notion (Cheema et. al., 2008). In a recent review study conducted by Cheema and Gaul et al., (2008) no exacerbation of objectively measured or subjectively reported lymphedema symptoms were reported in the 10 resistance training studies that were reviewed, some of which included upper body resistance based exercises. The authors concluded that breast cancer survivors can safely perform upper-body resistance training at an intensity equal to that recommended for the general population (8–12RM) (Cheema et. al., 2008).

2.12.4 Effect of Resistance Training on Inflammatory Markers in Cancer Survivors

It has been proposed that resistance training may have immunological and anti-inflammatory effects (Hagstrom et. al., 2016). Research investigation from aging individuals, and in those who experience chronic low-grade inflammation have suggested that resistance training may have an anti-inflammatory effect (Grewe et. al., 2001; Córdova et. al.,
While the underlying mechanism for positive change in inflammatory profiles is not presently known, it has been suggested that IL-6, released from contracting skeletal muscle may cause inhibition of inflammatory cytokines such as TNFα (Pedersen et. al., 2003; Gleeson et. al., 2011). Decreases in IL-6 and CPR has been previously observed in response to aerobic training; however comparable changes in relation to resistance training have yet to be observed.

Research investigation into resistance training and its effects on inflammatory markers in cancer survivors is limited. Galvão et. al. (2008) reported an upregulation in IL-8, with no other changes in markers including in an investigation involving 10 prostate cancer survivors. More research is required to improve our understanding of the interactions between resistance training and immune function in cancer survivors.

2.13 Justification for the Progressive Resistance Training Intervention

Resistance training is only one of a few interventions demonstrating significant efficacy for reducing self-reported fatigue symptoms in disease-free post-treatment cancer patients (Dimeo et. al., 1997; Dimeo et. al., 1998; Mock et. al., 2001). However, the physiological, neuromuscular, and performance adaptations associated with a reduction in fatigue symptoms related to resistance based exercise is currently unknown. Understanding the adaptive mechanisms that characterise improvements in fatigue symptoms severity following a chronic resistance training intervention may provide
new insights into the mechanisms responsible for fatigue symptoms reported within disease-free breast cancer survivors with cancer fatigue. Such knowledge may assist in the development of resistance based intervention to be used by health professional such as Exercise Physiologists and may improve current understanding of the underlying mechanisms associated with fatigue symptoms in cancer survivors.

Resistance exercise has been shown to produce neural learning and muscle adaptations that results in improved muscle activation following resistance training (de Lateur 1994). In the strength literature much of the early adaptation is believed to be central in origin (Chan et. al., 2003). Resistance training is thought to provide an anabolic stimulus with increase body mass (FFM), muscle fitness, and increase in functional status being observed following training in frail elderly subjects (Seynnes et. al., 2004). Other notable benefits of resistance based exercise may include increases in muscular endurance, bone mineral density and overall body composition (Evans, 1995; Al-Majid & McCarthy, 2001). Resistance training exercises provide a greater anabolic stimulus than aerobic training and are inherently regarded as the modality of choice for improving muscle strength, endurance, size, quality and power (Courneya, 2003). Total body resistance training has been previously reported to provide health-related benefits not attainable with aerobic training including the prevention of musculoskeletal injuries, reduced risk of falls, reduced frailty, improved self-efficacy and improved sleep and lesser symptoms of depression (Seguin & Nelson, 2003; Sagiv, 2009). Resistance training has even been shown to slightly increase aerobic capacity, associated with increases in muscle mass (Sagiv, 2009). Moreover, resistance training has the ability to reduce the risk of
osteoporosis and the signs and symptoms of numerous chronic diseases such as heart disease, arthritis, and type 2 diabetes (Seguin & Nelson, 2003). These benefits provide a robust rationale for the inclusion of a resistance based training intervention for disease-free, post-treatment cancer survivors.

2.14 Summary of the Literature

Results from available studies examining the relative contributions from central and peripheral mechanisms to exercise-induced fatigue in cancer survivors are conflicting and provide divergent results. In addition to the relatively small number of studies available, differences between studies may be related to the use of exercise fatigue tasks and/or neuromuscular assessment techniques. The exercise fatigue tasks used have involved different muscle groups, contraction intensities, contraction durations, and contraction protocols as well as different measurement techniques to assess neuromuscular fatigue. As neuromuscular fatigue is task dependent it is not surprising that results between studies are inconsistent. This problem is likely to be amplified through the use of different neuromuscular assessment techniques. Furthermore, many studies have include both men and women in their cohorts. It has been reported that women may exhibit a longer time to task failure than men during the performance of a sustained, submaximal isometric task of the knee extensors at 25% MVC (Clark et. al., 2005) and increased endurance time during submaximal isometric exercise of the elbow flexors at 15% MVC (Semmler et. al., 1999). Also, data indicates that different neural strategies may be evident between males and females during exercise fatigue tasks (Clark, Semmler et. al., 1999; Hunter & Enoka, 2001;
Therefore, the use of mixed male and female cohorts may also partly explain differences in results between studies.

A growing body of research indicates that regular physical exercise is a safe and beneficial non-pharmacological intervention for ameliorating cancer fatigue in cancer survivors. Previous studies have not specifically examined changes in fatigue. Rather fatigue is a secondary finding to improvements in the primary outcome of quality of life. Of the studies that have specifically examined fatigue symptoms, subjects included have not specifically consisted of cancer patients experiencing significant or severe fatigue levels. Thus our current knowledge regarding exercise as a suitable and effective non-pharmacological intervention for reducing cancer fatigue is greatly limited. By improving our understanding of potential mechanisms by which exercise based interventions may improve fatigue symptoms in disease-free, post treatment may lead to refinement and enhancement of current intervention strategies in addition to providing greater knowledge about factors that cause and contribute to cancer fatigue (Jacobsen et. al., 2007). Due to the involvement of the neuromuscular system in producing movement, it is possible that some of the improvements are related to changes in neuromuscular functioning. Therefore, further research examining the neuromuscular mechanisms contributing to cancer fatigue and performance adaptation associated with chronic resistance training exercise is warranted.
3 COMMON METHODOLOGY

3.1 Research Overview

This thesis consists of four independent studies which have utilised common methodological approaches. As such, a detailed description of shared methodology are presented within this chapter. Within each of the independent studies reference will be given to the relevant procedures detailed within this chapter and any study specific methodology will be described.

3.2 Participant Sample

Seven (7) breast cancer survivors and two (2) ovarian cancer survivors (PTCa) who had all completed curative cancer therapies and 17 healthy women (HW) healthy women with no known history of cancer and/or cancer-related treatment were recruited. Prior to commencing the resistance training the group of HW were assigned to either an exercise comparison group (HEx n=9) or a non-exercising control group (CON n=9); however, one of the control participants withdrew during the investigation due to reasons outside of the study. Therefore, data from the control group are reported for n= 8 for both study three and four.

Participants were recruited through advertising with local media, medical surgeries, and cancer support groups. Inclusion criteria required participants to be asymptomatic and free of significant musculoskeletal, cardiovascular, respiratory, metabolic, and/or neurological disorders that might influence the results of the study, other than cancer history in the
cancer survivor participants, which was determined using a health history questionnaire. Exclusion criteria for all participants included a hemoglobin level of less than <12 g/dL, a clinical diagnosis of depression or sleep disorder, and a history of any medications thought likely to influence the results of the study, such as beta-blockers or angiotension converting enzyme (ACE) inhibitors. All participants were community dwelling, non-smokers, and considered moderately active performing intermittent, light intensity habitual physical activity, such as walking and gardening 3-5 days a week (American College of Sports Medicine, 1998). No participant had any history of participation in structured exercise.

Cancer survivors were also excluded if they had a weight loss of >10% of pre-cancer diagnosis body weight prior to the study. Cancer survivors were required to complete a detailed medical history and obtain approval to participate in the study from their treating medical practitioner who was provided with details of the inclusion and exclusion criteria and asked to confirm they had no evidence of disease recurrence. Cancer survivors that participated in the study had diagnoses ranging from cancer stages 0-III. All survivors received surgery in addition to radiation therapy, chemotherapy, and/or hormonal therapy. The median time since the completion of curative primary cancer treatment was 26 months (range 7-102 months) prior to the study. Two (2) cancer survivors continued to receive an oestrogen receptor antagonist and a further two (2) continued to receive an aromatase inhibitor during the study.

Verbal and written informed consent was provided by all participants prior to participating in the study, which was approved by the
Institutional Ethics in Human Research, Biosafety, and Radiation Safety Committees.

### 3.2.1 Pre-screening

All participants attended the laboratory where they were interviewed by the Primary Investigator, whereby a thorough pre-exercise health screening process was conducted, and details of cancer treatment and health histories were obtained.

### 3.3 Physical Characteristics

#### 3.3.1 Fatigue, Depressive Symptoms, Sleep Quality, and Pain

Fatigue severity and the presence of clinical fatigue correlates were assessed using a variety of subjective self-report instruments, which were completed by participants in their homes at the same time of day following instructions by the primary investigator during familiarisation sessions. The Brief Fatigue Index (BFI) is a recommended tool for assessing fatigue associated with cancer (Seyidova-Khoshknabi et. al., 2010) and consists of a nine item questionnaire assessing current level of severity and impact on ability to function, including physical, emotional domains, over the preceding 24 hours. Each question is scored out of 10 with the mean score of all nine items used to provide a global measure (Chang et. al., 2007) in which higher scores represent greater fatigue (Mendoza et. al., 1999). The fatigue subscale of The European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-F) is recommended for
assessing fatigue associated with cancer (Seyidova-Khoshknabi et al., 2010) and consists of three questions examining the physical domain over the past week; “Did you need to rest?”, “Have you felt weak?”, and “Were you tired?” with each item scored out of 4. A raw score is calculated as the mean score of the three (3) questions, which is linearly transformed \[\frac{\text{mean score} - 1}{\text{range}} \times 100\] so that the overall fatigue is scored between 0 - 100; a higher score indicating greater fatigue (Holzner et. al., 2001; Knobel et. al., 2003).

The Revised Piper Fatigue Scale (RPFS) consists of a multidimensional questionnaire including sensory, affective meaning, cognitive/mood, and behavioural/severity domains where each item is scored out of 10 with the mean score across all domains used where a higher score corresponds with greater fatigue (Piper et. al., 1998). The 100mm visual analogue scale (VAS-F) consisted of a 100mm horizontal line anchored at each end by the word descriptors “No Fatigue” and “Very Severe Fatigue”. Participants were asked to place a vertical line at a point along the 100mm line that best represents their current level of fatigue. A numerical value is obtained by measuring the distance from the 0mm endpoint to the participant placed vertical line with a higher value indicating greater fatigue (Wewers & Lowe, 1990). The Beck Depression Inventory (BDI-II) consists of 21-items with a maximum overall score of 20 determined with higher scores indicating greater depressive symptoms (Beck et. al., 2004; Bailey et. al., 2005). The Pittsburgh Sleep Quality Index (PSQI) consists of 19 questions relating to quality of sleep over the preceding 30 days where an overall score out of 21 is calculated with higher scores indicating poorer sleep quality (Buysse et. al., 1989). The 101-point
numerical pain intensity rating scale (NRS-101) was used to quantify pain severity. The scale consisted of the numerical values of 0-10 anchored on the left by the word descriptors “No Pain” and on the right by “Worst Pain Imaginable” where participants were asked to circle the numerical value that best represents and quantifies their current level of pain (Williamson & Hoggart, 2005; Sharma et. al., 2009).

3.3.2 Blood Biochemistry

Fasting venous blood samples were taken to assess haemoglobin (Hb), glucose (GLU), and the concentrations of C-reactive protein (CRP), Interleukin 6 (IL-6), and Tumour Necrosis Factor-Alpha (TNFα). All participants were asked to refrain from strenuous activity, alcohol, and caffeine, and maintain normal nocturnal sleep habits (i.e. approximately 8 hours per night) for a period of 48 h prior to sample collection. Participants arrived to the laboratory between 0600-0900 hours in a fasted state (10-12 hrs). Following ~10 minutes of quiet sitting, a ~20mL sample of venous blood was collected using a 21GA winged infusion venipuncture set from the medial antecubital vein of the participant’s non-dominant arm. Hb and GLU concentrations were immediately assessed from a sample of the whole blood collected (ABL825 Radiometer, Copenhagen, Denmark) after which the remaining sample was aliquoted into SST tubes for analysis of CRP and EDTA tubes for the analysis of IL-6 and TNFα. The SST tubes were left to clot at room temperature for 20 min prior to centrifugation while EDTA tubes were centrifuged immediately at 3500rpm for 15min at 4°C. Supernatants for EDTA and SST, were immediately stored at -80°C or -20°C respectively. All biochemistry variables were analysed in duplicate
according to manufacturer’s instructions. Before analysis, the serum was allowed to reach room temperature and mixed gently via inversion. CRP was analysed using a particle enhanced turbidimetric immunoassay (Dimension Xpand Plus, Siemens Healthcare Diagnostics, Sydney, Australia) while IL-6 and TNF-α and were analysed using a bead-based multiplex immunoassay (MILLIPLEX MAP Human High Sensitivity T Cell Panel; Merck Millipore, Billerica, MA). A number of IL-6 and TNFα samples provided values below the expected range for these analytes and were therefore excluded from the analysis. As such, the results for IL-6 are from n= 5 and n= 3 and TNFα are from n= 6 and n= 4 for cancer survivors and healthy women, respectively.

### 3.3.3 Body Composition

Total body non-osseous lean tissue mass (TBLM), total body fat mass (TBFM), and right upper arm non-osseous lean tissue mass (RALM) was measured using dual x-ray absorptiometry (DXA) using (XR800™, Norland®, Cooper Surgical Company, CT, USA). For TBFM and TBLM, participants lay supine on the scanner bed, orientated parallel to the direction of detector movement, with their arms in anatomical position and hands touching their outer thighs. A whole body scan was performed at a speed of 260mm/sec and resolution of 6.5 x 13 mm starting from the top of the head to the bottom of feet. Whole body composition analysis was performed by identifying the chest, pelvis, and legs, which permitted the use of regionally weighted software algorithms (Figure 1). For RALM, participants lay supine on the scanner bed, orientated approximately perpendicular to the direction of detector movement, with their elbow fully
extended and shoulder abducted to 100° so the longitudinal axis of the abducted upper arm was parallel to the direction of scanner movement. A research scan was performed at speed of 90mm/sec and resolution of 3 x 3 mm starting from the sternal end of the clavicle to 3cm past the elbow. Total body composition analysis was performed on a region of interest (ROI) that included all tissues between the top of head and a horizontal line placed through the medial joint space of both ankles. Right upper arm composition analysis was performed on a ROI that included all tissue between an oblique line placed through the right glenohumeral joint, minimising the inclusion of the deltoid and latissimus dorsi musculature, to the distal portion of the humerus, bisecting the epicondylar space of the elbow. All analyses were performed using Illuminus DXA™ version 4.2.0 software (Cooper Surgical Company, CT, USA) with data reported in units of kilograms (kg).

3.4 Physical Performance

3.4.1 Aerobic Capacity

A submaximal aerobic capacity test was performed to assess aerobic power index (API) and rate of peak oxygen consumption ($\dot{V}O_{2}\text{peak}$). Testing was performed using an electronically braked cycle ergometer (LODE Excalibur Sport, LODE BV, Groningen, The Netherlands) and metabolic gas analysis system (Parvo-Medics, TrueOne 2400, Metabolic Measurement System, East Sandy, Utah, USA). Before each test, the gas analysers were calibrated with room air and a standard medical gas mixture of known oxygen and carbon dioxide concentrations and a flowmeter calibration was also performed. API was measured using a modified
protocol of the tri-level fitness profile (Wallman et. al., 2003), which has been previously been validated in a cancer population (Furzer et. al., 2012). Prior to testing, seat height was adjusted to ensure all participants were positioned on the cycle with their knee flexed to 15° (0° being full extension) when the right foot was placed on the pedal at its lowest point. Participants were then fitted with a heart rate monitor (Polar Instruments, Kempele, Finland), headgear, and mouthpiece connected to a low-resistance, two-way breathing valve. A nose clip was also positioned to eliminate nasal breathing. The prescribed target heart rate (THR) for test cessation was 75% predicted maximal heart rate (75% HRmax), which was calculated using the formula; THR (bpm) = [(220 – age) × 0.75] (Inbar et. al., 1994). Following a two minute warm-up consisting of low intensity cycling at 60 rpm, testing commenced at an initial workload of 25 Watts (W) for 1 min after which the load was increased by an additional 25 W each consecutive minute until THR was reached where the test was terminated at the end of that minute. Participants were instructed to maintain a cadence of 60 rpm through the test whilst heart rate was monitored throughout testing and recorded at the end of each minute.

The power output that coincided with THR was determined through interpolation techniques (Telford et. al., 1989). The difference between the heart rate recorded at the second last workload and at THR (HR1), as well as the difference in the heart rates recorded for the last two workloads (HR2) were calculated. These two values were represented as a fraction and multiplied by 0.25 (i.e. [HR1/HR2] × 25) to provide a single value. This single value was then summed with the power output achieved during the second last workload and the result obtained was divided by body mass,
which presents peak power output (PPO) data in units of W.kg\(^{-1}\) (Zupan et. al., 2009). For \(\dot{V}O_2\) peak, expired respiratory gases were continuously sampled throughout the test and analysed breath by breathe. The concentrations of oxygen and carbon dioxide were analysed through a sampling line after the gasses passed through a heated pneumotach and mixing chamber. Peak \(\dot{V}O_2\) was calculated offline as the highest mean rate of oxygen consumed during the final minute of the test with data presented in units of mL.kg\(^{1}\).min\(^{-1}\).

### 3.5 Neuromuscular Performance and Fatigue Testing

The assessment of neuromuscular performance and fatigue involved a combination of voluntary and evoked techniques performed on the right elbow flexors. Participants completed initial familiarisation with the neuromuscular (NM) assessment procedures to reduce any anxiety associated with any of the assessment procedures.

#### 3.5.1 Experimental Set-Up

Neuromuscular testing was performed on the right elbow flexors using an isokinetic dynamometer (Kin-Com model 125, Chattanooga Group Inc, Hixon, TN), electromyography, and constant current peripheral stimulator with all data captured synchronously using a customised data acquisition system with 16-bit A/D conversion at a rate of 4000Hz (LabVIEW™ 2010, National Instruments, Austin, TX). Participants were seated upright in the dynamometer with their right shoulder and elbow
flexed at 90˚ (0˚ being full extension) and the forearm supinated, which was a gravity neutral position. The forearm was attached to the lever arm of the dynamometer 1cm proximal to the wrist (Figure 3.1). Both shoulders and the pelvis were secured with straps to prevent any unwanted movements. Prior to testing, a standardised warm-up consisting of five progressive submaximal isometric contractions consisting of one contraction at ~50% maximal effort, two contractions at ~75% maximal effort, one contraction at ~90% maximal effort and one contraction at ~100% maximal effort was performed. A rest period of 1-min separated each of the warm up contractions, and 2-min elapsed prior to the commencement of testing.

3.5.2 Maximal Voluntary Isometric Force

Following a warm-up, participants performed 4-6 maximal voluntary isometric contractions of the right elbow flexors ensuring that the final three (3) attempts had values within ± 5% of each other. During all attempts, participants were instructed to flex their elbow as hard and rapidly as possible and continue to exert maximal effort until instructed to relax by the investigator with each contraction ~3-5 sec in duration. A 1-min rest period was provided between each attempt and instantaneous visual feedback of force output was provided to participants during all contractions using a computer display. For analysis, maximal voluntary torque (MVT) was taken as the single highest force value produced across the final three contractions. Additionally, normalised maximal voluntary force (MVF) values were determined to provide an indication of neuromuscular quality, which was calculated as: Normalised MVF (N.kg⁻¹) = MVT (N) / RALM (kg). The sum of the biceps brachii (BB) and brachioradialis (BR) EMG
Figure 3.1: Schematic representation of neuromuscular experimental testing setup. Erb’s point, anatomical site at the upper trunk of the brachial plexus located 2–3 cm above the clavicle; EMG, surface electromyography; BB, biceps brachii; BR, brachioradialis; Visual feedback, instantaneous force output was displayed on a computer screen; Coil, Transcranial magnetic stimulation was delivered using a high-power circular coil.
signals obtained during the contraction that produced MVF were bandpass filtered between 10-1000Hz using a zero-phase 4th order butterworth filter and quantified as the root-mean-square of the signal within a 500ms window centred about the moment of MVF normalised against the respective $M_{\text{max}}^{\text{RMS}}$ value and is herein referred to as $\text{EMG}_{\text{RMS}}$.

### 3.5.3 Surface Electromyography

Neuromuscular activity during voluntary and evoked testing was quantified from surface electromyographic (EMG) signals obtained from the active biceps brachii (BB), brachioradialis (BR), and triceps brachii (TB) muscles. EMG signals were detected using pairs of disposable 22mm diameter Ag/AgCl gel self-adhesive electrodes (Kendall 100 Medi-Trace, Chicopee, MA, USA) positioned over the belly of each muscle in a bipolar configuration, parallel with the muscle fibre orientation, with a 30mm inter-electrode distance and were captured using an isolated differential bio-amplifier with a gain of 500V/V, frequency bandwidth of 5-1000Hz, and a common mode rejection ratio of >110dB (i-EMG 100, GlobalTown Microtech, Inc, Sarasota, FL). A reference electrode was placed on the skin over the acromion process of the right shoulder. Prior to electrode attachment, the skin was shaved and cleaned with an abrasive cleaner and alcohol swabs to reduce skin impedance (De Luca, 1997).
3.6 Neuromuscular Performance and Fatigue Testing

3.6.1 Brachial Plexus Stimulation

To elicit maximal compound muscle action potentials ($M_{\text{max}}$) from BB, BR, and TB, a constant-current stimulator (DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK) delivered a series of single stimuli with pulse widths of 200μs using pairs of disposable 22mm diameter Ag/AgCL gel self-adhesive electrodes (Kendall 100 Medi-Trace, Chicopee, MA, USA). In order to stimulate the brachial plexus, the cathode was placed in the supraclavicular fossa over Erb’s point and the anode over the acromion. A stimulus-response curve was then completed to determine $M_{\text{max}}$ values across all muscles by increasing the current intensity in 10mA increments until both the negative peak to positive peak amplitude ($M_{\text{maxAMP}}$) and the total area under the negative and positive peaks of $M_{\text{max}}$ ($M_{\text{maxAREA}}$) for all muscles had plateaued. The current intensity at which both $M_{\text{maxAMP}}$ and $M_{\text{maxAREA}}$ plateaued was increased by a further 20% to ensure supramaximal stimulation. For testing, six (6) stimuli were delivered to resting muscle with a 30s rest between each. For processing, EMG signals were bandpass filtered between 10-1000Hz using a 2$^{nd}$ order butterworth filter whereby traces were averaged across trials and analysed for the $M_{\text{maxAMP}}$ (mV), $M_{\text{maxAREA}}$ (V.s), and root-mean-square across the $M_{\text{max}}$ negative and positive peaks ($M_{\text{maxRMS}}$; mV). These procedures were performed offline using custom software (LabVIEW™ 2010, National Instruments, Austin, TX).
3.6.2 Transcranial Magnetic Stimulation

To elicit motor evoked potentials (MEP) from BB, BR, and TB and determine the level of voluntary corticomotor activation, transcranial magnetic stimulation (TMS) was delivered using a high-power circular coil (13.5 cm outside diameter; Magstim 200, Whitlan UK). The direction of current flow was set to preferentially activate the left motor cortex and muscles of the right forearm. The optimal site for stimulation was determined as the location evoking the largest MEP negative peak to positive peak amplitude (MEP<sub>Amp</sub>) and total area under the negative and positive peaks (MEP<sub>Area</sub>) from the right elbow flexors. This was determined by systematically moving the coil in 0.5 cm steps in the anteroposterior and mediolateral directions whilst delivering single stimuli to the region during brief, steady-state submaximal (50% MVF) isometric contractions of the elbow flexor muscles with a fixed stimulator output of 50%. Once the optimal site was determined a mark was placed on the scalp using water-resistant ink and this position was used as the stimulation site for testing. A stimulus-response curve was then produced by increasing stimulator output from 30% of maximal stimulator output (MSO) by 5% steps during brief submaximal (50% MVC) isometric contractions of the elbow flexor muscles to determine the output required to elicit the largest possible MEP<sub>Amp</sub>/M<sub>max AMP</sub> and MEP<sub>Area</sub>/M<sub>max AREA</sub> ratios in BB and BR (ensuring a minimum values >0.5) with small MEP<sub>Amp</sub>/M<sub>max AMP</sub> and MEP<sub>Area</sub>/M<sub>max AREA</sub> ratios in the TB (<0.15) (Bowden et. al., 2014). The MEP<sub>Amp</sub>/M<sub>max AMP</sub> and MEP<sub>Area</sub>/M<sub>max AREA</sub> ratios for BB, BR, and TB were calculated to determine co-contraction of the agonist and antagonist.
muscles. The stimulator output used for testing then remained constant throughout testing (range 50–90% of MSO).

3.6.3 Assessment of Voluntary Muscle Activation

The interpolated twitch technique was used to assess the level of voluntary muscle activation (VA) of the right elbow flexors pre and post the sustained maximal voluntary contraction using the formula: VA (%) = [1 - (Interpolated Twitch Amplitude / Estimated Resting Twitch Amplitude)] × 100 (Todd et. al., 2003; Todd et. al., 2004); where interpolated twitch amplitude was calculated as the peak superimposed force produced during the 50–150 ms period following stimulation minus the mean voluntary force produced during the 25 ms prior to stimulus delivery. As cortical excitability increases with voluntary effort, cortically evoked resting twitch amplitude was estimated rather than measured directly as the elbow flexion force response following stimulation delivered to an inactive cortex is negligible. Thus, resting twitch amplitude was estimated from determining the y-intercept from a linear regression between interpolated twitch force and voluntary force for three (3) sets of three (3) contractions performed at intensities of 100%, 75%, and 50% of maximal voluntary effort as previously described (Todd et. al., 2004). Before the sustained maximal voluntary contraction, a 5 sec rest was provided between contractions within each set a 2-min rest period was provided between sets; while after the fatigue task all contractions and sets were performed as rapidly as possible to minimise recovery.
3.6.4 Cortical Silent Period

Cortical silent period (SP) duration was measured from the beginning of the MEP until the return of voluntary EMG activity during the 100% maximal effort contraction as measured during the CVA assessment (Molenaar et. al., 2013). Data was processed offline using custom software (LabVIEW™ 2010, National Instruments, Austin, TX).

3.6.5 Blood Lactate

Blood lactate concentrations (La-) were determined from a 100μL sample of fingertip capillary blood from the non-involved limb immediately prior to commencing the sustained maximal voluntary contraction and immediately after the assessment of voluntary muscle activation after completing the sustained contraction using a benchtop blood gas analyser (ABL825, Radiometer, Denmark).

3.6.6 Sustained Maximal Voluntary Contraction

Neuromuscular fatigue was induced using a 2-min sustained maximal voluntary isometric contraction. Participants were instructed to flex their elbow as hard and rapidly as possible and continue exerting maximal effort for the duration of the task until instructed to relax by the investigator. Strong verbal encouragement was provided throughout the task and continuous visual feedback of force output was provided on a computer display, but no feedback was provided to participants related to time elapsed or remaining was provided. During the sustained contraction, participants were cortically stimulated at the start of the contraction once force plateaued and at each 20 sec interval until task completion using the parameters
described above. An indication of the completeness of central motor drive during the sustained contraction was determined using the central activation ratio (CAR), which was calculated as: \( \text{CAR} (%) = \frac{\text{Peak Voluntary Force}}{\text{Peak Superimposed Force}} \times 100 \); where peak voluntary force was determined as the mean force produced during the 25 ms immediately prior to stimulation and peak superimposed force was determined as the peak force produced during the 50-150 ms period immediately after stimulation and was reported relative to initial values. The duration of the cortical silent period (SP) was also determined following stimulation during the sustained maximal voluntary contraction and was measured by cursor as the interval from the stimulus delivery to the return of continuous raw EMG (Taylor et al., 2000c) and reported relative to initial values. Voluntary force output during the sustained maximal voluntary contraction was determined during a 3 s window immediately prior to stimulus delivery and was reported relative to initial values. EMG signals obtained during the same 3 s windows used to determine MVF were used to evaluate signal amplitude and frequency characteristics. EMG signals were first bandpass filtered between 5-1000 Hz using a zero-phase 4th order butterworth filter. EMG amplitude was quantified as the root-mean-square (RMS) and normalised against the Mmax RMS value calculated across the negative and positive peaks and reported relative to initial values. EMG frequency was quantified as the median frequency (MDF) and calculated by performing a Fast Fourier Transformation using a Hanning window and determined as the frequency value at which the power spectrum was divided in two regions of equal integrated power and reported relative to initial values. These procedures
were performed offline using custom software (LabVIEW™ 2010, National Instruments, Austin, TX).

### 3.7 Resistance Training Program

PTCa and HEx participated in a fully supervised, whole body resistance training for a period of 12 weeks. A total of 34 training sessions were completed. These were performed on the same days of the weeks at a similar time of day with 2-3 days’ rest between sessions. All sessions were performed in a small group setting involving 2-4 participants to provide opportunities for socialisation and encourage training adherence. Each session involved three (3) sets of 8-12 maximal load repetitions (RM) for the 90° leg press, leg extension, bicep curl, lat pulldown, chest press, and shoulder press using plate or pin loaded machines (Panatta Sport, Apiro, Italy). Periodisation was applied across the training program by increasing training intensity while maintaining volume load. This was achieved by implementing three training phases each of 4 weeks’ duration in which phase one (weeks 1-4) involved a 12RM load, phase two (weeks 5-8) involved a 10RM load, and phase three (weeks 9-12) an 8RM load. Each repetition was 5 sec in duration with a 2 sec shortening phase, a 1 sec pause, and 2 sec lengthening phase. Each was performed in a controlled manner throughout the full range of motion ensuring that the active muscle groups remained loaded throughout each repetition. Training loads were adjusted across sets and sessions as necessary to ensure each set was performed with the required RM load. Minimal assistance was also provided towards the end of each set to ensure the load was moved through the full range of motion even as fatigue developed. A rest period of 90–120 sec separated
each of the three sets within each exercise and a 3-min rest period was allowed between exercises. A 5-min warm-up and cool-down involving gentle walking or stationary cycling and dynamic stretches was performed for all major muscle groups before and after each session.

### 3.7.1 Familiarisation

Participants completed initial familiarisation with the resistance training equipment, maximum repetition strength testing (1RM), and neuromuscular (NM) assessment procedures to reduce any anxiety associated with any of the assessment procedures.

### 3.7.2 Pre Training Data Collection

Following familiarisation the PTCa and HM groups (HEx and CON) attended three (3) pre-training phase laboratory based sessions involving voluntary and evoked neuromuscular assessments, as described in detail below. Each Pre-Training session was separated by ~7 days. During the final pre-training session descriptive measurements including anthropometric, body composition, sub-maximal aerobic capacity, self-reported fatigue and health-related questionnaires, in addition to the neuromuscular measurements were obtained. Venous blood was collected on a separate day, prior to the initial resistance training session, following a 10-12 hour overnight fast. Breakfast was provided following venous blood collection prior to undertaking any physical performance assessments. The CON group attended one (1) pre-training phase laboratory based sessions consisting of the neuromuscular assessments and descriptive measures as described in the final pre-training data collection session for the PTCa and HW. The CON
group were instructed to continue their normal physical activities and nutrition patterns for the duration of the 12 week intervention period.

### 3.7.3 Post Training Data Collection

All three (3) participant groups attended a post-training data collection session in the week immediately following completion of the 12 week resistance training period. All pre-training assessments were reassessed including anthropometric, body composition, sub-maximal aerobic capacity, self-reported fatigue and health-related questionnaires, venous blood and neuromuscular measurements.

All laboratory based data collection sessions were performed at a standardised time of day, where participants were required to have the same lead up to each trial, including continuing typical physical activities, sleep pattern and diet and refraining from heavy exercise and alcohol for the preceding 24 hours. A record of all food and beverage consumed in the 24-hour period prior to the first data collection session was kept in order to replicate for subsequent sessions.

### 3.7.4 Training Volume Load

Training volume load performed for each exercise for each session was calculated as sets × repetitions × load (kg) during which data were summed for the upper body (chest press, lat pulldown, bicep curl, shoulder press) and lower body (leg press and leg extension) exercises for each training phase to quantify the training volume loads completed across the training program.
3.7.5 Rating of Perceived Exertion

At the end of each set of resistance exercise, participants provided a rating of perceived exertion (RPE) using the Borg 1-10 scale. RPE data for each set of upper body (chest press, lat pulldown, bicep curl, shoulder press) and lower body (leg press and leg extension) exercise were summed across each phase of training to quantify each participant’s perceptual effort across the training program.

3.7.6 One Repetition Maximum (1RM) Muscular Strength

1RM muscular strength was assessed for each resistance exercise before the start of training, during the first training session of phases 2 and 3, and after the completion of the training program. Prior to each 1RM assessment, participants were instructed on proper technique including body positioning, required range of movement, and repetition velocity. A light, whole-body warm-up, consisting of 5-10 min of gentle walking or cycling at a self-selected pace was performed prior to assessments. For each specific resistance exercise, a warm-up set consisting of one set of 10 repetitions using a load of ~30% 1RM was initially performed after which single repetitions were performed with increasing loads until a 1RM value was obtained. A rest period of between three (3) to five (5) min was provided between attempts and of two (2) min between each specific exercise. 1RM data were pooled for the upper body (chest press, lat pulldown, bicep curl, shoulder press) and lower body (leg press and leg extension) exercises to quantify changes in muscular strength across the training program.
4 STUDY ONE

Persistent Fatigue, Systemic Inflammation, Neuromuscular Function and the Association Between Variables in Cancer Survivors and Healthy Women
Abstract

**Purpose:** To compare perceived fatigue, levels of circulating pro-inflammatory cytokines, aerobic exercise capacity, and neuromuscular function between disease-free, post primary treatment cancer survivors and healthy persons and examine the associations between variables.

**Methods:** Nine (9) disease-free, post-treatment cancer survivors (PTCa; 7 breast, 2 ovarian), aged 43-66 years and 17 healthy women (HW), aged 41-62 years were included. Mass, BMI, total body composition using dual-energy x-ray absorptiometry were assessed. Fasting venous blood samples were collected and analysed for haemoglobin (Hb) and inflammatory markers. Self-reported questionnaires for fatigue, sleep quality, depressive symptoms, and pain were completed. Physical performance including aerobic power output (API) and aerobic capacity (VO$_{2peak}$) were measured during a sub-maximal cycling protocol. Maximal voluntary isometric force (MVF) of the right elbow flexors performed on an isokinetic dynamometer at 90° shoulder and elbow flexion was assessed. EMG was recorded from the biceps brachii (BB) and brachioradialis (BR) and VA was measured using transcranial magnetic stimulation (TMS).

**Results:** Age, height, mass, BMI, body composition, CRP, IL-6 and TNFα, pain, API, VO$_{2peak}$, MVF and VA were comparable between groups (P>0.05). Hb was significantly higher for HW (P=0.01). Fatigue, sleep, depression were significantly higher for PTCa (P<0.05). EMG$_{RMS}$ for BB and BR were different between groups (P=0.01). Significant associations
between CRP and VA in PTCa (P=0.04); between CRP and $VO_{2peak}$ (P=0.01) and EMG (P=0.03) when pooled and between PSQI and EORTC-F (P=0.01) when pooled across groups.

**Conclusion:** PTCa experience higher self-reported fatigue symptoms, depressive symptoms, and poorer sleep quality compared to HW. Compared to HW, the PTCa did not have higher levels of CRP nor lower physical performance. Despite comparable physical performance, the perceptual fatigue experience appears to be more intense in PTCa. Findings suggest that cortical-subcortical factors may be involved in this high level of perceptual fatigue rather than peripheral based physical factors.
4.1 Introduction

In Australia, cancer (excluding basal and squamous cell carcinoma of the skin) has been the leading cause of total disease and injury burden since 2003 and currently accounts for approximately one fifth of the total national disease burden (AIHW, 2010; AIHW, 2012a; Horton, 2012). Although the incidence of cancer is expected to increase, cancer-related mortality is falling and survival rates are increasing due to improved sensitivity of diagnostic tests, the introduction of national cancer screening programs, and improved therapies (Bower et. al., 2014). In Australia, the 5-year all cancer survival rate increased between the periods 1982-1987 and 2006-2010 from 47% to 66% (AIHW, 2012b). As the number of survivors’ increase, the ability to manage the long-term and late effects of cancer and/or its treatment becomes increasingly important.

Cancer fatigue is defined as an unusual persistent sense of tiredness related to cancer and/or its treatment that interferences with usual functioning (Cella et. al., 1998), which is not relieved by sleep or rest (McNeely & Courneya, 2010; Sood & Barton, 2010). Fatigue is almost universally experienced during primary cancer treatment and 30-40% of disease-free survivors will continue to experience fatigue symptoms for up to 10 years post-treatment (Bower et. al., 2000; Cella et. al., 2001; Bower et. al., 2006; Ng et. al., 2007). Despite the severity and frequency of symptoms (Bower et. al., 2014), its negative effect on quality of life (Mishra et. al., 2015) and association with mortality (Chang et. al., 2007), the mechanisms contributing to cancer fatigue are largely unknown. This is probably because the aetiology of cancer fatigue is the result of multiple biologic processes involving the interaction between various disease and treatment related...
factors, patient susceptibility and comorbid conditions (e.g., sleep disturbance, depression, pain, anemia) (Wang, 2008; Saligan et. al., 2015). Several physiological systems, have been implicated in the etiology of cancer fatigue including the immune, nervous, musculoskeletal and cardiopulmonary (Berger et. al., 2012). To this end, a complex, multifactorial model of cancer fatigue has been proposed, which suggests that cancer and/or its treatment activates an immune response, involving primarily pro-inflammatory cytokine networks, which may exert an effect on the central nervous system (CNS) leading to symptoms of fatigue, which is associated with reduced physical capacity and impaired neuromuscular function (Bower et. al., 2002; Ng et. al., 2007; Alexander et. al., 2009; Saligan et. al., 2015).

Evidence to support an neuroimmune basis of cancer fatigue comes from studies demonstrating elevated circulating levels of pro-inflammatory cytokines, specifically interleukin (IL)-1, IL-6, C-reactive protein (CRP), and tumour necrosis factor-alpha (TNF)-α in both cancer patients undergoing treatment and disease-free survivors that experience symptoms of fatigue (Shor, 2003; Wyller et. al., 2009) and reports of a relationship between various pro-inflammatory cytokines and other clinical correlates of cancer fatigue, including impaired cognition (Kelley et. al., 2003), anaemia and cachexia (Barsevick et. al., 2010), depression (Raison et. al., 2006), and sleep disturbance (Roscoe et. al., 2007). However, a cause-effect relationship between a specific inflammatory marker/s and fatigue symptoms in cancer patients and/or survivors is yet to be established and reports of associations between various pro-inflammatory cytokines and
fatigue symptoms are inconsistent (Bower, 2007; Saligan & Kim, 2012; Pertl et. al., 2013).

Negative correlations between physical function and cancer fatigue have been reported (Dimeo, 2001; Luctkar-Flude et. al., 2007; Alexander et. al., 2009). However, such evidence has been obtained largely from self-report measures of physical activity and perceived levels of physical function (Alexander et. al., 2009), as such little is known about the relationship between cancer fatigue with objective measurements of physical capacity and performance. Although, physical capacity and physical activity levels are related, each represent separate domains of physical function, as such reduced physical activity levels do not automatic imply a reduction in physical capacity or vice versa (van Lummel et. al., 2015). Consequently, cause and effect relationships between physical function and cancer fatigue cannot be elucidated based on such measures.

Given that cancer fatigue appears to involve the activation of pro-inflammatory cytokines networks investigating physical capacity and its relationship with pro-inflammatory cytokines may be important to furthering our understanding of this symptom. A growing body of literature indicates that pro-inflammatory cytokines effect skeletal muscle function and physical performance in healthy older populations (Reid & Li, 2001; Wang, 2008). Several observation studies have reported lower skeletal muscle mass and poorer physical performance in well-functioning older persons with elevated plasma concentrations of TNF-α and IL-6 (Reuben et. al., 2002; Zoico & Roubenoff, 2002; Schaap et. al., 2009). Higher levels of circulating IL-6 and CRP have been found to be associated with poorer performance, including walking speed and grip strength, respectively.
(Taaffe et. al., 2000), and CRP has been shown to be associated with low hand grip strength in high-functioning older adults (Sousa et. al., 2016).

Whether elevated systemic pro-inflammatory cytokines is associated with lower muscle mass and poorer physical performance in cancer survivors with fatigue is not well established.

At present the causal pathway between declines in physical performance and elevated concentrations of inflammatory markers is not fully understood, however is thought to involve catabolic effects of pro-inflammatory cytokines on skeletal muscle (Sousa et. al., 2016). Recent investigations have found that TNF-α regulates skeletal muscle function via two mechanisms: 1) directly stimulating muscle cells protein loss, resulting in muscle atrophy and 2) the loss of contractile function, characterised by a loss in force per cross-sectional area, which occurs independent of muscle protein content (Reid & Li, 2001; Powers et. al., 2016), suggesting possible deficits in neuromuscular function.

Developing our understanding of the mechanisms contributing to cancer fatigue is complicated due to the fact that two distinct components must be considered: 1) a subjective component involving the assessment of perceived fatigue symptoms; and 2) an objective component related to the evaluation of physical performance. A range of self-report questionnaires have been used to evaluate the magnitude and/or intensity of perceived fatigue in persons with a history of cancer (Brown et. al., 2011). However, at present no gold-standard instrument exists (Bruera & Neil MacDonald, 1988; Prue et. al., 2006; Shen et. al., 2006) and methodological issues such as bias may be apparent when evaluating fatigue symptoms using self-report instruments (Breetvelt & Van Dam, 1991). In contrast, physical
performance can be objectively determined using highly precise and reliable laboratory-based assessments of exercise capacity. As such, examining different exercise capacities may provide insight into the dysfunction of various physiological systems and their contributions to the expression of cancer fatigue. However, available studies in this area have primarily examined aerobic exercise capacity while data pertaining to neuromuscular function is limited. This is surprising given that evidence for a neuroimmune basis of fatigue is growing (Dantzer et. al., 2014; Vargas & Marino, 2014).

Therefore, the purpose of this study is to examine perceived fatigue, indices of physical performance (aerobic exercise capacity and neuromuscular function), levels of circulating pro-inflammatory cytokines (CRP, TNFα, IL-6), and clinical symptoms associated with fatigue (depression, sleep and pain) in a group of disease-free, post primary treatment cancer survivors, with persistent fatigue compared to healthy persons to provide insight into their possible contributions to cancer fatigue. Due to the complex, multifactorial nature of cancer fatigue investigating the association between various physiological factors is important in developing our understanding of the mechanisms for cancer fatigue. As such a further purpose is to examine associations between variables including: associations between fatigue symptoms and pro-inflammatory cytokines with indices of physical performance and clinical correlates of fatigue (sleep, depression, pain) in the cancer survivors compared to healthy persons and within pooled group data. It is hypothesised that the cancer survivors will report higher perceived fatigue, associated symptoms of fatigue, pro-inflammatory cytokine concentrations and poorer physical performance compared to healthy persons. Based on previous literature, it is also hypothesised that
negative associations will be observed between fatigue and pro-inflammatory cytokines with sleep, depression, pain, indices of physical performance and that the strength of the associations will be different in the cancer survivors compared to healthy women.

4.2 Methods

A detailed description of all testing procedures is provided in Chapter 3.

4.2.1 Participant Sample

Seven (7) breast cancer survivors and two (2) ovarian cancer survivors (PTCa) who had all completed curative cancer therapies and 17 healthy women (HW) healthy women with no known history of cancer and/or cancer-related treatment participated in the study (Section 3.2).

4.2.2 Physical Characteristics

Fatigue, Depressive Symptoms, Sleep Quality, and Pain were assessed using a variety of subjective self-report instruments including: The Brief Fatigue Index (BFI); The fatigue subscale of European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-F); The Revised Piper Fatigue Scale (RPFS); The 100mm visual analogue scale (VAS-F); The Beck Depression (BDI-II); The Pittsburgh Sleep Quality Index (PSQI); and The 101-point numerical pain intensity rating scale (NRS-101) (Section 3.3.1). Fasting venous blood samples were taken to assess biochemistry measures including haemoglobin (Hb), glucose (GLU), and the concentrations of C-reactive protein (CRP), Interleukin 6
(IL-6), and Tumour Necrosis Factor-Alpha (TNFα) (Section 3.3.2). Mass, BMI, and measures of body composition including total body non-osseous lean tissue mass (TBLM), total body fat mass (TBFM), and right upper arm non-osseous lean tissue mass (RALM) was measured using dual x-ray absorptiometry (DXA) (Section 3.3.3).

4.2.3 Physical and neuromuscular performance

A submaximal aerobic capacity test was performed to assess aerobic power index (API) and volume of peak oxygen consumption ($\dot{V}O_2$peak) (Section 3.4.1). Following a standardised warm-up (Section 3.5.1), maximal voluntary isometric force (MVF) of the right elbow flexors performed on an isokinetic dynamometer at 90° shoulder and elbow flexion was assessed (Section 3.5.1). Neuromuscular activity during voluntary and evoked testing was quantified from surface electromyographic (EMG) signals obtained from the active biceps brachii (BB) and brachioradialis (BR) muscles (Section 3.5.3). Brachial Plexus Stimulation was used to elicit maximal compound muscle action potentials (Mmax) from BB, BR, and TB (Section 3.6.1). Transcranial Magnetic Stimulation was used to elicit motor evoked potentials (MEP) from BB, BR, and TB and determine the level of voluntary corticomotor activation (Section 3.6.2). Assessment of Voluntary Muscle Activation was measured using the interpolated twitch technique (Section 3.6.3).

4.2.4 Statistical Analysis

Before inferential statistics were completed, all data were natural log transformed using the equation $Y = \ln(x + 1)$ (Portney & Watkins, 2000). An
exploratory analysis was then performed to identify outliers and the
distribution of each independent variable was tested using the Shapiro-Wilk
W statistic (Ghasemi & Zahediasl, 2012). Between group differences in all
normally distributed variables were identified using a one-way analysis of
variance (ANOVA). Several variables were not normally distributed (body
mass, RALM, RALM, VO_{2\text{peak}}, PPO, and EORTC-F) and therefore a two-
sample Mann-Whitney rank sum test for non-parametric data was used
identify between group differences (Wilcoxon, 1945; Mann & Whitney,
1947). These statistical procedures were performed using SPSS (Statistical
Package for the Social Sciences version 20.0) software. Relationships
between variables were determined using a Pearson’s product moment
correlation using GraphPad Prism™ software (version 6, GraphPad
Software, Inc, La Jolla, CA). The critical level for significance was set at P≤
0.05 for all analyses. To determine the magnitude of statistically significant
differences between groups. All data are presented as the mean ± standard
development.
4.3 Results

4.3.1 Participant Characteristics

Physical characteristics for the cancer survivors and healthy women are presented in Table 4.1. Age was significantly different with cancer survivors older than the healthy women (P= 0.041). No other statistically significant differences were evident between groups for any other physical characteristics.

4.3.2 Blood Biochemistry

Blood biochemistry data for the cancer survivors and healthy women are presented in Table 4.2. Hb was observed to be higher for the cancer survivors than for the healthy women (P= 0.01). No other statistically significant differences were evident between groups for any other biochemical variable (P> 0.36).

4.3.3 Fatigue, Depressive Symptoms, Sleep Quality, and Pain Intensity

Fatigue severity, depressive symptoms, sleep quality, and pain intensity scores for the cancer survivors and healthy women are presented in Table 4.3. No significant differences in BFI, RPFS, VAS-F, or NRS-101 scores were evident between groups (P> 0.09). Scores for EORTC-F and BDI-II were significantly higher for the cancer survivors compared with the healthy women (P≤ 0.006); while a trend was evident for PSQI scores to be
Table 4.1: Participant characteristics for the cancer survivors and healthy women.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Mass (kg)</th>
<th>Body Mass Index (kg.m$^{-2}$)</th>
<th>TBLM (kg)</th>
<th>TBFM (kg)</th>
<th>RALM (kg)</th>
<th>API (W.kg$^{-1}$)</th>
<th>VO$_2$peak (ml.kg$^{-1}$.min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Survivors</td>
<td>56 ± 8</td>
<td>167 ± 8</td>
<td>73 ± 15</td>
<td>26.9 ± 4.9</td>
<td>41.2 ± 5.4</td>
<td>27.5 ± 12.0</td>
<td>1.1 ± 0.2</td>
<td>1.05 ± 0.70</td>
<td>22.3 ± 7.6</td>
</tr>
<tr>
<td>Healthy Women</td>
<td>49 ± 5*</td>
<td>164 ± 11</td>
<td>77 ± 10</td>
<td>29.1 ± 5.3</td>
<td>44.5 ± 4.8</td>
<td>32.4 ± 8.6</td>
<td>1.2 ± 0.1</td>
<td>1.07 ± 0.60</td>
<td>25.5 ± 5.9</td>
</tr>
<tr>
<td>Significance (P)</td>
<td>P= 0.04</td>
<td>P= 0.57</td>
<td>P= 0.44</td>
<td>P= 0.37</td>
<td>P= 0.61</td>
<td>P= 0.33</td>
<td>P= 0.73</td>
<td>P= 0.87</td>
<td>P= 0.33</td>
</tr>
</tbody>
</table>

TBLM, total body non-osseous lean mass; TBFM, total body fat mass; RALM, right upper arm non-osseous lean mass; API, aerobic power index; VO$_2$peak, peak oxygen consumption. Values presented as mean ± SD. *Indicates significance between groups (P= 0.04). Values presented as mean ± SD.
Table 4.2: Blood biochemistry data for the cancer survivors and healthy women.

<table>
<thead>
<tr>
<th>Group</th>
<th>Hb (mg/dL)</th>
<th>GLU (mmol/L)</th>
<th>CRP (mg/L)</th>
<th>IL-6* (pg/mL)</th>
<th>TNFα** (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Survivors</td>
<td>15.8 ± 0.8</td>
<td>4.9 ± 0.54</td>
<td>2.3 ± 1.0</td>
<td>1.1 ± 0.7</td>
<td>2.8 ± 2.3</td>
</tr>
<tr>
<td>Healthy Women</td>
<td>15.1 ± 2.4*</td>
<td>5.1 ± 0.6</td>
<td>2.8 ± 1.2</td>
<td>2.1 ± 1.4</td>
<td>2.4 ± 1.2</td>
</tr>
</tbody>
</table>

Significance (P)  
P= 0.01  
P= 0.36  
P= 0.34  
P= 0.23  
P= 0.75

Hb, haemoglobin; GLU, blood glucose; CRP, C-reactive protein; IL-6, interleukin-6; TNFα, tumor necrosis factor-alpha. *Indicates that n= 5 and n= 3 for the cancer survivors and healthy women, respectively. ** Indicates that n= 6 and n= 4 for the cancer survivors and healthy women, respectively. *Indicates a significant difference between groups (P= 0.01). Values presented as mean ± SD.
<table>
<thead>
<tr>
<th>Group</th>
<th>BFI</th>
<th>EORTC-F</th>
<th>RPFS</th>
<th>VAS-F</th>
<th>BDI-II</th>
<th>PSQI</th>
<th>NRS-101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Survivors</td>
<td>2.4 ± 1.5</td>
<td>24.7 ± 12.1</td>
<td>3.2 ± 1.9</td>
<td>2.5 ± 2.1</td>
<td>6.6 ± 2.9</td>
<td>7.3 ± 3.0</td>
<td>1.0 ± 1.3</td>
</tr>
<tr>
<td>Healthy Women</td>
<td>2.3 ± 1.3</td>
<td>11.5 ± 10.8*</td>
<td>1.3 ± 0.8</td>
<td>1.8 ± 2.0</td>
<td>2.5 ± 2.3*</td>
<td>5.2 ± 1.44</td>
<td>0.6 ± 0.9</td>
</tr>
<tr>
<td>Significance (P)</td>
<td>P= 0.81</td>
<td>P= 0.01</td>
<td>P= 0.09</td>
<td>P= 0.29</td>
<td>P= 0.006</td>
<td>P= 0.06</td>
<td>P= 0.47</td>
</tr>
</tbody>
</table>

BFI; Brief Fatigue Index; EORTC-F, European Organisation for Research and Treatment of Cancer Questionnaire- Fatigue Domain; RPFD, Revised Piper Fatigue Scale; VAS-F, Visual Analogue Scale- Fatigue; BDI-II, The Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; NRS-101, numerical pain intensity rating scale. *Indicates a significant difference between groups (P≤ 0.01). Values presented as mean ± SD.
higher for the cancer survivors compared with the healthy women (P= 0.06).

4.3.4 Maximal Voluntary Force

MVF and nMVF for the cancer survivors and healthy women are presented in Figure 4.1. No statistically significant differences were evident between groups in either variable (P> 0.21).

4.3.5 Neuromuscular Activity and Level of Voluntary Activation

EMG_RMS and VA data for the cancer survivors and healthy women are presented in Figure 4.2. EMG_RMS was statistically greater in the healthy women compared with the cancer survivors (P<0.01); while no statistically significant differences in VA were evident between groups (P> 0.73).
Figure 4:1: Maximum voluntary force (MVF) and normalised MVF (nMVF) for the cancer survivors and healthy women. Values presented as mean ± SD.
Figure 4: Neuromuscular activity (EMG$_{RMS}$) and the level of voluntary activation (VA) for the cancer survivors and healthy women. *Indicates a statistically significant difference between groups. Values presented as mean ± SD.
4.3.6 Associations Between Variables

Associations between variables in the cancer survivors and healthy women as well as in the pooled data between groups are presented in Table 4.4 and Table 4.5. A moderate positive association were observed between BD-II and EORTC-F in the cancer survivors; this association reached statistical significance when data from both groups were pooled (P= 0.01). A moderate negative association were observed between CRP and EORTC-F for healthy women. Moderate negative associations were also observed between EMG_RMS and CRP reaching statistical significance when data from both groups were pooled (P= 0.03). Statistical significance between VA and CRP was observed in the cancer survivors (P= 0.04); while a trend for a moderate negative association between VA and CRP was observed when data from both groups were pooled (P= 0.07). Trends for weak positive associations between VO2peak and CRP were observed in both the cancer survivors (P= 0.07) and healthy women (P= 0.08); while this association reached statistical significance when data from both groups were pooled (P= 0.01). No other trends or statistically significant associations in either group or when data were pooled between groups were observed.
Table 4.4: Associations between CRP with clinical fatigue correlates, indices of physical capacity and neuromuscular performance in the cancer survivors and healthy women.

<table>
<thead>
<tr>
<th>Group</th>
<th>CRP and EORTC-F</th>
<th>CRP and BD-II</th>
<th>CRP and PSQI</th>
<th>CRP and NRS-101</th>
<th>CRP and MVF</th>
<th>CRP and nMVF</th>
<th>CRP and EMGrms</th>
<th>CRP and VA</th>
<th>CRP and API</th>
<th>CRP and VO₂peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Survivors (n= 9)</td>
<td>r= 0.08 (P= 0.84)</td>
<td>r= 0.40 (P= 0.07)</td>
<td>r= 0.06 (P= 0.57)</td>
<td>r= 0.03 (P= 0.68)</td>
<td>r= -0.04 (P= 0.91)</td>
<td>r= -0.03 (P= 0.95)</td>
<td>r= -0.53 (P= 0.14)</td>
<td>r= -0.67* (P= 0.04)</td>
<td>r= 0.14 (P= 0.36)</td>
<td>r= 0.39 (P= 0.07)</td>
</tr>
<tr>
<td>Healthy Women (n= 17)</td>
<td>r= -0.34 (P= 0.37)</td>
<td>r= 0.00 (P= 0.93)</td>
<td>r= 0.09 (P= 0.21)</td>
<td>r= 0.01 (P= 0.74)</td>
<td>r= 0.18 (P= 0.65)</td>
<td>r= 0.42 (P= 0.25)</td>
<td>r= -0.51 (P= 0.17)</td>
<td>r= 0.16 (P= 0.68)</td>
<td>r= 0.01 (P= 0.64)</td>
<td>r= 0.18 (P= 0.08)</td>
</tr>
<tr>
<td>Pooled Data Between Groups (n= 26)</td>
<td>r= -0.01 (P= 0.91)</td>
<td>r= -0.02 (P= 0.52)</td>
<td>r= 0.09 (P= 0.65)</td>
<td>r= 0.00 (P= 0.93)</td>
<td>r= 0.03 (P= 0.91)</td>
<td>r= 0.15 (P= 0.54)</td>
<td>r= -0.51* (P= 0.03)</td>
<td>r= -0.44 (P= 0.07)</td>
<td>r= 0.004 (P= 0.31)</td>
<td>r= 0.29* (P= 0.01)</td>
</tr>
</tbody>
</table>

EORTC-F, fatigue subscale of European Organisation for Research and Treatment of Cancer quality of life questionnaire; BD-II, Beck’s Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; NRS-101, 101-point numerical pain intensity rating scale; MVF, maximal voluntary force; nMVF, maximal voluntary force normalised for lean muscle mass; EMGrms, neuromuscular activity; VA, level of voluntary muscle activation; API, aerobic power index; VO₂peak, peak oxygen consumption; CRP, C-reactive protein; r, Pearson’s product-moment correlation; and P, level of significance.

*Indicates statistically significant association (P < 0.05).
Table 4.5: Associations between EORTC-F with clinical fatigue correlates, indices of physical capacity and neuromuscular performance in the cancer survivors and healthy women.

<table>
<thead>
<tr>
<th>Group</th>
<th>EORTC-F and BD-II</th>
<th>EORTC-F and PSQI</th>
<th>EORTC-F and NRS-101</th>
<th>EORTC-F and MVF</th>
<th>EORTC-F and nMVF</th>
<th>EORTC-F and EMG&lt;sub&gt;RMS&lt;/sub&gt;</th>
<th>EORTC-F and VA</th>
<th>EORTC-F and API</th>
<th>EORTC-F and VO&lt;sub&gt;2peak&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Survivors (n= 9)</td>
<td>r= 0.40 (P= 0.07)</td>
<td>r= 0.31 (P= 0.15)</td>
<td>r= 0.22 (P= 0.24)</td>
<td>r= -0.04 (P= 0.91)</td>
<td>r= -0.03 (P= 0.95)</td>
<td>r= -0.53 (P= 0.14)</td>
<td>r= -0.67* (P= 0.04)</td>
<td>r= 0.004 (P= 0.)</td>
<td>r= 0.39 (P= 0.07)</td>
</tr>
<tr>
<td>Healthy Women (n= 17)</td>
<td>r= 0.00 (P= 0.93)</td>
<td>r= 0.22 (P= 0.05)</td>
<td>r= 0.11 (P= 0.18)</td>
<td>r= 0.18 (P= 0.65)</td>
<td>r= 0.42 (P= 0.25)</td>
<td>r= -0.51 (P= 0.17)</td>
<td>r= 0.16 (P= 0.68)</td>
<td>r= 0.0003 (P= 0.94)</td>
<td>r= 0.18 (P= 0.08)</td>
</tr>
<tr>
<td>Pooled Data Between Groups (n= 26)</td>
<td>r= -0.02 (P= 0.52)</td>
<td>r= 0.37* (P= 0.001)</td>
<td>r= 0.10 (P= 0.12)</td>
<td>r= 0.03 (P= 0.91)</td>
<td>r= 0.15 (P= 0.54)</td>
<td>r= -0.51* (P= 0.03)</td>
<td>r= -0.44 (P= 0.07)</td>
<td>r= 0.001 (P= 0.86)</td>
<td>r= 0.29* (P= 0.01)</td>
</tr>
</tbody>
</table>

EORTC-F, fatigue subscale of European Organisation for Research and Treatment of Cancer quality of life questionnaire; BD-II, Beck’s Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; NRS-101, 101-point numerical pain intensity rating scale; MVF, maximal voluntary force; nMVF, maximal voluntary force normalised for lean muscle mass; EMG<sub>RMS</sub>, neuromuscular activity; VA, level of voluntary muscle activation; API, aerobic power index; VO<sub>2peak</sub>, peak oxygen consumption; r, Pearson’s product-moment correlation; and P, level of significance. *Indicates statistically significant association (P< 0.05).
4.4 Discussion

4.4.1 Major Findings

Despite increased self-reported fatigue in the cancer survivors, levels of circulating CRP, MVF, nMVF, and VA were comparable to the healthy women. Negative associations were observed between CRP and VA in the cancer survivors and between CRP with $\text{EMG}_{\text{RMS}}$ when pooled between groups, suggesting that cancer survivors experiencing increased perceived fatigue symptoms may retain their capacity for maximal strength performance during a single, acute task. Although CRP was not associated with fatigue symptoms or maximal neuromuscular performance in either group individually or when data was pooled between groups, it appears CRP may still influence discrete elements of neuromuscular function.

4.4.2 Fatigue, Depressive Symptoms, Sleep Quality, and Pain

As there is no gold standard instrument currently available several self-report fatigue questionnaires were used in this study (Minton & Stone, 2009). Consistent with previous findings, the present cancer survivors demonstrated higher self-reported fatigue based on EORTC-F scores compared with the healthy women (Andrykowski et. al., 1998; Broeckel et. al., 1998; Woo et. al., 1998; Bower et. al., 2000; Servaes et. al., 2001; Servaes et. al., 2002). The mean EORTC-F score exceeded the >20 point criteria previously established for clinical fatigue in cancer patients using this instrument (Snyder et. al., 2010). Differences between groups were
more pronounced using the EORTC-F compared with the RPFS, BFI, RPFS, or VAS-F. This may be explained by the RPFS scores relating to fatigue experienced during the past 24 hours; whilst the EORTC-F involves fatigue during the past week. Similarly, the BFI also evaluates fatigue during the past 24 hours; while the VAS-F evaluates fatigue during the past two weeks. However, unlike multidimensional self-report fatigue scales such as the RPFS and EORTC-F, which capture characteristics and manifestations of fatigue across multiple domains, the BFI and VAS-F are unidimensional assessments which evaluate symptoms without consideration of the complex nature of fatigue (Ng et. al., 2007a; Minton & Stone, 2009). Suffice to say, that the discrepancy between the various self-report fatigue questionnaires across groups supports the notion that such instruments are not interchangeable and assess difference aspects of the fatigue experience. Additionally, evidence in cancer patients undergoing chemotherapy suggests that fatigue symptoms may be highly variable and change over the course of a day and across a treatment cycle (Bower et. al., 2000; Schwartz, 2000; Jacobsen, 2004; Dimsdale et. al., 2007). Therefore, it is possible that such variability may continue into survivorship and acute self-report fatigue assessments may not adequately capture the fatigue experience. Accordingly, future studies seeking to evaluate fatigue in cancer survivors may benefit from using a battery of multidimensional self-report questionnaires that are administered on multiple occasions.

Fatigue in cancer survivors is frequently related to depressive symptoms (Andrykowski et. al., 1998; Broeckel et. al., 1998; Bower et. al., 2000; Okuyama et. al., 2000), sleep quality (Andrykowski et. al., 1998; Broeckel et. al., 1998; Bower et. al., 2000; Okuyama et. al., 2000; Servaes
et. al., 2001), and pain (Smets et. al., 1998; Bower et. al., 2000; Servaes et. al., 2002). As such, higher depressive symptoms and a trend for reduced sleep quality in the cancer survivors observed in the present study was not unexpected. The relationship between fatigue, depression, and poor sleep quality observed in cancer is highly complex whereby fatigue is a symptom of clinical depression, but persistent fatigue may induce depression (Visser & Smets, 1998); while poor sleep is an independent risk factor for depression (Irwin et. al., 2013) and a strong clinical correlate of fatigue (Roscoe et. al., 2007). While the BDI-II scores in the present study were higher in the cancer survivors their values are considered normal, the criteria for mild depression being ≥ 13 (Mota et. al., 2012). Although PSQI scores tended to be higher in the cancer survivors, both groups may be affected by poor sleep as a cut-off score of 5 has been suggested (Buysse et. al., 1989). However, the PQSI has been criticised as being more of a measure of negative attitude and dissatisfaction rather than physiological sleep quality (Grandner et. al., 2006) and the validity of this data may be questioned. Unfortunately, it was not feasible in the present study to directly monitor participants’ sleep or physical activity levels using actigraphy or other objective instrument. In contrast, pain scores were very low and were comparable between groups. Although the precise mechanisms explaining the association between self-reported fatigue with depressive symptoms, impaired sleep, and/or pain are unknown, it is reasonable to suggest that given the similarity of the data obtained between groups that the influence of these correlates on fatigue status was likely minimal and clearly demonstrates the complexity of the problem.
4.4.3 Physical and Neuromuscular Performance

4.4.3.1 Aerobic Capacity

Declines in aerobic capacity due to the negative physiological effects of cancer and/or its treatment, coupled with deconditioning has been suggested to contribute to persistent fatigue in cancer survivors (Dimeo et. al., 1998; Ng et. al., 2007a; Alexander et. al., 2009). Aerobic capacity was similar between groups, and neither group were anaemic (Hb levels >12g/dL) (Cook & Finch, 1979). Neil et. al. (2013) reported a lower absolute age-adjusted VO$_2$peak during a maximal cycle test in breast cancer survivors with persistent fatigue compared to non-fatigued survivors; however, relative VO$_2$peak was comparable between groups (Neil et. al., 2013). Additionally, Herrero et. al. (2006) reported that absolute and relative VO$_2$peak as well as peak aerobic power during a maximal cycling test was not significantly different between fatigued and non-fatigued breast cancer survivors (Herrero et. al., 2006). The present data are in agreement with such findings; although the VO$_2$peak data obtained in this study appears to be relatively low compared with age-related norms (Shvartz & Reibold, 1990; Heyward & Gibson, 2014). Nonetheless, it appears that aerobic deconditioning may be precluded as a potential factor contributing to the persistent fatigue symptoms experienced by the present sample of cancer survivors.

4.4.3.2 Maximal Voluntary Force

Contrary to previous reports we found MVF was highly comparable between both the cancer survivors and healthy women. Harrington et. al. (2011) reported 20-30% lower maximal upper body strength, as measured
using a hand held dynamometer, in breast cancer survivors following the completion of primary treatment compared to a group of healthy women. Although, non-significant differences in lower body strength, as measured during a 3 sec isometric maximum voluntary contraction of the quadriceps, have been previously reported between fatigued (105.4 ± 39.4 Nm) and non-fatigued breast cancer survivors (100.0 ± 25.9 Nm) (Neil et. al., 2013). Such results offer some support for our finding, suggesting that the perceived fatigue experienced by PTCa may not be due to reduced physical capacity during brief, maximal isometric efforts. Comparisons between studies is problematic due to different methods utilised to assess strength.

Peak force per unit of muscle mass, used to evaluated muscle quality, was highly comparable between groups. This quantitative approach assesses the relationship between the quantity of skeletal muscle present and quality of muscle force produced to determine whether impairments in neuromuscular performance may mediate force generated (Girard et. al., 2014). When taken together, muscular strength, mass and normalised force was similar between the groups, suggesting that the groups were well matched in terms of factors involving contractile elements of muscle cells, descending neural drive, motor unit function, changes in the, excitation–contraction coupling mechanisms. However, further research is needed to confirm this.

As pre cancer diagnosis physical performance measures are not available for comparative purposes it is not known whether the PTCa experienced a change in their level of physical performance since diagnosis. The current findings provide further evidence that the two groups investigated were well matched for physical performance (aerobic capacity
and neuromuscular function), reducing the potential influence that physical performance had on participants self-reported perceived fatigue level that would arise if cancer related fatigue symptoms were largely related to physical deconditioning.

4.4.3.3 Neuromuscular Activity and the Level of Voluntary Activation

Non-significant differences between groups for EMGrms or VA suggests that descending motor drive from spinal and supraspinal sites was similar between groups for the MVC contraction. Although the cancer survivors were 7 year older than the healthy women, this difference in age is unlikely to result in major differences in physical performance based on current understandings of the rate of age-related loss in muscle mass and motor unit recruitment. Our findings support those reported by Kisiel-Sajewicz et al. (2012) whereby no difference in peak twitch force production as measured using peripheral electrical stimulation during an isometric maximal contraction involving the biceps brachii were reported between 10 advanced cancer survivors with fatigue and 12 healthy. Similarly, in a recent randomised control study Prinsen et al. (2013) found no significant differences in force production in response to peripheral electrical stimulation during an isometric maximal contraction involving the biceps brachii in 20 fatigued and 20 non fatigued post treatment cancer survivors. Although EMG was recorded only force values were reported. These findings are inconclusive in determining whether reduced neuromotor function is evident in cancer survivors. Although we found no difference in VA between groups we did observe greater EMGrms in the healthy women.
compared to cancer survivors and healthy women. The discrepancies may be related to the greater sensitivity of EMG to detect increases in myoelectrical activity compared to the force based VA measures. As no difference was observed in MVF the differences in EMG\textsubscript{RMS} may relate to factors such as antagonist coactivation, or alternatively may indicate possible enhanced contractility in the cancer survivors.

\subsection*{4.4.4 Systemic Inflammation}

No significant differences were found in pro-inflammatory cytokines, including CRP, IL-6, and TNF\(\alpha\) between groups. Elevated circulating levels of pro-inflammatory cytokines, including CRP, IL-1, IL-6, and/or TNF\(\alpha\), as well as increased markers of pro-inflammatory cytokine activity, such as IL-1 receptor agonist, soluble IL-6 receptor, and/or soluble TNF receptor type II, have been observed in fatigued post treatment cancer survivors in follow-up studies (Orre et. al., 2011; Reinertsen et. al., 2011) and cross-sectional comparisons with non-fatigued survivors (Bower et. al., 2002; Collado-Hidalgo et. al., 2006; Alexander et. al., 2009) or healthy participants (Bower et. al., 2011). However, observations differ between studies in terms of which pro-inflammatory cytokines are elevated and data supporting a link between inflammation and persistent fatigue in cancer survivors remains inconclusive (Bower et. al., 2002; Collado-Hidalgo et. al., 2006; Saligan & Kim, 2012). Alexander et. al. (2009) found significant elevations in CRP in 60 breast cancer survivors who met stringent criteria for cancer-related fatigue syndrome compared to 104 non-fatigued controls. Similarly, in sample of 299 disease-free survivors, Orre et. al. (2011) found a positive association between CRP and fatigue that remained significant.
after controlling for age, BMI, depressive symptoms, sleep disturbance, medication use, and self-rated health. In a recent study by (Alfano et. al., 2012) higher CRP was associated with increased probabilities of being classified as fatigued, controlling for age, race, menopausal status, antidepressant/anxiolytic use, comorbidities, and BMI, in a sample of 633 breast cancer survivors. This study also found a significant linear association between CRP levels and fatigue, particularly physical and behavioural dimensions of fatigue; however, these associations were attenuated to non-significant after controlling for use of antidepressants/anxiolytics, comorbidities, and BMI. These studies suggest that low grade inflammation could contributes to the development of fatigue in cancer survivors.

Conversely, Bower et. al. (2011) reported that neither IL-1ra nor CRP were elevated in 103 women with clinically significant fatigue who had recently finished treatment (surgery, radiation, chemotherapy) for early-stage breast cancer. As such, no specific inflammatory marker has been observed directly implicated in pathogenesis of cancer fatigue (Saligan & Kim, 2012). Serum concentrations of CRP were similar between groups. Although considerable care was taken with all blood samples with analyses performed in duplicate, only a small number of usable measurements where obtained for TNFα and IL-6 due to sample errors. A larger participant sample size than that used in the current study may also assist to minimise such issues.
4.4.5 Associations Between Variables

No evidence of a relationship between CRP and fatigue scores on the EORCT-F scores was observed. However, previous studies have reported elevated levels of pro-inflammatory markers with positive associations with the magnitude of self-reported fatigue in post treatment cancer survivors in some (Alexander et. al., 2009; Orre et. al., 2009; Orre et. al., 2011; Alfano et. al., 2012) but not all studies (Bower et. al., 2011). In a sample of 299 disease-free cancer survivors, Orre et al., (2011) found a positive association between CRP and fatigue levels which remained significant after controlling for age, BMI, depressive symptoms, sleep disturbance, medication use, and self-rated health.

In a recent study investigating relationship between CPR and fatigue in a sample of 633 breast cancer survivors, Alfano et. al. (2012) reported a significant linear association between CRP levels and fatigue, particularly physical and behavioural dimensions of fatigue; however, these associations were attenuated to non-significant after controlling for use of antidepressants/anxiolytics, comorbidities, and BMI. Association between fatigue and elevations in plasma levels of the soluble TNF receptor type II (sTNF-RII), a downstream marker of TNF activity have been reported in breast cancer survivors within a month following treatment; this association was particularly strong among women treated with chemotherapy (Bower et. al., 2011). Other studies that have investigated the link between IL-6 and TNFa and fatigue (Von Ah et. al., 2008; Orre et. al., 2011; Pertl et. al., 2013) however due to the low sample numbers of the current study comparing results is not appropriate.
It has been suggested that increased pro-inflammatory cytokine levels could contribute to the symptoms of fatigue related to cancer by signalling the central nervous system (Bower & Lamkin, 2013), although present understanding of the neural mechanisms involved are incomplete (Pertl et. al., 2013). The nervous and immune systems are known to communicate in a bidirectional manner (Silverman et. al., 2010). Inflammation originating in the periphery is communicated to the central nervous system (CNS) by several pathways, including activation of sensory nerves (Dantzer et. al., 2012). Prostaglandins released in response to cytokine activation (Saligan & Kim, 2012) can alter blood brain barrier (BBB) permeability to interleukin (IL)-1α and IL-1β, IL-1 receptor antagonist (IL-1ra), IL-6, TNFα (Pan et. al., 2011). This leads to an increased production of prostaglandins and pro-inflammatory cytokines by endothelial cells, macrophages, and microglia located within the CNS (LaVoy et. al., 2016). Pro-inflammatory cytokines in particular IL-6, IL-1β, and TNF-α are known to act on brain structures thereby altering behaviour leading to the symptom of fatigue (Fung et. al., 2012; Saligan & Kim, 2012). These CNS inflammatory mediators then influence neurons directly or indirectly by modifying astrocyte, oligodendrocyte, and endothelial cell functions effecting supraspinal neuraxial function thereby contributing to fatigue (LaVoy et. al., 2016).

Inflammation is also implicated in the pathogenesis of depression, and depression is a strong predictor of CRF. Thus, the role of the pro-inflammatory cytokines in CRF may be mediated by depression or both conditions may share similar underlying physiological processes (Pertl et. al., 2013). We observed significant associations between BD-II and
EORTC-F scores in the pooled dataset. Significant associations have been previously observed between fatigue and depressive symptoms (BDI-II) in a group of 103 breast cancer survivors who had recently completed primary treatment (Bower et. al., 2011). Links between CRP and depression have been previously reported (Bower et. al., 2011; Becking et. al., 2013; Miller et. al., 2013) suggesting a possible role for CRP in persistent fatigue in cancer survivors given the relations with depression. However, such relationships have not been consistently shown, with no relationship reported in post-treatment breast cancer survivors (Bower et. al., 2011)

We found significant correlations between EMG_{RMS} and CRP in the pooled dataset and for VA and CRP in PTCa providing suggestive evidence that inflammatory mediators might influence descending motor drive and motor unit excitation. This is the first study to demonstrate such a relationship, suggesting that in the presence of higher level of inflammatory markers in cancer-related fatigue that muscle activation may be impaired. However, no evidence of a relationship between CRP and MVF or nMVF was found. We observed significant associations between CRP and VO_{2peak} in the pooled dataset. This finding has previously been reported in a group of 40 asymptomatic women (45 ± 4.2 years) in which higher circulating levels of IL-6, CRP were associated with lower VO_{2peak} (Omran et. al., 2013).

These novel findings may have implications for our understanding of the mechanisms contributing to persistent fatigue symptoms and neuromuscular performance in cancer survivors and healthy persons.
5 STUDY TWO

Central Neuromuscular Manifestations Associated With A Sustained Maximal Voluntary Contraction Between Cancer Survivors with Fatigue Symptoms and Healthy Women
Abstract

**Purpose:** We compared the acute neuromuscular manifestations associated with a sustained maximal voluntary isometric contraction of the elbow flexors between cancer survivors and healthy women.

**Methods:** Nine (9) disease-free, post-treatment cancer survivors (PTCa; 7 breast, 2 ovarian), aged 43-66 years and 17 healthy women (HW), aged 41-62 years were included. A 2-min sustained, maximal voluntary isometric contraction of the right elbow flexors at 90° shoulder and elbow flexion was performed. Blood lactate (La-) and resting muscle compound potentials (Mmax) from the biceps brachii were assessed before and after fatigue; while maximal voluntary torque (MVT), voluntary surface electromyography (EMG) from the biceps brachii, and indices of corticomotor excitability using transcranial magnetic stimulation (TMS) were assessed before, during, and after fatigue.

**Results:** No differences were observed between groups before exercise in any of the variables. MVT progressively decreased during exercise so that values after exercise were ~60% of those observed before exercise. La- was higher after exercise in both groups. EMG root-mean-square (rms) normalised to Mmax and EMG median frequency progressively decreased over time during exercise; however, values immediately after exercise were similar to before exercise in both groups. Superimposed twitch responses to TMS during exercise normalised to the background, showed that the level of torque progressively decreased over time during exercise; however, the level of corticomotor activation after exercise were similar to before exercise.
exercise values in both groups. However, the duration of the TMS cortical silent period progressively increased during exercise and was longer after exercise in the PTCa group. The level of corticomotor activation after exercise was similar to before exercise values in both groups.

**Conclusion:** Despite increased self-reported fatigue in the PCTa group the contribution of central mechanisms in the progressive development of fatigue during the sustained maximal voluntary contraction task was highly comparable to that observed in HW. Such findings provide further evidence to suggest that the underlying pathophysiological mechanisms contributing to the increased self-reported fatigue in post-treatment cancer survivors may be more related to alterations in perception rather than impaired sensory-motor function.
5.1 Introduction

Cancer and/or its treatment/s are associated with multiple side-effects that may cause considerable distress and a significant loss of function. Of these side-effects, fatigue is reportedly the most frequent symptom experienced and is perceived by patients to be more distressing than pain, nausea, and depression (Vogelzang et. al., 1997; Holley, 2000; Hickok et. al., 2005). As many as 70-80% of patients undergoing primary cancer therapies will experience fatigue symptoms depending on the sample, type of treatment, and method of fatigue assessment (Stone et. al., 2000b; Cella et. al., 2001; Servaes et. al., 2002b; Bower et. al., 2006b). Although fatigue levels generally dissipate within one year after the completion of treatment, 25-33% of disease-free cancer survivors may continue to experience ongoing fatigue symptoms for up to 10 years following their cancer diagnosis (Servaes et. al., 2007; Siegel et. al., 2012; Wang et. al., 2014). The presence of fatigue has serious implications for cancer patients as it may interfere with the timing and/or completion of primary cancer treatments (Hofman et. al., 2007), hinder post-treatment interventions (Cleeland, 2007), and has been associated with reduced survival (Groenvold et. al., 2007). For disease-free cancer survivors, fatigue is associated with disease recurrence (Groenvold et. al., 2007) and significantly impairs work output (Calvio et. al., 2010), cognitive function (Wilbers et. al., 2015), social activity (Syrjala et. al., 2005), and mood (Kuhnt et. al., 2009), which ultimately decreases overall quality of life (Weaver et. al., 2012; Koch et. al., 2013). Yet, despite the fatigue burden associated with cancer and/or its treatment/s the underlying
pathophysiological mechanisms involved remain largely elusive (Lee et. al., 2004; Wang & Woodruff, 2015).

Numerous hypotheses to explain the development of fatigue symptoms with cancer and/or its treatment have been proposed. However, these hypotheses have largely been developed based on observed associations between variables that have led to mechanisms being proposed that are yet to be properly tested and fully established (Lee et. al., 2004; Ryan et. al., 2007; Wang, 2008; Bower, 2014b). Despite this, relatively few studies have directly examined the neuromotor mechanisms associated with exercise-induced fatigue in cancer patients. This is surprising as this approach has been used successfully to identify altered fatigue mechanisms associated with ageing (Callahan et. al., 2009), gender (Hunter, 2009), exercise related training (Lepers et. al., 2002b), muscle injury (Dugan & Frontera, 2000) and other disease states, including Chronic Fatigue Syndrome (Samii et. al., 1997), Multiple Sclerosis (Steens et. al., 2012), Parkinson’s disease and Fibromyalgia (Gur & Oktayoglu, 2008). The classic approach to characterising neuromotor fatigue includes distinguishing between central and peripheral based mechanisms. Central fatigue results from the inability of nervous system to adequately drive motoneurons and may originate in any region of the motor pathway proximal to the neuromuscular junction (Gandevia, 2001). Peripheral fatigue is the associated decline in the force-generating capacity of motor units due to changes at, or distal to, the neuromuscular junction (Gandevia, 2001). As such, the ability to identify differences in the contributions of central and/or peripheral factors of fatigue in relation to cancer may provide new insights
into the underlying pathophysiological mechanisms responsible for ongoing fatigue in cancer patients and the development of mechanistic-driven interventions to ameliorate patient symptoms.

Available evidence indicates the central and/or peripheral contributions to fatigue may differ between cancer survivors with persistent fatigue symptoms and non-fatigued counterparts or healthy persons, which suggests that altered neuromotor processes may be implicated in the manifestation of fatigue in this population (Bruera, et al., 1988; Monga et. al., 1997; Yavuzsen et. al., 2009). However, available data are limited and results are somewhat conflicting (Bruera, et al., 1988; Yavuzsen et. al., 2009; Alt et. al., 2011). With regard to central mechanisms, previous studies investigating cancer fatigue have examined the level of voluntary muscle activation to estimate central motor drive during voluntary muscle contractions by supramaximally stimulating peripheral motor nerves (Yavuzsen et. al., 2009; Kisiel-Sajewicz et. al., 2012; Neil et. al., 2013; Cai et. al., 2014; Platt et. al., 2014; Prinsen et. al., 2015). Voluntary muscle activation is considered to be less than maximal, or otherwise incomplete, if the stimulus delivered to the nerve during a voluntary contraction evokes additional force from the active muscle. Alternately, if the supramaximal stimulus fails to elicit more force then activation is considered to be complete (Merton, 1954; Herbert & Gandevia, 1999b). To quantify the level of voluntary muscle activation, the amplitude of the interpolated twitch evoked during contraction following stimulation is compared with the amplitude of the twitch evoked when a stimulus of the same intensity is delivered to the resting potentiated muscle (Allen et. al., 1995b; Goodall et. al., 2009). By stimulating peripheral motor nerves, the location of central
motor drive impairment contributing to incomplete voluntary muscle activation cannot be determined and the sites responsible are generalised as being at or above the alpha-motor neurons (Gandevia, 2001).

To further localise the site contributing to impaired central motor drive during contraction, the more advanced method of transcranial magnetic stimulation (TMS) may be used to quantify the level of voluntary muscle activation (Todd et. al., 2004; Sidhu et. al., 2009). TMS uses a short duration electromagnetic pulse to induce excitation of corticomotor axons that project to the muscle of interest (Siebner et. al., 2009). Although the level of voluntary activation is quantified in a similar, but not identical (Todd et. al., 2004; Sidhu et. al., 2009), manner to that of peripheral motor nerve stimulation, the presence of an interpolated twitch during contraction indicates sub-maximal drive from a site at or above the motor cortex (Todd et. al., 2004; Sidhu et. al., 2009). In addition to the mechanical twitch response used to quantify the level of voluntary activation, TMS also evokes a short latency electrical response that can be recorded through surface electromyography, which is referred to as a motor evoked potential (MEP). The size of the MEP is dependent on several factors, but likely reflects the excitability of both corticomotor neurones and alpha-motor neurons (Gandevia, 2001). Immediately following the MEP, voluntary EMG activity is suppressed for a short time as a result of TMS-induced interruption to corticomotor output, which appears to be influenced by the level of intracortical inhibition at the time of stimulation (Inghilleri et. al., 1993; Wilson et. al., 1993). As such, the use of TMS may permit a more comprehensive evaluation of corticomotor function during exercise-induced fatigue compared with peripheral motor nerve stimulation techniques and
provide greater insight into the underlying pathophysiological mechanisms
associated with fatigue in cancer patients.

Additionally, many studies examining cancer fatigue have used
sustained submaximal tasks for their exercise-induced fatigue protocols
(Yavuzsen et. al., 2009; Alt et. al., 2011; Kisiel-Sajewicz et. al., 2012;
Kisiel-Sajewicz et. al., 2013; Neil et. al., 2013; Cai et. al., 2014; Platt et. al.,
2014). However, interpreting evoked mechanical and electrical responses
following either peripheral motor nerve or cortical stimulation during
prolonged submaximal efforts is difficult as a criterion level of central
motor drive during contraction cannot be determined as motor neuron
activity increases with time in an attempt to maintain target force output and
compensate for the progressive weakness in those active motor units. Thus,
the use of a sustained maximal voluntary effort may be informative when
evaluating central mechanisms contributing to fatigue. Therefore, the
purpose of the present study was to compare the central contributions to
exercise-induced fatigue associated with a sustained maximal voluntary
isometric contraction of the elbow flexors between disease-free cancer
survivors with persistent fatigue symptoms and healthy participants. It is
hypothesised that the cancer survivors, with persistent fatigue will exhibit
lower maximal voluntary torque immediately before exercise, greater
relative decline in force output during exercise and greater reductions in
maximal voluntary torque immediately after exercise which can be
explained by impaired central motor mechanisms and as demonstrated by
reductions in descending neuromotor drive and increased cortical inhibition.
5.2 Methods

A detailed description of all testing procedures is provided in Chapter 3.

5.2.1 Participant sample

Seven (7) breast cancer survivors and two (2) ovarian cancer survivors (PTCa) who had all completed curative cancer therapies and 17 healthy women (HW) healthy women with no known history of cancer and/or cancer-related treatment participated in the study (Section 3.2).

5.2.2 Physical characteristics

Fatigue, Depressive Symptoms, Sleep Quality, and Pain were assessed using a variety of subjective self-report instruments including: The Brief Fatigue Index (BFI); The fatigue subscale of European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-F); The Revised Piper Fatigue Scale (RPFS); The 100mm visual analogue scale (VAS-F); The Beck Depression (BDI-II); The Pittsburgh Sleep Quality Index (PSQI); and The 101-point numerical pain intensity rating scale (NRS-101) (Section 3.3.1). Mass, BMI, and measures of body composition including total body non-osseous lean tissue mass (TBLM), total body fat mass (TBFM), and right upper arm non-osseous lean tissue mass (RALM) was measured using dual x-ray absorptiometry (DXA) (Section 3.3.3). A submaximal aerobic capacity test was performed to assess aerobic power index (API) and volume of peak oxygen consumption (\(\dot{V}O_2\text{peak}\)) (Section 3.4.1).
5.2.3 Neuromuscular Performance and Fatigue Testing

The assessment of neuromuscular performance and fatigue was performed on the right elbow flexors using a combination of voluntary and evoked techniques (Section 3.5). A 2-min sustained, maximal voluntary isometric contraction of the right elbow flexors at 90° shoulder and elbow flexion was performed (Section 3.6.6). Blood lactate (La-) (Section 3.6.5) and resting muscle compound potentials (Mmax) from the biceps brachii were assessed before and after fatigue (Section 3.6.1). Maximal voluntary torque (MVT) (Section 3.5.2), voluntary surface electromyography (EMG) from the biceps brachii (Section 3.5.3), and indices of corticomotor excitability (Section 3.6.3) using transcranial magnetic stimulation (TMS) (Section 3.6.2) were assessed before, during, and after fatigue.

Following a standardised warm-up (Section 3.5.1), testing commenced, which involved the assessment of the following parameters in this sequence: 1) Compound muscle action potentials (Mmax); 2) the level of voluntary muscle activation; 3) blood lactate; 4) 2-min sustained maximal voluntary contraction; 5) Mmax; 6) the level of voluntary muscle activation; and 7) blood lactate. A 1-min rest period was provided between assessment of Mmax and the level of voluntary muscle activation and a 2-min rest period was provided between the assessment of voluntary muscle activation and the commencement of the sustained maximal voluntary contraction. All assessments following the completion of the sustained maximal voluntary contraction were performed as rapidly as possible to minimise the amount of recovery.
5.2.4 Statistical Analysis

Before inferential statistics were performed, the normality of distribution of each independent variable was tested using the Shapiro-Wilk W statistic as recommended for sample sizes of less than 50 (Ghasemi & Zahediasl, 2012). Descriptive characteristics related to anthropometry measures, body composition, VO2peak, fatigue status, depressive symptoms, sleep quality, and pain were analysed using a one-way analysis of variance (ANOVA). For all neuromuscular variables, a mixed factorial ANOVA was used to identify significant main effects for group and time and their interactions. Where Mauchy’s test of sphericity was significant and $\epsilon \leq 0.75$ or $\epsilon \geq 0.75$, a Greenhouse-Geisser or Huynh-Feldt correction, respectively, was applied to the within-participant analyses. Levene’s test of equality of error variance between participants did not show statistical significance for any of the analyses. When a significant main effect and/or interaction were observed, a one-way ANOVA with a Bonferroni correction for multiple-comparisons was used, where appropriate, to determine the source of significance. All statistical procedures were performed using Predictive Analytic Software (PASW) (Statistical Package for the Social Sciences version 20.0, Chicago, IL, USA) software with the critical level for significance was set at $P< 0.05$. To determine the magnitude of differences observed between groups. All data are reported as mean ± standard deviation (SD).
5.3 Results

5.3.1 Participant Characteristics

Physical characteristics for the cancer survivors and healthy women are presented in Table 5.1. Age was significantly different with cancer survivors older than the healthy women (P= 0.041). No other statistically significant differences were evident between groups for any other physical characteristics.

5.3.2 Fatigue, Depressive Symptoms, Sleep Quality, and Pain Intensity

Fatigue severity, depressive symptoms, sleep quality, and pain intensity scores for the cancer survivors and healthy women are presented in Table 5.2. No significant differences in BFI, RPFS, VAS-F, or NRS-101 scores were evident between groups (P> 0.09). Scores for EORTC-F and BDI-II were significantly higher for the cancer survivors compared with the healthy women (P≤ 0.006); while a trend was evident for PSQI scores to be higher for the cancer survivors compared with the healthy women (P= 0.06).
Table 5.1 Participant characteristics for the cancer survivors and healthy women.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Mass (kg)</th>
<th>Body Mass Index (kg.m$^2$)</th>
<th>TBLM (kg)</th>
<th>TBFM (kg)</th>
<th>RALM (kg)</th>
<th>API (W.kg$^{-1}$)</th>
<th>VO$_2$peak (ml.kg$^{-1}$.min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Survivors</td>
<td>56 ± 8</td>
<td>167 ± 8</td>
<td>73 ± 15</td>
<td>26.9 ± 4.9</td>
<td>41.2 ± 5.4</td>
<td>27.5 ± 12.0</td>
<td>1.1 ± 0.2</td>
<td>1.05 ± 0.70</td>
<td>22.3 ± 7.6</td>
</tr>
<tr>
<td>Healthy Women</td>
<td>49 ± 5*</td>
<td>164 ± 11</td>
<td>77 ± 10</td>
<td>29.1 ± 5.3</td>
<td>44.5 ± 4.8</td>
<td>32.4 ± 8.6</td>
<td>1.2 ± 0.1</td>
<td>1.07 ± 0.60</td>
<td>25.5 ± 5.9</td>
</tr>
<tr>
<td>Significance (P)</td>
<td>P= 0.04</td>
<td>P= 0.57</td>
<td>P= 0.44</td>
<td>P= 0.37</td>
<td>P= 0.61</td>
<td>P= 0.33</td>
<td>P= 0.73</td>
<td>P= 0.87</td>
<td>P= 0.33</td>
</tr>
</tbody>
</table>

TBLM, total body non-osseous lean mass; TBFM, total body fat mass; RALM, right upper arm non-osseous lean mass; API, aerobic power index; VO$_2$peak, peak oxygen consumption. Values presented as mean ± SD. *Indicates significance between groups (P= 0.04). Values presented as mean ± SD.
Table 5.2 Fatigue severity and clinical fatigue correlate scores for the cancer survivors and healthy women.

<table>
<thead>
<tr>
<th>Group</th>
<th>BFI</th>
<th>EORTC-F</th>
<th>RPFS</th>
<th>VAS-F</th>
<th>BDI-II</th>
<th>PSQI</th>
<th>NRS-101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Survivors</td>
<td>2.4 ± 1.5</td>
<td>24.7 ± 12.1</td>
<td>3.2 ± 1.9</td>
<td>2.5 ± 2.1</td>
<td>6.6 ± 2.9</td>
<td>7.3 ± 3.0</td>
<td>1.0 ± 1.3</td>
</tr>
<tr>
<td>Healthy Women</td>
<td>2.3 ± 1.3</td>
<td>11.5 ± 10.8*</td>
<td>1.3 ± 0.8</td>
<td>1.8 ± 2.0</td>
<td>2.5 ± 2.3*</td>
<td>5.2 ± 1.44</td>
<td>0.6 ± 0.9</td>
</tr>
<tr>
<td>Significance (P)</td>
<td>P= 0.81</td>
<td>P= 0.01</td>
<td>P= 0.09</td>
<td>P= 0.29</td>
<td>P= 0.006</td>
<td>P= 0.06</td>
<td>P= 0.47</td>
</tr>
</tbody>
</table>

BFI; Brief Fatigue Index; EORTC-F, European Organisation for Research and Treatment of Cancer Questionnaire- Fatigue Domain; RPFS, Revised Piper Fatigue Scale; VAS-F, Visual Analogue Scale- Fatigue; BDI-II, The Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; NRS-101, numerical pain intensity rating scale. *Indicates a significant difference between groups (P≤ 0.01). Values presented as mean ± SD.
5.3.3 Pre and Post Sustained Contraction Data

5.3.3.1 Mmax Amplitude

No main effects for group ([F1.0, 24.0] = 1.86; P= 0.18) or time ([F1.0, 24.0] = 4.54; P= 0.506) nor a group x time interaction ([F1.00, 24.0] = 0.44; P= 0.65) were observed for MmaxAMP pre and post for the sustained maximal voluntary contraction.

5.3.3.2 Maximal Voluntary Isometric Force

MVF data pre and post the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women are presented in Figure 5.1. No main effect for group ([F1.0, 24.0] =0.001; P= 0.97) nor a group x time interaction ([F1.0, 24.0] = 2.19; P= 0.15) were apparent for MVF; however, a main effect for time ([F1.0, 24.0] =162.46; P < 0.001) was evident in which a significant reduction in MVF was observed from pre- to post-task in both groups.

5.3.3.3 Level of Voluntary Muscle Activation

VA data pre and post the 2-min sustained maximal voluntary isometric task for the cancer survivors and healthy women are presented in Figure 5.2. No main effects for group ([F1.0, 24.0] = 0.61; P= 0.441) nor a group x time interaction ([F1.0, 24.0] = 0.01; P= 0.92), were observed for VA; however there was a main effect for time ([F1.0, 24.0] =5.02; P= 0.04) in which a significant reduction in VA was observed from pre- to post-task in both groups.
Figure 5.1 Maximal voluntary force (MVF) data pre and post the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women. *Indicates significant differences for time within both groups (P<0.001). Values presented as mean ± standard deviation.
Figure 5.2 The level of voluntary activation (VA) data pre and post the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women. *Indicates significant differences for time within both groups (P<0.05). Values presented as mean ± standard deviation.
5.3.3.4 Blood Lactate

La− data pre and post the 2-min sustained maximal voluntary isometric task for the cancer survivors and healthy women are presented in Figure 5.3. No main effect for group ([F1.0, 24.0] = 0.08; P= 0.78) nor a group x time interaction ([F1.0, 24.0] = 1.89; P= 0.18) were observed for La−; however a main effect for time was evident so that La− increased from pre- to post-fatigue task ([F 1.0, 24.0] = 50.34; P< 0.001).

5.3.4 During Sustained Contraction Data

5.3.4.1 Voluntary Force

Voluntary force data during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women are presented in Figure 5.4. No main effect for group ([F1.0, 24.0] =2.041; P= 0.17) nor a group x time interaction ([F2.81, 67.5] = 0.70; P= 0.55) were observed for voluntary force across the 2-min fatigue task; however, a main effect for time was apparent ([F2.81, 67.5 = 179.4; P< 0.001) in which voluntary force decreased across all consecutive time points from initial values to 120s in both groups with reductions of 49 ± 9% and 52 ± 7% pre to post in the cancer survivors and healthy women, respectively.
Figure 5.3 Blood lactate concentration (La−) data pre and post the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women. *Indicates a significant increase in La− from pre- to post- task within both groups (P<0.001). Values presented as mean ± standard deviation.
Figure 5.4 Voluntary force during the 2-min sustained maximal voluntary isometric contraction. *Indicates a significant difference in voluntary force among all time points within both groups (P<0.001). Data are reported as a percentage of initial values and presented as the mean ± standard deviation.
5.3.4.2 Central Activation Ratio

CAR data during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women are presented in Figure 5.5. No main effect for group ([F1.0, 24.0] = 6.33; P= 0.433) nor a group x time interaction ([F3.56, 85.34] = 0.22; P= 0.97 were evident for CAR across the fatigue task; however, a main effect for time ([F3.56, 85.34] = 5.77; P= 0.001) was observed so that CAR decreased across all consecutive time points from 40-120 s compared with initial values in both groups with reductions of 5.8 ±7.6 and 6.5 ± 7.4% from pre to post in the cancer survivors and healthy women, respectively.

5.3.4.3 Cortical Silent Period

SP during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women are presented in Figure 5.6. No main effect for group ([F1.0, 24.0] = 3.18; P= 0.093) was observed for SP; however, a main effect for time ([F2.5, 62.2] = 19.2; P < 0.001) was observed in which SP was longer from 80-120 s compared with initial values. A group x time interaction was also observed SP ([F2.5, 62.2] = 3.12; P = 0.037) whereby the increase in SP with time was greater for the cancer survivors compared with the healthy women (P< 0.05).
Figure 5.5 Central activation ratio (CAR) during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women. \(^a\)Indicates a significant decrease in CAR compared with initial values within both groups (P<0.001). \(^b\)Indicates a significant decrease in CAR compared with initial values within both groups (P<0.01). \(^c\)Indicates a significant decrease in CAR compared with initial values within both groups (P<0.05). Data are reported as a percentage of initial values and presented as the mean ± standard deviation.
Figure 5.6 Cortical silent period (SP) during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women. 

\(^a\)Indicates a significant differences for time compared with initial values in the cancer survivors (P<0.001). \(^b\)Indicates a significant differences for time compared with initial values in the cancer survivors (P<0.01). \(^c\)Indicates a significant differences for time compared with initial values in the cancer survivors (P<0.05). Data are reported as a percentage of initial values and presented as the mean ± standard deviation.
5.3.4.4 EMG Amplitude and Frequency

RMS data during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women is presented in Figure 5.7. No main effect for group ([F1.0, 24.0] = 0.360; P= 0.554) or time ([F1.0, 24.0] = 0.597; P= 0.447) nor a group x time interaction ([F1.0, 24.0] = 0.540; P= 0.470) were observed for RMS across the 2-min fatigue task.

MDF data during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women is presented in Figure 5.8. No main effect for group ([F1.0, 24.0] = 1.86; P= 0.185) nor a group x time interaction ([F1.41, 33.9] = 1.11; P= 0.322) was evident in MDF; however a main effect for time ([F1.41, 33.9] = 28.4; P= 0.001) was observed in which MDF was significantly lower at 20-120 s compared with initial values (P<0.05).
Figure 5.7 Normalised EMG root-mean-square (RMS) data during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women. Data are reported as a percentage of initial values and presented as the mean ± standard deviation.
Figure 5.8 EMG median frequency (MDF) data during the 2-min sustained maximal voluntary isometric contraction for the cancer survivors and healthy women. 

- Indicates a significant differences for time compared with initial values within both groups (P<0.001).
- Indicates a significant differences for time within both groups (P<0.01).
- Indicates a significant within differences for time within both groups (P<0.05).

Data are reported as a percentage of initial values and presented as the mean ± standard deviation.
5.4 Discussion

5.4.1 Major Findings

To the best of our knowledge, this is the first study to investigate central fatigue using TMS in a group of post-treatment cancer survivors. We found no evidence for greater central manifestation of fatigue during a 2 minute sustained maximal voluntary contraction of the elbow flexors in the PTCa compared to HW. This observation indicates that despite increased self-reported fatigue in the PCTa group, the underlying pathophysiological mechanisms contributing to persistent fatigue do not appear to involve impairments in sensory-motor function rather the underlying contributor it is more likely to involve alterations in perception.

5.4.2 Voluntary Force

Contrary to expectations we did not observe any significant difference in maximal voluntary force over the two minute fatigue task between the groups. We observed significant declines in maximal voluntary force production in both PTCa and HW over the 2 min sustained maximal task, indicating the development of neuromuscular fatigue. This suggests that the 2 minute task provided an appropriate challenge to the motor pathways of both groups, thereby offering suitable test conditions in which to examine the manifestation of fatigue. We found that the magnitude of the decline in force was similar between the two groups, indicating that the groups experienced comparable degrees of neuromuscular fatigue. Such findings are in agreement with a previous investigation (Prinsen et. al., 2015).
5.4.3 EMG and Voluntary Activation

The data from this investigation indicate that the central manifestation of fatigue during a 2 minute sustained maximal voluntary contraction involving the elbow flexors is highly comparable between the PTCa and HW. Evidence in support of this come from a number of observations. The TMS evoked superimposed force responses during the 2min task increased in both PTCa and HW, which indicates that voluntary cortical drive from the motor cortex to the elbow flexors (BB and/or BR) increased as the task progressed suggests the presence of suprasinal fatigue (Gandevia et. al., 1996; Hunter et. al., 2006; Thomas et. al., 2014). In addition, we found significant reductions in VA pre-post 2min task and CAR during the 2min task proving further evidence of supraspinal fatigue. However, the significant reduction in CAR was only observed from 45sec onwards during the 2minute task, suggesting that there was no change in corticomotor drive during initial phase of the 2 min sustained task. We also observed a decrease MDF during the sustained 2min task providing additional evidence for the development of neuromuscular fatigue during the 2 minute maximal sustained task which suggest a possible slowing of motor unit firing rates. These findings were not significantly different between the two groups. We found no significant difference in $\text{Mmax}_{\text{AMP}}$ over the two minute task demonstrating that any change observed in $\text{EMG}_{\text{RMS}}$ was robust and that change in neuromuscular input was not an artefact from impaired neuromuscular junction or peripheral excitability (Sheean et. al., 1997; Fowles et. al., 2002). Overall, these findings were highly comparable between both groups suggesting that the PTCa were able to maintain comparable corticomotor excitability as were the HW (Sacco et.}
al., 1999). Therefore, evidence of greater impairments in neuromotor function and/or output in PTCa with persistent fatigue for this specific task was not found and are in agreement with previous findings demonstrated comparable motor pathway function between CRF and non-fatigued Ca survivors (Neil et. al., 2013; Prinsen et. al., 2015).

However, other studies have found evidence of altered central processing in persons with CRF compared to non-fatigued participants (Yavuzsen et. al., 2009; Kisiel-Sajewicz et. al., 2012; Kisiel-Sajewicz et. al., 2013; Cai et. al., 2014). In a cross-sectional investigation (Yavuzsen et. al., 2009) examined the contributions of peripheral and central fatigue during a fatigue induced exercise task involving the elbow flexors in cancer patient in palliative care. Patients were a minimum of 4 week post treatment, consisting of 16 patients with CRF, as measured using the BFI, and 16 healthy-matched persons. Endurance time (ET) associated with a sustained 30% MVC performed to exhaustion and PNS delivered at 30 sec intervals during task to measure maximal recruitment were recorded. Baseline and immediately post task neuromotor indices including CMAP, $M_{\text{max}}$ and evoked twitch force using twitch interpolation technique were obtained. CRF were observed to have a significantly shorter ET and greater TF at end of sustained contraction compared to the healthy group. No changes in $M_{\text{max}}$ pre-post task were observed. It was concluded that the CRF patients demonstrated greater central fatigue as evidenced by significantly greater twitch force at the completion of the task and impaired neuromuscular junction conduction as evidenced by significantly lower $M_{\text{max}}$ amplitude compared to the healthy group. The discrepancies between previous findings demonstrates the complexities associated with cancer fatigue.
5.4.4 Limitations

Limitations of this study include the small sample size, although current sample size is comparable to other studies of this topic (Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2013; Cai et al., 2014). Moreover, single pulse TMS protocols are limited to determining whether the integrity of the neuromotor pathway is altered or not, and cannot be used to identify specific higher order processes. Further investigations involving other neuro-imaging techniques such as paired pulse TMS protocols, with the concurrent use of EEG, and/or NIRS to assess possible involvement and activation of distinct regions of the cortex could provide additional information regarding other possible centrally based processes involved in the processing and manifestations of fatigue (Chen, 2000; Farzan et al., 2013). However, it is was important to first identify whether higher order processes were involved using this single pulse protocol to determine whether further investigations are required. Due to the task specific nature of the development and manifestations of fatigue, additional investigations may need to focus on neuromotor performance under different task conditions (Enoka, 1995). An elbow flexion task was selected due to the minimal contributions of the antagonist muscle group to the evoked forces (Taylor et al., 2006; Todd et al., 2007). We did not assess for any potential contributions caused by coactivation. Other limitations include not including the use of peripheral fatigue data (e.g. twitch properties) obtained using peripheral electrical stimulations which would help identify other possible mechanisms involved that could potentially be different between the PTCa and HW. However, our findings of comparable declines in force during the
2 minute task combined with similar decrements if MVF post-task suggest this may not have been a factor to consider in this investigation.

5.5 Conclusion

In conclusion, it was found that the contribution of central mechanisms in the development of fatigue during the sustained maximal voluntary contraction task was highly comparable between healthy women and post-treatment cancer survivors irrespective of greater self-reported fatigue symptoms in this group. Such findings provide evidence to suggest that the underlying mechanisms contributing to the increased self-reported fatigue in post-treatment cancer survivors is not likely to be related to impaired sensory-motor function but are rather due to alterations in perception function. However, it is unknown whether other fatigue tasks produce similar findings between post-treatment cancer survivors and healthy women. It is anticipated that these findings add to the current literature investigating the central neuromuscular pathways as a potential contributor to persistent fatigue symptoms in cancer survivors.
6 STUDY THREE

Effects of Short-Term Resistance Training

On Muscular Strength and Central Adaptations In Cancer Survivors With Fatigue Symptoms Compared to Healthy Women
Abstract

**Purpose:** To compare the effects of 12-weeks of resistance training on muscle mass, muscular strength and neuromuscular performance between cancer survivors with persistent fatigue symptoms and healthy women.

**Methods:** Nine disease-free, post-treatment cancer survivors (PTCa; 7 breast, 2 ovarian), nine healthy women (HEx) and eight healthy control participants (Con) were recruited. PTCa and HEx undertook a progressive RT program consisting of six machine based exercises, three times a week for 12 weeks. A range of functional and clinical measures were obtained before and after RT including: body composition measured using DXA, indices included total body lean mass (TBLM), total body fat mass (TBFM), right arm lean mass (RALM); cardiorespiratory fitness measured using a sub-maximal cycling protocol to measure a range of indices including peak oxygen consumption (VO$_2$ peak) and aerobic power index (API). Several health related variables including sleep, depression, pain, fatigue, HR-Qol were measured using self-report questionnaires. During RT measures included one repetition maximum (1RM), training volume, and rating of perceived exertion (RPE). Clinical measures obtained before and after RT included maximal voluntary force (MVF) of the right elbow flexors at 0°/s recorded using an isokinetic dynamometer, maximal voluntary force normalised to RALM (nMVF), and surface electromyography recordings of the biceps brachii and brachioradialis (EMG). Maximal muscle compound action potential (Mmax) of the brachial plexus was used to normalise EMG data. Single pulse transcranial magnetic stimulation (TMS) was delivered to
the motor cortex to determine voluntary activation (VA), and cortical silent period (SP) duration was measured.

**Results:** Age, height, weight, BMI, VO\textsubscript{2}\text{peak}, API and indices of body composition were comparable before RT between groups (P> 0.05). Fatigue symptoms were higher in the HEx compared to PTCa at baseline as measured using the RPFS (P= 0.016) and ECORT fatigue subscale (P=0.045). No significant difference in clinical outcome measures including MVF, nMVF, VA, SP, TBLM or TBFM were apparent between or within groups after RT (P> 0.05). 1RM was significantly higher in the HEx compared to PTCa before RT and following the initial 4 weeks of RT; however after RT 1RM values were comparable (P>0.05). RALM increased significantly in all groups after RT (P= 0.007. EMG decreased after RT across all 3 groups (P< 0.037).

**Conclusion:** Resistance training for 12 weeks appears to induce similar functional and clinical neuromuscular adaptations in untrained women with a history of cancer and treatment compared to healthy women. RT as a single modality exercise regime positively increases muscular strength and right arm lean mass in both post-treatment cancer survivors and healthy women.
6.1 Introduction

Cancer represents a major health problem within the Australian population (AIHW, 2014). In 2014, it was estimated that 123,920 people would be diagnosed with cancer and 45,780 people would die from cancer in Australia (AIHW, 2014). Between 16% and 19% of the total disease burden in Australia is caused by cancer (Horton, 2012). A convergence of factors including advances in the detection, diagnosis and management of cancer has seen an increase in the life expectancy of cancer survivors post-treatment (Eakin et. al., 2007). It is being increasingly recognised that cancer and/or its treatment is associated with the presence of adverse, long-term side-effects including fatigue, pain, and sleep problems (Beckjord et. al., 2014) which are known to contribute to a decline in physical function and overall health-related quality of life (Battaglini et. al., 2006).

Fatigue is a notable clinical problem in cancer survivors (Jones et. al., 2015). It may appear as a symptom prior to cancer diagnosis, become evident during the treatment (Smets et. al., 1993), or continue long after the cessation of treatment (Prue et. al., 2006). Between 25-35% of cancer survivors report persistent fatigue following the completion of cancer-related treatments (Servaes et. al., 2007; Bower, 2014a). The significance of cancer fatigue is that it interferes with usual functioning, limiting the ability to carrying out essential activities of daily living and reduces quality of life (Bower et. al., 2002; Anderson et. al., 2003; Berger et. al., 2010). Current understanding of cancer fatigue is incomplete, having no known etiology or any effective pharmacological intervention (Minton et. al., 2008; Wang, 2008). Possible biological mechanisms include dysregulation of the
hypothalamic-pituitary-adrenal axis, 5-hydroxytryptophan (5-HT)
neurotransmitter dysregulation, circadian rhythm disruption, alterations in
adenosine triphosphate (ATP) and muscle metabolism, and vagal afferent
activation and inflammatory processes (Collado-Hidalgo et. al., 2006;
Neefjes et. al., 2013; Bower, 2014a). Limited understanding of the
mechanisms involved in cancer fatigue has impaired the development of
objective diagnostic criteria and successful mechanistic-driven interventions
for this disabling symptom.

Evidence indicates that exercise is one of only a few therapeutic
treatments demonstrating significant efficacy in reducing persistent fatigue
(Courneya et. al., 2003; Pinto et. al., 2009). Exercise also has the ability to
simultaneously attenuate other cancer and/or treatment related side-effects
such as pain, sleep, depression, QoL and overall physical performance in
cancer survivors (Mustian et. al., 2009). Recent observational studies have
suggested that participation in regular moderate to vigorous exercise may
lower overall risk of mortality by approximately 50% in cancer survivors
with a range of cancer types (Buffart et. al., 2014).

To date, the majority of research examining exercise as an
intervention for cancer fatigue has utilized aerobic-based programs
(Battaglini et. al., 2006; Culos-Reed et. al., 2007) and/or the effects of
combined aerobic and resistance training activities (Cramp & Byron-Daniel,
2012); few studies have evaluated the effectiveness of resistance-based
training as a stand-alone intervention (De Backer et. al., 2009; Hayes et. al.,
2009). A recent Cochrane systematic review examining the role of exercise
in the management of cancer fatigue reported that aerobic exercise
significantly reduces cancer fatigue; however resistance training as a stand-alone modality did not produce significant changes (Cramp & Byron-Daniel, 2012). This finding is likely to be influenced by the comparatively smaller number of studies investigating resistance-based training (6 studies) compared to aerobic based training (29 studies). The authors advocate that further research into resistance training should be undertaken (Cramp & Byron-Daniel, 2012). Consequently the current evidence-based recommendations regarding the appropriate prescription of resistance training exercise for post-treatment cancer survivors is limited. Existing recommendations for resistance training for this population are based primarily on the general guidelines for healthy adults (Hayes et. al., 2009; Schmitz et. al., 2010).

It is well established that resistance training can have a positive effect on a range of musculoskeletal and health-related parameters such as muscular strength and power, fat-free mass, bone density, and physical function including improvements in balance (O'Connor et. al., 2010; Baker et. al., 2013). Such outcomes can assist in attenuating the risk of muscle sarcopenia, osteoporosis and the number of falls, thereby assisting in maintenance of functional capacity and independence (Kraemer et. al., 2002; O'Connor et. al., 2010; Garber et. al., 2011). Resistance training has the potential to have a positive and meaningful impact on a wide range of health-related indices in the post-treatment cancer population.

Due to the lack of research of the effects of resistance training as a stand-alone intervention, it is not known what effect a short term resistance training stimulus has on muscular strength and the associated central
adaptations in post-treatment cancer survivors and/or if such adaptations are comparable to those measured in healthy women. To the author’s knowledge, no previous studies have reported the neuromuscular adaptations to resistance training by concurrently investigating the functional and clinical adaptations to this form of exercise in post-treatment cancer survivors. Therefore the purpose of this investigation was to compare the effects of a 12-week program of resistance training on muscle mass, muscular strength and neuromuscular performance between cancer survivors with persistent fatigue symptoms and healthy women without such symptoms. It is hypothesised that the cancer survivors, with persistent fatigue will demonstrate positive functional and clinical adaptations to RT including increases in muscular strength and right arm lean mass, maximal voluntary force, maximal voluntary force normalised to RALM and surface electromyography recordings of the biceps brachii and brachioradialis (EMG) which is explained by central adaptations demonstrated by increases in descending neuromotor drive and decreased cortical inhibition. These changes will occur to a lesser extent in the cancer survivors compared to the healthy participants. It is anticipated that the study findings will generate new knowledge regarding the effects of a short term resistance training program on muscular strength and the neuromuscular adaptations of post-treatment cancer survivors compared to healthy women. The results of this study may contribute to better informing health care professional regarding the most appropriate form of exercise therapy for post-primary treatment cancer survivors.
6.2 Methods

A detailed description of all testing procedures is provided in Chapter 3.

6.2.1 Participant Sample

Seven (7) breast cancer survivors and two (2) ovarian cancer survivors (PTCa) who were post-treatment and had completed curative cancer therapies and 17 healthy women with no known history of cancer and/or cancer-related treatment participated in the study (Section 3.2). Prior to commencing the study, the healthy women were assigned to either an exercise comparison group (HEx n=9) or a non-exercising control group (CON n= 9); however, one of the control participants withdrew during the investigation due to reasons outside of the study. Therefore, data from the control group are reported for n= 8.

6.2.2 Research Design

The investigation consisted of a 17-week data collection period, which included a 3-week familiarisation and baseline data collection period, a 12-week progressive resistance training period, and a 1-week data collection period after the completion of the training period. In week -4, all participants were interviewed by the Primary Investigator where exercise pre-screening was performed (Section 3.2.1) and descriptive measures, aerobic capacity, and detailed cancer treatment and health histories were obtained. In week -3, participants attended the laboratory and completed initial familiarisation with the resistance training equipment, maximum repetition strength testing (1RM), and neuromuscular assessment.
procedures. In week -2, participants completed follow-up familiarisation sessions (Section 3.7.2), performed dual energy X-ray absorptiometry testing, and completed the self-report health questionnaires. In week -1, participants completed formal baseline 1RM and neuromuscular testing and completed a battery of validated self-report questionnaires to quantify fatigue severity and clinical fatigue correlates of depressive symptoms, sleep quality, and pain. From weeks 1-12, PTCa and HEx participated in a fully supervised, whole body progressive resisting training program and CON continued their usual activities. At the end of weeks 4 and 8, PTCa and HEx performed 1RM and neuromuscular testing, which were completed again in week 13 after training by all participants in addition to completing the self-report questionnaires (Section 3.7.3). All test sessions were performed at the same time of day to reduce the effect of diurnal variation. Throughout the study, participants were instructed to avoid any changes in diet and to continue participating in normal habitual activities of daily living. Participants were also asked to refrain from intense physical activity and the consumption of caffeine and alcohol as well as obtain a minimum of 8 hours of sleep in the 48 hours and 24 hours, respectively, prior to all test sessions. A record of all food and beverage consumed in the 24-hour period prior to the first neuromuscular test session was kept and replicated for all subsequent sessions. Prior to and throughout the study, all participants were reminded to avoid undertaking any regular physical activities to which they were previously unaccustomed and maintain their usual physical activity and nutritional patterns for the duration of the study.
6.2.3 Physical characteristics

Fatigue, Depressive Symptoms, Sleep Quality, and Pain were assessed using a variety of subjective self-report instruments including: The Brief Fatigue Index (BFI); The fatigue subscale of European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-F); The Revised Piper Fatigue Scale (RPFS); The 100mm visual analogue scale (VAS-F); The Beck Depression (BDI-II); The Pittsburgh Sleep Quality Index (PSQI); and The 101-point numerical pain intensity rating scale (NRS-101) (Section 3.3.1). Mass, BMI, and measures of body composition including total body non-osseous lean tissue mass (TBLM), total body fat mass (TBFM), and right upper arm non-osseous lean tissue mass (RALM) was measured using dual x-ray absorptiometry (DXA) (Section 3.3.3). A submaximal aerobic capacity test was performed to assess aerobic power index (API) and volume of peak oxygen consumption (VO₂peak) (Section 3.4.1).

6.2.4 Neuromuscular Testing

The assessment of neuromuscular performance and fatigue was performed on the right elbow flexors using a combination of voluntary and evoked techniques (Section 3.5.1). Neuromuscular testing assessed compound action potentials of the elbow flexors and extensors (Mmax) using brachial plexus stimulation (Section 3.6.1), maximum voluntary isometric force (MVF) (Section 3.5.2), voluntary surface electromyography (EMG) (Section 3.5.3), voluntary muscle activation (VA) using the interpolated twitch technique (Section 3.6.3) and cortical silent period (SP) (Section 3.6.4) using transcranial magnetic stimulation (Section 3.6.2).
6.2.5 Resistance Training Program

PTCa and HEx participated in a fully supervised, whole body resistance training for a period of 12 weeks. A detailed description of the resistance training program (Section 3.7) and procedures for 1RM muscular strength testing (Section 3.7.6), the collection of RPE (Section 3.7.5) and calculation of training volume load (Section 3.7.4) is provided in Chapter 3.

6.2.6 Statistical Analysis

Before inferential statistics were performed, the distribution of each independent variable was tested using the Shapiro-Wilk W statistic as recommended for sample sizes of less than 50 (Ghasemi & Zahediasl, 2012). Descriptive characteristics were analysed using a one-way analysis of variance (ANOVA). Resistance training and neuromuscular data were analysed using a two-way (group x time) ANOVA. Where Mauchy’s test of sphericity was significant and $\epsilon \leq 0.75$ or $\epsilon \geq 0.75$, a Greenhouse-Geisser or Huynh-Feldt correction, respectively, was applied to the within-participant analyses. Levene’s test of equality of error variance between participants did not show statistical significance for any of the analyses. When a significant main effect and/or interaction were observed, a one-way ANOVA with a Bonferroni correction for multiple-comparisons was used, where appropriate, to determine the source of significance. All statistical procedures were performed using Predictive Analytic Software (PASW) (Statistical Package for the Social Sciences version 20.0, Chicago, IL, USA) software with the critical level for significance was set at $P < 0.05$. To determine the magnitude of differences observed between groups. All data are reported as mean ± standard deviation (SD).
6.3 Results

6.3.1 Participant Characteristics

Physical characteristics for the participants are presented in Table 6.1. Age was significantly different between PTCa and HEx (P= 0.041). No other statistically significant differences were evident between groups for any other physical characteristics (P >0.05).

6.3.2 Exercise Adherence, Training Volume Loads, and Ratings of Perceived Exertion

No difference was observed in exercise adherence between groups across the 12-week resistance training period with HEx and PTCa attending 92.2 ± 1.7% and 95.4 ± 2.0% of sessions, respectively ([F1.0, 16.0] = 2.27; P= 0.91).

Training volume loads across phases 1-3 for PTCa and HEx are presented in Figure 6.1. For upper body volume load, no main effect for group ([F1.0, 8] = 2.92; P= 0.126) or group x time interaction ([F 2, 16] = 2.68; P= 0.100) were observed; however, a main effect for time was apparent ([F 2, 16] = 17.6; P= 0.001) in which volume load completed during phase 3 was lower compared with phases 1 and 2 (P= 0.002). For lower body volume load, main effects for group ([F1.0, 8] = 9.8; P= 0.014) and time ([F2.0, 16] = 6.65; P= 0.008) were observed so that volume loads completed during phases 1 and 2 were higher for HEx (P= 0.03) and were lower during phase 3 compared with phases 1 and 2 in HEx (P= 0.04). RPE across phases 1-3 for PTCa and HEx are presented in Figure 6.2. For the
Table 6.1: Participant characteristics for the cancer survivors, healthy women and non-exercising control group.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Mass (kg)</th>
<th>Body Mass Index (kg.m^{-2})</th>
<th>TBLM (kg)</th>
<th>TBFM (kg)</th>
<th>API (W.kg^{-1})</th>
<th>VO_{2peak} (ml.kg^{-1}.min^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCa</td>
<td>56 ± 8</td>
<td>167 ± 8</td>
<td>73 ± 15</td>
<td>26.9 ± 4.9</td>
<td>41.2 ± 5.4</td>
<td>27.5 ± 12.0</td>
<td>1.05 ± 0.70</td>
<td>22.3 ± 7.6</td>
</tr>
<tr>
<td>HEx</td>
<td>49 ± 5*</td>
<td>164 ± 11</td>
<td>77 ± 10</td>
<td>29.1 ± 5.3</td>
<td>44.5 ± 4.8</td>
<td>32.4 ± 8.6</td>
<td>1.07 ± 0.60</td>
<td>25.5 ± 5.9</td>
</tr>
<tr>
<td>CON</td>
<td>52 ± 6</td>
<td>169 ± 6</td>
<td>81 ± 21</td>
<td>28.5 ± 9.3</td>
<td>46.1 ± 5.2</td>
<td>32.7 ± 18.7</td>
<td>1.3 ± 0.7</td>
<td>25.2 ± 6.6</td>
</tr>
</tbody>
</table>

TBLM, total body non-osseous lean mass; TBFM, total body fat mass; RALM, right upper arm non-osseous lean mass; API, aerobic power index; VO_{2peak}, peak oxygen consumption. *Indicates significance between PTCA and HEx (P= 0.04). Values presented as mean ± SD.
Figure 6.1: Training volume loads for the upper body (A) and lower body (B) exercises completed by the cancer survivors (PTCa) and healthy women (HEx) across the resistance training program. 

*Indicates a significance difference in phase 3 compared with phases 1 and 2 in both groups (P=0.002). 

^b^ Indicates a significance difference in HEx compared with PTCa in phases 1 and 2 (P=0.03). 

^c^ Indicates a significance difference in phase 3 compared with phases 1 and 2 in HEx (P=0.04).
Figure 6.2: Ratings of perceived exertion (RPE) for the upper body (A) and lower body (B) exercises completed by the cancer survivors (PTCa) and healthy women (HEx) across the resistance training program. a Indicates a significance difference in phase compared with phases 1 and 2 in both groups (P= 0.002). b Indicates a significance difference in phase 2 compared with phases 1 and 2 in both groups (P= 0.002).
upper body, no main effect for group ([F1.0, 8] = 3.29; P= 0.09) or group x
time interaction ([F 2, 16] = 2.44; P= 0.156) were observed; however, a
main effect for time was apparent ([F 2, 16] = 13.92; P= 0.0001) in which
RPE during phase 3 was lower compared with phases 1 and 2 (P= 0.002).
For the lower body, no main effects for group ([F1.0, 16.0] = 3.96;
P=0.105), nor a group x time interaction ([F 1.02, 8.16= 2.44; P= 0.119)
were observed; however, a main effect for time ([F 1.089, 8.7] =13.92; P=
0.0001) was apparent in which lower body RPE during phase 3 was lower
compared with phases 1 and 2 (P= 0.002).

6.3.3 Muscle Mass

Changes in TBLM and RALM for PTCa, HEx, and CON before and
after resistance training are presented in Figure 6.3. No main effects for
group ([F2.0, 23.0] =0.907; P= 0.418) or time ([F1.0, 23.0] =1.045; P=
0.317), nor a group x time interaction ([F2.0, 23.0] = 1.015; P= 0.378), were
observed for TBLM. No main effect for group ([F2.0, 23.0] = 0.907; P=
0.418), nor a group x time interaction ([F2.0, 23.0 = 2.474; P= 0.106), were
observed for RALM; however, a main effect for time ([F2.0, 23.0] = 8.841;
P= 0.007) whereby RALM was increased after training.

6.3.4 1RM Muscular Strength

Changes in 1RM strength in the upper body and lower body for
PTCa and HEx before training after completing phases 1, 2 and 3 are
presented in Figure 6.4. In the upper body, a main effect for group ([F1.0,
16.0] = 5.529; P= 0.032) was observed in which 1RM strength was higher
for HEx before training (P= 0.03) and at the end of phase 1 compared with
Figure 6.3: Changes in lean body mass (A) and right arm lean mass (B) for the cancer survivors (PTCa), healthy women (HEx), and controls (CON) before and after the resistance training. *Indicates a significance after training in PTCa and HEx (P<0.01;).
Figure 6.4: Changes in 1RM strength for the upper body, lower body for PTCa and HEx before training and after phases 1, 2, and 3. 

- Indicates a significance difference between PTCa and HEx before training and at the end of phase 1 (P< 0.03).
- Indicates a significance difference compared with before training in both groups (P= 0.001).
- Indicates a significance difference compared with before training and end of phase 1 in both groups (P= 0.001).
PTCa (P = 0.03). A main effect for time ([F2.1, 48.0] = 20.917; P=0.0001) was also observed in which upper body 1RM strength was higher at end the phase 1 compared with before training; however, a group x time interaction ([F2.056, 48] = 1.432; P=0.253) was not apparent. In the lower body, a main effect for group ([F1.0, 16.0] = 6.721; P= 0.02) was observed in which 1RM strength was higher for HEx before training (P=0.01) and at the end of phase 1 (P=0.01) compared with PTCa. A main effect for time ([F1.9, 48.0] = 9.091; P=0.001) was also observed whereby lower body 1RM had increased after phase 1 (P =0.012) and increased further at the end of phase 3 (P< 0.024); but no group x time interaction ([F1.924, 48] = 0.196; P=0.815) was observed.

6.3.5 Maximal Voluntary Force

MVF for PTCa, HEx, and CON before training and after completing phases 1, 2 and 3 is presented in Figure 6.5. No main effect for group ([F1.0, 16.0] = 0.062; P=0.807) nor a group x time interaction ([F3.0, 48] = 1.202; P=0.312) were observed for MVF. However, a main effect for time ([F1.835, 48.0] =3.742; P= 0.04) was observed in which MVF increased from before training to the end of phase 1 in both PTCa and HEx (P= 0.001).

6.3.6 Maximal Voluntary Force RMS

A main effect for group ([F2.0, 23.0] = 3.752; P= 0.039) was observed whereby before RT \( MVF_{RMS} \) was higher for the CON compared with PTCa (P=0.001). A main effect for time ([F1.0, 23.0] = 4.899; P< 0.037) was also apparent in which \( MVF_{RMS} \) decreased from before to after
Figure 6.5: Maximal voluntary force (MVF) for PTCa, HEx, and CON before training and after phases 1, 2, and/or 3. *Indicates a significance difference compared with before training in both PTCa and HEx (P < 0.001). Values presented as mean ± standard deviation.
RT across all 3 groups. A group x time interaction ([F2.0, 23.0] = 7.156; P= 0.004) was observed whereby $MVF_{RMS}$ increased from before to after RT in PTCa; however, decreased for HEx and CON before to after RT. No main effects for group ([F1.0, 16.0] = 1.660; P= 0.216) or time ([F3.0, 48.0] =0.976; P= 0.341), nor a group x time interaction ([F3.0, 48] = 0.719; P=0.414), were observed for PTCa or HEx for $MVF_{RMS}$ across the training period.

6.3.7 Level of Voluntary Muscle Activation

No main effects for group ([F2.0, 23.0] = 2.472; P=0.107), time ([F1.0, 23.0] =0.068 P= 0.797), nor a group x time interaction ([F2.0, 23.0] = 1.099; P=0.350) were observed for VA across the training program.

6.3.8 Cortical Silent Period

No main effect for group ([F2.0, 23.0] = 0.526; P= 0.598), nor a group x time interaction ([F2.0, 23.0] = 0.319; P= 0.730), were observed for SP; however, there was a trend for time ([F1.0, 23.0] = 4.098; P= 0.055) in which SP increased from before to after RT across all groups.
6.4 Discussion

6.4.1 Major Findings

Primary findings of this study include significant improvements in muscular strength and RALM with comparable neuromuscular adaptations to resistance training between the PTCa and HEx. Findings also indicate that increases in volume load of training rather than increased training intensity only may be necessary to promote positive strength related adaptations. Significantly higher fatigue was observed in the cancer survivor groups compared to the healthy women at baseline; however, all other self-reported measures including sleep, depression, and pain were comparable between the groups. Clinical based neuromuscular measure including MVF, nMVF, VA and SP remained unchanged following 12 weeks of resistance training.

6.4.2 Exercise Adherence, Training Volume Loads, and Ratings of Perceived Exertion

All participants who commenced the RT program completed the 12 weeks, there were no dropouts in the RT groups. The adherence rate for RT sessions was 92% and 95% for the HEx and PTCa groups respectively, which is well above average for quality of life interventions. The high adherence rates are likely due to the supervision by an Accredited Exercise Physiologist during training sessions, the individualization of the training loads and the small group setting.
Upper body training loads were comparable between HEx and PTCa across all phases of the RT program. Training volume load for the upper body increased from phase one to phase two; however decreased from phase two to phase three. Lower body training volume loads were greater in HEx during phase one and two of the RT program compared to PTCa; however by phase 3 lower body training volume was comparable between groups. This indicates that following 8 weeks of RT (phase one and two) the PTCa had reached an equivalent lower body training load as the HEx. Training volume load for the lower body decreased from phase two to phase three of the RT program.

The training volume is calculated as the product of repetitions performed by set undertaken by the exercise load (rep x sets x load). The RT program design consisted of 3 phases in which the repetitions and sets performed during each phase of the program was keep consistent across both groups, thus the observed difference in training volume load appear to be related to training volume rather than intensity.

RPE for both upper body and lower body resistance exercises over the 3 phases of the RT program were comparable between the groups, suggesting that the perceptions of effort associated with the RT exercises were similar and that the RT intervention utilised for this investigation was well tolerated by PTCa. Both lower and upper body RPE decreased between phases two and three which coincided with a decrease in the lower body training volume load. No between groups differences in lower body RPE was found for phase one and phase two despite significantly greater training volume load for the HEx compared to PTCa during both phase one and phase two of the RT program. This suggests that PTCa may require a lower
initial training volume load with a slower rate of progression during the initial 8 weeks of resistance training compared to HEx. RPE is a common tool used to measure physical activity intensity levels which relates specifically to how hard a person feels like their body is working based on the physical sensations they experiences during physical activity and should be considered as a separate phenomenon to cancer fatigue. Cancer fatigue is a term used to describe the symptom of fatigue associated with cancer and or its treatment (Piper & Cella, 2010), that is not proportional to recent activity (Berger et. al., 2015b). As such these findings does not suggest that the PTCa group were not experiencing any cancer-related fatigue.

6.4.3 Muscle Mass

RALM increased over the RT period demonstrating that the resistance training program had a positive effect on the regional muscle mass of the upper arm, even in the absence of any change in total body lean mass. Previous investigation of the effects of resistance training on body composition in cancer survivors have provided mixed results. In a randomized controlled trial Schmitz et. al. (2005a) reported significant increases in total body lean mass, measured using dual energy X-ray absorptiometry, in 85 breast cancer survivors performing resistance training twice-weekly following the RT intervention. Conversely, Ligibel et. al. (2008) reported no significant change in body composition following resistance training in 101 sedentary, overweight breast cancer survivors. Participants were randomly assigned either to a 16 week cardiovascular and strength training exercise intervention or to a usual care control group. The exercise consisted of two 50 minute supervised resistance training sessions
in addition to completing 90 minutes of home based aerobic per week. Body composition was measured using bioelectric impedance which unlike DXA is not considered a gold standard method of assessing body composition.

6.4.4 1RM Muscular Strength

The present study shows significant improvements in muscle strength after 4 weeks of RT. We found upper and lower body 1RM values increased significantly from baseline to the end of training phase one, values increased by 58.0 ± 32.4% and 18.7 ± 34.7% for upper and lower body respectively. Compared to PTCa, the HEx has significantly higher 1RM values at baseline for lower body and after phase 1 for upper body 1RM. No further increases in 1RM strength were found beyond initial 4 weeks of RT (phase one). As the training volume load for the upper body only increased significantly from phase one to phase two; this observation suggests that in order to promote positive muscular strength adaptation with RT increases in training volume, rather than increases in training intensity alone is necessary. A recent meta-analysis investigating the efficacy of exercise as an intervention to reduce cancer fatigue among cancer survivors reported that engaging in moderate-intensity resistance exercise modulated cancer fatigue levels more than engaging in low-intensity resistance exercise (Brown et. al., 2011a). Resistance training intensity may be an important training consideration for promoting positive change in fatigue symptoms; however muscular strength gains may relate to training volume in cancer survivors. Investigations aimed at delineating this phenomenon are necessary before this observation can be confirmed.
Our findings of improvements in muscular strength is in agreement with Segal and colleagues (2009), who reported increases in upper and lower body strength in a sample of cancer survivors in response to resistance training. 41 men with prostate cancer (PCa) undergoing androgen deprivation therapy (ADT) undertook a RCT consisting of 24 weeks of RT, performed 3 days a week, in which two sets of eight to twelve repetitions for ten different exercises (leg extension, leg curl, seated chest fly, latissimus pulldown, overhead press, triceps extension, biceps curls, calf raises, low back extension, and modified curl-ups) were performed at an intensity of between 60-70% of estimated 1RM. Improvement in upper and lower body muscular strength of 22% and 24%, respectively, were reported following RT compared with a group of PCa undertaking usual care. Other research support comes from a RCT of 83 BCa survivors during chemotherapy, who participated in a RT program consisting of nine exercises (leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, biceps curls, and modified curl-ups). Participants performed two set of eight to twelve repetitions, 3 times a week, at an intensity between 60% to 70% of their estimated 1RM. Muscular strength was assessed using an 8RM protocol for bench press and leg extension exercises. 8RM values increased by 25% to 35%, following training for the upper and lower body exercises respectively (Courneya et. al., 2007). A limitation of this study was that training duration varied according to each cancer patient’s length of treatment, with a median length of 17±4 weeks. These findings in addition to the present study demonstrate that post-treatment cancer survivors are capable of performing resistance exercise at a sufficient intensity to stimulate physiologic adaptation in muscle strength. Whether the PTCa
groups improvements in ability to lift heavier loads (1RM) is due to muscle based, neural based and/or perceptual based factors has not been previously reported.

6.4.5 Maximal Voluntary Force

Although increased strength as evidence by increased training volume and 1RM was observed over the training period; this was not paralleled by improvements in clinical based measurements of voluntary force production. An improvement in MVF was observed between baseline and the end of RT phase 2; however this increase was not continued across the remaining RT period. Evidence indicates most of the early adaptations in muscular strength upon commencing a resistance based program is of central (neural) origin (Chan et. al., 2003).

Studies using laboratory based measurement of force production following RT intervention in the cancer survivors population are lacking; most studies have utilised functional based assessment techniques namely 1RM testing. As results are comparable for both exercise groups this finding may be attributed to the lack of specificity as the resistance training program consisting of dynamic isotonic based resistance training performed on pin loaded equipment and the maximal isometric voluntary contraction elbow flexion assessment being performed on an isokinetic dynamometer. Based on previous literature in other clinical populations it would be expected that isometric strength would improve with the resistance training intervention.

In a RCT investigating the effects of 15 weeks of RT (n = 56) compared to relaxation therapy (n = 49) in women with fibromyalgia, significant improvements in isometric elbow flexion force (P = 0.02) in the RT group
when compared to the relaxation group as assessed using an isokinetic dynamometer. The resistance training intervention consisted of supervised twice weekly session involving the large muscle groups and core stability exercises.

Although increased RALM was observed following RT, muscle quality as measured by peak muscle force per unit of right arm muscle mass did not change over the training period for either the PTCa or HEx group. As such the increase in RALM was unlikely to have contributed to the increases in muscular strength observed.

6.4.6 Root Mean Square During Maximal Voluntary Torque

EMG signal from the BB and BR during maximal voluntary contraction decreased from before to after RT across all groups. Although, the raw/mean group values indicate that the PTCa $MV_{RMS}$ increased from before to after RT; however this was not significantly different compared to the HEx. It is currently unclear what effect resistance training has on EMG activity. Previous evidence indicates that $MV_{RMS}$ increases following resistance training, indicating that the number of motor units recruited has increased, or alternatively that motor units are firing at higher rates, or a combination of these factors has occurred, suggesting an increase in neural drive (Gabriel et. al., 2006). It is possible that the lack of observed increase in $MV_{RMS}$ with RT could be associated with the absence of significant gains in maximal voluntary torque over the RT period. Many factors that can influence the measurement of the EMG signal including placement of electrodes between session, changes in muscle temperature, skin electrode
contact could all have contributed to distorted results (Luca, 2006). Future investigations using such an isometric MVF assessment protocol should consider incorporating a isometric elbow flexion specific training task into resistance training interventions.

6.4.7 Voluntary Activation and Cortical Silent Period

To our knowledge this is the first study to investigate neuromuscular adaptations to a resistance based exercise program using TMS techniques in this clinical population. We did not observe a significant change in VA or SP, suggesting the possibility that cortical activation and descending drive was not greatly influenced by the RT intervention. It is possible that the increases in 1RM observed in this study was related to muscle based factors such as altered contractile characteristics and muscle architectural (Gabriel et. al., 2006). However, the lack of significance found for VA and SP does not discount the potential involvement of centrally based factors in physiological adaptation to resistance training; rather these may be related in part to the training intervention design and the limited increased in MVF observed in the current study (Carroll et. al., 2011). The dynamic isotonic RT intervention used in this study was not specific to the isometric conditions under which cortical voluntary activation was assessed. In addition, it has been suggested by Carroll et. al. (2011) that changes in voluntary activation following a resistance training intervention may only be detectible when training leads to sizeable increases in MVF. Accordingly, Lee et. al. (2009b) used TMS to examine the influence of unilateral dynamic strength training on the ability of the motor cortex to drive the untrained wrist muscles following 4 weeks of dynamic wrist abduction (range of
motion was from 5° abduction to 30° adduction). Subjects were randomly allocated to either a RT group (n = 12) or a control group (n = 11). The authors reported a small but significant increase in MVF during wrist abduction by 11.0 ± 8.7% (P < 0.01), however they found no significant increase in cortical voluntary activation of the wrist abductors following training.

In a subsequent study involving isometric based RT intervention by Lee et. al. (2010), found a significant 30% increase in MVC in the trained limb of participants (n =21) compared to controls (n=8) and significant change in cortical voluntary activation increased for the wrist extensors in the limb contralateral to the trained side. The increased voluntary activation was observed with a concomitant increase in MVF using an isometric based training was obtained. Hence, the design of the current RT intervention, the clinical testing techniques used and/or the lack of increase in MVF may have limited our clinical neuromuscular findings.

A trend for increased SP was apparent with training for both RT groups; thus it appears that some neural based changes may have occurred. SP has been reported as representing inhibitory processes thought to be in the motor cortex or other higher order sites (Fisher et. al., 2008). A similar increased SP following exercise was reported by Fisher 2008 (2008) while investigated the effects of a high-intensity treadmill based exercise training program in a group of patients with Parkinson Disease (PD). The authors of this RCT suggested that the exercise training may have induced activity dependant neuroplasticity as evidenced by changes observed in corticomotor excitability. However, previous TMS studies have reported consistently shorter SP in PD patients compared to healthy matched
controls; an effect which has not been previously reported in cancer survivors. In order to better understand the possible neuromuscular adaptations of associated with resistance training such as in the present study, future research should consider investigating the effect of resistance training on the development of fatigue during an exercise-based fatigue task. This may assist in clarifying potential underlying neuromuscular mechanisms.

6.4.8 Limitations

The strengths of this study include the supervised training program, the high adherence rates, and the inclusion of a control group for comparative purposes. Several limitations exist in our study. The small sample size may not have provided the statistical power required to discern a significant difference in clinical measurements including maximal voluntary force and voluntary activation and limits the ability to generalize the findings; however the consistency of positive effect on several functional and clinical measures we observed suggest the results are likely to be real. The PTCa were older than the HEx; although this does not seem to have affected the study findings. A specific isometric based resistance training protocol may be more useful in demonstrating evidence of cortical voluntary activation changes than a dynamic isotonic based intervention. However, the purpose of this investigation was to investigate the adaptations associated with a clinical based intervention that could be implemented by Exercise Physiologists when working with post-treatment cancer survivors; hence a laboratory-based isometric training protocol was not of research interest. The 12 week intervention period may not have been long enough
for significant cortical adaptations to be measured using TMS and interpolated twitch techniques as used within this investigation to occur.

6.5 Conclusion

We have provided evidence that a 12 week progressive resistance training is well tolerated by post-treatment cancer survivors and improvements in muscular strength comparable to healthy women can be attained. It is anticipated that these findings may assist in providing evidence of the effects of resistance training on muscular strength central adaptations in untrained post-treatment cancer survivors and healthy women to be used in the development of prospective exercise prescription guidelines. More research into the possibility of an effect of training volume versus intensity should be examined further.
7  STUDY FOUR

Effects of Short-Term Resistance Training
On Fatigue Symptoms And Neuromuscular
Manifestations Associated With A Sustained
Maximal Voluntary Contraction In Cancer
Survivors And Healthy Women
Abstract

**Purpose:** Current understandings of the development and manifestation of neuromuscular fatigue associated with a progressive resistance training intervention in post-treatment cancer survivors are yet to be reported. This study compared neuromotor performance associated with a 2min sustained, isometric elbow flexion task before and after 12 weeks of resistance training (RT) between post-treatment cancer survivors (PTCa) and healthy women (HEx).

**Methods:** Nine (9) disease-free, post-treatment cancer survivors (PTCa; 7 breast, 2 ovarian), nine (9) healthy women (HEx) and eight (8) healthy control participants (CON) were recruited. PTCa and HEx participated in a 12 week total body progressive resistance training program (RT), consisting of six exercises, during which three (3) sets of eight to twelve (8-12) repetitions were performed thrice weekly at a workload of between 70- 85% of one repetition maximum (1RM). All groups performed a 2 min sustained, maximal isometric task involving the right elbow flexors using an isokinetic dynamometer before and after RT. Neuromuscular measures included maximal voluntary torque (MVF) at 0°/s, surface EMG recordings of the biceps brachii (BB) and brachioradialis (BR), maximal muscle compound action potential (M$_{\text{max}}$) of the brachial plexus, were used to normalise EMG data and blood lactate (La$^-$) concentrations. Single pulse transcranial magnetic stimulation (TMS) was delivered to the motor cortex (M1) and used to measure both cortical voluntary activation (VA) using the superimposed interpolation twitch technique (SITT) and cortical silent
period (SP). During the 2 min task, maximal voluntary torque (MVF) at 0°/s, surface EMG reported as median frequency (MDF), central activation ratio (CAR) and cortical silent period (SP) were measured. Self-reported fatigue was measured using The European organisation for research and treatment of cancer fatigue subscale (ECORT-F). Descriptive measurements including height, weight, total body fat mass (FM), total body non-osseous lean tissue mass (LBM), and right upper arm non-osseous lean tissue (RA-FFM) mass measured using dual x-ray absorptiometry (DXA) and VO\textsubscript{2peak} were obtained at baseline.

**Results:** Age, height, weight, BMI and indices of body composition were comparable between groups (P> 0.05). ECORT-F and Hb was significantly higher in the PTCa compared with HEx before training (P=0.02; P = 0.01). Significant between group differences were observed for after training maximal force during the 2 minute task which were higher in PTCa compared to HEx at 45, 65, and 85 sec (P<0.01) and for before training SP with shorter duration observed in HEx and CON compared to PTCa at 65 and 85 sec during the 2min task; (P= <0.05). After training SP was significantly different being shorter in the CON compared to PTCa across all consecutive time points (5, 25, 45, 65, 85, 105; P<0.05) during the 2min task. Main effect for time were observed pre to post-task for MVF decreased significantly before and after training (P<0.001) and VA decreased pre to post-task after training for all groups (P= 0.02). During task force decreased before and after training by 53.6 ± 8.8% and 49.7 ± 11.1% respectively, across all consecutive time points during task (P<0.001). MDF during task decreased before and after training across all consecutive time points (25,
EMG$_{RMS}$ before training decreased between 0 sec and 45 sec, 65, 85, 105 and 120 sec (P = 0.02). CAR during task decreased before training between 5 sec, and 45, 105 and 120 sec (P<0.05) and after training between 5, 45, 85 and 105 sec (P<0.05). A group x time interaction was observed whereby EMG during MVC increasing from pre-task to post- task before and after training in PTCa; decreasing from pre-task to post- task before and after training in CON; however remained unchanged from pre-task to post- task before training in HEx and then decreased from pre-task to post- task after training (P= 0.030).

**Conclusion:** 12 weeks of resistance training positively improved persistent fatigue symptoms in post-treatment cancer survivors. The neuromuscular manifestations of fatigue associated with an exercise-induced fatigue were comparable between cancer survivors and healthy women. We found some evidence for longer SP duration associated with a 2 minute sustained maximal isometric task involving the right elbow flexors before resistance training in cancer survivors compared to health women providing evidence of greater cortical inhibition. Further studies should investigate possible inhibitory mechanisms associated with changes in SP through the use of a paired pulse TMS protocol. Due to the task specific nature of the development and manifestations of fatigue additional investigation may need to focus on neuromuscular performance under different task conditions.
7.1 Introduction

As many as 30-40% of disease-free cancer survivors report persistent fatigue symptoms for up to 10 years following the completion of cancer treatment (Bower et. al., 2000; Cella et. al., 2001; Bower et. al., 2006c). Cancer-related fatigue is a complex and multifactorial symptom (Targum et. al., 2014), which often occurs together with poor sleep quality and depressive symptoms (Miller et. al., 2008; Illi et. al., 2012). Alterations in centrally based neural circuitry have been implicated in the genesis of sleep disorders and depression (Miller et. al., 2008). It has been proposed that altered neural function may be a potential contributor to the development and/or continuation of persistent fatigue symptoms associated with cancer (Miller et. al., 2008; Harrington, 2012; Dantzer et. al., 2014). Indeed some authors have reported deficits in neuromuscular function of cancer survivors (Yavuzsen et. al., 2009; Kisiel-Sajewicz et. al., 2013; Cai et. al., 2014); however, studies are limited and results are conflicting (Bruera, et al., 1988; Yavuzsen et. al., 2009; Alt et. al., 2011).

Neuromuscular fatigue has been described as having peripheral and central components (Davis & Walsh, 2010) depending on whether a loss in capacity to generate maximal voluntary force originates in the muscle tissues or in the nervous system respectively (Schillings et. al., 2007). Greater contributions from central factors compared to peripheral factors have been reported in this population compared to non-fatigued cancer survivors and/or healthy persons (Yavuzsen et. al., 2009; Kisiel-Sajewicz et. al., 2012; Kisiel-Sajewicz et. al., 2013; Cai et. al., 2014; Platt et. al., 2014). A recent study Platt et. al. (2014) reported impaired muscle function at task
failure in cancer survivors performing a 30% maximal handgrip compared to controls as evidenced by increased twitch force by motor nerve stimulation indicating greater levels of central fatigue. Although other authors have failed to confirm reports of central based mechanisms within this setting (Prinsen et. al., 2012; Neil et. al., 2013). Other evidence suggestive of centrally based neural changes includes difference in electroencephalography frequency power dynamics in cancer survivors reporting persistent fatigue during a sustained elbow flexion task compared to non-fatigued healthy persons (Khoshknabi, 2006; Platt et. al., 2014). Moreover, distinct patterns of resting brain connectivity, measured by functional connectivity magnetic resonance imaging, between fatigued compared to non-fatigued breast cancer survivors (Hampson et. al., 2015). Based on these findings, current understanding of the involvement of the neural pathways in persistent fatigue in cancer survivors is uncertain.

At present, limited options are available for the management of persistent fatigue in cancer survivors (Harrington, 2012). However, evidence of the benefits of exercise in ameliorating persistent fatigue in cancer survivors is accumulating (McMillan & Newhouse, 2011) with several guidelines for the prescription of exercise in cancer survivors recently being developed by key professional bodies, including Exercise in Sport Science Australia and the American College of Sport Medicine (Hayes et. al., 2009; Schmitz et. al., 2010; Campbell et. al., 2012). Although exercise has shown some efficacy in managing fatigue symptoms in cancer survivors, previous exercise interventions have mostly encompassed aerobic activities (McMillan & Newhouse, 2011) while studies examining the effects of resistance training on persistent fatigue symptoms are limited.
(McMillan & Newhouse, 2011) and additional research is necessary before any definitive conclusions can be drawn. Furthermore, it remains unknown if resistance training may influence the neuromuscular manifestations associated with exercise-induced fatigue in cancer survivors. Such data could provide evidence of mechanisms by which resistance training may ameliorates persistent fatigue symptoms in cancer survivors. Therefore, the purpose of this study was to compare the effects of 12 weeks of resistance training on persistent fatigue symptoms and neuromuscular manifestations associated with an exercise-induced fatigue task before and after training between cancer survivors and healthy women. It is hypothesised that the cancer survivors, with persistent fatigue will exhibit improvements in persistent fatigue symptoms as demonstrated by reduced fatigue ECORT-F scores, increased maximal voluntary torque immediately before and after an exercise-induced fatigue task, with reduced relative decline in force output during exercise after training compared to before training. Such changes will be largely explained by central motor mechanisms and as demonstrated by increased descending neuromotor drive and decreased cortical inhibition associated with an exercise-induced fatigue task after training.
7.2 Methods

A detailed description of all testing procedures is provided in Chapter 3.

7.2.1 Participant Sample

Seven (7) breast cancer survivors and two (2) ovarian cancer survivors (PTCa) who were post-treatment and had completed curative cancer therapies and 17 healthy women with no known history of cancer and/or cancer-related treatment participated in the study (Section 3.2). Prior commencing the study, the healthy women were assigned to either an exercise comparison group (HEx n=9) or a non-exercising control group (CON n= 9); however, one of the control participants withdrew during the investigation due to reasons outside of the study. Therefore, data from the control group are report for n= 8.

7.2.2 Physical characteristics

Fatigue, Depressive Symptoms, Sleep Quality, and Pain were assessed using a variety of subjective self-report instruments including: The Brief Fatigue Index (BFI); The fatigue subscale of European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-F); The Revised Piper Fatigue Scale (RPFS); The 100mm visual analogue scale (VAS-F); The Beck Depression (BDI-II); The Pittsburgh Sleep Quality Index (PSQI); and The 101-point numerical pain intensity rating scale (NRS-101) (Section 3.3.1). Mass, BMI, and measures of body composition including total body non-osseous lean tissue mass (TBLM),
total body fat mass (TBFM), and right upper arm non-osseous lean tissue mass (RALM) was measured using dual x-ray absorptiometry (DXA) (Section 3.3.3). A submaximal aerobic capacity test was performed to assess aerobic power index (API) and volume of peak oxygen consumption (VO2peak) (Section 3.4.1).

7.2.3 Neuromuscular Performance and Fatigue Testing

The assessment of neuromuscular performance and fatigue was performed on the right elbow flexors using a combination of voluntary and evoked techniques (Section 3.5). A 2-min sustained, maximal voluntary isometric contraction of the right elbow flexors at 90° shoulder and elbow flexion was performed (Section 3.6.6). Blood lactate (La-) (Section 3.6.5) and resting muscle compound potentials (Mmax) from the biceps brachii were assessed before and after fatigue (Section 3.6.1). Maximal voluntary torque (MVT) (Section 3.5.2), voluntary surface electromyography (EMG) from the biceps brachii (Section 3.5.3), and indices of corticomotor excitability (Section 3.6.3) using transcranial magnetic stimulation (TMS) (Section 3.6.2) were assessed before, during (0, 20, 40, 60, 80, 100 and 120 sec), and after fatigue.

Following a standardised warm-up (Section 3.5.1), testing commenced, which involved the assessment of the following parameters in this sequence: 1) Compound muscle action potentials (Mmax); 2) the level of voluntary muscle activation; 3) blood lactate; 4) 2-min sustained maximal voluntary contraction; 5) Mmax; 6) the level of voluntary muscle activation; and 7) blood lactate. A 1-min rest period was provided between assessment of Mmax and the level of voluntary muscle activation and a 2-min rest period...
was provided between the assessment of voluntary muscle activation and the commencement of the sustained maximal voluntary contraction. All assessments following the completion of the sustained maximal voluntary contraction were performed as rapidly as possible to minimise the amount recovery.

### 7.2.4 Resistance Training Program

PTCa and HEx participated in a fully supervised, whole body resistance training for a period of 12 weeks. A detailed description of the resistance training program (RT) (Section 3.7) and procedures for 1RM muscular strength testing (Section 3.7.6), the collection of RPE (Section 3.7.5), calculation of training volume load (Section 3.7.4) and post training data collection (Section 3.7.3) is provided in Chapter 3.

Following the 12 week training period the PTCa and HEx performed 1RM testing. All three (3) participant groups attended a post-training data collection session in the week immediately following completion of the 12 week resistance training period (Section 3.7.3).

### 7.2.5 Statistical Analysis

Before inferential statistics were performed, the distribution of each independent variable was tested using the Shapiro-Wilk W statistic as recommended for sample sizes of less than 50 (Ghasemi & Zahediasl, 2012). Descriptive characteristics were analysed using a one-way analysis of variance (ANOVA). Resistance training and neuromuscular data were analysed using a two-way (group x time) ANOVA. Where Mauchy’s test of sphericity was significant and $\epsilon \leq 0.75$ or $\epsilon \geq 0.75$, a Greenhouse-Geisser or
Huynh-Feldt correction, respectively, was applied to the within-participant analyses. Levene’s test of equality of error variance between participants did not show statistical significance for any of the analyses. When a significant main effect and/or interaction were observed, a one-way ANOVA with a Bonferroni correction for multiple-comparisons was used, where appropriate, to determine the source of significance. All statistical procedures were performed using Predictive Analytic Software (PASW) (Statistical Package for the Social Sciences version 20.0, Chicago, IL, USA) software with the critical level for significance was set at P< 0.05. To determine the magnitude of differences observed between groups. All data are reported as mean ± standard deviation (SD). All data are reported as mean ± standard deviation (SD).
7.3 Results

7.3.1 Physical Characteristics

Physical characteristics for the participants are presented in Table 7.1. Age was significantly different between PTCa and HEx (P= 0.041). No other statistically significant differences were evident between groups for any other physical characteristics (P >0.05).

7.3.2 Muscle Mass

No main effects for group ([F2.0, 23.0] = 0.907; P= 0.418) or time ([F1.0, 23.0] = 1.045; P= 0.317), nor a group x time interaction ([F2.0, 23.0] = 1.015; P= 0.378), were observed for TBLM. No main effect for group ([F2.0, 23.0] = 0.907; P= 0.418), nor a group x time interaction ([F2.0, 23.0] = 2.474; P= 0.106), were observed for RALM; however, a main effect for time ([F2.0, 23.0] = 8.841; P= 0.007) in which RALM was increased after RT.

7.3.3 1RM Strength

A main effect for group ([F1.0, 16.0] = 5.529; P= 0.032) was observed whereby upper body 1RM strength was higher for HEx before RT compared with PTCa (P= 0.030); however, no main effects for time ([F2.1, 48.0] = 20.917; P=0.0001) nor a group x time interaction ([F2.056, 48] = 1.432; P=0.253) were observed. No main effects for group ([F1.0, 16.0] = 6.721; P= 0.020) or time ([F1.924, 30.78] = 9.091; P=0.001), nor a group x time interaction ([F1.924, 30.78] = 0.196; P=0.815), were observed for lower body 1RM strength.
Table 7.1: Participant characteristics for the cancer survivors, healthy women and control participants.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Mass (kg)</th>
<th>Body Mass Index (kg.m^{-2})</th>
<th>TBLM (kg)</th>
<th>TBFM (kg)</th>
<th>API (W.kg^{-1})</th>
<th>VO_2peak (ml.kg^{-1}.min^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCa (n= 9)</td>
<td>56 ± 8</td>
<td>167 ± 8</td>
<td>73 ± 15</td>
<td>26.9 ± 4.9</td>
<td>41.2 ± 5.4</td>
<td>27.5 ± 12.0</td>
<td>1.05 ± 0.70</td>
<td>22.3 ± 7.6</td>
</tr>
<tr>
<td>HEx (n= 9)</td>
<td>49 ± 5*</td>
<td>164 ± 11</td>
<td>77 ± 10</td>
<td>29.1 ± 5.3</td>
<td>44.5 ± 4.8</td>
<td>32.4 ± 8.6</td>
<td>1.07 ± 0.60</td>
<td>25.5 ± 5.9</td>
</tr>
<tr>
<td>CON (n= 8)</td>
<td>52 ± 6</td>
<td>169 ± 6</td>
<td>81 ± 21</td>
<td>28.5 ± 9.3</td>
<td>46.1 ± 5.2</td>
<td>32.7 ± 18.7</td>
<td>1.3 ± 0.7</td>
<td>25.2 ± 6.6</td>
</tr>
</tbody>
</table>

TBLM, total body non-osseous lean mass; TBFM, total body fat mass; RALM, right upper arm non-osseous lean mass; API, aerobic power index; VO_2peak, peak oxygen consumption; PTCa, post-treatment cancer survivors; HEx, healthy women; CON, non-exercising control group. *Indicates significance between PTCa and HEx (P= 0.04). Values presented as mean ± SD.
7.3.4 Self-Reported Fatigue

Self-report fatigue for PTCa and HEx before and after resistance training are presented in Table 7.2. No main effects for group ([F2.0, 23.0] =1.903; P=0.172) or time ([F1.0, 23.0] =1.918; P= 0.179), nor a group x time interaction ([F2.0, 23.0] =0.455; P=0.640), were observed for BFI between all groups before or after RT. No main effects for group ([F2.0, 21.0] =2.438; P= 0.112) nor a main effect for time ([F2.0, 21.0] = 0.187; P=0.670), were observed for RPFS from before to after RT; however a group x time interaction ([F2.0, 21.0] =5.033; P= 0.016) was observed whereby RPFS improved from before to after RT in PTCa and HEx groups; however was poorer in CON group after RT compare to before RT. ECORT-F was significantly different between PTCa and HEx with higher fatigue symptoms observed in PTCa before training (P<0.05).
Table 7.2: Self-reported fatigue measures for cancer survivors, healthy women and non-exercising control group.

<table>
<thead>
<tr>
<th>Group</th>
<th>BFI</th>
<th>VAS-F</th>
<th>RPFs</th>
<th>EORTC-F</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCa (n=9)</td>
<td>2.4 ± 1.5</td>
<td>3.7 ± 3.6</td>
<td>3.1 ± 2.0</td>
<td>24.7 ± 12.5</td>
</tr>
<tr>
<td>HW (n=9)</td>
<td>1.91 ± 1.01</td>
<td>1.8 ± 1.8</td>
<td>1.8 ± 0.54</td>
<td>8.3 ± 9.8</td>
</tr>
<tr>
<td>Con (n=8)</td>
<td>2.7 ± 1.6</td>
<td>1.3 ± 0.9</td>
<td>1.6 ± 0.8</td>
<td>15.7 ± 11.3</td>
</tr>
<tr>
<td>Significance</td>
<td>P=0.44</td>
<td>P=0.12</td>
<td>P=0.07</td>
<td>P=0.02*</td>
</tr>
</tbody>
</table>

BFI; Brief Fatigue Index; VAS-F, Visual Analogue Scale- Fatigue; RPFs, Revised Piper Fatigue Scale; EORTC-F, European Organisation for Research and Treatment of Cancer Questionnaire- Fatigue Domain. PTCa, post-treatment cancer survivors; HEx, healthy women; CON, non-exercising control group. *Indicates a significant difference between groups (P≤ 0.05). Values presented as mean ± SD.
7.3.5 Pre and Post Sustained Contraction Data

7.3.5.1 Lactate

Lactate data for PTCa and HEx before and after resistance training are presented in Figure 7.1. No main effects for group ([F2.0, 23.0] = 0.72; P= 0.498) nor a group x time interaction ([F4.3, 49.2] = 0.396; P= 0.822) were observed for La⁻. However, a main effect for time ([F 2.1, 49.2] = 20.71; P< 0.001) was evident in which La⁻ increased from pre to immediately post-task before and after RT.

7.3.5.2 Resting Maximal Compound Action Potential

M_max data for PTCa and HEx before and after resistance training are presented in Figure 7.2. A main effect for M_max between groups was observed in which M_max was greater in PTCa compared to CON pre and post task before RT and post-task after RT ([F2, 22] = 3.9; P<0.05). No significant differences for time [F1.2, 27.2] = 3.09; P= 0.082) nor a group x time interaction ([F2.4, 27.2] = 1.38; P= 0.271) were observed for M_max.
Figure 7.1: Lactate (La⁻) immediately pre-task before training, post-task before training, pre-task after training, post-task after training in post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON). *Significant within differences for time (P<0.001). Values presented as Mean ± Standard deviation.
Figure 7.2: $M_{\text{max}}$ immediately pre-task before training, post-task before training, pre-task after training, post-task after training for post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON). *Indicates a significant difference between groups ($P < 0.05$). Values presented as Mean ± Standard deviation.
7.3.5.3 Maximal Voluntary Force and Normalised Voluntary Force

Changes in MVF for PTCa and HEx before and after resistance training are presented in Figure 7.3. No main effect for group ([F2.0, 23] = 2.3; P= 0.123) nor a group x time interaction ([F6, 69] = 0.823; P= 0.556) were evident for MVF before and after RT; however, a main effect for time was observed in which MVF decreased significantly pre to post-task by 25.5±7.8% before RT and by 28.2±11.1% after RT ([F2.0, 23] = 2.3; P<0.001). No main effect for group ([F2.0, 23] = 0.25 P= 0.781) or a main effect for time ([F2.0, 23.0] = 0.012 P= 0.913); nor a group x time interaction ([F 2.0, 23.0] = 3.221; P= 0.058) were evident for nMVF before and after RT.

7.3.5.4 Level of Voluntary Activation

Changes in VA for PTCa and HEx before and after resistance training are presented in Figure 7.4. No main effect for group ([F2.0, 22] = 2.4; P= 0.113) nor a group x time interaction ([F3.4, 34.5] = 0.881; P= 0.465) were observed for VA before or after RT; however, there was a main effect for time whereby VA decreased significantly by 6.5 ± 12.4 pre to post-task after RT for all groups ([F1.6, 34.5] =4.8; P= 0.02) Figure 4). VA decreased by 10.2 ± 5.5 pre to post-task before RT for both PTCa and HEx groups however this was not statistically significant (P>0.05).
Figure 7.3: Maximum voluntary force (MVF) and normalised MVF (nMVF) for post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON). \(^b\) Significant within differences for time (P<0.001). Values presented as mean ± SD.
Figure 7.4: Voluntary activation (VA) immediately pre-task before training, post-task before training, pre-task after training, post-task after training for post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON). a Significant within differences for time after training (P<0.05). Values presented as Mean ± Standard deviation.
7.3.6 During Sustained Contraction Data

7.3.6.1 Voluntary Force

Force data for PTCa and HEx are presented in Figure 7.5. A main effect for group ([F2.0, 23] = 5.4; P= 0.012) in which after RT force was observed as being significantly higher in PTCa compared to HEx at 40, 60, and 80 sec (P<0.01). A main effect for time was observed whereby force decreased before and after RT by 53.6 ± 8.8% and 49.7 ± 11.1% respectively, across all consecutive time points during task (0, 5, 20, 40, 60, 80 100 and 120 sec) [F 4.1, 95.4] = 115.1; P<0.001). No group x time interaction was observed for force during the 2min task ([F8.3, 95.4] = 1.9; P= 0.67).

7.3.6.2 Central Activation Ratio

CAR data for PTCa and HEx are presented in Figure 7.6. No main effect for group ([F2.0, 23.0] =2.93; P= 0.073) nor a group x time interaction ([F269.7, 111.9] = 1.33; P= 0.223) were observed for CAR during the 2min task before and after RT; however a main effect for time was observed whereby CAR during the 2min task decreased before RT between 5 sec, and 40, 100 and 120sec ([F4.8, 299] = 6.9; P<0.05) and after training between 5, 40, 80 and 100 sec ([F4.8, 299] = 4.7; P<0.05). CAR decreased by 6.3 ± 7.0% between 0 and 120sec before training and by 5.2 ± 8.2% between 0 and 105 sec after RT.
Figure 7.5: Force (N) during the 2min task (0, 5, 20, 40, 60, 80, 100 and 120 sec) before and after training for post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON). aSignificance between PTCa and HEx during task after training (P<0.01). bSignificant within differences for time before and after training (P<0.01). Values presented as Mean ± Standard deviation.
Figure 7.6: Central Activation Ratio during the 2min task before and after training for post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON). aSignificant within differences between 5 and 120 sec before training (P<0.01). bSignificant within differences time points 5 and 100 sec before training (P<0.001). cSignificant within differences between 5 and 40, 80 sec after training (P<0.05). dSignificant within differences between 5 and 80 sec after training (P<0.01). Values presented as Mean ± Standard deviation.
7.3.6.3  Cortical Silent Period

SP data for PTCa and HEx are presented in Figure 7.7. A main effect for group was observed whereby SP before RT was significantly shorter in HEx and CON compared to PTCa at 60 and 80 sec during the 2min task; [F2.0, 23.0] = 7.5; P= <0.05). After training SP was significantly shorter in the CON compared to PTCa across all consecutive time points (5, 20, 40, 60, 80, 100, 120 sec; P<0.05) during the 2min task. SP increased before and after RT by 14.8 ± 0.2% and 3.25 ± 0.1% respectively between 5 and 120sec. However no main effect for time ([F1.4, 33.1] = 1.44; P= 0.247) nor a group x time was observed were observed for SP before and after RT ([F2.9, 33.1] = 0.896; P= 0.450).

7.3.6.4  Median Frequency

EMG\textsubscript{MDF} data for PTCa and HEx are presented in Figure 7.8. No main effect for group ([F2.0, 23] = 2.38 P= 0.115) nor a group x time interaction ([F30, 345] = 0.961; P= 0.0.528); however a main effect for time whereby MDF during task decreased before and after RT by 40.0 ± 12.0% and 41.4 ± 7.9% respectively, from 0 seconds compared to all consecutive time points (20, 40, 60, 80, 10 and 120 sec; P <0.001).
Figure 7.7: Cortical silent period during the 2min task (5, 20, 40, 60, 80, 100, 120 sec) before and after training for post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON). 

aSignificance between PTCa and HEx and between PTCa and CON before training (P<0.05). bSignificance between PTCa and HEx and PTCa and CON after training (P<0.05). Values presented as Mean ± Standard deviation.
Figure 7.8: MDF (Hz) during the 2min task (0, 5, 20, 40, 60, 80 100 and 120 sec) before and after training for post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON). *Significant within differences for time before and after training (P<0.001). Values presented as Mean ± Standard deviation.
7.3.6.5 Root Mean Square

$\text{EMG}_{\text{RMS}}$ data for PTCa and HEx are presented in Figure 7.9. A main effect for group was observed after RT whereby $\text{EMG}_{\text{RMS}}$ during task was higher in the PTCa compared to CON groups at 0, 40, 60, 80, 100 and 120 sec ($F_{2, 23} = 4.3 P = 0.026$). A main effect for time was also observed ($F_{2.6, 58.8} = 2.9; P = 0.049$) whereby $\text{EMG}_{\text{RMS}}$ before RT decreased between 0 sec and 40 sec, 60, 80, 100 and 120 sec ($P = 0.02$). This was a reduction in RMS by $24.7 \pm 24.8\%$ between 0 and 120 sec, before training. No group x time interaction ($F_{5.1, 58.9} = 0.92 P = 0.475$) was observed.
Figure 7.9: RMS (mV) during the 2min task (0, 5, 20, 40, 60, 80, 100 and 120 sec) before and after training for post-treatment cancer survivors (PTCa), Healthy women (HEx) and non-exercising control group (CON).

Significance between PTCa and CON after training (P<0.01). bSignificance Significant within differences for time before training (P<0.05). Values presented as Mean ± Standard deviation.
7.4 Discussion

7.4.1 Major Findings

The purpose of this study was to compare the effects of 12 weeks of resistance training on persistent fatigue symptoms and neuromuscular manifestations associated with an exercise-induced fatigue task before and after training comparing cancer survivors and healthy women. Our measures indicated that persistent fatigue symptoms improved following 12 weeks of resistance training in post-treatment cancer survivors. We also found that the neuromuscular manifestations of fatigue associated with an exercise-induced fatigue were comparable between cancer survivors and healthy women. In addition we reported evidence of longer SP duration associated with a 2 minute sustained maximal isometric task involving the right elbow flexors before resistance training in cancer survivors compared to healthy women providing evidence of greater cortical inhibition in the post-treatment cancer survivors. In addition the pattern of EMG_RMS activity immediately pre and post task MVF before and after training varied between groups, indicating the potential for altered muscle recruitment strategies between cancer survivors with fatigue symptoms and HEx.

7.4.2 Muscle Mass

After 12 weeks of resistance training program regional muscle mass of the upper arm increased in PTCa and HEx despite no change in total body lean mass. Schmitz et. al. (2005a) reported significant increases in total body lean mass in 85 breast cancer survivors performing resistance training twice-weekly following the RT intervention, as measured using
dual energy X-ray absorptiometry. Conversely, Ligibel et. al. (2008) reported no significant change in body composition following resistance training in 101 sedentary, overweight breast cancer survivors. However, others have also failed to observe significant change in total body composition following resistance training (Ligibel et. al., 2008).

7.4.3 1RM Strength

Compared to PTCa, the HEx has significantly higher 1RM values at baseline for the lower body; however this was not observed for the upper body 1RM. However, 1RM strength did not significantly increase following 12 weeks of resistance training. This finding may be due to the design of the resistance training program in which the training intensity progressively increased whilst volume load was keep constant over the 12 week program. Consequently, in order to promote positive muscular strength adaptation as evidenced by increases in 1RM with RT, increases in training volume rather than increases in training intensity only may be required; although additional research is necessary in order for this to be confirmed. Based on previous research it was anticipated that 1RM would increase following 12 weeks of resistance training. Courneya et. al. (2007) reported significant increases in 1RM in a group of breast cancer survivors (n=83) who were undergoing chemotherapy following resistance training. The cancer survivors performed nine different exercises (leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, biceps curls, and modified curl-ups), 3 times a week at an intensity of 60% to 70% of their estimated 1RM for two sets of eight to twelve repetitions. Muscular strength was assessed using an 8RM protocol for both bench press and leg extension.
Following resistance training 1RM values increased by 25% to 35% for the bench press and leg extension respectively. Limitations of the study include a variable training period according to the individual’s length of treatment, with a median length of between 17±4 weeks. Alternatively a longer period of resistance training may have been necessary for gains in strength to be observed in the present study.

7.4.4 Self-Reported Fatigue

Fatigue as measured on the fatigue subscale of the ECORT-F was significantly higher in PTCa (24.7 ±12.5; 0 – 33.3) compared to HEx (8.3 ± 9.8; 0 – 22.2) indicating that fatigue symptoms were different between the two groups before training. It was anticipated that if any differences in neuromuscular mechanisms existed between the groups that the variances in self-reported fatigue symptoms between groups would enable this phenomenon to be examined. Following 12 weeks’ resistance training ECORT-F scores were no longer significantly different between groups; the ECORT-F scores for the PTCa group improved after RT demonstrating a positive effect of resistance training on fatigue symptoms in this population. This finding is supported by a recent meta-analysis investigating the efficacy of exercise as an intervention to reduce cancer fatigue among cancer survivors, which reported that moderate intensity resistance exercise reduces cancer fatigue in breast and prostate cancer survivors and cancer survivors of older age (Brown et. al., 2011a).
7.4.5 Pre and Post Sustained Contraction Data

7.4.5.1 Lactate

In the present study, lactate increased pre to post task both before and after training in all groups, suggesting that metabolic demands during the task performance increased over time which was comparable between groups. Lactate production is a protective response by the body to allow cellular energy production to continue when tissue oxygen supply is inadequate for aerobic metabolism during sustained muscular contractions. It has been observed that lactate accumulates proportionally to increases in plasma metabolites, during high-intensity exercise (Todd, 2014). Recent studies indicate lactate as a biomarker rather than a direct cause of fatigue.

7.4.5.2 Resting Maximal Compound Action Potential

No change in $M_{\text{max}}$ was observed during MVF pre to post task, before or after training; indicating that propagation and neuromuscular transmission were not impaired following the 2 minute task before and after resistance training.

7.4.5.3 Maximal Voluntary Force and Normalised Voluntary Force

We found comparable declines in the ability to produce maximal voluntary force across all groups, pre to post-task, before training and after training. This suggesting that the development of muscle fatigue, defined as a reduced capacity to generate muscle force in response to exercise was similar between all groups (Lanza et. al., 2004). Similarly, maximal
voluntary force normalised to right arm fat free mass (nMVF) was comparable between group before and after training. After training differences between groups was not unexpected given the lack of significant increase in voluntary muscle force following resistance training. Previous research has demonstrated improvements in muscle quality following a resistance training intervention in groups of older healthy adults (Fragala et. al., 2014). Muscle quality, defined as muscle strength per unit of muscle mass, provides an estimation of the contribution of neuromuscular factors associated with strength development (Fragala et. al., 2014). If muscular strength improved to a greater extent than changes in muscle mass, indices of muscle quality could provide some evidence of neural adaptations to training (Pinto et. al., 2014). Hence, if peak force per unit of mass increased, improvements in neuromuscular capacity, either through learning or altered patterns of muscle and motor unit recruitment would have been expected (Gandevia, 2001; Pinto et. al., 2014).

7.4.5.4 Level of Voluntary Activation

Voluntary activation (VA) of the biceps brachii and brachialis muscles, using transcranial magnetic stimulation over the motor cortex, was incomplete (<100%) pre-task before training in all groups. However, VA values were within normal acceptable ranges (~92-94%) for individuals without a previous history of undertaking structured resistance training. Consistent with previous studies, a significant decline in VA was revealed following the performance of a 2 minute maximal isometric task after the training period for all groups. This decrease suggests the development of central fatigue (supraspinal drive) (Gandevia, 2001). Such findings were not
found pre to post-task, before training. The reduced cortical drive pre to post-task following 12 weeks’ resistance training, suggests that participants may have performed at a sub-maximal intensity thereby activating previously inactive motor units and/or increasing the discharge rate of those motor units already recruited (Enoka, 2008; Taylor & Gandevia, 2008) after training compared to before training resulting in a greater reduction in cortical drive. Alternatively, the greater deficits in voluntary activation may be related to greater work output during the 2 minute task after training as compared to before training. However, as no difference in force production were observed after training this explanation it unlikely. Another possible explanation for the lack of significance in VA pre-post task before training may be attributed to a learning effect (pattern of muscle activation required for the 2 minute task) following the resistance training period, as all three groups including the control group performed similarly after training (Gandevia, 2001). Alternatively, the small deficit in voluntary activation observed before training may provide little scope for improvement following resistance training.

7.4.6 During Sustained Contraction Data

7.4.6.1 Voluntary Force

As anticipated, force decreased in all groups before and after training during the performance of the 2 minutes task indicating the presence of neuromuscular fatigue, evidenced by a decrease in maximal force-generating capacity in response to exercise (Lanza et. al., 2004). A between group difference was observed after training in which force production was
significantly higher in PTCa compared to HEx during the task at 45, 65, and 85 sec. This finding provides some evidence of improved voluntary muscle strength and/or resistance to neuromuscular fatigue during the middle portion of the 2 minute task in the PTCa groups in response to the 12 week training intervention. However, maximal force output was comparable between groups at the commencement and completion of the task, thus, voluntary force during the task performance was not significantly improved following training at the start and end of the 2 minutes. The increased force production observed in the PTCa group during the 2 minute task after training may be due to factors other than increases in neural drive (EMG) to the agonist, such as motor control changes, increases in reflex potentiation, and protein synthesis that are often reported with resistance training (Behm & St-Pierre, 1998).

The lack of improvement in voluntary force during the task performance after resistance training compared to before training may be due to a variety of factors such as specificity between the neuromuscular testing versus resistance training modes, training volume and task complexity (Lee et. al., 2009a; Carroll et. al., 2011). Although the resistance training intervention for this study included an elbow flexion exercise, the contraction type was isotonic and not isometric. It is feasible the lack of overall improvement in maximal force generation following training is due to notable differences between the training intervention which involved whole body, dynamic isotonic contractions and the task requirements for the performance of the 2 minute elbow flexion task which involved an isometric, maximal, elbow flexion task. Hence, the stimuli for inducing cortical changes (neural plasticity) lacked specificity to the 2 minute
isometric elbow flexion task (Gandevia, 2001). The transferability of the muscular strength gains associated with a whole body dynamic resistance training program as performed by study participants and sustained, isometric based elbow flexion testing protocol may not be possible. Indeed, Sale et al., (1992) reported no change in maximal voluntary isometric knee extension strength following 19 weeks of dynamic-based resistance training, despite large improvements in 1RM leg press strength (P<0.01). The resistance training program involved three sets of between 10-20 repetitions (based on the participants’ repetition maximum) performed thrice-weekly. Others have reported significant increases in maximal strength capacity using dynamic isotonic (horizontal leg press) and isometric (leg extension) assessment protocols following a dynamic-based resistance training interventions (Latella et. al., 2012). These results indicate that the adaptations that occur within the corticospinal tract are likely to be task specific and thus the principle of specificity must be considered when designing appropriate neuromuscular testing protocols for investigating resistance-based interventions in this population.

From a functional perspective, muscular strength and resistance to neuromuscular fatigue are important, as they are essential for the performance of habitual daily activities such as walking and stair climbing (Behm & St-Pierre, 1998). As most activities of daily living involve dynamic isotonic (concentric and eccentric) contractions, an isotonic based resistance training program is advocated for improving muscular strength capacity in chronic disease populations, including post-treatment cancer related fatigue survivors (Hayes et. al., 2009; Schmitz et. al., 2010). Future investigations may consider implementing an isometric or mixed
isotonic/isometric based training intervention to observe possible
neuromuscular adaptations. A study investigating the combine effects of
dynamic isotonic and isometric seated knee extension exercises following
six weeks of training reported a small (2%) but statistically significant
increase in the CAR of the quadriceps in both young and older men after
training (Knight & Kamen, 2001).

Moreover, the training intervention include only one elbow flexion
task hence a greater volume of specific elbow flexion loading and duration
of contraction may be required in order for observable changes to be found
during the performance of the 2 minute task. Alternatively, a longer training
intervention period may offer greater period for which changes in neural
plasticity could occur.

### 7.4.6.2 Central Activation Ratio

The magnitude of the superimposed twitch increased during the 2
minute task before and after training for all groups. This indicates a reduced
ability to produce optimal drive from the motor cortex, suggesting that the
reductions in maximal torque observed during the task were in part due to
centrally based factor at a site at or above the motor cortical output (Hunter
et. al., 2008). This finding is consistent with reports of limited change in
voluntary activation following resistance training in healthy participants
(Shield & Zhou, 2004). A small number of investigations have reported
statistically significant improvements in voluntary activation following
resistance training involving the quadriceps femoris (Knight & Kamen,
2001) and ankle plantar flexor (Knight & Kamen, 2001) muscles. However
comparable results have not been demonstrated in the biceps brachii
(Herbert & Gandevia, 1999a). The limited changes observed for CAR and EMG
MDF data from this study indicates that resistance training did not
appear to greatly influence supraspinal fatigue developed during the
sustained contraction and that persistent fatigue related to cancer and its
treatment does not appear to have diminished any training induced
performance adaptations of the PTCa.

The complexity of the training intervention for the current
investigation may not have provided a larger enough stimulus to induce
changes in cortical plasticity. It has been suggested that corticospinal
excitability may be unchanged following a period of resistance training due
to low task complexity (Kidgell et al., 2010). It is possible that more
complex resistance based interventions involving dual task and/or cognitive
based activities may be required in order for clinically significant changes in
cortical voluntary activation to be discernible using acute isometric
laboratory based fatigue inducing task involving the elbow flexors. For
example, Perez et al., (2006) investigating corticospinal adaptations
following a training intervention consisting of a visuo-motor tracking task
involving the ankle muscles which emphasised a large degree of attention
and precision. The author reported significant improvements in corticospinal
input to spinal motoneurones. Similarly, following a 4 weeks’ ballistic
strength training intervention involving acceleration and deceleration forces
of the tibialis anterior muscles significant increases in corticospinal
excitability were reported (Beck et. al., 2007). These findings highlight the
importance of adequately challenging the nervous system by incorporating
sufficiently complex motor tasks and skill based movements that stimulate
processes involved in sensorimotor integration between cortex and muscle into resistance training programs (Kidgell et. al., 2010).

7.4.6.3 Cortical Silent Period

Cortical silent period is a characteristic interruption in EMG signal that occurs following the delivery of the TMS pulse, resulting from a temporary interruption of corticomotor output (Sacco et. al., 1999). When suprathreshold TMS stimulation is delivered to the M1 of healthy persons during a voluntary isometric contraction a SP lasting up to several hundred milliseconds is observed (Taylor & Gandevia, 2001; Furzer et. al., 2012). Previous research indicates that the length of the SP increases during the performance of sustained maximal contractions (Taylor & Gandevia, 2001). The underlying mechanisms responsible for this phenomenon are not well understood, although it is generally agreed that spinal mechanisms, for example Renshaw inhibition, account for the initial portion of the SP (50–100 ms), whereas the latter is explained by reduced excitability of the M1, known as cortical inhibition (Chen, Lozano, & Ashby, 1999). The duration of SP can be used an index of the strength or time course of corticospinal inhibitory function at the time of the stimuli (Macdonell et. al., 2001).

The average duration of the silent period in the current investigation was ~200 ms. We found SP to be significantly shorter in HEx (185 – 188 ms) and CON (176 -178 ms) compared to PTCa (243 – 244 ms) before training during the 2min task at 65 and 85 sec. After training SP was significantly shorter in the CON compared to PTCa across all consecutive time points during the 2min task, however, no difference was observed between the HEx compared to PTCa after training. It has been proposed that
SP reflects GABA receptor function mediated by dopaminergic processes (Farzan et al., 2013). A prolonged SP duration may be regarded as results of an imbalance in cortical excitability toward a state of enhanced inhibition (Grippo et al., 2005) via increased GABAergic mechanisms (Chen, 2000). The silent period duration increases during fatiguing exercise, indicating that there is a build-up of intracortical inhibition that may limit central motor drive (Sacco et al., 1999). It is not known whether SP reflects impairment of the inhibitory processes involving the stimulated M1, or within other motor-related areas and/or non-motor regions (Farzan et al., 2013). Sensory input from the peripheral system is one potential mechanism underlying the increased inhibitory input to M1. This may occur via the activation of small-diameter (groups III and IV) muscle afferents (Tanaka & Watanabe, 2012), that are sensitive to noxious mechanical and chemical stimuli. However, current understanding of the actions of these fatigue-sensitive afferents to M1 is contentious (Taylor & Gandevia, 2008).

The longer SP before training in the PTCa compared to the HEx may provide some evidence of greater deficits in central motor drive (central fatigue). Abnormally long SP durations have been observed in other patient populations including depression, obstructive sleep apnoea disorder, Huntington’s disease and epileptic disorders when compared to healthy persons (Macdonell et al., 2001; Farzan et al., 2013). Interestingly, health conditions with characteristics fatigue symptoms including chronic fatigue syndrome, fibromyalgia and Parkinsonism have been found to have shorter SP duration compared to healthy persons (Priori et al., 1994; Sacco et al., 1999; Farzan et al., 2013). Similarly, old adults have been reported to have shorter SP duration compared with young counterparts (Hunter et al.,
Paradoxically, it has been reported that decreased psychological stress, anti-psychotic medications, meditation and cognitive behavioural therapy are associated with SP lengthening (Santa Mina et. al., 2014).

As resistance training improved self-reported fatigue symptoms in PTCa as measured using the ECROTC fatigue subscale following resistance training, with no concomitant change in SP after training the underlying basis for this finding is unclear. However, the absence of difference in SP duration between PTCa and HEx after training suggests a possible improvement in cortical drive to muscle during a maximal fatiguing elbow flexion task in the PTCa. As no previously published studies have investigated SP in a fatigued cancer population it is not known whether these findings are consistently observed across CRF sub-populations. Overall, the combined SP and twitch interpolation data provide some support for increased central fatigue originating upstream of the motor cortex.

Further TMS investigations using paired pulse techniques to investigate short and long interval cortical inhibition could be used to confirm these observations. Paired-pulse TMS stimulation is a technique that provides two stimuli at different time intervals, a conditioning response (initial stimulus) and a test response (subsequent stimulus) which can be used to quantify corticospinal inhibition and facilitation processes (Liepert et. al., 2005). The test responses are compared to the conditioned responses: if the amplitude of the test responses is enhanced, facilitation is indicated; conversely when responses are diminished inhibition is thought to be present. Functional magnetic resonance imaging (fMRI) studies can be used to investigate how far throughout the motor network fatigue related
processes might extend and whether areas not directly involved with movement might also be influenced.

### 7.4.6.4 Root Mean Square

Root mean square is a widely utilised technique which provides a measure of EMG signal amplitude (Arabadzhiev et. al., 2010), reflecting the mean power of the signal (Enoka, 2008). EMG\textsubscript{RMS} can provide information about number and location of active motor units, recruitment of motor units and shape of motor unit action potentials (Ahmadi et. al., 2007). We found EMG\textsubscript{RMS} decreased in all groups between 0 sec and 45 sec, 65, 85, 105 and 120 sec during the 2 minute task; however this was not observed after training. This finding is consistent with previous studies in which EMG\textsubscript{RMS} decreased during the performance of maximal sustained voluntary contractions of the biceps brachii (Rainoldi et. al., 1999). As EMG\textsubscript{RMS} offers information relating to the net motor unit activity (Farina et. al., 2004), the decrease on EMG amplitude suggests a reduction in motor unit activity over the duration of the task. This may be due to alterations in the pattern of motor units’ activation strategy, attributed to changes in motor unit firing rate, synchronisation of motor units and the duration of the contributing action potentials (Farina et. al., 2004). This may represent a protective mechanism aimed at preventing conduction failure in order to optimise input to motor units as their contractile properties changes.

### 7.4.6.5 Median Frequency

Surface EMG can be used to indicate changes in recruitment pattern of skeletal muscle motor units (Gandevia, 2001). EMG represents the
electrical potentials generated by the contracting muscle, which provides both temporal and frequency information regarding neural drive to the contracting muscle (Gandevia et. al., 1996). Median frequency is considered a gold standard measurement, used to determine changes in the power spectrum content of EMG signals (González-Izal et. al., 2012). EMG power spectrum is divided into two regions of equal amplitude. MDF is defined as a half of the total power (quantified by dividing the total power area into two equal parts (Phinyomark et. al., 2012).

We found a decrease in EMG\textsubscript{MDF} signal over the duration of the task, before and after training for all groups. This supports previous studies demonstrating a decrease in EMG\textsubscript{MDF} activity during the performance of maximal isometric tasks, resulting in a slowing of EMG signal, associated with a shift of the frequency spectrum to lower frequencies (González-Izal et. al., 2012). Due to the comparable pattern of EMG\textsubscript{MDF} during the task performance between the groups both before and after training, it appears that resistance training had little effect on neural drive as measured with surface EMG. This is consistent with the lack of significant change observed in muscular force production and/or voluntary activation during the task before and after training. Hence evidence suggestive of neural adaptations with the resistance training intervention has not been observed in the present investigation.

7.5 Conclusion

In conclusion, 12 weeks of resistance training positively improved persistent fatigue symptoms in post-treatment cancer survivors compared to health women. Our results provided some evidence of comparable
neuromuscular manifestations of fatigue associated with an exercise-induced fatigue between cancer survivors and healthy women. We found some evidence of longer SP duration associated with a 2 minute sustained maximal isometric task involving the right elbow flexors before resistance training in cancer survivors compared to health women providing evidence of greater cortical inhibition. Further studies should investigate possible inhibitory mechanisms associated with changes in SP through the use of a paired pulse TMS protocol.
8 CONCLUSION

8.1 Overview

The aim of this thesis was to examine the neuromuscular mechanisms contributing to self-reported post-treatment cancer fatigue and the effect of resistance training exercise in ameliorating fatigue symptoms. This chapter provides a summary of the research findings presented, general conclusions to the research questions, practical applications to the research findings and outlines areas of future research.

8.2 Summary and Conclusion of the Research Findings

Collectively the findings presented within this thesis have intended to provide new knowledge and understanding including: the accuracy of the proposed complex model of cancer-related fatigue within a sample of disease-free post-primary treatment cancer survivors; possible links between cancer-related fatigue and altered functioning of central (neural) processing, using an exercise-induced fatigue model to investigate the neuromuscular pathways; the effect of resistance training exercise as a stand-alone intervention in ameliorating fatigue symptoms, and the physiological and neuromuscular adaptations in post-treatment cancer survivors, with persistent fatigue compared to healthy women.

The first objective of this thesis was to provide preliminary evidence regarding the accuracy of the proposed complex, multifaceted model of
cancer-related fatigue, in a sample of disease-free, post primary treatment cancer survivors. This was achieved by comparing perceived fatigue and clinical correlates associated with fatigue (depression, sleep, pain), levels of circulating pro-inflammatory cytokines, aerobic exercise capacity, and neuromuscular function between disease-free, post primary treatment cancer survivors and healthy persons, and examining the associations between these variables using basic correlation analyses.

The PTCa experienced higher self-reported fatigue symptoms, depressive symptoms and poorer sleep quality scores compared to HW. This finding is consistent with previous literature and provide evidence to support the complex model of cancer-related fatigue under investigation, in which dysfunction in sleep and depression are associated with the presence of cancer fatigue. Systemic inflammatory markers were not found to be different between PTCa and HW. This finding diverges from previous reports of elevated systemic inflammation in this population and does not support the suggestion of pro-inflammatory signaling within the CNS, triggering behavioral changes such as fatigue, sleep disturbance, and depressive-like symptoms, as per the model of cancer-related fatigue. Although data regarding elevated inflammatory markers in this population varies greatly between studies. The lack of observed differences were most likely due to technical issues experienced during the analysis of blood. Alternatively, this finding may have been due to a lack of specificity in the inflammatory markers investigated as CRP, IL-6 and TNFα do not necessarily reflect levels in the brain where the symptoms of cancer fatigue are likely to originate.
Physical capacity and neuromuscular performance were similar between the PTCa and HW, as evidenced by comparable aerobic power index and VO$_{2\text{peak}}$ measures recorded during a submaximal aerobic capacity test and MVT performance during an acute maximal voluntary contraction involving the elbow flexors. These findings diverge from the proposed model in which cancer-fatigue is associated with reduced physical capacity and impaired neuromuscular function via physical inactivity and resultant deconditioning. This was unexpected as an association between cancer fatigue, physical inactivity, deconditioning and reduced physical function is frequently reported in cancer patients. The current research specifically measured indices of physical capacity and not physical activity levels; these represent related but separate domains of physical function. As such, reduced physical capacity does not imply an automatic reduction in physical activity levels. Although this outcome was unexpected, the present findings are in agreement with previous data in which absolute and relative VO$_{2\text{peak}}$ as well as peak aerobic power during a maximal cycling test were not significantly different between fatigued and non-fatigued breast cancer survivors. Based on the current evidence, aerobic deconditioning and MVT performance during an acute maximal voluntary contraction may be excluded as potential factors contributing to the persistent fatigue symptoms experienced by the current sample of PTCa. This suggests that persistent fatigue, at least in some cancer survivors, may exist independently from impairments in physiological performance. As such it appears that the higher level of perceptual fatigue experience is not due to peripheral based physical factors rather cortical-subcortical factors may be involved. It is plausible that the MVT and submaximal cycle tasks included in this study
were not of sufficient intensity to permit relationships between fatigue and physical performance to be observed (or different relationships may occur during different tasks conditions) in the current sample of moderately fatigued cancer participants. Alternatively, the current group of PTCa, represented a sample of reasonably healthy, high functioning post-treatment cancer survivors with fatigue. Although the PTCa reported higher self-reported fatigue than the HW, the fatigue scores were within the lower cut-off limits for clinically relevant fatigue. This may be due to the PTCa experiencing moderate levels of fatigue severity, which was not of a large enough magnitude to impact greatly upon physical capacity and performance.

Associations between the aforementioned variables were also examined. Novel findings included significant associations between CRP and VA in cancer survivors, which suggests the possibility of an association between cortical-subcortical factors and a higher level of perceptual fatigue in post treatment survivors. In addition, significant associations between CRP and VO\textsubscript{peak}, CRP and EMG and between BD-II and EORTC when pooled across groups were found. However, due to the cross-sectional research design, and the small sample size, the direction of causality between these variables cannot be determined with certainty.

Collectively, these findings suggest that despite comparable physical performance, the perceptual fatigue experience appears to be more intense in post-treatment cancer survivors, suggesting that cortical-subcortical factors rather than peripheral based physical factors may be involved. Evidence regarding the accuracy of the proposed complex, multifaceted model of cancer-related fatigue was mixed. Support for the model of cancer-
related fatigue included higher depressive symptoms and poorer sleep quality scores in the cancer survivors; however limited evidence exists for an association between elevated pro-inflammatory markers and impaired physical performance with cancer fatigue.

The second objective of this thesis was to investigate the central neuromuscular pathways as a potential contributor to persistent fatigue symptoms in cancer survivors. This was achieved by comparing the acute neuromuscular manifestations associated with a 2-min sustained maximal voluntary isometric contraction task involving the elbow flexors between PTCa and HW. Support for this approach comes from a proposed model of cancer-related fatigue in which the neuromuscular system is implicated as a possible contributor to the genesis of fatigue symptoms.

The contribution of central motor mechanisms to the progressive development of fatigue before, during and after the sustained maximal voluntary contraction task were highly comparable between the PTCa and the HW as evidenced by equivalent declines in MVT, surface EMG signals and superimposed twitch responses to TMS during exercise and higher La-concentrations after exercise between the groups. Similarly, the level of corticomotor activation (descending neuromotor drive) after exercise were similar to before exercise values in both groups. Together these findings suggest that the motor pathways are not likely involved in the manifestation of fatigue. This finding was somewhat unanticipated, although, previous evidence regarding the contribution of central mechanisms to cancer fatigue are conflicting. Current findings are in agreement with several prior studies demonstrating comparable motor pathway function between fatigued and non-fatigued cancer survivors; however, others studies have conversely
provided evidence of altered central processing in this population. The previous studies have relied on peripheral electrical stimulation techniques including twitch interpolation and central activation ratio to assess voluntary activation, which do not permit the differentiation between spinal and supraspinal components of central fatigue to determine the location of central motor drive impairment. The current investigation used TMS to assess voluntary muscle activation, which offers greater insight into potential sites contributing to impaired central motor drive, although no such evidence was observed. The only evidence for central mechanisms was a longer cortical SP duration after exercise in the PTCa compared to HW, providing possible evidence of cortical inhibition occurring upstream of the corticospinal motor neuron pool. As this is the first study to use TMS to assess the motor pathway of cancer survivors with persistent fatigue symptoms, further investigations to confirm this observation and to determine the underlying cause are required. This provides additional evidence that supraspinal factors are involved in cancer-related fatigue.

Accordingly, these findings provide limited support for impairments in neuromuscular function, suggesting that the motor pathways are not likely involved in the manifestation of fatigue. Such findings provide further evidence to suggest that the underlying pathophysiological mechanisms contributing to the increased self-reported fatigue in post-treatment cancer survivors may be more related to alterations in perception rather than impaired sensory-motor function. It is important to note that these findings are only generalizable to the current exercise based model under investigation. As neuromuscular fatigue is task dependent, other exercise based tasks and/or muscle groups may demonstrate different outcomes.
Therefore, it is not known whether other fatigue tasks produce similar findings in post-treatment cancer survivors with persistent fatigue symptoms.

The third objective of this thesis was to examine the physiological and neuromuscular adaptations to 12 weeks resistance training in post-treatment cancer survivors compared to healthy women. This was achieved by comparing the effects of a 12-week program of resistance training on muscle mass, muscular strength, and acute neuromuscular manifestations before and after training between PTCa with persistent fatigue symptoms and HW.

Improvements in right arm lean mass were found in those who undertook 12 weeks of resistance training; however no effect on total body lean mass, or fat mass were evident in either the cancer fatigue or the healthy group. This was somewhat unexpected as previous literature indicates that resistance training for a duration of 12 weeks may lead to increases in total body lean mass, and decrease in fat mass; although results regarding this are mixed. Although changes in total body composition were not found the resistance training positively improved cancer survivors’ functional-based muscular strength capacity over the 12 week training period.

1RM values were significantly higher in the HW compared to PTCa prior to commencing resistance training; however by week 8 of the training program 1RM values were comparable between the PTCa and HW. Current findings are in agreement with previous research reporting improvements in muscular strength with resistance training. Such findings provide additional evidence for advocating resistance training as an exercise intervention for
post-treatment cancer survivors, with persistent fatigue symptoms. Interestingly the increases in 1RM data were not paralleled by improvements in clinical based measurements of voluntary force production (MVT). A possible explanation may be the lack of specificity between the resistance training exercises and the assessment techniques employed; the resistance training program consisted of dynamic isotonic based exercises performed on pin loaded equipment and the MVT assessment consisted of an isometric contraction performed on an isokinetic dynamometer.

No effect on normalised force per unit of right arm mass in both the cancer fatigue and the healthy group were found in those who undertook resistance training. As such the increase in right arm lean mass was unlikely to have contributed to the increases in muscular strength observed. This is an important finding as whether the post-treatment cancer survivors improvements in ability to lift heavier loads (1RM) is due to muscle based, neural based and /or perceptual based factors has not been previously reported. This evidence indicates that most of the early adaptations in muscular strength upon commencing a resistance based program is likely to be of central (neural) origin.

A novel finding included increases in training intensity with maintenance of total training volume over the 12 week resistance training program having little effect on increasing isometric muscle based strength beyond the initial 4 weeks training period. Although this finding aligns with previous research demonstrating large neural adaptations early on following the commencement of a resistance based training program with reduced rates of improvement following the initial 4 week training period. More research into the possibility of an effect of training volume versus intensity
should be examined further to assist in establishing optimal resistance training guidelines for exercise prescription for this population. Together these findings provide evidence that 12 weeks of resistance training is well tolerated by post-treatment cancer survivors and that they are capable of performing resistance exercise at a sufficient intensity to stimulate physiologic adaptation in muscle strength. Collectively, resistance training for 12 weeks appears to induce similar functional and clinical neuromuscular adaptations in untrained women with a history of cancer and treatment compared to HW.

The fourth objective of this thesis was to examine the effect of 12 weeks resistance training, as a stand-alone intervention, in ameliorating fatigue symptoms and mechanisms by which resistance training may ameliorate persistent fatigue symptoms in post-treatment cancer survivors compared to healthy women. This was achieved by comparing the effects of a 12-week program of resistance training on persistent fatigue symptoms and neuromuscular manifestations associated with an exercise-induced fatigue task before and after training between PTCa with persistent fatigue symptoms and HW.

A major finding included positive improvements in persistent fatigue symptoms in post-treatment cancer survivors, indicating that short-term (≤12 weeks) resistance training is an effective exercise-based intervention for this population. Presently limited evidence supports the effectiveness of resistance training as a stand-alone modality for reducing cancer fatigue; although strong evidence for aerobic-based exercise exist. This is partly due to few published resistance training only studies, with the majority of previous work focusing on aerobic and or mixed modality interventions. As
such, the current findings expands upon the current literature base supporting the effectiveness of resistance training as a stand-alone intervention. It is anticipated that this finding will help to inform clinical practitioners working with fatigued post-treatment cancer survivors regarding resistance training being an appropriate and effective exercise based invention.

The neuromuscular manifestations of fatigue associated with an exercise-induced fatigue task following 12 weeks of resistance training were comparable between PTCa and HW. This finding supports the previous thesis findings in which neuromuscular mechanisms do not appear to be associated with cancer-related fatigue in post-treatment cancer survivors with persistent fatigue. This is the first study to investigate the neuromuscular manifestations of fatigue associated with an exercise-induced fatigue following resistance training in this population; as such further investigations are required to confirm this observation. No evidence was found to suggest that resistance training had an effect on cortical VA following the 12 weeks, indicating that neuromuscular functioning was not altered as a result of resistance training. Accordingly, these findings suggest that the cancer fatigue group did not have an impaired level of cortical activation. Alternatively, the isotonic-based resistance training program was not specific enough to induce such changes in the isometric-based assessment techniques used within this thesis. Additional investigations may need to focus on neuromuscular performance under different task conditions, due to the task specific nature of the development and manifestations of fatigue. Some evidence of increased cortical silent period duration were found to be associated with a 2 minute sustained maximal
isometric task involving the right elbow flexors before resistance training in the PTCa compared to HW, providing evidence of possible cortical inhibition. Until additional studies are undertaken to assess the motor pathway using TMS in this population, this finding will remain unconfirmed and the underlying mechanisms unknown.

In conclusion, the findings from the four studies included within this thesis indicate that the post-treatment cancer survivors experienced higher self-reported fatigue symptoms, depressive symptoms compared to HW. The acute physical performance is comparable to HW. Such findings were not supportive of the complex model of cancer fatigue, involving elevated inflammatory markers, physical inactivity, and impaired neuromuscular function. This may be due to the moderate severity of fatigue experienced by post-treatment, cancer survivors included in this research. As such the findings presented in this thesis should be applied cautiously as the participants may not have been entirely representative of the wider patient population. Evidence of impairments in neuromuscular function were not found, suggesting that the motor pathways are not likely involved in the manifestation of fatigue. Due to the greater perceptual experience of fatigue in the post-treatment cancer survivors it is possible that higher subcortical processing may be a possible contributor. Resistance training appears to induce similar functional and clinical neuromuscular adaptations in untrained women with a history of cancer and treatment compared to HW following a 12 week resistance training protocol. Fatigue symptoms are positively improved following a RT only exercise regime.
8.3 Practical Applications of the Findings

Based on the findings of this thesis, several practical applications are provided:

- From a clinical perspective, untrained post-treatment cancer survivors, with persistent fatigue symptoms, undertaking resistance training as a stand-alone intervention appear to experience improvements in fatigue and comparable, functional and clinical neuromuscular adaptations to HW following a 12 week resistance training protocol. No adverse outcomes were reported by study participants. As such, post-treatment cancer survivors, with persistent fatigue symptoms should be encouraged to participate in regular resistance training sessions.

- The findings from this thesis support the application of existing resistance training guidelines for healthy older adults and guidelines for cancer survivors, as applied within this research.

- Given that positive musculoskeletal adaptations, including increased muscular strength and right arm lean mass, were observed following the 12 week exercise program, resistance training has the potential to have a meaningful impact on reducing risk factors associated with developing long-term musculoskeletal side-effects associated with cancer and/or its treatment including muscle sarcopenia, osteoporosis and the number of falls. As such resistance training should be considered as a suitable intervention for post-treatment
cancer survivors, with persistent fatigue symptoms for these additional health-related outcomes.

- Comparable physical performances were observed; however the perceptual fatigue experience appears to be more intense in post-treatment cancer survivors, with persistent fatigue symptoms. This suggests that persistent fatigue in some cancer survivors may exist independently from impairments in physiological performance and that physical performance indices alone should not direct clinical treatment or decision making.

- From a research perspective, the neuromuscular exercise-induced fatigue model used within this research, did not find any evidence of any links between cancer fatigue and alterations in the function of central (neural) processing via investigating the neuromuscular pathways. This suggests that the motor pathways are not likely involved in the manifestation of fatigue. As such, other avenues should be explored, as described on the future research direction section.

- However, due to limitations in the research design and moderate levels of fatigue reported by the cancer survivors these findings may not apply to other post-treatment cancer survivors.
8.4 Future Research Directions

Based upon the current thesis findings a number of future research directions have been proposed.

- Comparable physical performance were observed; however the perceptual fatigue experience appears to be more intense in post-treatment cancer survivors, with persistent fatigue symptoms. This suggests that persistent fatigue in some cancer survivors may exist independently from impairments in physiological performance. These results should be confirmed during other performance tasks, such as a sustained maximal contraction. It is possible that the MVT and submaximal cycle tasks included in this study were not of sufficient intensity to permit relationships between fatigue and physical performance to be observed (or different relationships may occur during different task conditions) in the current sample of moderately fatigued post-treatment cancer survivors, with persistent fatigue symptoms participants

- A limitation of the current research design was the use of isometric testing protocol to measures strength changes associated with an isotonic based resistance training intervention. Future investigations should consider implementing an isometric or mixed isotonic/isometric based training intervention to observe possible neuromuscular adaptations. This is important as most activities of daily living involve dynamic isotonic (concentric and eccentric) contractions.
• Limitations in the techniques used within this research to assess neuromuscular fatigue exist. As such future studies should examine subcortical processing associated with the performance of exercise induced fatigue tasks using other central neurophysiological techniques including a combination of EEG, paired pulse TMS and FMRI imaging. This will assist in determining whether the fatigue experienced by cancer survivors is related to impairments in central (neural) processing.

• Studies should investigate possible inhibitory mechanisms associated with changes in CSP through the use of a paired-pulse TMS protocol, to assess intracortical facilitatory and inhibitory properties by combining a conditioning stimulus and a test stimulus at different interstimulus intervals and investigate cortical mechanisms upstream to the corticospinal motor neuron that may be associated with central fatigue and sense of effort during and after a fatigue task.

• Significant associations between CRP and cortical VA in post-treatment cancer survivors, with persistent fatigue symptoms group is highly suggestive of association between cortical-subcortical factors and higher level of perceptual fatigue in post treatment survivors. Further research is needed to confirm such associations.

• Given the complex nature of cancer-related fatigue, concurrent appraisal of neural, endocrine, and immune biomarkers may help inform the design of more effective exercise based interventions and
understanding of the mechanisms by which these interventions act and how successful they are in altering the endocrinologic and immunoregulatory aspects of fatigue.

- Evidence suggests that the symptom of cancer-related fatigue appears to be greater than the normal sense of effort for any given task. In order to provide a more systematic evaluation of the perceptual difference observed between cancer survivors with fatigue and healthy participants, proceeding investigations should consider the inclusion of perceptual scales such as RPE or VAS to be collected during the neuromuscular testing session including measurements taken before, during and after the exercise-induced fatigue exercise.

- As the underlying mechanisms involved in cancer fatigue are complex and that no one questionnaire is currently capable of capturing concurrently all the complexities of this phenomenon, future studies should consider the use of multiple self-report fatigue questionnaire in order to gain a holistic measurement of fatigue.

- The symptoms of fatigue is known to vary throughout the day and at present all available self-report instruments are limited to capturing information from one time point, further studies should consider using an ecological momentary assessment approach, in which data is collected several times a day, over several days to assist in conforming the level of fatigue.
• While the fatigue assessments instruments used within this research were considered as being psychometrically valid and reliable, their clinical significance remains unclear. Further research should establish thresholds to define clinically significant fatigue levels for commonly used fatigue questionnaires. This will assist future studies examining exercise interventions aimed at reducing cancer-related fatigue when interpreting their results in the context of clinical significance.

• Although the current sample of cancer survivors reported higher self-reported fatigue than the HW, the fatigue scores were within the lower limits of cut-off scores for clinically relevant fatigue. As such they were not considered to be experiencing severe levels of fatigue. Future studies investigating cancer-related fatigue should aim to recruit a large sample size to enable comparison across sub-groups of participants based on discrete levels of cancer fatigue (low/moderate/high).

• The current findings indicate that the early-phase adaptations to the resistance training program were comparable between the post-treatment cancer survivors with fatigue and HW. Due to the limited training duration of 12 weeks, it is not currently known what the longer term adaptations are or whether this may lead to adverse side-effects such as overtraining. Future studies should investigate the longitudinal (>12 weeks) effect of resistance training on fatigue and overall health, adaptations to resistance training.
• The novel finding that increases in training intensity without an increase in total training volume load in untrained cancer survivors during a 12 week progressive resistance training program was not associated with an increase in isometric strength beyond the initial 4 weeks of training suggests that the total volume load of exercise performed may be important. Future studies should investigate the effects of manipulating the training volume load interaction in stimulating adaptations in isometric strength in post-treatment cancer survivors with fatigue. This knowledge may assist in establishing optimal resistance training guidelines for exercise prescription for this population.

• Previous research has provided strong support for the use of aerobic training for improving self-reported fatigue in cancer survivors; however few studies have examined the effects of resistance training. The findings of the current work indicate that resistance training can have a positive effect on self-reported fatigue. As such, future work should explore possible differences between resistance compared to aerobic based training and the possible benefits derived from mixed exercise-based training programs to determine the combined effects of both training modalities on improvements in fatigue and neuromuscular function.

• Prospective resistance training intervention studies should include outcome measures that aim to elucidate the mechanisms by which resistance training yields its effect, such as longitudinal observations of changes in immune system activation and function. Where
possible measurements should go beyond measuring circulating cytokines, as serum or plasma levels of cytokines do not necessarily reflect levels in the brain where the symptoms of cancer fatigue likely originate.

• One major drawback of the current research was the use of a convenience recruitment strategy. Although there was no reason to suspect a systematic bias in participant recruitment, it is possible that the study subjects were not entirely representative of the wider clinical population. Future studies should considered using randomised approach and ensuring that the control participants are age-matched to the cancer fatigue participants.

• Finally, future research should focus on cancers other than breast cancer and there is a need for higher quality randomised controlled trials with larger sample sizes and increased duration of follow-up measures.
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APPENDICES
Appendix A

Human Ethics Approval Letter
22 December 2011

Ms Danielle Girard
Allen House (N1)
School of Human Movement Studies
BATHURST CAMPUS

Dear Ms Girard,

Thank you for the additional information forwarded in response to a request from the Human Research Ethics Committee (HREC).

The CSU HREC reviews projects in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Research Involving Humans.

I am pleased to advise that your project entitled “A Comparison Of The Physiological, Neuromuscular, Perceptual And Performance Adaptations During Different Exercise Fatigue Tasks And Following 12 Weeks Between Disease-Free Breast Cancer Survivors With Post Cancer Fatigue And Healthy Matched Persons” meets the requirements of the National Statement; and ethical approval for this research is granted for a twelve month period from 22/12/2011.

The protocol number issued with respect to this project is 2011/173. Please be sure to quote this number when responding to any request made by the Committee.

Please note the following conditions of approval:

- all Consent Forms and Information Sheets are to be printed on Charles Sturt University letterhead. Students should liaise with their Supervisor to arrange to have these documents printed;
- you must notify the Committee immediately in writing should your research differ in any way from that proposed. Forms are available at www.csu.edu.au/research/committees/human/forms/ehrc_amnrep.doc;
- you must notify the Committee immediately if any serious and or unexpected adverse events or outcomes occur associated with your research, that might affect the participants and therefore ethical acceptability of the project. An Adverse Incident form is available from the website; as above;
- amendments to the research design must be reviewed and approved by the Human Research Ethics Committee before commencement. Forms are available at the website above;

Version 2

FIA

www.csu.edu.au

CRICOS Provider Numbers for Charles Sturt University are 00005F (NSW), 019473 M (VIC) and 029006D (ACT). ABN: 83 878 706 651
• if an extension of the approval period is required, a request must be submitted to the Human Research Ethics Committee. Forms are available at the website above;
• you are required to complete a Progress Report form, which can be downloaded as above, by 22/12/2012 if your research has not been completed by that date;
• you are required to submit a final report, the form is available from the website above.

You are reminded that an approval letter from the CSU HREC constitutes ethical approval only.

If your research involves the use of radiation, biological materials, chemicals or animals a separate approval is required from the appropriate University Committee.

The Committee wishes you well in your research and please do not hesitate to contact the Executive Officer on telephone (02) 6338 4628 or email ethics@csu.edu.au if you have any enquiries.

Yours sincerely

Julie Hicks
Executive Officer
Human Research Ethics Committee
Direct Telephone: (02) 6338 4628
Email: ethics@csu.edu.au
Cc: Dr Jack Cannon

Version 2
Appendix B

Information Sheet
Information Sheet

A Comparison Of Neuromuscular Performance, Fatigue Responses, Musculoskeletal Health, And Health-Related Quality Of Life Between Cancer Survivors And Healthy Matched Persons And The Effect Of 12 Weeks Of Resistance Training

Thank you for expressing interest in this research. Please read and retain this information sheet. Should you have any questions regarding this study the Chief Investigator and Research Supervisor may be contacted at the following:

Principal Investigator (PhD Student) Research Supervisor
Miss Danielle Girard Dr Jack Cannon
School of Human Movement Studies School of Human Movement Studies
Allen House, N1 Allen
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Panorama Ave Panorama Ave
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6338 4065
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Research Project Summary
This research project aims to examine the science behind resistance training during post treatment cancer survivorship by investigating the effect of resistance training on Fatigue Responses, Musculoskeletal Health, and Health-Related Quality Of Life in four groups of participants including: 1) disease-free, post primary treatment cancer survivors; 2) post primary treatment cancer survivors with fatigue symptoms and; 3) healthy matched persons 4) non-exercising control group.

Participant Inclusion Criteria:
Disease-free, post primary treatment cancer survivors (this may include persons receiving ongoing endocrine therapies who are not considered to have active disease).
Disease-free, post primary treatment cancer survivors with fatigue symptoms (this may include persons receiving ongoing endocrine therapies who are not considered to have active disease).

Healthy matched persons.
- Aged between 40-85 years
- No current musculoskeletal, metabolic, or cardiovascular conditions
- Commit to resistance training exercise: 3/wk x ~45 min for 12 weeks
- Non-exercise control group
- Aged between 40-85 years
- No current musculoskeletal, metabolic, or cardiovascular conditions
- Continue normal physical activity and nutrition patterns for 12 weeks.
Following the completion of data collection, participants within the control groups will be invited to attend the CSU gymnasium to commence an individually tailored resistance exercise training program.

**Data Collection will involve:**
- Body composition
- Strength testing
- Aerobic capacity testing
- Neuromuscular and Fatigue measurements
- Blood sampling

**Expectations of Research Participants**
If you agree to participate in this study you will be required to attend:

**Exercise Group**
- 1 x Sub maximal aerobic capacity test (~45 minutes)
- 1 x Familiarisation session (~2 hr)
- 2 x Pre-training data collection sessions (~1.5 – 2 hrs each session)
- 36 x Resistance training sessions (~45 - 60 minutes each session)
- 2 x Post-training data collection sessions (~1 - 1.5 hrs each session)

**Non-Exercise Group**
- 2 x data collection sessions conducted 12 week apart (~3 - 4 hrs each session)
**Participant Benefits:**

Comprehensive health screening appraisal, providing information regarding risk of developing secondary health conditions (e.g. heart disease, diabetes, body composition, etc). Improve fatigue responses, quality of life, and musculoskeletal health including: increase bone mineral density and fat free mass, reduce fat mass and increased muscular strength.

We invite you to participate in this exciting research project.
Purpose of the Research
The primary purpose of this research is to compare neuromuscular performance, exercise-induced fatigue responses, musculoskeletal health, and health-related quality of life (HRQOL) and examine the effect of 12-weeks of resistance training between three (3) participant groups:

1. Disease-free post primary treatment cancer survivors, aged 40-85 years.
2. Disease-free post primary treatment cancer survivors with cancer fatigue symptoms, aged 40-85 years.
3. Healthy matched persons, aged 40-85 years.
4. Control group, aged 40-85 years

An additional purpose is to compare the reproducibility of neuromuscular performance and the exercise-induced fatigue response between the three (3) aforementioned participant groups.

Specifically, the aims of this study are to:

- Examine the reproducibility of neuromuscular performance and exercise-induced fatigue responses between participant groups;
- Compare neuromuscular performance, exercise-induced fatigue responses, musculoskeletal health, and HRQOL between participant groups.
- Compare the magnitude of resistance training-induced neuromuscular and musculoskeletal adaptations and effects on HRQOL between participant groups.
- Compare the effect of resistance training on the neuromuscular responses to exercise-induced fatigue and recovery between participant groups.
Background

Previous literature indicates that exercise is one of only a few interventions demonstrating significant efficacy in reducing cancer and/or treatment related side-effects, including reducing fatigue symptoms, increasing HRQOL, and improving overall physical performance in disease-free post-treatment cancer patients.

Exercise-related intervention studies demonstrating improvements in functional status and fatigue symptoms of cancer survivors have focused mostly on the benefits of aerobic and/or mixed aerobic and resistance training modalities. Knowledge of whether resistance training exercise alone can improve neuromuscular performance, musculoskeletal health and HRQOL and/or reduce fatigue symptoms in disease-free post-treatment cancer survivors, including those with fatigue symptoms, is not presently known. This study aims to generate new knowledge regarding these issues, which may contribute to better informing health care professional regarding the most appropriate form of exercise therapy for post primary treatment cancer survivors.

Furthermore, limited evidence-based recommendations exist regarding the prescription of resistance training exercise for disease-free, post-treatment cancer survivors, including those with fatigue symptoms. Current recommendations for resistance training program for this population are based on the general guidelines for healthy persons. However, it is not known whether disease-free post-treatment cancer survivors and healthy persons experience comparable adaptations in neuromuscular performance, musculoskeletal health, fatigue responses, and/or similar improvements in HRQOL associated with chronic resistance training. Such knowledge may assist in the development of practical guidelines that can be implemented by exercise physiologists when working with cancer survivors.
Participant and Study Requirements

PRE-SCREENING
Prior to involvement, you will need to:

Complete three health related screening questionnaires including:

1. **Pre-Exercise Screening Form**
Complete a Pre-Exercise Screening form used to determine your safety or possible risk of exercising and information regarding your overall health status. As part of this screening process, you will be required to obtain a referral from your medical practitioner to a pathology clinic to undertake a full blood count analysis including fasting lipid profile and blood glucose levels. Any costs associated with the medical appointment and referral for blood analysis will be at the expense of the participant.

2. **Transcranial Magnetic Stimulation Screening Questionnaire**
Complete a standard screening questionnaire to identify any possible reason to be excluded from undertaking Transcranial magnetic Stimulation (TMS).

3. **Cancer Diagnosis and Treatment History Review**
Cancer survivors will be required to complete a detailed medical history review questionnaire to provide descriptive data related to their cancer diagnosis and treatment history.
Obtain clearance and approval to participate in the study from a medical practitioner who will be provided with a ‘GP Information Sheet’ informing them of participant inclusion and exclusion criteria.
To be eligible for inclusion:
All subjects must have no acute or chronic health conditions, nor take any medications thought likely to influence the results of the study,
such as betablockers or angiotension converting enzyme (ACE) inhibitors.

**Cancer survivors must be:**

Disease-free, post primary treatment cancer survivors (this may include persons receiving ongoing endocrine therapies who are not considered to have active disease).

- Disease-free, post primary treatment cancer survivors with fatigue symptoms (this may include persons receiving ongoing endocrine therapies who are not considered to have active disease). Cancer survivors with fatigue must also satisfy established criteria for cancer-related fatigue as stated in the International Classification of Diseases 10th Revision-Clinical Modification. Specifically, cancer survivors must experience significant fatigue, diminished energy or increased need to rest that is disproportionate to any recent change in activity level every day or nearly every day during the same 2-week period in the past month. In addition, subjects must also exercise five or more of the following symptoms;

- Complaints of generalised weakness or limb heaviness;
- Diminished concentration or attention;
- Decreased motivation or interest in engaging in usual activities;
- Experience of sleep as unrefreshing or non restorative;
- Perceived need to struggle to overcome inactivity;
- Marked emotional reactivity (e.g. sadness, frustration, or irritability) to feeling fatigued;
- Difficulty completing daily tasks attributed to feeling fatigued;
- Perceived problems with short-term memory; and/or
- Post exceptional malaise lasting several hours.
• Cancer survivors must not have a current weight loss of greater than 10% of pre-cancer diagnosis body weight, and have a haemoglobin level greater than 12 g/dL.

• Healthy persons must have no known history of cancer and/or cancer-related treatment, and have a haemoglobin level greater than 12 g/dL.

Participants may be ineligible to participate in the study if they have: clinically diagnosed depression, a clinically diagnosed sleep disorder; a history of epilepsy; a heart pacemaker; metallic implants in the eye or brain; are pregnant; and/or have a history of ingesting medications known to influence motor cortex excitability, such as antidepressants, benzodiazepines, neuroleptics, and anticonvulsants.

Expectations of Research Participants
All participants will attend the familiarisation, pre-training and post-training data collection sessions, and complete the self-report questionnaires before, during and after the resistance training period. Sessions will be conducted at Charles Sturt University, Bathurst campus in either the Exercise or Sport Science Laboratories building S21 or the Gymnasium building E1. Each visit you will need to bring comfortable clothing for exercise, including shorts and enclosed shoes. Shower and changing facilities are available for your use after each session. Cancer survivors will be encouraged to bring a support person with them to all sessions, to aid to returning home after the completion of each session.

A brief overview of the study timeline and requirements is provided in the table
### Study Timeline and Weekly Requirements

<table>
<thead>
<tr>
<th>Week -4</th>
<th>Week -3</th>
<th>Week -2</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 5</th>
<th>Week 9</th>
<th>Week 12</th>
<th>Week 13</th>
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<tbody>
<tr>
<td>Fatigue assessments</td>
<td>*Pre-training neuromuscular and fatigue assessments</td>
<td>*Pre-training neuromuscular and fatigue assessments</td>
<td>*Pre-training neuromuscular and fatigue assessments (a)</td>
<td>Resistance Training Program 3 x weekly training session</td>
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<td></td>
<td>Post-training measures</td>
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<tr>
<td>Questionnaires</td>
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<td>Questionnaires</td>
<td>1-RM assessment</td>
<td>1-RM Neuromuscular and fatigue measures</td>
<td>1-RM Neuromuscular and fatigue measures</td>
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<td>Questionnaires</td>
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<td>DXA and Anthropometric (a)</td>
<td></td>
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<td></td>
<td>DXA and Anthropometric</td>
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<td>Submaximal Aerobic Capacity</td>
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<td>Submaximal Aerobic Capacity</td>
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<td>Blood Collection (b)</td>
<td></td>
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<td></td>
<td>Blood Collection</td>
</tr>
</tbody>
</table>
FAMILARISATION
During the familiarisation session you will be familiarised with the neuromuscular assessments and perform a practice trial for the exercise fatigue task consisting of a 2 minute sustained, maximal voluntary isometric contraction of the right elbow flexors, as outlined below (session 1). Participants will undertake a practice of the exercises involved in the resistance training program. This session is expected to take ~ 1.5 hours.

PRE-TRAINING DATA COLLECTION SESSION
During the pre-training data collection period you will visit the Exercise and Sports Science Laboratories on three (3) separate occasions, performed at a standardised time of day. For these three (3) sessions you will be required to have the same lead up to each trial, including continuing your normal physical activities, sleep pattern and diet and refraining from heavy exercise and alcohol for the preceding 24 hours. We will also need you to refrain from caffeine on the day of the experiment. You will be asked to keep a record of the food and beverage consumed in the 24-hour period prior to the first data collection session and to replicate for each remaining sessions. Cancer participants are advised to bring a support person to all data collection sessions in the event that they require assistance returning home after the sessions. During the 24 hours following each session you will receive a follow up phone call by the Chief Investigator to ensure that you have adequately recovered and to provide the opportunity for any concerns to be communicated.

An overview of what to expect at each of the three (3) pre-training data collection sessions is outlined below.

**Session 1 (Week -4)**
The first pre-training data collection session will involve:
- Fatigue Rating
You will report your current fatigue levels using the brief fatigue index (BFI) and fatigue, visual analogue scale (VAS) and fatigue and recovery questionnaire.

- Capillary Blood Collection

A small sample of blood will be taken from your ear (100 μL), which will be analysed for hemoglobin (Hb) concentration. This measure will be used to indicate the condition of anaemia, defined as a haemoglobin level less than 12g/dL. You may be excluded from participating in the study if you are anaemic.

- Submaximal Aerobic Capacity Assessment

Following an adequate period of recovery, you will perform a submaximal aerobic capacity test on a stationary bicycle. This test will be used to determine your aerobic capacity (level of fitness). You will be positioned on the bicycle and begin cycling at a light intensity which will increase each minute. This test will finish once your heart rate has reached 75% of your age-predicted heart rate. This test will take between ~ 6-12 minutes to complete. You will spend another minute or so cycling to ensure that you have recovered adequately.

**Session 2 (Week -3)**

**Pre-Training Neuromuscular and Fatigue Assessments**

- You will be fitted with a heart rate monitor chest strap, where heart rate data recorded throughout the session.

- You will report your current rating of perceived exertion (RPE)

- A sample of blood will be taken from your ear. This will be immediately analysed for lactate (La⁻), glucose (Glu), pH, bicarbonate (HCO₃⁻) and hemoglobin (Hb).

- You will be positioned, seated upright on the computerized strength testing chair with your knee flexed to 90° (0° being full extension).

As part of this process we will:
• Electrically stimulate the nerves to your right upper arm muscles using a mild electric current and

• Magnetically stimulate the right upper arm muscles via the motor cortex (brain).

• Your right upper arm will be prepared and fitted for the placement of two (2) recording electrodes. Prior to electrode placement, the skin will be shaved, abraded and any oil and dirt on the skin will be removed using an alcohol swab.

• Your right leg, waist and shoulders will be secured via straps to the dynamometer.

• You will warm-up on the dynamometer by performing five progressive submaximal isometric contractions of the right elbow flexors. You will be given a 30 second rest period between each contraction, and a 2-minute period will elapse prior to the commencing the following testing procedures.

**Neuromuscular Assessment Protocol**

**Peripheral Nerve Stimulation**

Electrical stimulation will be achieved by placing an electrode on the front of your right upper arm and another on the side of your right hip, which will be used to electrically stimulate the brachial plexus (the nerve branch to your upper arm).

**Transcranial Magnetic Stimulation**

Magnetic stimulation will be achieved by placing a plastic coil over the top of your skull which produces a magnetic field that will trigger the region of your motor cortex (part of your brain) which activates the muscles that produces movement in your right upper arm.

You will perform four (4) sets of four (4) muscle contractions. Each set will consist of one (1) 100% maximal effort contraction, during the contraction an electrical stimulus will be applied to your brachial plexus (of the upper arm) during the contraction and immediately after the contraction. Following a sixty (60) second rest, you will...
perform three (3) contractions; one (1) 100% maximal effort; one (1) 75% of maximal effort and; one (1) 50% of maximal effort contraction with a five (5) second rest between each contraction.

Immediately following this, you will perform a 10% of maximal voluntary contraction (MVC) of the right elbow flexors. Eight (8) single and eight 8 paired magnetic pulses, with a 5-7 second rest period between each, will be delivered to the motor cortex using TMS.

You will then rest for ~sixty (60) seconds each set of contractions. Muscle activation can be uncomfortable for some participants, however it is expected that the familiarisation sessions with this procedure will reduce any associated anxiety. Importantly, the stimulus delivered to the muscle will not be greater than tolerated and you are free to end testing at any time.

Following this, you will perform the exercise fatigue task, as outlined below.

**Exercise Fatigue Task**

A two minute sustained, maximal voluntary isometric contraction of the right elbow flexors will be performed. This task will be performed on the Kin-Com dynamometer. Participants will be instructed to produce maximal voluntary effort from the commencement of the contraction and to continue exerting maximal effort for a 2 minute period. Strong verbal encouragement will be provided throughout the task.

**Post Task Measurements**

All pre task measurement will be repeatedly performed immediately after, 1, 2, 3, 4, 5 and 6 -min after the exercise fatigue task. The recording electrodes and heart rate monitor will be removed.

Test completion and debriefing

This session is expected to take ~ 2 hours.

**Session 3 (Week -2)**
Following arrival at the laboratory, you will undertake a repeated assessment of the "pre-training neuromuscular and fatigue" measurements as previously undertaken during session 2.

This session is expected to take ~ 1 1/2 hours.

**Session 4a: (Week 0)**
The fourth pre training laboratory session will include anthropometric, dual energy x-ray absorptiometry (DXA) scanning, pre-training neuromuscular and fatigue measurements and venous blood collection. Before attending the third pre training laboratory session you will be given a series of questionnaires to be completed at home on a set day and time. These questionnaires include;

**Fatigue**
You will be asked to report your fatigue symptoms using four independent self-report questionnaires including the brief fatigue inventory (BFI), revised piper fatigue scale, fatigue and recovery questionnaire and a visual analogue scale (VAS).

**Quality of Life**
You will be asked to complete the EORTC quality of life questionnaire (QLQ-C30) and the MOS 36-Item Short-form (SF36).

**Depression**
You will be asked to complete the beck depression inventory (BDI-II).

**Sleep**
You will be asked to report your sleep quality over the preceding 30 days using the Pittsburgh sleep quality index (PSQI).

**Physical Activity**
You will be asked to report your usual amount and intensity of physical activity currently performed throughout the day, using the Stanford Brief Activity Survey.

**Nutrition**
You will be asked to record all beverages & food consumed over a three (3) day period. The three days examined will include two week days and one weekend day during the week.

**Anthropometric Measurements**
After reporting to the Human Performance Laboratory a measure of your height, weight and waist circumference will be taken.

**DXA Scanning**

Next, you will receive a whole body and right upper arm DXA scan, performed by the Principal Investigator which will allow us to determine your body composition. This information will allow us to assessed total non-osseous fat-free mass and fat mass. During these tests you will lie on you back on a special scanner table for approximately 10 minutes. This session is expected to take ~ 2.5 hours.

**Session 4b: (Week 0)**

You will be required to arrive at this session in a fasted (8-10 hr previous) state for the purposes of blood collection.

**Venous Blood Collection**

A 4 x 5mL sample of venous blood will be collected (on two occasions; before and after the training period) following ~10 minutes of quiet sitting in a seated or reclined position, to be collected from your non-dominant arm. The blood collected will be assessed for the concentration of blood markers associated with systemic inflammation tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and Cortisol (Cort).

**12 WEEK RESISTANCE TRAINING PROGRAM**

Following the three (3) pre-training data collection sessions, participants will be allocated to either the exercising or non-exercising groups. The exercising participants will participate in a 12 week supervised progressive resistance training program at gymnasium, CSU Bathurst Campus. You will be required to attend a total of 36 resistance training sessions over the 12 week intervention period. The intervention will consist of structured resistance training sessions performed three times a week. Each session will consist of a i) warm-up, ii) conditioning and iii) cool-down phase, as outlined below. The control groups will receive no exercise training during the
12 week intervention period. Following the post-training data collection, participants in the control groups will be offered the opportunity to participate in a resistance training program similar to that involved in the training intervention.

An overview of the procedure involved in the typical resistance training session is outlined.

**Standardised Warm-up**
Each resistance training session will consist of a 5-10 minute warm-up phase involving gentle exercise, for example walking or stationary cycling and gentle dynamic stretches for all muscle groups trained during the session (i.e. quadriceps, hamstring, chest, back, and shoulders).

**Resistance Training Exercise Protocol**
The resistance training exercises will consist of pin loaded machines. Specifically, the exercise program will consist of a whole-body workout and involve six (6) exercises (see Table 1). You will be required to complete between eight (8) to fifteen (15) repetitions for a total of three (3) sets per exercise. The training load for each exercise will be performed at 60-80% maximal effort. A two (2) minute rest will be provided between each set.

**Table 1: Resistance Training Exercise Protocol**

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Repetitions</th>
<th>Sets</th>
<th>Tempo</th>
<th>Rest</th>
<th>Intensity (% 1RM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg Press</td>
<td>8 – 15</td>
<td>3</td>
<td>2:1:2</td>
<td>2 min</td>
<td>50-80%</td>
</tr>
<tr>
<td>Leg Extension</td>
<td>8 – 15</td>
<td>3</td>
<td>2:1:2</td>
<td>2 min</td>
<td>50-80%</td>
</tr>
<tr>
<td>Bicep Curl</td>
<td>8 – 15</td>
<td>3</td>
<td>2:1:2</td>
<td>2 min</td>
<td>50-80%</td>
</tr>
<tr>
<td>Latpulldown</td>
<td>8 – 15</td>
<td>3</td>
<td>2:1:2</td>
<td>2 min</td>
<td>50-80%</td>
</tr>
<tr>
<td>Chest Press</td>
<td>8 – 15</td>
<td>3</td>
<td>2:1:2</td>
<td>2 min</td>
<td>50-80%</td>
</tr>
<tr>
<td>Shoulder Press</td>
<td>8 – 15</td>
<td>3</td>
<td>2:1:2</td>
<td>2 min</td>
<td>50-80%</td>
</tr>
</tbody>
</table>
To facilitate continued adaptation, training intensity (i.e. load) will be progressively increased throughout the twelve (12) week training phase, to attenuate the onset of a plateau in physiological adaptation.

**Standardised Cool-down**

A 5-minute cool-down phase involving gentle dynamic and static stretching for each major muscle group (quadriceps, hamstring, chest, back, and shoulders) will be performed. Sessions will be conducted in a small group setting consisting of between five (5) to six (6) participants. Each session will be supervised by several trained exercise supervisors, who will provide verbal encouragement and feedback regarding exercise technique throughout each exercise performed. A minimum of 24 hours will be provided between each resistance training session, to allow for adequate recovery.

During each resistance training session performance, perceptual, fatigue and training data will be collected, as described below.

- **Perceptual Measures**

The intensity resistance training exercise will be rated on the Borg RPE scale at the end of each exercise set.

**Fatigue Measures**

Fatigue symptoms as measured using the brief fatigue inventory (BFI), a visual analogue scale (VAS) and a fatigue and recovery questionnaire will be taken prior to commencing each resistance training session.

**Study Training Diary**

You will be provided with a study training diary to keep a record of the activities performed during each training session. Specifically, the diary will be used record session training loads, the number of repetitions completed per set, the number of sets completed per exercise, rating of perceived exertion (RPE), any injuries or
complaints of excessive muscle soreness, and any additional exercise or physical activity you undertaken outside of the training session.

**One Repetition Maximal Assessment**

An assessment of muscular strength using a one repetition maximal (1RM) protocol will be conducted during the first training session, of weeks 1, 5, 9 and during their last training session. This data will be used to determine your individual weight requirement for the initial resistance training program. In addition, this assessment will be used to determine your progress following the 12 week resistance training program. Prior to each exercise assessment you will be instructed on proper technique including body position, and starting and stopping points of each movement. Before the assessment is commenced a light warm-up, consisting of 5-10 minutes of gentle walking or cycling at a self-selected pace will be performed. Testing will involve the six (6) exercises outlined in Table 1. The assessment will begin with one (1) set of ten (10) repetitions at a relatively light load. Resistance in the form of additional weight will be added until the subject rates the difficulty as maximal, refuses to attempt lifting more weight, is unable to lift more weight with proper technique, or reports any other symptoms that required stopping. A rest period of between three (3) to five (5) minutes will be provided between attempts, and two (2) minutes between each specific exercise.

**POST-TRAINING DATA COLLECTION SESSION**

Seven (7) days following the final resistance training session in week twelve you will complete one (1) post-training data collection session. Prior to attending this session, you will complete the self-report questionnaires previously completed. This session will involve the repeated performance of the exercise fatigue task, capillary and venous blood collection, anthropometric, DXA scanning and submaximal aerobic capacity assessments, as described previously.
Potential Risks and Side Effects

The potential risks and side effects of participating in this study are minimal and similar to those associated with any form of physical exercise. As with all exercise there is the possibility of injury. Such injuries that may occur during training or testing are primarily restricted to soft tissue injuries, such as musculoskeletal/tendon strains. All testing will be performed either in the CSU Human performance Laboratory in building S21 or the Exercise Physiology and Functional Rehabilitation Clinic located within the CSU gymnasium. The Chief Investigator and research supervisor are trained first aiders and will be available to provide assistance if required. A telephone is readily accessible to contact emergency services if necessary. To minimise the risk of injury, a thorough warm-up will be performed before all tasks performances. In the event that any injury may occur from your participation in the study, any associated costs will lie with you, unless the injury was solely related to the negligence of CSU. However, CSU will assist where possible in obtaining appropriate medical assistance.

It is possible that the participation in some of the physical activities will result in some amount of discomfort, muscle stiffness, soreness and continued physical fatigue, following maximal muscle contractions and electrical stimulations. In addition you may experience delayed muscle soreness, especially in the day or two following the tests. This is Delayed muscle soreness which is a normal body response to unaccustomed physical activity and should subside over the course of a few days. Delayed muscle soreness will not cause any permanent damage and should not stop you completing any normal activities of daily living. The warm-up procedures performed prior to testing will assist in minimising the extent of muscle soreness experienced.

A small percentage of participants may experience a headache during and immediately following transcranial magnetic stimulation, which can be alleviated with over-the-counter pain medications such as aspirin or ibuprofen. Another potential discomfort is ringing in the
ears caused by the noise associated with the stimulating coil. When the magnetic pulse is applied, participants can hear a loud clicking noise. As a safety measure, earplugs will be provided to participants to be worn during the procedure to avoid such discomfort. Individuals with neurologic disorders or other conditions such as stroke, brain tumor, or Multiple Sclerosis are advised to not undertake TMS, as this procedure could be associated with the risk of seizure. All prospective participants will be carefully screened for conditions that would put them at higher risk for complications related to TMS.

This research involves participants being exposed to a small amount of radiation in order to assess body composition and bone mineral density. As part of everyday living, everyone is exposed to naturally occurring background (cosmic) radiation that is equivalent to a dose of approximately 2000 microsieverts (μSv) each year. The effective radiation dose you will be exposed to in this research is 67 μSv. At these radiation dose levels, no harmful effects have been demonstrated as any effect is too small to measure. As such, the risk is believed to be low and theoretically is approximately equivalent to risk category I (minimal) - <1:100,000.

You should retain the information about the DEXA procedure (including the radiation dose) for at least five years in case you decide to participate in any future research projects involving exposure to ionizing radiation.

**Benefits**
The results obtained from this study will assist generate new knowledge regarding whether resistance training exercise can improve muscular strength, indices of body composition, neuromuscular parameters, improving HRQOL, and reducing fatigue symptoms in disease-free, cancer survivors and cancer survivors receiving ongoing hormonal therapies. This information may be used in the development of resistance training exercise guidelines aimed at minimising fatigue symptoms and improving quality of life and
general well-being in this population. This information will be important for all allied health professionals involved in the management of post cancer fatigue survivors, such as General practitioners, Oncologists, and Exercise physiologists.

This project will provide an opportunity for all participants involved to have body composition, and muscular strength assessed, providing meaningful health-related information for the participant involved. In addition, provides participants the opportunity to participate in structured resistance training program.

Use of Collected Data
The data collected in this project will be used for the purpose of the Principal Researcher PhD thesis, which will be presented at national and/or international scientific conferences and submitted for publication in international health related journals.

Privacy and Confidentiality
Your name and personal details will not be disclosed to anyone apart from the Principal Investigators. Each participant will be assigned a number (01, 02, 03, etc) which will be the only identification used if we need to describe a specific participants results. If any identifying photographs are taken during the data collection period, they will not be used without your written consent.
Personal information will be kept on a laptop computer during data collection and transferred to hard copies and stored in a locked filing cabinet within the School of Human Movement Studies. Each participant will have access to their personal results at their request.

Voluntary Nature of Participation
Participation in this research project is entirely voluntary. You are not obliged to participate in this study and if you start you are free to withdraw at anytime without fear of penalty or discrimination.

Contact Details
If participants have any queries throughout the testing procedures, they can contact the researcher on the contact detailed provided on the first page of the document.

Institutional Review Board
Note: Charles Sturt University’s Ethics in Human Research Committee has approved this project. If you have any complaints or reservations about the ethical conduct of this project, you may contact the Committee treatment through the executive Officer:

The Executive Officer
Ethics in Human Research Committee
Academic Secretariat
Charles Sturt University
Private Mail Bag 29
Bathurst, NSW, 2795.

Tel: (02) 6338 4628
Fax: (02) 6338 4194

Any issues you raise will be treated in confidence and investigated fully and you will be informed of the outcome.

Thank you for expressing an interest in this research. If you agree to participate in this study, please sign the following consent form.
Appendix C

Informed Consent
Informed Consent

Questions concerning the study can be directed to:

Chief Investigator

Miss Danielle Girard
PhD Student
School of Human Movement Studies
Allen House, N1
University
Charles Sturt University
Panorama Ave
Bathurst, NSW
2795
Tel: (02) 6338 6101
Fax: (02) 6338 4065
Email: dgirard@csu.edu.au

Research Supervisor

Dr Jack Cannon
School of Human Movement Studies
Allen House, N1
Charles Sturt

Email: jcannon@csu.edu.au

I, (print your name) _________________________________ have read the information sheet regarding the research study ‘A Comparison Of Neuromuscular Performance, Fatigue Responses, Musculoskeletal Health, And Health-Related Quality Of Life Between Cancer Survivors And Healthy Matched Persons And The Effect Of 12 Weeks Of Resistance Training’ and consent to my participation based on the following understandings:
• I am free to withdraw my participation at any time without being subject to any penalty or discriminatory treatment.

• I have been given the opportunity to ask questions about the research and received satisfactory answers.

• The purpose of this research and potential risks or discomforts involved with the testing procedures has been sufficiently explained to me, with the opportunity to ask questions.

• I am aware of the risk associated with the procedure involved in this study, including the risks associated with Transcranial Magnetic Stimulation (TMS) and have answered all screening questionnaires to the best of my knowledge.

• That any information or personal details gathered in the course of this research about me is confidential and that neither my name nor any other identifying information will be used or published without my written permission.

• If I experience any acute incident (e.g. continued discomfort, pain, ringing in ears) during and/or following each session, I will directly notify the Chief Investigator and/or Research Supervisor that such an incident has arisen. Such an incident will be followed up Chief Investigator and/or Research Supervisor and may result in an official incident report being lodged.

• I am aware that as part of the Pre-Exercise Screening process, I am required to obtain a referral from a medical practitioner to a pathology clinic to undertake a full blood count analysis including fasting lipid profile and blood glucose levels.
and that any costs associated with the participant suitability screening process will not be funded by the researchers.

- I do/do not (circle) give consent to be photographed or videotaped during the study. Photos and video recording will be used in future conference presentations related to the study and findings. All photos will be de-identified with faces masked.

That Charles Sturt University’s Human Research Ethics Committee and Radiation Safety Committee have approved this study.

I understand that if I have any complaints or concerns about this research I can contact:

**Executive Officer**

**Human Research Ethics Committee, Office of Academic Governance**

**Charles Sturt University**

**Panorama Avenue, Bathurst NSW 2795**

Ph: (02) 63384628  Fax: (02) 63384194

_________________________________________  __________________________
Signature of participant                                                                                  Date

_________________________________________
Signature of investigator                            Date
Appendix D

GP Information Sheet
RESEARCH TITLE:

*A Comparison Of Neuromuscular Performance, Fatigue Responses, Musculoskeletal Health, And Health-Related Quality Of Life Between Cancer Survivors And Healthy Matched Persons And The Effect Of 12 Weeks Of Resistance Training*

**Principal Investigator**
Ms Danielle Girard  
*PhD Candidate*
School of Human Movement Studies  
Allen House, N1  
Charles Sturt University  
Panorama Ave, Bathurst, NSW  
2795

**Research Supervisor**
Dr Jack Cannon  
*PhD Supervisor*
School of Human Movement Studies  
Allen House, N1  
Charles Sturt University  
Panorama Ave, Bathurst, NSW  
2795

**Purpose:**
The purpose of this research is to compare neuromuscular performance, exercise-induced fatigue responses, musculoskeletal health, and health-related quality of life (HRQOL) and examine the effect of 12-weeks of resistance training between four (4) participant groups:

1. Disease-free post primary treatment cancer survivors, aged 40-85 years.
2. Disease-free post primary treatment cancer survivors with cancer fatigue symptoms, aged 40-85 years.
3. Healthy matched persons, aged 40-85 years.
4. Control group, aged 40-85 years
An additional purpose is to compare the reproducibility of neuromuscular performance and the exercise-induced fatigue response between the three (3) aforementioned participant groups.

Specifically, the aims of this study are to:

- Examine the reproducibility of neuromuscular performance and exercise-induced fatigue responses between participant groups;
- Compare neuromuscular performance, exercise-induced fatigue responses, musculoskeletal health, and HRQOL between participant groups.
- Compare the magnitude of resistance training-induced neuromuscular and musculoskeletal adaptations and effects on HRQOL between participant groups.
- Compare the effect of resistance training on the neuromuscular responses to exercise-induced fatigue and recovery between participant groups.

**Background:**
Previous literature indicates that exercise is one of only a few interventions demonstrating significant efficacy in reducing cancer and/or treatment related side-effects, including reducing fatigue symptoms, increasing HRQOL, and improving overall physical performance in disease-free post-treatment cancer patients.

Exercise-related intervention studies demonstrating improvements in functional status and fatigue symptoms of cancer survivors have focused mostly on the benefits of aerobic and/or mixed aerobic and resistance training modalities. Knowledge of whether resistance training exercise alone can improve neuromuscular performance, musculoskeletal health and HRQOL and/or reduce fatigue symptoms in disease-free post-treatment cancer survivors, including those with
fatigue symptoms, is not presently known. This study aims to generate new knowledge regarding these issues, which may contribute to better informing health care professional regarding the most appropriate form of exercise therapy for post primary treatment cancer survivors.

Furthermore, limited evidence-based recommendations exist regarding the prescription of resistance training exercise for disease-free, post-treatment cancer survivors, including those with fatigue symptoms. Current recommendations for resistance training program for this population are based on the general guidelines for healthy persons. However, it is not known whether disease-free post-treatment cancer survivors and healthy persons experience comparable adaptations in neuromuscular performance, musculoskeletal health, fatigue responses, and/or similar improvements in HRQOL associated with chronic resistance training. Such knowledge may assist in the development of practical guidelines that can be implemented by exercise physiologists when working with cancer survivors.

Persons interested in participating in this study have been requested to seek consultation with their GP to determine their suitability for participation.

In brief, the testing sessions will consist of:

- Submaximal aerobic capacity test on Bike
- Exercise to 75% of maximal heart rate
- DXA Scan
- a whole body and right upper arm scan
- Neuromuscular and Strength testing

This will involve peripheral electrical stimulation and transcranial magnetic stimulation and maximal voluntary isometric contractions of
the right upper arm muscles. A 2 minute maximal isometric contraction involving the right upper arm will be performed. The interested participant has been provided with an Information Sheet which outlines the specifics of the research study should you require it. Your advice regarding the following selection criteria would be appreciated.

**Participation Criteria for Cancer Survivors:**
- Patient has been cancer free for 6 months
- Patient is has the capacity to participate in an exercise program involving total body resistance training exercise
- Patient does not have any co-morbid conditions for which exercise is contraindicated
- Patient must meet one of the two following criteria:
  - Disease-free, post primary treatment cancer survivors (this may include persons receiving ongoing endocrine therapies who are not considered to have active disease).
  - Post primary treatment cancer survivors with fatigue symptoms (this may include persons receiving ongoing endocrine therapies who are not considered to have active disease).

**Participation Criteria for Healthy Controls:**
- Patient does not have any co-morbid conditions for which exercise is contraindicated

**PARTICIPATION CRITERIA:**

________________________ (Patient name) meets /does not meet (please circle) participate eligibility criteria for participation in this study.
PARTICIPATION CAPACITY:
In my opinion________________________ (patient name) does /does not (please circle) have the physical capacity to participate in resistance training intervention.
Signed___________________________ (GP)               Date___________________
If you (patients GP) would like any additional information or have any question regarding this study and your patient involvement and suitability please feel welcome to contact either the Primary Investigator or Research Supervisor on the contact details listed above.
Appendix E

Revised Piper Fatigue Scale
Revised Piper Fatigue Scale

Directions: Many individuals can experience a sense of unusual or excessive tiredness whenever they become ill, receive treatment, or recover from their illness/treatment. This unusual sense of tiredness is not usually relieved by either a good night’s sleep or by rest. Some call this symptom “fatigue” to distinguish it from the usual sense of tiredness.

For each of the following questions, please fill in the space provided for that response that best describes the fatigue you are experiencing now or for today. Please make every effort to answer each question to the best of your ability. If you are not experiencing fatigue now or for today, fill in the circle indicating “0” for your response.

1. How long have you been feeling fatigue? (Please circle; one response only).
   1. Not feeling fatigue
   2. Minutes
   3. Hours
   4. Days
   5. Weeks
   6. Months
   7. Other (Please describe)

2. To what degree is the fatigue you are feeling now causing you distress?
   1 2 3 4 5 6 7 8 9 10
   (No Distress) (A Great Deal)

3. To what degree is the fatigue you are feeling now interfering with your ability to complete your work or school activities?
   1 2 3 4 5 6 7 8 9 10
   (None) (A Great Deal)

4. To what degree is the fatigue you are feeling now interfering with your ability to socialize with your friends?
   1 2 3 4 5 6 7 8 9 10
   (None) (A Great Deal)

5. To what degree is the fatigue you are feeling now interfering with your ability to engage in sexual activity?
   1 2 3 4 5 6 7 8 9 10
   (None) (A Great Deal)
6. Overall, how much is the fatigue which you are now experiencing interfering with your ability to engage in the kind of activities you enjoy doing?

   1 2 3 4 5 6 7 8 9 10
   (None)                           (A Great Deal)

7. How would you describe the degree of intensity or severity of the fatigue which you are experiencing now?

   1 2 3 4 5 6 7 8 9 10
   (Mild)                                                              (Severe)

8. To what degree would you describe the fatigue which you are experiencing now as being?

   1 2 3 4 5 6 7 8 9 10
   (Pleasant)                                                          (Unpleasant)

9. To what degree would you describe the fatigue which you are experiencing now as being?

   1 2 3 4 5 6 7 8 9 10
   (Agreeable)                                                          (Disagreeable)

10. To what degree would you describe the fatigue which you are experiencing now as being?

     1 2 3 4 5 6 7 8 9 10
     (Protective)                                                      (Destructive)

11. To what degree would you describe the fatigue which you are experiencing now as being?

     1 2 3 4 5 6 7 8 9 10
     (Positive)                                                   (Negative)

12. To what degree would you describe the fatigue which you are experiencing now as being:

     1 2 3 4 5 6 7 8 9 10
     (Normal)                                                  (Abnormal)

13. To what degree are you now feeling:

     1 2 3 4 5 6 7 8 9 10
     (Strong)                                             (Weak)
14. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Awake)                                                             (Sleepy)

15. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Lively)                                                              (Listless)

16. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Refreshed)                                                               (Tired)

17. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Energetic)                                                             (Unenergetic)

18. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Patient)                                                              (Impatient)

19. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Relaxed)                                                             (Tense)

20. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Exhilarated)                                                   (Depressed)

21. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Able to Concentrate)                         (Unable to Concentrate)

22. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Able to Remember)                             (Unable to Remember)

23. To what degree are you now feeling:

1  2  3  4  5  6  7  8  9  10
(Able to Think Clearly)                              (Unable to Think Clearly)
24. Overall, what do you believe is *most* directly contributing to or causing your fatigue?

__________________________________________________________________________

__________________________________________________________________________

25. Overall, the *best* thing you have found to relieve your fatigue is:

__________________________________________________________________________

__________________________________________________________________________

26. Is there anything else you would like to add that would describe your fatigue better to us?

__________________________________________________________________________

__________________________________________________________________________

27. Are you experiencing any other symptoms right now?

__________________________________________________________________________
Appendix F

Brief Fatigue Inventory
Brief Fatigue Inventory

Date:________________                            Time:___________
Name:_______________

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week?
(Please circle) Yes      No

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<tr>
<th>Symptom</th>
<th>1 to 10 ranking</th>
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<tbody>
<tr>
<td></td>
<td><em>1 is most favourable and 10 least favourable</em></td>
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Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right **NOW**

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Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **USUAL** level of fatigue during the past 24 hours

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Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **WORST, level of fatigue during the past 24 hours**

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Appendix G

Visual Analogue Scale
Instruct the patient to point to the position on the line between the faces to indicate how much fatigue they are currently feeling. The far left end indicates ‘No fatigue’ and the far right end indicates ‘Worst fatigue ever’.
Appendix H

The European Organization for Research and Treatment of Cancer
EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no “right” or “wrong” answers. The information that you provide will remain strictly confidential.

Please fill in your first initial: [____]

Your birth date (Day, Month, Year): [____] [____] [____]

Today’s date (Day, Month, Year): [____] [____] [____]

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<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tbody>
</table>

During the past week:

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<tr>
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<th>Not at All</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
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<tbody>
<tr>
<td>6</td>
<td>Were you limited in doing</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Question</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had diarrhoea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Has your physical condition or medical</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>treatment interfered with your family life?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>------------------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>27</td>
<td>Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>28</td>
<td>Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you:

29. How would you rate your overall health during the past week?

   1  2  3  4  5  6  7  Excellent

   Very poor

30. How would you rate your overall quality of life during the past week?

   1  2  3  4  5  6  7  Excellent

   Very poor
Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems, please answer by circling the number that best applies to you.

During the past week:

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Have you had cramps in your abdomen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>32</td>
<td>Have you had difficulty in controlling your bowels?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>33</td>
<td>Have you had blood in your stools (motions)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>34</td>
<td>Did you pass water/urine frequently?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>35</td>
<td>Have you had pain or a burning feeling when passing water/urinating?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>36</td>
<td>Have you had leaking of urine?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>37</td>
<td>Have you had difficulty emptying your bladder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>38</td>
<td>Have you had swelling in one or both legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>39</td>
<td>Have you had pain in your lower back?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>40</td>
<td>Have you had tingling or numbness in your hands or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>41</td>
<td>Have you had irritation or soreness in your vagina or vulva?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>42</td>
<td>Have you had discharge from your vagina?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>43</td>
<td>Have you had abnormal bleeding from your vagina?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>44</td>
<td>Have you had hot flushes and/or sweats?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Have you felt physically less attractive as a result of your disease or treatment?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Have you felt less feminine as a result of your disease or treatment?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Have you felt dissatisfied with your body?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Have you worried that sex would be painful?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Have you been sexually active?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Answer these questions only if you have been sexually active during the past 4 weeks:

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Not at All</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Has your vagina felt dry during sexual activity?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51</td>
<td>Has your vagina felt short?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>52</td>
<td>Has your vagina felt tight?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>53</td>
<td>Have you had pain during sexual intercourse or other sexual activity?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>54</td>
<td>Was sexual activity enjoyable for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**EORTC QLQ - OV28 (subscale)**

*During the past week:*

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Not at All</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>Did you have a bloated feeling in your abdomen / stomach?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>56</td>
<td>Were you troubled by passing wind / gas / flatulence?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------------------------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>57</td>
<td>Have you lost any hair?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>58</td>
<td>Answer this question only if you had any hair loss:</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Were you upset by the loss of your hair?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>59</td>
<td>Did food and drink taste different from usual?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>60</td>
<td>Have you had tingling hands or feet?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>61</td>
<td>Have you had numbness in your fingers or toes?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>62</td>
<td>Have you felt weak in your arms or legs?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>63</td>
<td>Did you have aches or pains in your muscles or joints?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>64</td>
<td>Did you have problems with hearing?</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Appendix I

Medical Outcomes Short Survey 36
**SF36 Health Survey**

**INSTRUCTIONS:** This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. **In general, would you say your health is?** (Please tick one box.)
   - Excellent
   - Very Good
   - Good
   - Fair
   - Poor

2. **Compared to one year ago, how would you rate your health in general now?** (Please tick one box.)
   - Much better than one year ago
   - Somewhat better now than one year ago
   - About the same as one year ago
   - Somewhat worse now than one year ago
   - Much worse now than one year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Please circle one number on each line.)

<table>
<thead>
<tr>
<th>Activities</th>
<th>Yes, Limited A Lot</th>
<th>Yes, Limited Little</th>
<th>Not Limited At All</th>
</tr>
</thead>
<tbody>
<tr>
<td>3(a) Vigorous activities, such as running, lifting heavy objects,</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>particularly strenuous sports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3(b) Moderate activities, such as moving a table, pushing a</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>vacuum cleaner, bowling, or playing golf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3(c) Lifting or carrying groceries</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3(d) Climbing several flights of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3(e) Climbing one flight of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3(f) Bending, kneeling, or stooping</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3(g) Walking more than a mile</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3(h) Walking several blocks</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3(i) Walking one block</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3(j) Bathing or dressing yourself</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

4. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?** (Please circle one number on each line.)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>4(a) Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4(b) Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4(c) Were limited in the kind of work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4(d) Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

5. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?** (Please circle one number on each line.)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5(a) Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5(b) Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5(c) Didn't do work or other activities as carefully as usual</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick one box.)
   - Not at all
   - Slightly
   - Moderately
   - Quite a bit
   - Extremely

7. How much physical pain have you had during the past 4 weeks? (Please tick one box.)
   - None
   - Very mild
   - Mild
   - Moderate
   - Severe
   - Very Severe

8. During the past 4 weeks, how much pain interfered with your normal work (including both work outside the home and housework)? (Please tick one box.)
   - Not at all
   - A little bit
   - Moderately
   - Quite a bit
   - Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.
   (Please circle one number on each line.)

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9(a) Did you feel full of life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9(b) Have you been a very nervous person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9(c) Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9(d) Have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9(e) Did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9(f) Have you felt downhearted and blue?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9(g) Did you feel worn out?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9(h) Have you been a happy person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9(i) Did you feel tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick one box.)

   - All of the time
   - Most of the time
   - Some of the time
   - A little of the time
   - None of the time

11. How TRUE or FALSE is each of the following statements for you?
    (Please circle one number on each line.)

<table>
<thead>
<tr>
<th>Question</th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Don't Know</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>11(a) I seem to get sick a little easier than other people.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11(b) I am as healthy as anybody I know.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11(c) I expect my health to get worse.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11(d) My health is excellent.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thank You!
Appendix J

Health Screening Tool
# ADULT PRE-EXERCISE SCREENING TOOL

This screening tool does not provide advice on a particular matter, nor does it substitute for advice from an appropriately qualified medical professional. No warranty of safety should result from its use. The screening system in no way guarantees against injury or death. No responsibility or liability whatsoever can be accepted by Exercise and Sports Science Australia, Fitness Australia or Sports Medicine Australia for any loss, damage or injury that may arise from any person acting on any statement or information contained in this tool.

**Name:**

**Date of Birth:**

**Male** □ **Female** □ **Date:**

## STAGE 1 (COMPULSORY)

**AIM:** To identify those individuals with a known disease, or signs or symptoms of disease, who may be at a higher risk of an adverse event during physical activity/exercise. This stage is self-administered and self-evaluated.

Please circle response

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has your doctor ever told you that you have a heart condition or have you ever suffered a stroke?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you ever experience unexplained pains in your chest at rest or during physical activity/exercise?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you ever feel faint or have spells of dizziness during physical activity/exercise that causes you to lose balance?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Have you had an asthma attack requiring immediate medical attention at any time over the last 12 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. If you have diabetes (type 1 or type 2) have you had trouble controlling your blood glucose in the last 3 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you have any diagnosed muscle, bone or joint problems that you have been told could be made worse by participating in physical activity/exercise?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you have any other medical condition(s) that may make it dangerous for you to participate in physical activity/exercise?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IF YOU ANSWERED YES to any of the 7 questions, please seek guidance from your GP or appropriate allied health professional prior to undertaking physical activity/exercise.

**IF YOU ANSWERED NO to all of the 7 questions, and you have no other concerns about your health, you may proceed to undertake light-moderate intensity physical activity/exercise.**

I declare that to the best of my knowledge, all of the information I have supplied within this tool is correct.

**Signature** ___________________________ **Date** ___________________________
<table>
<thead>
<tr>
<th>INTENSITY CATEGORY</th>
<th>HEART RATE MEASURES</th>
<th>PERCEIVED EXERTION MEASURES</th>
<th>DESCRIPTIVE MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEDENTARY</td>
<td>&lt; 40% HRmax</td>
<td>Very, very light RPE&lt;1</td>
<td>Activities that usually involve sitting or lying and that have little additional movement and a low energy requirement</td>
</tr>
<tr>
<td>LIGHT</td>
<td>40 to &lt;55% HRmax</td>
<td>Very light to light RPE 1-2</td>
<td>An aerobic activity that does not cause a noticeable change in breathing rate</td>
</tr>
<tr>
<td>MODERATE</td>
<td>55 to &lt;70% HRmax</td>
<td>Moderate to somewhat hard RPE 3-4</td>
<td>An aerobic activity that can be sustained for at least 60 minutes</td>
</tr>
<tr>
<td>VIGOROUS</td>
<td>70 to &lt;90% HRmax</td>
<td>Hard RPE 5-6</td>
<td>An aerobic activity in which a conversation cannot be maintained uninterrupted</td>
</tr>
<tr>
<td>HIGH</td>
<td>≥ 90% HRmax</td>
<td>Very hard RPE ≥ 7</td>
<td>An intensity that generally cannot be sustained for longer than about 10 minutes</td>
</tr>
</tbody>
</table>

# = Borg's Rating of Perceived Exertion (RPE) scale, category scale 0-10

V1 (2011)
### ADULT PRE-EXERCISE SCREENING TOOL
#### STAGE 2 (OPTIONAL)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Family history of heart disease (e.g., stroke, heart attack)</td>
<td></td>
</tr>
<tr>
<td>Relative</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td></td>
</tr>
<tr>
<td>Brother</td>
<td></td>
</tr>
<tr>
<td>Son</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td></td>
</tr>
<tr>
<td>Sister</td>
<td></td>
</tr>
<tr>
<td>Daughter</td>
<td></td>
</tr>
<tr>
<td>Do you smoke cigarettes on a daily or weekly basis or have you quit smoking in the last 6 months? Yes No</td>
<td></td>
</tr>
<tr>
<td>If currently smoking, how many per day or week?</td>
<td></td>
</tr>
<tr>
<td>Describe your current physical activity/exercise levels</td>
<td></td>
</tr>
<tr>
<td>Frequency (sessions per week)</td>
<td></td>
</tr>
<tr>
<td>Duration (minutes per week)</td>
<td></td>
</tr>
<tr>
<td>Please state your height (cm)</td>
<td></td>
</tr>
<tr>
<td>weight (kg)</td>
<td></td>
</tr>
<tr>
<td>BMI =</td>
<td></td>
</tr>
<tr>
<td>BMI ≤ 30 kg/m² = +1 risk factor</td>
<td></td>
</tr>
<tr>
<td>Have you been told that you have high blood pressure? Yes No</td>
<td></td>
</tr>
<tr>
<td>Have you been told that you have high cholesterol? Yes No</td>
<td></td>
</tr>
<tr>
<td>Have you been told that you have high blood sugar? Yes No</td>
<td></td>
</tr>
</tbody>
</table>

Note: Refer over page for risk stratification.

**STAGE 2 Total Risk Factors =**
### Stage 3 (Optional)

**Aim:** To obtain pre-exercise baseline measurements of other recognised cardiovascular and metabolic risk factors. This stage is to be administered by a qualified exercise professional. (Measures 1, 2 & 3 – minimum qualification, Certificate III in Fitness; Measures 4 and 5 minimum level, Exercise Physiologist*).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RESULTS</th>
<th>RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BMI (kg/m²)</td>
<td>BMI ≥ 30 kg/m² = +1 risk factor</td>
<td></td>
</tr>
<tr>
<td>2. Waist girth (cm)</td>
<td>Waist &gt; 94 cm for men and &gt; 80 cm for women = +1 risk factor</td>
<td></td>
</tr>
<tr>
<td>3. Resting BP (mmHg)</td>
<td>SBP ≥ 140 mmHg or DBP ≥ 90 mmHg = +1 risk factor</td>
<td></td>
</tr>
<tr>
<td>4. Fasting lipid profile*</td>
<td>Total cholesterol ≥ 5.20 mmol/L = +1 risk factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol &gt; 1.55 mmol/L = -1 risk factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol &lt; 1.00 mmol/L = +1 risk factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triglycerides &gt; 1.70 mmol/L = +1 risk factor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDL cholesterol ≥ 3.40 mmol/L = +1 risk factor</td>
<td></td>
</tr>
<tr>
<td>5. Fasting blood glucose*</td>
<td>Fasting glucose &gt; 5.60 mmol/L = +1 risk factor</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Stratification**

- ≥ 2 risk factors – Moderate Risk Clients
  - Individuals at moderate risk may participate in aerobic physical activity/exercise at a light or moderate intensity (refer to the exercise intensity table on page 2).

- < 2 risk factors – Low Risk Clients
  - Individuals at low risk may participate in aerobic physical activity/exercise up to a vigorous or high intensity (Refer to the exercise intensity table on page 2).

Note: If stage 2 is completed, identified risk factors from stage 2 (Q1–Q4) and stage 3 should be combined to indicate risk. If there are extreme or multiple risk factors, the exercise professional should use professional judgment to decide whether further medical advice is required.
Blood collection and analyses setup.
Participants during the resistance training and data collection sessions.