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Fatigue and exercise in cancer

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FATIGUE AND EXERCISE IN CANCER

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In memory of my Mum, Jo Wilson...

CONTENTS

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FORMAT OF THE THESIS

In brief, this thesis consists of stand-alone manuscripts either submitted or to be submitted to relevant peer review journals. There may be necessary overlap between chapters. This thesis comprises a general introduction, three experimental chapters and a general discussion.

A single reference section appears at the end of this thesis. Abbreviations are defined at first use in each chapter and a list of abbreviations is included. Tables and figures are numbered consecutively, restarting in each chapter. [Square brackets] and/or **bold type** is used when referring to sections elsewhere in the thesis.

There is no commonly accepted definition for a person diagnosed with cancer; it is a complex area under continual debate. 'Macmillan cancer support' define someone who is living with or beyond cancer as a 'cancer survivor', however this definition is still not widely accepted by researchers, clinicians and the patients themselves (Twombly *et al.*, 2004). For the purpose of the experimental chapters in this thesis, an individual undergoing active treatment for cancer will be defined as a 'patient' and an individual who has completed initial treatment for cancer and has no apparent evidence of active disease will be defined as a 'patient on follow-up.'

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LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ACSM:	American College of Sports Medicine
ADT:	Androgen deprivation therapy
ANOVA:	Analysis of variance
BP:	Blood pressure
BFI:	Brief fatigue inventory
CFS:	Chronic fatigue syndrome
CRF:	Cancer related fatigue
CNS :	Central nervous system
CO:	Cardiac output
CV:	Coefficient of variation
DXA	Duel energy X-ray absorptiometry
ECG:	Electrocardiogram
FACT	Functional assessment of cancer therapy
Hb:	Heamoglobin
HPA	Hypothalamic-pituitary-adrenal
HR:	Heart rate
HRQoL	Health related quality of life
IL-1	Interlukin-1
IL-6	Interlukin-6
MDASI	MD Anderson symptom inventory
MAP:	Mean arterial pressure
METs	Metabolic equivalents
NCCN	National Comprehensive Cancer Network
PSA	Prostate specific antigen

O_2 pulse:	Oxygen pulse (VO_2/HR)
QoL	Quality of life
r:	Pearson's product-moment correlation
RER:	Respiratory exchange ratio (VO_2/VCO_2)
RPE:	Ratings of perceived exertion
SD:	Standard deviation
SV:	Stroke Volume
TPR:	Total peripheral resistance
VCO_2	Ventilatory equivalent of carbon dioxide
VO_2	Ventilatory equivalent of oxygen
VO_{2max}	Maximal oxygen consumption

SUMMARY

Recent advances in the diagnosis and treatment of cancer have produced significant improvements in survival rates for many cancer types. The sequential combinations of treatment modalities (chemotherapy, radiotherapy, immunotherapy and hormonal therapy) aim to cure or prolong life. However, they are also related to debilitating side effects that negatively impact upon quality of life. Consequently, research and interventions that target these treatment related toxicities will have considerable benefit in this population.

In this thesis, the results from three studies are presented. The first study **[chapter two]** is experimental in nature and investigates the mechanisms of physical fatigue in patients with breast cancer receiving adjuvant chemotherapy. The study identifies the importance of investigating a subtype of fatigue, operationally defined as an increase in perceived exertion during a physical task. As hypothesised, there was an increase in perceived exertion at baseline and post chemotherapy in these patients, and the study had the capability to relate this increased perception of effort to different physiological and psychological processes associated with cancer therapy.

The second randomised controlled experiment **[chapter three]** indentifies a safe and effective exercise intervention appropriate for reversing physiological and psychological side effects associated with cancer therapy in patients with prostate cancer. As hypothesised, a high intensity progressive resistance training programme improves body composition, physical function, fatigue and quality of life. Interestingly, this study identifies improved mental aspects, as well as physical aspects of fatigue in response to an exercise training programme.

The third cross sectional study **[chapter four]** identifies treatment related barriers to exercise in patients on follow-up from breast cancer treatment. This study identified treatment related side effects, such as fatigue and increased perception of effort to be the most common reasons for not engaging in physical activity after treatment for breast cancer. This study provides novel targets for future research and treatment of fatigue with this patient population.

In conclusion, this thesis presents mechanisms by which fatigue is increased in breast cancer patients during adjuvant chemotherapy; identifies potential barriers to physical activity in breast cancer patients on follow-up from treatment; and also adds to existing literature that exercise can alleviate the side effects of treatment from cancer. Overall, the studies in this thesis provide a better understanding of the increased perception of effort associated with fatigue in patients treated for cancer and provides novel targets for intervention strategies.

CHAPTER ONE

GENERAL INTRODUCTION

This chapter presents the main areas covered in the thesis by reviewing the relevant literature and explaining the research questions. As the thesis has a multidisciplinary approach, the first section provides information on the most common side effects experienced by patients both during and post treatment for cancer, focussing on fatigue. The second section discusses the evidence related to managing these side effects, with a focus on topics associated with exercise rehabilitation.

The four most common cancers in the UK are lung, breast, colorectal and prostate and together, they account for over half (54%) of all cancers (ICD, 2008). This thesis focuses on breast and prostate cancer, as these are the most common sites in women and men, accounting for 46% and 31% of all female and male cases respectively.

Breast cancer

Breast cancer is the second most common cause of cancer death after lung cancer (Office for National Statistics, 2010), and 1 in 8 women are diagnosed with the disease in their lifetime (Sasieni *et al.*, 2011). Over the last 30 years, in the UK, the incidence rate for breast cancer in women has increased by more than half (65%) (Office for National Statistics, 2010). However, survival rates are high when the cancer is detected early and treated according to best practice, therefore mortality rates have decreased. For example, in England and Wales, 80% of breast cancer patients will live for 5 years and 72% will live for at least 10 years after diagnosis (Rachet *et al.*, 2009).

Most female breast cancer starts in the ducts of the breast (ductal breast cancer); however, it can also start in the glands (lobular breast cancer) or other tissues such as connective and fatty tissue. Breast cancer cells can spread to other organs of the body through the lymph

system, which is part of the body's capability to fight infections or foreign organisms. In-situ breast cancer is non-invasive cancer that has not spread further than the ducts or the lobules (Stage 0). A breast cancer is invasive when the malignant cells have infiltrated beyond the layer of cells where it started (Stage I-IV).

In most cases, treatment for breast cancer begins with surgery; either part of the breast (lumpectomy) or the whole breast (mastectomy) is removed and completed with an axillary node dissection (the nodes most likely to contain cancer are removed). Post surgery, women undergo a variety of adjuvant treatments in order to lower the chances of recurrence. These include chemotherapy, radiotherapy, hormone therapy (i.e. anti-oestrogens such as Tamoxifen) and biological therapies (i.e monoclonal antibodies such as Herceptin), solely or in combination with each other.

Prostate cancer

Prostate cancer is the most common solid organ cancer in men, accounting for approximately 19% of cancers amongst men in developed countries (Parkin *et al.*, 2002). Although prostate cancer continues to rise, mortality is proportionately much less, with the overall 5 year survival rate for 1996-2003 being 98.4% (Howlader *et al.*, 2008). The increases in survival rates are due to both increased screening techniques (resulting in early detection of the disease) and advances in treatments (Baade *et al.*, 2004).

Prostate cancer starts in the prostate gland and can spread through the lymph glands and into other organs of the body, normally the bones and liver. When the cancer is contained to the prostate, it is considered localised (Stage I and II). Locally advanced prostate cancer describes when the cancer has spread to the surrounding areas, such as the seminal vesicles

(Stage III). When the cancer spreads beyond the surrounding areas, such as the lymph nodes or other organs, it is known as advanced prostate cancer (Stage IV).

One of the most common forms of adjuvant treatment for prostate cancer is Androgen Deprivation Therapy (ADT) (Cooperberg *et al.,* 2003), which involves castration either surgically (i.e. orchiectomy) or chemically (with gonadtropin-releasing hormones (GnRH) i.e Flutamine, Zolodex) which causes reductions in circulating androgen levels. ADT is used increasingly as adjuvant therapy with radiotherapy for localised prostate cancers and as salvage therapy for increasing prostate-specific antigen (PSA) levels after localized treatment. ADT is effective at alleviating disease specific symptoms and some evidence suggests that it is effective at prolonging survival when used as an adjuvant with radiation therapy in patients with locally advanced prostate cancer (Bolla *et al.,* 1997).

Side effects of cancer treatment

Although modern treatments for cancer are essential for curing the cancer or prolonging life, unfortunately, they are associated with serious toxicities (Hoffman *et al.,* 2007). The effects of cancer and its treatment can lead to long-term ill health in those who survive. The general physiological side effects of modern cancer treatments are displayed in Table 1. Of interest to the reader at this point is that the majority of treatment related side effects listed in the table are suggested to be associated with symptoms of fatigue. It is important to note the psychological side effects from cancer treatment which include; altered body image due to factors such as loss of hair, loss of body parts, such as the breast, colon and jaw, an increase or decrease in body mass, and swelling from lymphoedema; and psychological distress such as stress, depression and anxiety (Piper 1990).

The most commonly reported symptoms affecting patients with cancer are pain, nausea and fatigue (Hofman *et al.*, 2007), with fatigue the most prevalent (Escalante *et al.*, 2001; Mock 2004). Since little is known about its pathogenesis, fatigue remains underecognised and undertreated (Ryan *et al.*, 2007).

Fatigue

Cancer related fatigue (CRF) is a debilitating form of fatigue, which usually begins before cancer diagnosis, is increased during the course of cancer treatment (Stone *et al.*, 2000), and persists at a higher rate than baseline after treatment has completed and clinical remission have been achieved (Bower *et al.*, 2006). It is also present in at the end of life (Morrow *et al.*, 2002; Ahlberg *et al.*, 2003).

CRF has been defined as 'an unusual persistent, subjective sense of tiredness' attributed to the cancer or cancer treatment that can affect both physical and mental capacity (Sobrero *et al.*, 2001) and interferes with the usual functioning of the individual (Mock *et al.*, 2000), worsening QoL (Mock *et al.*, 2007). More recently, the Fatigue Task Force (Assessing Symptoms of Cancer using Reported-Patient Outcomes) defined CRF as 'the perception of unusual tiredness that varies in pattern or severity and has a negative impact on the ability to function in people who have or have had cancer' (Barsevick *et al.*, 2010). CRF is distinct from the fatigue experienced by healthy individuals; by its severity, that it is not relieved by rest or sleep, (Piper 1990) and that it is not necessarily associated with the patient's level of previous physical exertion (Morrow *et al.*, 2005; Mustian *et al.*, 2007).

The severity and prevalence of CRF varies in different studies, with prevalence rates ranging from 17-100% (Curt *et al.*, 2000; Servaes *et al.*, 2002; Hofman *et al.*, 2007;

Higginson & Costantini 2008), with the majority of studies reporting prevalence rates of above 60% (Cella *et al.*, 2001). This variety is due to the different definitions of fatigue, the assessment technique (Minton *et al.*, 2008), stage of the cancer, treatment regimes, and the patient population (Hofman *et al.*, 2007). For example, studies that involve more stringent criteria for assessing fatigue report lower prevalence (17%) in patients (Cella *et al.*, 2001). Most patients with advanced stages of cancer will experience fatigue more than those with lower stages, with the prevalence of fatigue at the end of life being up to 100% in some studies (Stone *et al.*, 1999).

Patients undergoing chemotherapy, radiotherapy and biologic response modifiers will develop fatigue compared with those who do not receive these treatments (Jacobsen *et al.*, 1999). For those who have completed treatment for cancer, the prevalence rates are lower than those on active treatment, but fatigue is higher than the general population, with 17-38 % of patients reporting severe CRF 6 months or longer after completion of treatment (Mustian *et al.*, 2007). In support, Bower *et al.*, (2006) found that of 763 women treated for breast cancer, 35% reported fatigue 1-5 years after completion of their treatment, and 34% reported fatigue 5-10 years after completion of treatment. These similar percentages highlight the persistent nature of the fatigue.

In relation to breast and prostate cancer, estimates of incidences of fatigue during treatment have been reported to vary between 28-91% in breast cancer patients (Hofman *et al.*, 2007) and between 15 and 78% in prostate cancer patients (Monga *et al.*, 2007). Forlenza *et al.*, (2005) reported that prostate cancer patients were most likely to report feelings of fatigue for greater than 6 months compared to other cancers.

Contributing factors to cancer related fatigue

A combination of different factors is thought to contribute to CRF, but the precise mechanisms are poorly understood (Wu & McSweeney 2001). Within the literature, the general understanding into cancer related fatigue is provided via the basic mechanisms of muscular fatigue, broadly categorised into two main components; central and peripheral. Central fatigue, which is proposed to develop in the central nervous system (CNS), is the progressive failure to transmit motor neuron impulses (Gandevia 2001). Peripheral fatigue results in the inability of the musculoskeletal system to perform a task in response to central stimulation, which occurs in the neuromuscular junctions and muscle tissues.

Although the research is currently emerging (Yavuzsen *et al.*, 2009), the evidence for the central vs. peripheral muscular fatigue hypothesis within patients with cancer is limited. Also, as CRF is likely to have a different etiology compared with populations that have already been studied in the context of this hypothesis (such as chronic fatigue and rheumatoid arthritis), there are limitations to using this hypothesis within cancer. So, for the purpose of this chapter, the potential contributing factors to CRF are discussed using a more holistic approach, focussing on the symptoms of fatigue as opposed to more specific physiological fatigue. There is support for a symptom based approach to understanding the mechanisms and measuring cancer related fatigue (Mendoza *et al.*, 1999; Hwang *et al.*, 2003). Therefore, the following section is broken down into the mechanisms of fatigue that are associated with 1) the central nervous system 2) other physiological systems.

Mechanisms associated with the central nervous system

Cancer and its treatments are associated with increases in plasma levels of proinflammatory cytokines (Levey *et al.*, 2001), such as interleukin (IL)-1, IL-6 and tumor

necrosis factor-alpha (TNF-α). These cytokines, which are associated with changes in the central nervous system (Ryan *et al.*, 2007) can induce "sickness behaviours" and symptoms of fatigue such as loss of energy and motivation, increased sleep, inability to concentrate, subjective reports of poor memory, and decreased appetite (Blesch *et al.*, 1991; Kelley *et al.*, 2003). The mechanisms for the exact pathways by which cytokines induce fatigue are not well understood, but TNF-α has been associated with alterations in central nervous system neurotransmission (Ryan *et al.*, 2007).

Schubert *et al.*, (2007) reviewed the link between fatigue and proinflammatory cytokines, and although there were limited studies and small sample sizes, they demonstrate that in general there is a significant positive correlation between fatigue and levels of circulating inflammatory markers (specifically IL-6) (Mills *et al.*, 2005; Bower *et al.*, 2002). However, there are a number of studies that do not support this relationship (Ahlberg *et al.*, 2004; Meyers *et al.*, 2005; Pusztai *et al.*, 2004). In general, the support for the role of cytokines in CRF has emerged from the chronic fatigue and rheumatoid arthritis literature, but the evidence related to cancer, particularly experimental, remains limited and inconsistent.

Another hypothesis proposed for CRF is the disturbance of the hypothalamic-pituitary-adrenal (HPA) axis, which can cause changes in the endocrine system. The HPA axis controls the release of coritsol in response to physical, biological or psychological stress. There is some evidence for an association between reduced cortisol output and fatigue in cancer (Bower *et al.*, 2002), however, the evidence for increased levels of cortisol remains inconclusive (Bower 2005). Proinflammatory cytokines stimulate the HPA axis, while cortisol has been shown to have a suppressive effect on proinflamatory cytokine

production (Bower *et al.*, 2007). Therefore, levels of cortisol may result from the direct suppression of the HPA axis by cancer treatment or changes in serotonin levels (5-HT) in the brain. As the direct functions of 5- HT include control of appetite, sleep, memory, mood, behaviour, muscle contraction and endocrine regulation (Passik *et al.*, 2002), 5-HT dysregulation could contribute to CRF.

However, many cancer patients suffer from CRF even in the absence of any identifiable cause (Lipman & Lawrence 2004). For example, it has been shown that even with a decrease in psychosocial correlates such as depression there was no effect on fatigue (Morrow *et al.*, 2003). More recently, a randomised controlled trial suggests that fatigue in cancer patients receiving chemotherapy is not associated with abnormalities in serotonin metabolism and depression (Roscoe *et al.*, 2005).

It has been suggested that cancer and its associated treatments can also have an effect on the brain (Vodermaier 2009; Mohile *et al.*, 2008; Alibhai *et al.*, 2006). Studies have found that both chemotherapy and ADT can have an effect on cognitive function. However, there is little literature investigating this in relation to fatigue.

In summary, there appear to be correlations between factors that arise from the central nervous system such as cytokines, cortisol, serotonin levels, and fatigue, but there is little experimental evidence to support the mechanisms behind these contributors towards fatigue, and the exact mechanism by which these cause the sensation of fatigue is yet to be determined.

Mechanisms related to other physiological systems

CRF is often accompanied by other treatable co-morbid conditions; the most commonly proposed include pain, anaemia and cachexia (Mock *et al.,* 2000). Anaemia (a haemoglobin level of < 12 and 14 g/dL in women and men respectively) is a common complication of treatment for cancer (Groopman & Itri 1999), with one third of patients undergoing chemotherapy becoming anaemic (Glaspy 2002; Cramp & Daniel 2008). The National Comprehensive Cancer Network (NCCN) (2011) identifies anaemia as one of the treatable factors that contribute to CRF. Earlier studies exploring the link between anaemia and fatigue failed to demonstrate a clear correlation between haemoglobin (Hb) and levels of fatigue in patients with cancer (Morant *et al.,* 1994). However, studies using the Functional Assessment of Cancer Therapy (FACT) questionnaire have reported a relationship between Hb levels and fatigue (Cella *et al.,* 2002). Yellen *et al.,* (1997) administered the FACT to 3 groups (non anaemic cancer patients, anaemic cancer patients, and the general population) and found that fatigue scores were significantly worse in the anaemic group compared with the non anaemic group, which in turn, were worse than those in the general population. Additionally, the degree of anaemia was predictive of the degree of fatigue.

Sobrero *et al.,* (2001) found that general QoL scores and subjective physical and functional well-being were significantly higher in patients with Hb levels of greater the 12g/dL when compared with patients with levels lower than 12 g/dL. In support of this, treatment of aneamia with erythropoietin-a has been shown in randomised controlled trials to improve fatigue in patients with cancer (Glaspy 2002).

Although anaemia and reduced haemoglobin levels explain the difference in fatigue levels compared with the general population, there are other contributing factors towards fatigue in cancer. In support of this, the overall fatigue level of cancer patients without anaemia has been reported to be greater than that of the general population (Cella *et al.*, 2002), suggesting that anaemia is only a partial contributor towards CRF. Also, the mechanism by which anaemia or reduced haemoglobin is sensed as a feeling of fatigue in these patients remains poorly understood.

There is a negative correlation between physical function and CRF (Brown *et al.*, 2005; Lee *et al.*, 2003). It has been hypothesised that cancer and its treatment could lead to a defect in the mechanism for regenerating ATP in skeletal muscle, compromising the ability to perform mechanical tasks and increasing physical fatigue. Although increased levels of uncoupling proteins accompanied by a reduction in ATP level have been reported in the skeletal muscle of patients with cancer (Ouimet *et al.*, 2009; Isaksson *et al.*, 2003), evidence is limited for the disruption of ATP metabolism (Ryan *et al.*, 2007). Perhaps more important is the reduction in physical activity that is seen in patients with cancer undergoing treatment. Sedentary habits and bed rest can lead to severe atrophy of muscle mass, which compromise physical function and lead to increases in the relative intensity of daily tasks. Reductions in muscle mass can lead to weakness which again increases the relative intensity of activities of daily living and thus contributes to the perception of fatigue.

The ongoing research into the 'mechanisms' contributing to fatigue provides little evidence to explain how the changes in physiological and psychological processes are interpreted as perceptions of fatigue. The neurophysiological basis for fatigue i.e. the perception and

sensation of fatigue is not well understood, although a number of hypotheses on how fatigue is sensed have been proposed. The perception of fatigue and effort exerted during a task may involve mechanisms such as signalling from the motor cortex to the primary somatosensory cortex (Enoka *et al.,* 1992). However, there is little research investigating the effects of cancer and treatment on the perceptions of fatigue during rest and activities of daily living.

Cook *et al.*, (2003) found perceived exertion was elevated in chronic fatigue syndrome (CFS) patients and that this contributed to increases in fatigue. Some authors have argued that CFS is a disease of increased effort sense (Edwards *et al.*, 1993). Wallman *et al.*, (2004) have looked at the physiological responses during submaximal exercise in patients with CFS compared with healthy controls and found that ratings of perceived exertion (RPE) were the only significantly different variable between the two groups. However, there is little research relating fatigue to the sense of effort in patients treated for cancer.

Treatment for cancer related fatigue

The NCCN (2011) propose guidelines for treatment of fatigue which include both pharmacologic strategies, combined with rest and energy conservation, and/or a variety of nonpharmacologic behavioural strategies. Evidence from pharmacologic treatments show that although there is some effect of treatment (in particular for psychostimulants such as methylphenidate and modafinil), there is also quite a large placebo effect observed in randomised controlled trials (de la Cruz *et al.,* 2010). Also, many patients continue to experience CRF even after clinical treatment of fatigue related symptoms (Mustian *et al.,* 2007). Consequently, the NCCN (2011) recommend that physicians treat patients with pharmacological interventions after other causes of fatigue have been excluded. However,

as CRF may be experienced without contributing clinical factors, pharmacological treatment is sometimes difficult and therefore it is best practice to consider a combination of pharmacologic and nonpharmacologic behavioural interventions for the treatment of CRF.

The strongest evidence for non pharmacologic treatment strategies are for physical activity enhancement, physical-based therapies and psychosocial interventions (support interventions, education, stress management, coping strategy training and behavioural interventions). Other strategies include integrative interventions (yoga, mindfulness-based stress reduction, and nutrition and sleep consultations).

Both psychosocial and integrative interventions have been reviewed as effective treatments for the management of CRF (Mustian *et al.*, 2007). However, of the non-pharmacological approaches to manage CRF, exercise has the most evidence for effectiveness (Galvao & Newton 2005; Knols *et al.*, 2005; McNeely *et al.*, 2006; Cramp & Daniel 2008).

Exercise as therapy to alleviate side effects from cancer treatment

It is beyond the scope of this thesis to provide an in-depth review on the effects of exercise in patients with cancer. However, this section provides the main evidence to support exercise as a form of therapy to alleviate CRF. It briefly explores reviews that have described exercise in patients on treatment for cancer and in patients on follow-up from cancer treatment.

Exercise is defined as the planned, structured, and repetitive bodily movement performed to improve or maintain specific components of physical fitness. It is performed in a

systematic manner (specific frequency, intensity, duration, and mode) with the intention of improving health-related outcomes, such as cardiovascular fitness, muscular strength, body composition, depression, anxiety, sleep, cognition, and fatigue. Periods of rest and inactivity (which are often increased during cancer treatment) lead to muscle wasting and loss of cardiorespiratory fitness, which in turn increase the perception of fatigue and ultimately reduce QoL. In contrast, exercise can improve functional capacity, thus reducing perceived effort and improving the perception of fatigue and QoL (Courneya *et al.*, 2003). It is increasingly being recognised that exercise is important in the recovery and rehabilitation from cancer and that changes brought about by exercise training may counteract the negative side effects that cancer and cancer treatment have upon physical capacity (Dimeo 2002). In addition, exercise may also improve the psychological complaints from cancer (Spence *et al.*, 2009) by improving mood, body image, and reducing anxiety and depression (Dimeo 2001).

Exercise interventions have been shown to be effective in alleviating fatigue experienced by cancer patients during treatment (Mock *et al.*, 2005; Mutrie *et al.*, 2007) and on follow-up from treatment (Burnham & Wilcox 2002; Daley *et al.*, 2007). However, due to different exercise prescriptions and assessment techniques, the most appropriate type of exercise for the alleviation of CRF remains to be explained and there is no agreement on the optimal components of exercise, particularly for different cancer types.

The results from three meta-analyses examining the effects of a combination of aerobic and resistance exercise, two in mixed cancer patients (Cramp & Daniel 2008; Kangas *et al.*, 2008) and one specifically in breast cancer patients (McNeely *et al.*, 2006) collectively support a reduction in fatigue during and post cancer treatment. Kanga *et al.*, (2008) found

that 35 % of 17 RCTs found an improvement in fatigue, with the effect size for the pooled mean effect being 'moderate' and considered clinically significant. The effect for exercise intervention during cancer treatment was higher than that post treatment, with the largest effect being in breast cancer patients.

Cramp & Daniel (2008) reported 28 RCTs examining the effects of exercise training on fatigue for both cancer patients and patients on follow-up from treatment. Those patients who received an exercise intervention experienced significantly less fatigue compared with the control conditions (standardised mean differences (SMD) -0.23). Exercise was statistically more effective at reducing fatigue than the control intervention for both participants during and post treatment; however, in contrast to Kanga *et al.*, (2008) exercise was more effective post treatment (SMD -0.37) than during treatment (-0.18). Thirteen studies included patients with specific cancer types and it was noted that fatigue improved the most in patients with breast and prostate cancer.

McNeely *et al.*, (2006) investigated the effect of exercise on fatigue in breast cancer patients only. They found that although there were significant improvements for fatigue in 6 studies, the studies that contributed most to this effect were two studies where exercise was undertaken post cancer treatment. The results of these meta-analyses should be interpreted carefully, as different cancer populations and different time points of the exercise intervention have different effects on fatigue.

Although more research is needed to determine the individual benefits of each exercise mode (aerobic, resistance or flexibility), there is evidence for a moderate to large effect of exercise training on improvements in aerobic and muscular fitness, quality of life and

fatigue in patients with breast and prostate cancer both during therapy and post treatment. The current guidelines on exercise testing and prescription (American College of Sports Medicine (ACSM), for patients with cancer (2010) reflect the American Cancer Society's recommendation of 30 to 60 minutes of moderate to vigorous intensity physical activity at least five days per week for patients who are otherwise healthy.

There is a wealth of evidence investigating the effects of exercise interventions in patients with breast cancer. The evidence is not as strong for the effect of exercise on the different aspects of fatigue in patients with prostate cancer. For this reason, the exercise intervention study in this thesis concentrated on patients treated for prostate cancer.

Barriers to exercise

Despite the evidence to suggest exercise as a therapy, it is not routinely undertaken by patients during and post treatment for cancer, nor is it routinely promoted by health care providers. It is estimated that patients with breast cancer decrease their physical activity levels 1 year post treatment compared with pre diagnosis levels (Irwin *et al.*, 2003). Vallance *et al.*, (2010) found that 30% of patients meet the ACSM recommended physical activity levels, whilst Irwin (2004) found that 32% of patients participate in the recommended weekly amount of physical activity (150 minutes per week of moderate to vigorous activity), this adherence, in fact, is slightly higher than the general population. Considering the beneficial effects of exercise in these population, it is important to both promote exercise and understand why a large proportion of patents to not engage in physical activity or exercise training.

Understanding the reasons why patients do not engage in exercise is a challenging topic. Previous studies have identified multiple barriers to physical activity within breast cancer patients. These include social, biological and psychological variables (Emery *et al.*, 2009) and also symptoms of disease and treatment related QoL (Courneya *et al.*, 2009). Biopsychosocial, health belief and self-efficacy models (Bandura, 1977) have been used to explain exercise behaviour in healthy populations. However, although these theories should not be disregarded within cancer patients, it appears that disease and treatment-related side effects are also a fundamental part of understanding the barriers to physical activity within breast cancer patients.

Knobf (1990) summarized potential and predictable effects of treatment for primary breast cancer and categorised them as those associated with mastectomy (i.e. reconstruction), with radiation therapy (i.e. breast soreness), and with symptomatology associated with both treatments (i.e. pain and fatigue). In addition, negative impacts of treatment on body image and weight gain (Smith & Reilly, 1994) are associated problems. Prolonged fatigue or muscle weakness and shortness of breath may also compromise patients' involvement in physical activity.

In summary, cancer patients will experience similar barriers as healthy population, but will also experience many treatment related side effects, such as fatigue and nausea, that could also act as barriers towards exercise. More understanding is needed regarding the relationship between fatigue and barriers to physical activity in this patient population.

Summary and outline of thesis

To date, while the full aetiology of CRF is yet to be clarified; it is evident that it is a multifactorial construct. As a consequence it is unsurprising that the symptoms of CRF may vary amongst cancer patients. Therefore, the general aim of this research programme was to investigate specific aspects or subtypes of fatigue and interventions that can ameliorate the symptoms of CRF.

There is a wealth of literature investigating fatigue in patients with cancer; however, the exact pathophysiology is not well understood. For the purpose of this thesis, a particular aspect of fatigue was studied, defined as 'physical fatigue'. This includes symptoms such as increased general exertion required to perform previously effortless daily tasks, limb heaviness, shortness of breath, dizziness and muscle pain during moderate tasks. The rationale for this definition of fatigue can be based upon research from patients receiving chemotherapy, where patients repeatedly report activities of daily living such as chores around the house and walking as being more effortful when they are fatigued (Curt, 2000). Qualitative data from a 'Cancerbackup' leaflet (2005) confirms this research with the following quotation 'Everything is too much effort. Just to comb your hair or get dressed is too much effort.' More recently Ryan *et al.*, (2007) suggest that 'fatigue is a sense of greater effort required to accomplish a task'.

The first study **[chapter two]** in this thesis was exploratory in nature, but was designed to investigate the hypothesised increase in perceived exertion in patients with cancer related fatigue, after chemotherapy. More specifically, it aimed to assess the physiological and/or psychological parameters associated with this increase in fatigue and perceived exertion reported both in previous published studies and anecdotally.

As previously discussed, the introduction of an exercise training programme is effective non-pharmacological treatment for CRF. There is strong evidence to support the use of exercise interventions in patients with fatigue, particularly in breast and prostate cancer. However, there is no consensus on the amount and type of exercise required to alleviate treatment related side effects, particularly in relation to prostate cancer patients undergoing treatment. The second study **[chapter three]** was based on previous literature that has looked at the effect of resistance training in prostate cancer patients receiving ADT. There is limited literature in relation to high intensity resistance training and its effect on both mental and physical fatigue. Therefore, the aim of **chapter three** was to assess the efficacy of a high intensity resistance training programme in alleviating side effects related to ADT treatment, such as increases in fatigue and reductions in muscle mass, strength and function.

Despite the well-known benefits of the effect of physical activity and exercise in patients treated for cancer, the majority of patients do not meet the recommended weekly physical activity guidelines. Therefore, the majority of patients are not gaining the benefits from exercise such as improved physical capacity, fatigue and QoL. Understanding the reasons for this are important when considering promoting exercise in these patients. Past literature has focused on psychosocial and treatment related side effects as barriers towards exercise, although the latter is less explored. Although studies have investigated the relationship between fatigue and physical activity levels in cancer patients, there is little research investigating perceived exertion as a barrier towards exercise. There is evidence to suggest that in healthy populations there is a negative relationship between physical activity levels and perceived exertion; and as patients undergoing treatment for cancer have

been reported to find activities of daily living more effortful, the last study **[chapter four]** aimed to further investigate this in relation to barriers towards physical activity.

Eventually the three studies included in the research programme should advance the knowledge-base regarding CRF and introduce targets for intervention to alleviate CRF in patients treated for cancer. Finally, this will enhance patient QoL and well-being, and will ultimately aid full recovery from cancer and/or its treatment.

In summary, the aims of this research programme were to;

- Gain a better understanding of the mechanisms of cancer related fatigue, with a particular focus on perceived exertion.
- Confirm the findings that exercise training can improve side effects associated with cancer and/or its treatment, such as fatigue.
- Understand further why patients might not engage in exercise despite the well known benefits of, with a focus on perceived exertion and fatigue.

Hypotheses

Chapter Two: There will be an increase in fatigue and perception of effort during treatment for breast cancer. This increase in perception of effort will be associated with the physiological or psychological parameters that are affected by cancer treatment.

Chapter Three: Exercise training will improve fatigue and quality of life in patients treated for prostate cancer. Exercise training will also improve muscle mass, strength, and physical functioning in these patients.

Chapter Four: Patients on follow-up for treatment for breast cancer will not engage in the recommended physical activity levels due to treatment related factors, such as fatigue and increased perceived effort.

Table 1. Physiological side effects of cancer treatment

System	Changes to the physiological system	Side effect or outcome
Immune system	Myelosuppression	Susceptible to infections Bruise more easily
Cardiovascular	Cardiotoxicity	Fatigue Anaemia
Pulmonary	Pulmonary fibrosis	Coughing Dyspnoea Fatigue
Gastrointestinal	Intestinal changes Narrowing of the bowel	Constipation Diarrhoea Loss of appetite Nausea/vomiting
Musculoskeletal	Sarcolema and mitochondrial changes	Muscle force changes Muscle weakness Fatigue Muscle imbalances Decreased range of motion
Neuroendocrine	Changes in the hypothalamus and pituitary glands Changes to the central nervous system Necrosis and atrophy	Confusion Numbness in hands and feet Muscle weakness Blurred vision Balance problems Urinary incontinence Memory loss Sleep disturbances
Nephrotoxicity	Hyperuricemia (abnormal amounts of uric acid in the blood)	Gout Kidney and bladder abnormalities Oedema
Dermatological	Destruction of healthy cells	Hair loss Skin infections and lesions Dermatitis

CHAPTER TWO

THE PSYCHOPHYSIOLOGICAL MEDIATORS OF PHYSICAL FATIGUE IN BREAST CANCER PATIENTS RECIEIVNG ADJUVANT CHEMOTHERAPY

Recent advances in cancer therapy have produced significant improvements in survival rates for many cancer types. However, modern treatments are associated with serious toxicity and the effects of cancer and its treatment can lead to long-term ill health in those who survive.

The most common side effects of cancer and cancer therapy include pain, nausea, vomiting, exertional dyspnea (Travers *et al.*, 2008) and fatigue (Sobrero *et al.*, 2001; Hofman *et al.*, 2007). Fatigue associated with cancer is distinct from the typical fatigue experienced by people as a result of normal daily life. Cancer related fatigue (CRF) is a complex syndrome that can be defined as a 'persistent sense of tiredness related to cancer and cancer treatment that interferes with usual functioning' (Mock 2004; Watson & Mock 2004). It can be characterised by an abnormal whole-body experience of tiredness, decreased capacity for both physical and mental work and persistent exhaustion that is not related to previous activity or exertion and is not relieved by rest (Glaus *et al.*, 1996; Morrow *et al.*, 2005) .

CRF is very common, with most studies reporting prevalence rates between 60 and 90% (Cella *et al.*, 2000). CRF is one of the symptoms frequently reported by patients at diagnosis; it increases during treatment including radiotherapy, chemotherapy and immunotherapy, and is still present in 1/3 of patients on completion of treatment (Minton *et al.*, 2008).

CRF can have a negative impact on patients' quality of life, ability to perform activities of daily living, and relationships with family. Despite CRF being the most prevalent and frequently reported symptom by cancer patients, until recently is has been underecognised

and undertreated (Ryan *et al.*, 2007). In fact, until recently, the most common advice given to cancer patients by health care professionals was to rest (Curt *et al.*, 2000). Unlike other subjective symptoms, such as pain and nausea, there is little focussed research into specific types of CRF and as a result, the pathogenesis of this symptom is poorly understood; as a consequence there is no specific medical treatment for CRF.

In terms of existing research into CRF, management of CRF has focussed on correcting sleep disturbances, hypothyroidism, anaemia, infections, depression and physical deconditioning (Morrow 2007). However, although there is an association between these physiological contributors and fatigue, the contributors do not necessarily cause fatigue, therefore the research does not explain the underlying mechanisms. Most research into the mechanisms of fatigue has focussed on psychosocial correlates such as depression or on biological mediators such as cytokines. However, many cancer patients suffer from CRF even in the absence of any identifiable, reversible cause (Lipman & Lawrence 2004). For example, it has been shown that even with a decrease in psychosocial correlates such as depression, there was no effect on fatigue (Morrow *et al.*, 2003).

One problem with the research onto the mechanisms of CRF is the definition of fatigue itself. Fatigue is a multifaceted symptom with different physical, cognitive and affective dimensions (Wessley *et al.*, 1998). As with other subjective symptoms, such as pain and nausea, it might be of interest to study a particular type or sub-type of fatigue, as different aspects of fatigue could potentially have different pathophyisologies and mechanisms. One of the main features of fatigue is the sense of effort in relation to a task (Wessley, *et al.*,1998). This study proposed to look at this aspect of fatigue, and in particular operationally defined physical fatigue as 'the sense of effort in relation to a physical task'.

The support for the use of this definition of fatigue is based on research from patients receiving chemotherapy, where patients repeatedly report activities of daily living such as chores around the house and walking as being more effortful when they are fatigued (Curt *et al.*, 2000). Qualitative data from a 'Cancerbackup' leaflet (Coping with fatigue, 2005) confirms this research with the following quotation 'Everything is too much effort. Just to comb your hair or get dressed is too much effort.' More recently Ryan *et al.*, (2007) suggest that 'fatigue is a sense of greater effort required to accomplish a task', and also suggest that the relationship between the sense of effort and fatigue has not yet been explored within the cancer related fatigue literature. Although perceived exertion has been measured in cancer patients during exercise (Evans *et al.*, 2009), it has not been investigated in the context of fatigue.

A rating of perceived exertion involves an individual actually interpreting and measuring their perceived exertion or sense of effort on a predefined semantic scale. A measure of perceived exertion is the 'degree of heaviness and strain experienced in physical work as estimated according to a specific rating method' (such as the Borg rating of perceived exertion (RPE) scale) (Noble & Robertson, 1996).

Several physiological parameters including ventilation, oxygen consumption (VO_2) and metabolic acidosis have been shown to be associated with RPE (Noble & Robertson, 1996). Studies have also demonstrated the role of respiratory and peripheral muscle weakness in mediating the sense of effort and dyspnea during exercise in patients with pulmonary and cardiac disorders (Jones & Killian 2000). More recently Travers *et al.*, (2008) have discussed the mechanisms of exertional dyspnea in cancer patients and the

role of weakened respiratory muscles and Marcora *et al.*, (2009) have discussed the role of mental fatigue in relation to perceived exertion.

The effects of chemotherapy on cardiorespiratory and metabolic responses to exercise have not been fully investigated, but studies have shown that various cytotoxic agents can have an effect on hemoglobin concentration and also cardiac function, vascular reactivity and blood rheology (i.e. causing reductions in blood flow). It is also possible that several other factors, such as mood and sleep disturbances, could affect RPE, without significant changes in physiological parameters. Therefore, based on previous literature where associations have been found between physiological and psychological parameters and perceived exertion, changes within the body during treatment for cancer could affect perceived exertion.

The aims of this study were 1) to provide psychophysiological evidence to existing anecdotal observations that chemotherapy increases perceived exertion during physical tasks and 2) to investigate whether this increase in perceived exertion was associated with alterations in cardiorespiratory, metabolic and muscular function or mood.

Methods

Participants

After ethical approval from the North West Wales NHS Trust, 13 female patients treated for stage II-III breast cancer by definitive surgery and receiving outpatient adjuvant chemotherapy were recruited for the study. Recruitment was undertaken by Oncology consultants and researchers at the outpatient's clinic at the local hospital. The mean time since cancer diagnosis was 5.2 ± 0.7 months and surgery history consisted of lumpectomy (n = 3), mastectomy (n = 6), lumpectomy plus mastectomy (n = 2) and double mastectomy (n = 2). Chemotherapy treatment consisted of Epirubicin (EPI) in n = 6; Cyclophosphamide, Methotrexate and Fluorouracil (CMF) in n = 4; and Fluorouracil, Epirubicin and Cyclophosphamide (FEC) in n = 3. Mean number of chemotherapy cycles was 4.5 ± 1.2 (range; 3 to 7). Thirteen sex and age matched healthy (no history of cancer) controls were recruited from the local community via word of mouth. Both patients and controls were excluded if they had any significant cardiovascular (e.g. ischemic heart disease, cerebravascular disease, severe anaemia or uncontrolled hypertension), pulmonary (emphysema or asthma), metabolic (gross obesity or uncontrolled diabetes), renal or neuromuscular disease. Further exclusion criteria included the prescription of any drug known to affect the normal physiological response to exercise (e.g. beta blockers) (see Table 1 for baseline subject characteristics).

Design

This was a repeated (pre/post) experimental design. All participants visited the laboratory on two different occasions. In patients, visit 1 occurred 1-2 days before scheduled chemotherapy treatment, the patients then visited the laboratory on a second occasion (visit 2) where all procedures were repeated. Visit 2 was 3-5 days post chemotherapy as this is

when patients report more severe feelings of fatigue (Ryan *et al.*, 2007). The same time period between visits (4-7 days) was observed for controls.

Procedures

During the first visit, the study and its aims were explained, and a medical and lifestyle questionnaire was administered. Eligible participants signed an informed consent form and anthropometric measures were taken. Leisure and work time physical activity was assessed using a 4 category scale (ranging from sedentary to very active). The cancer patients were also asked to recall their leisure and work time physical activity levels pre treatment. During both visits, grip strength, fatigue, cancer symptoms, affect and physiological and perceptual responses to exercise were measured.

Fatigue

Clinical fatigue was assessed using the brief fatigue inventory (BFI) (Mendoza *et al.*, 1999). The BFI includes a 3-item fatigue severity scale and a 6-item interference scale. The first 3-items describe the patient's severity of fatigue, with 0 being "no fatigue" and 10 being "fatigue as bad as you can imagine". The last six items assess how much fatigue symptoms interfere with various aspects of the patient's life (general activity, mood, walking ability, normal work (including housework and work outside the home), relationships with others, and enjoyment of life) during the past 24 hours; with 0 being "does not interfere" and 10 being "completely interferes." Thus, higher scores represent more severe fatigue.

Cancer symptoms

Cancer symptoms were assessed using the MD Anderson Cancer Symptom Inventory (MDASI) (Cleeland 2000). The MDASI includes a 13-item symptom scale and a 6-item

interference scale. The first 13 items describe the patient's symptoms during the last 24 hours, with 0 being "not at all" and 10 being "as bad as you can imagine." Similar to the BFI, the last six items assess how much the symptoms interfere with various aspects of the patient's life during the past 24 hours. Again, higher scores represent more severe cancer symptoms. The validity and reliability of the BFI and MDASI have been established (Cleeland 2000).

Affect

Mood was assessed using the positive and negative affect scale (PANAS). The scale consists of a number of words that describe different feelings and emotions. The participants were asked to rate on a 5-point scale the extent to which they experienced each mood state at that particular moment. The points of the scale are labelled "very slightly or not at all", "a little", "moderately", "quite a bit", and "very much". The scores were summed to produce one positive (P) and one negative affect score (N). The validity and reliability of the PANAS has been established (Watson *et al.,* 1988).

Physiological and perceptual responses to exercise

A submaximal exercise test (2 min at 0, 25, 50, 75 W) was performed on a cycle ergometer (Corival, Lode). Tidal volume (L), breathing frequency (min^{-1}), ventilation ($L.min^{-1}$), oxygen consumption (VO_2; $L.min^{-1}$), and carbon dioxide production (VCO_2; $L.min^{-1}$) were measured breath-by-breath using computerised metabolic gas analysis systems (600Ergo Test, ZAN Messgera, Germany: MetaLyzer 3B, Cortex Biophysik, Leipzig, Germany). These automated devices were calibrated before each test using certified gases of known concentration (11.5% O_2 and 5.1% CO_2) and a 3.0 L calibration syringe (series 5530; Hans

Rudolph). All respiratory gas exchange data were averaged over 30-sec periods for statistical analysis. Repeated tests were performed on the same breath-by-breath system. During rest and 1 min after the end of the submaxiaml exercise test, a 5 µl sample of whole fresh blood was taken from the right earlobe and analysed for lactate concentration ($mMoL^{-1}$) using a portable analyzer (Lactate Pro LT-1710; Arkray, Shiga, Japan). Lactate production was calculated by subtracting the resting value from the value obtained post exercise. Resting haemoglobin concentration was also measured using a B-heamoglobin photomoter (Hemocue, Sweden). During the final 15s of each minute of exercise, subjects were asked to give their overall rating of perceived exertion (RPE) using the 15-point scale (Borg, 1986). Subjects were given standard instructions for overall rating of perceived exertion developed by Borg.

A bioimpedance device (Physioflow PF05L1; Manatec, Petit-Ebersviller, France) was used to measure heart rate (HR), stroke volume (SV), and cardiac output (CO). Two sets of two electrodes (AmbuBlue Sensor VL; Ambu, Ballerup, Denmark), one transmitting and the other one receiving a low amperage alternating electrical current, were applied on the supraclavicular fossa at the left base of the neck and along the xiphoid. Another set of two electrodes was used to monitor a single ECG lead in the V1/V6 position. All electrode placement areas were cleaned with an alcohol pad, and dried with a paper towel. Wires connected to the electrodes were fixed on the body using tape to reduce movement artifacts. SV (ml) was estimated by this computerized device from changes in transthoracic impedance during cardiac ejection. CO ($L.min^{-1}$) was calculated as CO = (HR x SVi x BSA)/1,000, where BSA is body surface area (m^2) calculated according to the Haycock formula [BSA = 0.02465 x body mass $(kg)^{0.5378}$ x height $(cm)^{0.3964}$] and SVi (ml/m^2) = SV/BSA. HR (min^{-1}) was based on the R-R interval determined from the first

derivative of the ECG. These data were averaged over 30-sec periods before statistical analysis. Before each test, the Physioflow was autocalibrated using a procedure based on 1) 30 consecutive heartbeats recorded while the participant was resting in a seated position on the cycle ergometer, 2) anthropometric data, and 3) resting systolic and diastolic blood pressure values (mmHg). These values were the averages of two separate blood pressure recordings taken before and after the Physioflow autocalibration using an automated blood pressure monitor (Tango; SunTech Medical, Morrisville, NC). Blood pressure was also monitored at the end of each 2 min stage. Mean arterial pressure (MAP) (mmHg) was calculated as MAP = [(2 x diastolic pressure) + systolic pressure]/3. Total peripheral resistance (TPR) ($mmHg \cdot l^{-1} \cdot min^{-1}$) was calculated as TPR = MAP/CO.

Statistical analyses

All data are presented as means ± standard deviation (SD), unless otherwise stated. The effects of cancer and chemotherapy on RPE and physiological data were analysed using multiple mixed model (group x time x workload) factor analyses of variance (ANOVA) with repeated measures for time and power output. Clinical fatigue (BFI), cancer symptoms, blood lactate production, haemoglobin concentration, hand-grip strength, and affect were analysed using mixed model (group x time) ANOVAs. For all ANOVAs, if a significant group x time interaction was revealed, *post hoc* analyses were performed using the bonferroni *t*-test method. The assumptions of sphericity and normality of distribution were verified by Mauchly's test and the Kolmogorov-Smirnov test, respectively. Significance was set at $p < 0.05$ for all analyses, which were conducted using the Statistical Package for the Social Sciences Version 12.0.

Results

A total of 107 patients were approached, of whom 52 met all the eligibility criteria. Of these, 27 declined participation due to time and travel concerns and 8 had further medical complications. Seventeen were enrolled in the study and 13 completed all testing procedures. Reasons for not completing testing included the following; Too fatigued (n =1), medical complications (n = 2) and unable to tolerate the exercise protocol (n = 1). The 13 patients were age and sex matched to healthy controls who were recruited by word of mouth.

Comparison of demographic data between groups is shown in Table 1. There were no significant differences between the groups for age, height and body mass. There were differences in self reported leisure time physical activity; however, these differences were not apparent when 'pre treatment leisure time physical activity' was used for the cancer patients ($p = 0.33$). Comparison of baseline resting physiological values demonstrated significant differences between the two groups for heart rate, resting hemoglobin and systolic blood pressure. There were no significant differences between the two groups for baseline resting blood lactate and diastolic blood pressure.

Subjective reported symptoms

Using the MDASI, patients reported significantly more symptoms associated with cancer compared to the controls (main effect of group; $p = 0.00 - 0.04$). There were no main effects of group for vomiting ($p = 0.28$) and numbness/tingling ($p = 0.24$). There were group x time interactions for the following symptoms; fatigue ($p = 0.04$), disturbed sleep ($p = 0.02$), shortness of breath ($p = 0.01$) and lack of appetite ($p = 0.03$), where patients rated these symptoms significantly higher post chemotherapy compared to baseline (Figure 1).

There was a significant main effect of group for fatigue measured using the BFI, where patients reported significantly higher global fatigue compared with controls ($p < 0.001$). There was also a significant group x time interaction ($p < 0.001$); where patients reported higher global fatigue scores post chemotherapy compared to baseline (Figure 2).

Ratings of perceived exertion

There were no triple interactions (group x time x workload) for any of the measured variables, therefore, two-way (group x time) repeated measures ANOVAs were used to analyse the data, using the grand mean from all four workloads. Data are presented in figures as the grand mean for all four workloads at each time point (pre and post chemotherapy) for each group (cancer and control) (Data for each workload are presented in Appendices, p152).

Patients reported significantly higher ratings of perceived exertion across all power outputs compared with controls (main effect of group; $p < 0.001$). A group x time ANOVA revealed a significant interaction for RPE ($p = 0.037$), where patients reported higher ratings of perceived exertion post chemotherapy (Figure 2) (See Appendices, p153: Table 1 for full data).

Cardiovascular parameters

The cardiovascular data are presented in Figure 3 (Full raw data are tabulated in Appendices, p154: Table 2). There were main effects of group for exercising heart rate ($p = 0.050$), systolic, ($p = 0.007$) diastolic ($p = 0.004$), mean arterial blood pressure ($p = 0.003$) and total peripheral resistance ($p = 0.048$). The cancer patients had significantly elevated heart rate and lowered systolic, diastolic, mean arterial blood pressure and total

peripheral resistance at all power outputs, compared with controls. There were no main effects of group for cardiac output ($p = 0.949$) or stroke volume ($p = 0.193$). There were no group by time interactions for any of the cardiac variables, indicating no changes in these variables post chemotherapy. Resting Hb concentration was consistently lower in the cancer patients compared with the controls with two out of the 13 patients being classed as anaemic (<12 g/dL). There was a main effect of group for Hb concentration ($p = 0.001$), indicating that it was consistently lower in the cancer patients compared with the controls (Figure 3*H*).

Respiratory and metabolic parameters

There was a main effect of group for respiratory exchange ratio (RER), with cancer patients having a higher RER at both time points compared with the controls; however this did not change over time (no interaction). There were no main effects of group or interactions for any of the other respiratory data (VO_2, VCO_2, VE, VT and BF), indicating no differences between the two groups at baseline and no changes in these data post chemotherapy (Figure 4) (Full data are tabulated in Appendices, p154: Table 3).

There were no significant differences in resting blood lactate between the two groups ($p = 0.23$). However, there was a significant main effect for blood lactate production, where cancer patients had significantly higher blood lactate production than controls at both time points ($p = 0.03$). There were no changes in blood lactate production in either group post chemotherapy (Figure 5).

The workloads were designed to replicate activities of daily living; therefore, each workload was converted into metabolic equivalents (METs) (Absolute VO_2 was converted

to relative VO_2 using body mass is kgs, which was divided by 3.5 ml). The 0, 25, 50 and 75w stages corresponded to an average of 2.1, 2.7, 3.6 and 4.7 METs respectively (Figure 6). There were no significant differences between the cancer and control group for each METs values ($p = 0.567$). There were no changes in VO_2 data post chemotherapy; therefore, the METs value for each workload did not change over time.

Muscle function

There was no main effect of group ($p = 0.22$) or group by time interaction for grip strength ($p = 0.20$) (Figure 7).

Mood

There was no main effect of group ($p = 0.22$) or group by time interaction for either positive or negative mood ($p = 0.20$) (Figure 8).

Discussion

The purpose of this study was to provide psychophysiological evidence to existing observations that chemotherapy increases perceived exertion during physical tasks, and to investigate whether this increase in perceived exertion was associated with alterations in cardiorespiratory, metabolic and muscular function or mood. For the purpose of this discussion, the baseline differences between cancer patients and healthy controls will be discussed first, which examines the effects of cancer and previous treatment on the measured parameters. This is followed by comparisons between pre and post treatment, which discusses the effects of an acute bout of chemotherapy on the measured parameters.

Effects of cancer and previous chemotherapy

The main findings of this study suggest that breast cancer patients have significantly elevated feelings of fatigue when compared with healthy controls. The patients reported significantly higher global fatigue using the BFI and fatigue on the subscale of the MDASI at baseline compared with the controls. This is in agreement with the literature that one of the main side effects from cancer and its treatment is fatigue (Hofman *et al.*, 2007; Ryan *et al.*, 2007).

Most importantly, the findings from this study revealed that the breast cancer patients reported significantly higher ratings of perceived exertion during cycle ergometry than the controls. The elevated baseline perception of effort can be explained in part by the decreased exercise capacity in the breast cancer patients. The cardiovascular and metabolic parameters suggest that the cancer patients physical fitness is reduced compared with the controls; this is reflected by elevated resting and exercising heart rate, reduced stroke volume (although not significant), increased blood lactate production and

respiratory exchange ratio. The reductions in physical fitness could be explained by reduced physical activity levels in the breast cancer patients. In the present study the patients reported significantly lower levels of leisure physical activity compared to the controls. Also, pre-treatment physical activity levels were significantly higher than during treatment in the cancer patients, suggesting a decline in leisure time physical activity after commencing chemotherapy treatment. It has been observed that physical activity is reduced in breast cancer patients undergoing adjuvant chemotherapy treatment (Irvine *et al.*, 1994).

There were no baseline differences at rest or during exercise between the cancer patients and controls for VO_2, VCO_2, VE, BF and VT. Ventilation was slightly higher in the cancer patients, but not significant and this was due to a slightly higher breathing frequency, although not significant. It is common for cancer and treatment to cause breathlessness, which is often present without anaemia (Travers *et al.*, 2008). The cancer patients reported significantly higher subjective feelings of breathlessness at baseline compared with the controls, which is in line with previous research; however, there was no statistically significant difference in the breathing frequency data. RER was significantly increased in the cancer patients compared with the controls; this was due to a slightly lower VO_2 and higher VCO_2 in the cancer patients, although neither of these were significant. At the end of the 50W stage, the cancer patients had reached an RER of 1.0, therefore, using predominately more anaerobic respiration than the controls (RER of 0.88).

Although only two out of the 13 breast cancer patients were classed as anaemic (9.6 and 10.7 g/dL), the breast cancer patients had significantly lower baseline Hb concentration compared with healthy controls, with an average of 12.7 vs. 14.9 g/dL. The reduction in

Hb concentration is expected in cancer patients undergoing chemotherapy and is in line with previous literature, where Glaspy (2002) suggest that 1/3 of cancer patients undergoing chemotherapy will become anaemic after 3 cycles of treatment. The reasons for reduced levels of Hb concentration within the present study are multifactorial, but are likely to be due to the cytotoxic effects of chemotherapy on both the production (Ryan *et al.*, 2007) and life span of erythrocytes (Bron *et al.*, 2001).

There is a known association between cancer-related fatigue and low Hb levels (Cella *et al.*, 2002; Glaspy 2002), with one of the hypotheses for this relationship being organ tissue hypoxia (Ryan *et al.*, 2007). Within the present study, arterial oxygen content (CaO_2) was significantly lower in the cancer patients compared with the controls at rest and after exercise (data not shown). This difference was due to the reduced amounts of Hb in the blood as opposed to reduced oxygen saturation of the Hb (SaO_2). Previous studies have looked at the physiological adjustments to compensate for reduced oxygen carrying capacity during anaemia or reduced Hb concentrations. It is well established that anaemia or low Hb concentration influences exercise capacity and cardiopulmonary responses to exercise. In contrast to maximal exercise, it appears that during acute anaemia, at submaxmimal workloads, CO is elevated, compensating for impaired O_2 delivery (Ekblom, 1972). It has been suggested that the more rapid the onset of anaemia, the larger the increase in CO. Woodson *et al.*, (1978) found that the rapid increase in CO at rest and during exercise in response to acute anaemia (15.3 to 10.0 g/dL) decreased to within baseline levels after a 2 week period of established anaemia, which caused a reduction in O_2 delivery. This supports the present study where the cancer patients had significantly lower Hb concentration than the controls, with no difference in CO. However, there were no significant differences in O_2 delivery between the two groups, but this is probably a

reflection of the Hb concentrations not being as low as in Woodson's study. In support of this, Brannon *et al.*, (1945) found that whilst observing 18 anaemic patients, CO at rest was only increased in patients with severe anaemia (less than 7 g/dL). This suggests that the reduction in Hb within the cancer patients is not severe enough to elicit the compensatory changes to CO seen in acute (Ekblom, 1972) and more severe chronic anaemia (Brannon *et al.*, 1945). As CO is not increased, O_2 delivery is probably slightly reduced in the cancer patients, which could contribute to increased feelings of effort.

Within the present study, the lower hemoglobin levels cannot fully explain the increased feelings of fatigue within this population, as estimated whole body O_2 delivery was not significantly reduced. Interestingly, there was no correlation between Hb concentration and feelings of fatigue using the BFI and ratings of perceived exertion. In support of this, the overall fatigue level of cancer patients without anaemia has been reported to be greater than that of the general population (Cella *et al.*, 2002), suggesting that anaemia is only a partial contributor to cancer related fatigue.

The breast cancer patients have the same CO as the controls, so they do not appear to be compensating for a reduced Hb level. Therefore there is reduced systemic O_2 delivery, which is likely to limit O_2 delivery to the muscle. In line with this, the patients have increased lactate production, so is it could be that the patients are using predominately more anaerobic respiration compared to the healthy controls.

In summary, there is an increase in fatigue compared with healthy controls which is apparent using RPE during cycle ergometry and clinical fatigue questionnaires. The advantage of using RPE as opposed to clinical questionnaires is that it allows real time

assessment of physical fatigue which allows the concurrent measurement of physiological parameters. The explanations for this elevated RPE include a reduced physical fitness, indicated by elevated HR, RER and blood lactate production for the same absolute workloads. Even though the cancer patients have decreased Hb levels (oxygen availability), this is not compensated for by elevated cardiac output (oxygen delivery).

The effects of an acute bout of chemotherapy

Post chemotherapy, the cancer patients had significantly elevated fatigue, measured using the BFI and the MDASI. This is in agreement with the literature, where it is suggested that patients receiving chemotherapy will experience increased feelings of fatigue 3-5 days post treatment (Ryan *et al.*, 2007). Some symptoms on the MDASI, such as lack of appetite, disturbed sleep and breathlessness were also significantly increased. The most interesting finding was that the breast cancer patients had a significant elevation in RPE during exercise compared with baseline. There were no concurrent changes in any of the physiological data, which suggests that the increase in RPE is not due to any of the physiological variables measured in this study.

Although the effects of chemotherapy on the body have been studied, there appears to be a lack of evidence for direct effects of chemotherapy on cardiovascular and metabolic processes, but studies have shown that various cytotoxic agents can have an effect on haemoglobin concentration and also cardiac function, vascular reactivity and blood rheology (causing reductions in blood flow). This is one of the first studies to investigate the effects of chemotherapy on the metabolic and perceptual responses to exercise. Although there appear to be chronic effects of cancer and previous treatment on parameters such as Hb, blood lactate (although we can not tell whether these are just because of

reduced physical capacity), there are no acute effects (i.e. the effects of one bout) of chemotherapy on any of these measured cardiorespiratory and metabolic parameters. The data suggest that the acute increase in perceived exertion after one bout of chemotherapy is not due to the direct effects of chemotherapy on the physiological parameters measured.

It is possible that several other factors could affect RPE, such as mood and sleep disturbances, without any significant changes in physiological parameters. The increase in RPE post chemotherapy was associated with increases in the subjective self-reported feelings of breathlessness, disturbed sleep and lack of appetite.

The increase in disturbed sleep could be a reason for the increase in RPE, however, future research is needed to investigate whether one bout of chemotherapy does in fact reduce sleep quality using an objective measure such as an actigraph. It is worth noting that the majority of chemotherapy patients receive dexamethasone for 1-3 days to prevent vomiting, which is known to cause sleep disturbances. Within the exercise physiology literature, sleep deprivation has been shown to affect RPE (Oliver *et al.*, 2009), however, these are very severe periods of sleep deprivation (30 h with no sleep), with only modest increases in RPE. Therefore research that objectively measures these self-reported changes would be useful in determining if they are associated with changes in RPE.

In summary, there is an increase in perceived exertion and clinical fatigue after one bout of chemotherapy, which can not be explained by the measured physiological and psychological variables within this study. This study provides evidence to suggest that chemotherapy can have an effect on the central nervous system. Future research is needed

within this area to determine what the direct effects on the CNS system are and how they relate to perceived exertion in these patients.

In conclusion, this study provides quantitative evidence to suggest that compared with healthy matched controls, this population of cancer patients has a significantly elevated baseline perception of effort during physical tasks. The reasons for this are multifactorial, but can be explained partly by decreased exercise capacity, possibly due to a reduction in physical activity, a reduced resting heamoglobin (although not anaemic), and an increase in blood lactate production and RER.

However, the acute effects of one bout of chemotherapy on perception of effort cannot be explained by any of the measured physiological and psychological parameters. Possible future research might look to explain in more depth the mechanisms for the acute effects of chemotherapy on physical fatigue and in particular focus on the possible direct effects of the central nervous system on perception of effort in this population.

Clinical recommendations based on past literature and this study should try to promote physical activity in breast cancer patients during treatment. The baseline differences in fatigue could be corrected in part by increased levels of physical activity; decreasing HR, reducing lactate production and possibly improving Hb levels, which would reduce perception of effort. In turn this would reduce the abnormal effort these patients perceive during activities of daily living.

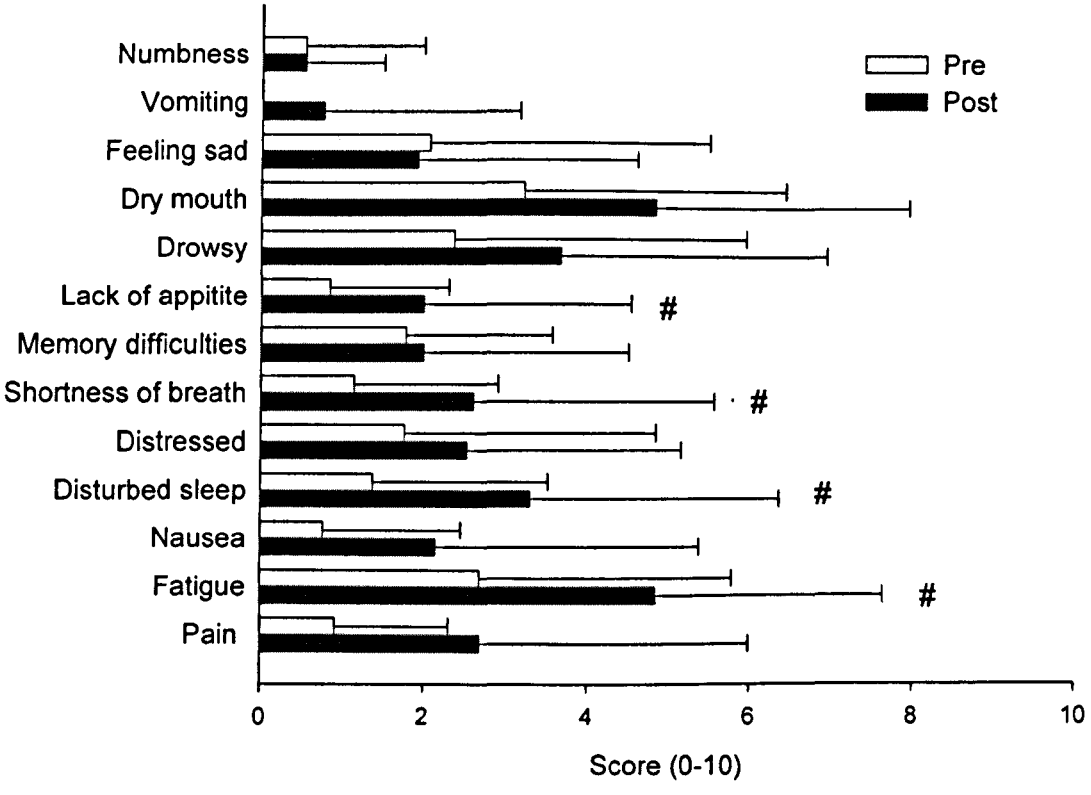
Tables and figures

Table 1. Demographic and baseline resting physiological data for breast cancer patients and age matched healthy controls

	Breast cancer	**Healthy controls**	***p* value**
Age (yr)	48.7 ± 11.1	50.2 ± 7.7	0.701
Cancer Stage (*n*)			
II	4	Not Applicable	
III	9		
Cancer type (*n*)			
Ductal carcinoma	10	Not Applicable	
Lobular carcinoma	3		
Treatment cycle	5 (3-7)†	Not Applicable	
Height (cm)	164 ± 5.6	164 ± 3.9	0.990
Body Mass (kg)	74.1 ± 13.9	68.6 ± 10.0	0.258
Body Fat (%)	36.6 ± 7.5	34.3 ± 6.6	0.410
Physical activity (1-4)			
Work	1.6 ± 0.8	2.0 ± 1.0	0.236
Leisure	1.6 ± 0.7	2.4 ± 0.5	0.003 *
Resting Heart Rate (bpm)	85 ± 16	73 ± 9	0.031 *
Systolic BP (mm Hg)	111 ± 15	128 ± 16	0.007 *
Diastolic BP (mm Hg)	75 ± 9	77 ± 10	0.486
Blood Lactate (mM)	1.1 ± 0.4	1.0 ± 0.1	0.278
Resting Heamoglobin (g/dL)	12.7 ± 1.5	14.9 ± 1.3	0.000*

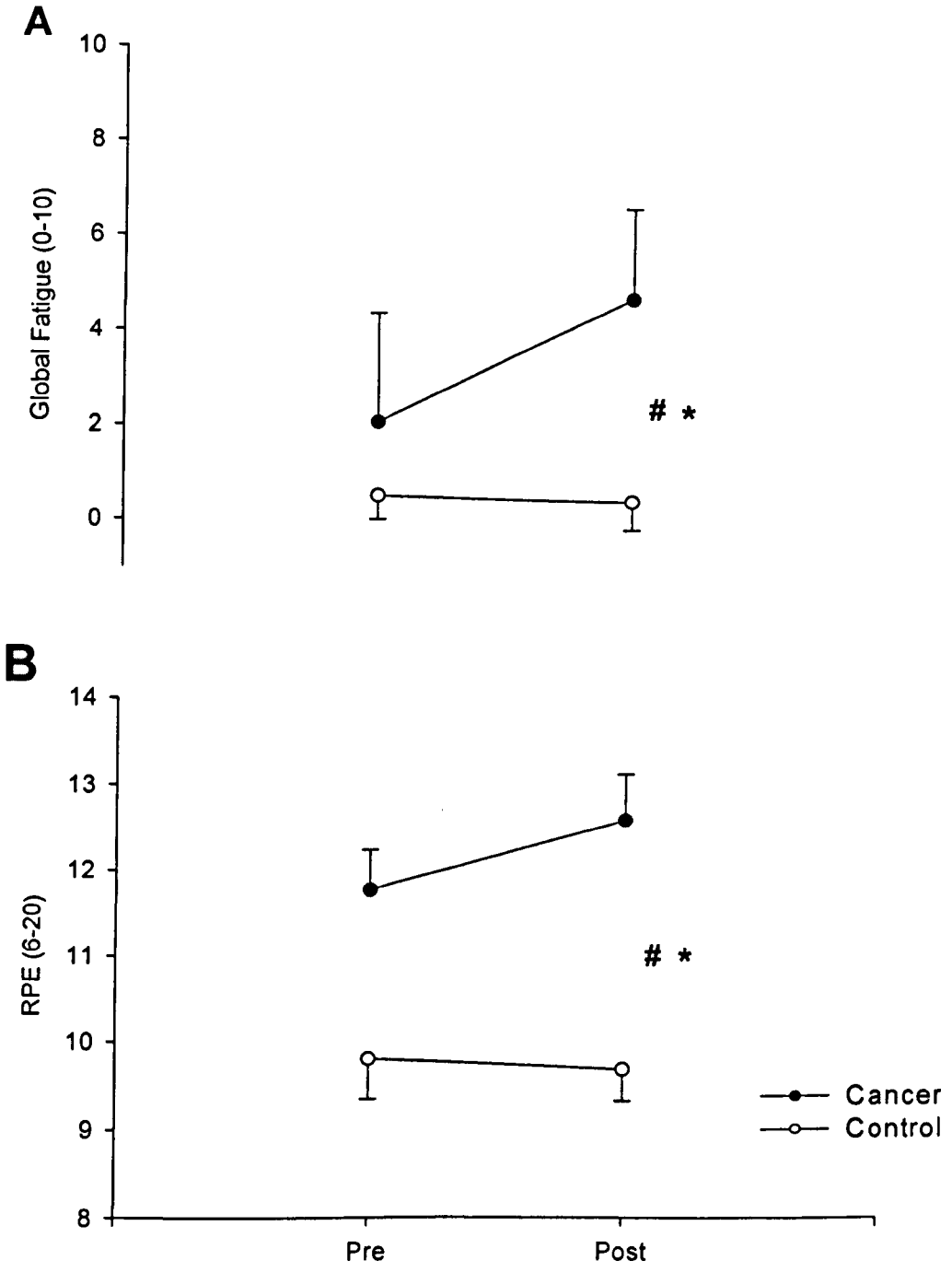
Data are means ± SD or no. of subjects (n). † Data are median with range. * significant difference between groups ($p < 0.05$) ($n = 26$)

Figure 1. The effects of cancer and chemotherapy on reported cancer symptoms using the MD Anderson Symptom Inventory



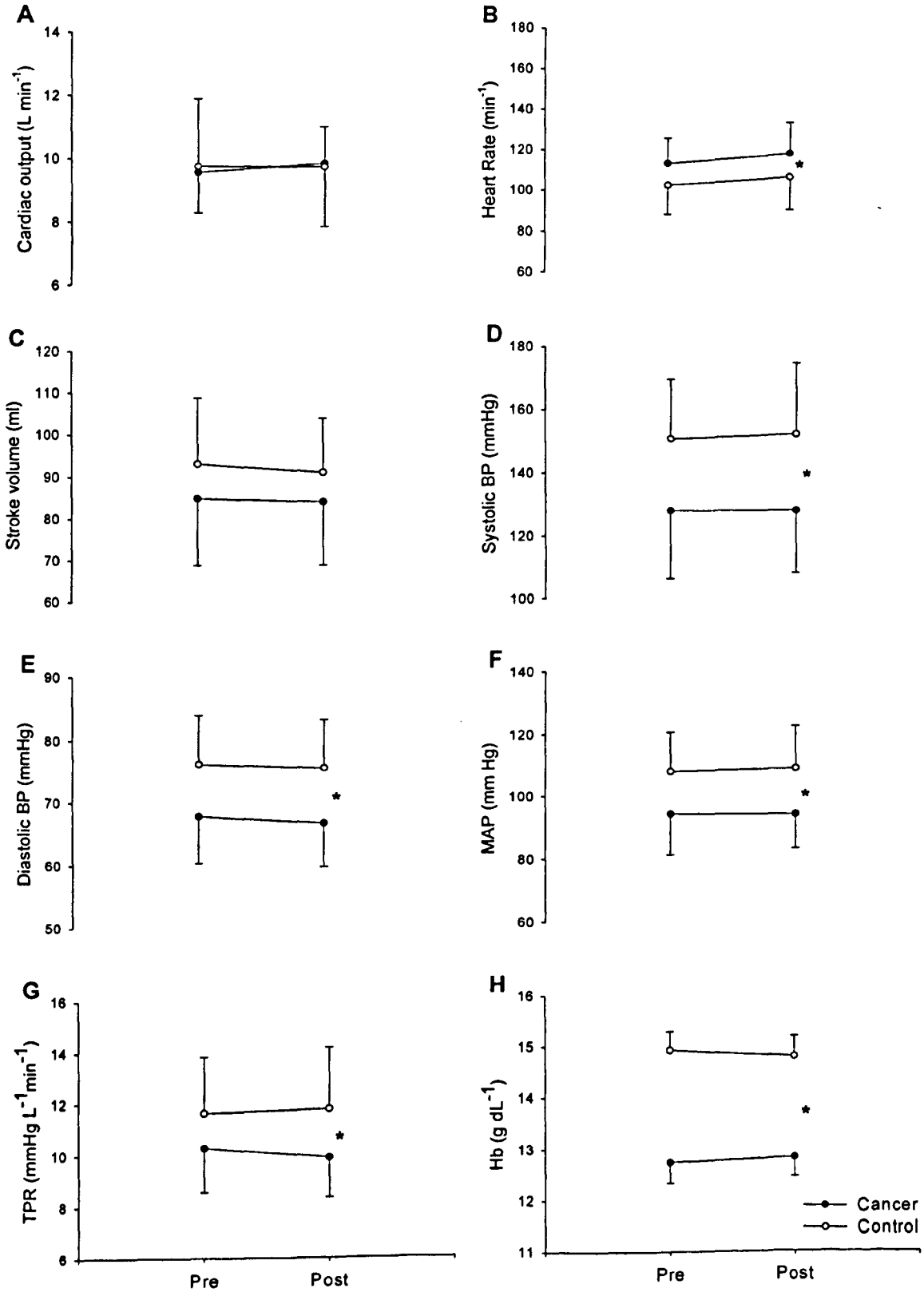
Data are means ± SD. Severity of symptoms in the preceding 24 hours on a 0-10 scale, with 0 being 'not present' and 10 being 'as bad as you can imagine'. # Significant interaction ($p < 0.05$) ($n = 13$)

Figure 2. The effect of cancer and chemotherapy on fatigue measured using the brief fatigue inventory (A) and ratings of perceived exertion using the 6-20 RPE scale (B)



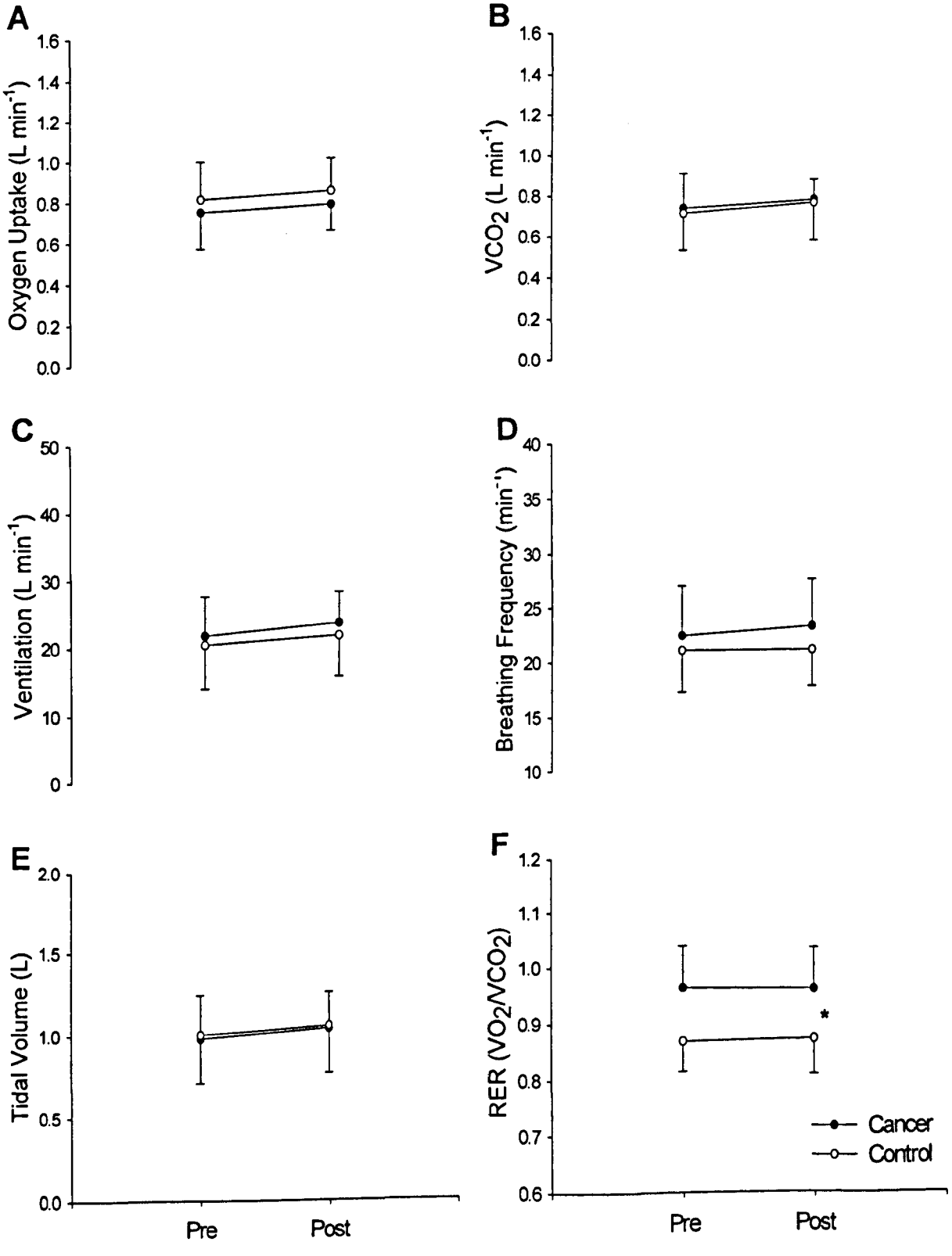
Data are means ± SD. # significant interaction ($p < 0.05$). * significant main effect of group ($p < 0.05$) ($n = 26$).

Figure 3. The effect of cancer and chemotherapy on cardiovascular parameters



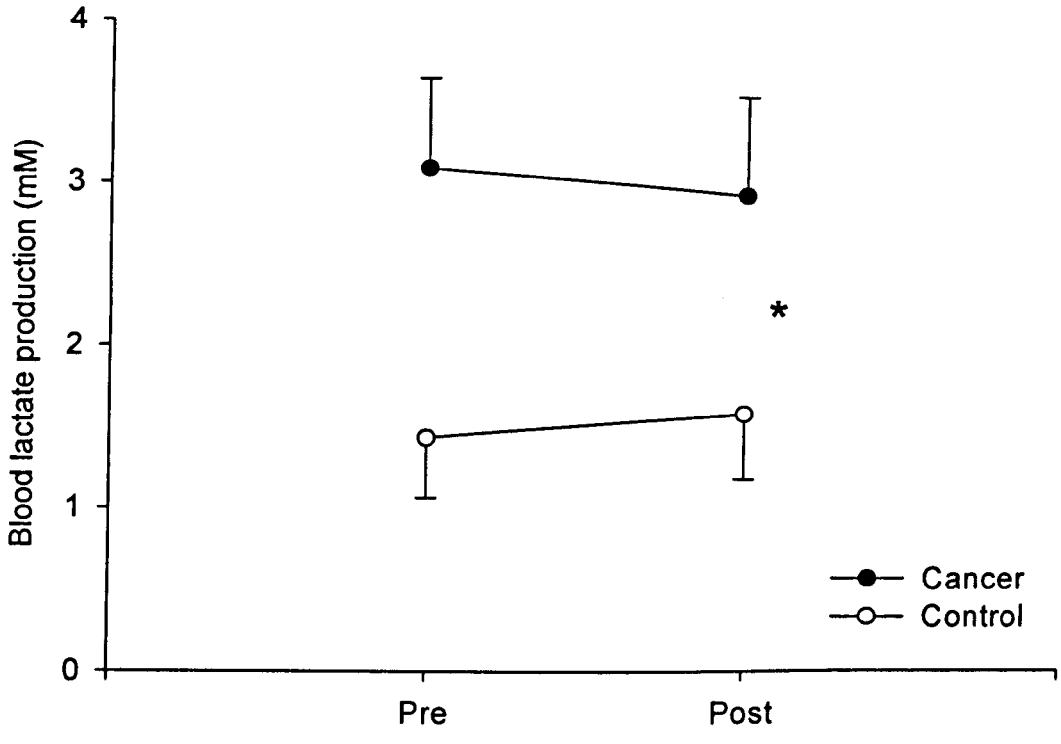
Data are means ± SD. * significant main effect of group ($P < 0.05$). MAP, mean arterial pressure, TPR, total peripheral resistance Hb, haemoglobin concentration ($n = 26$)

Figure 4. The effect of cancer and chemotherapy on respiratory and metabolic parameters



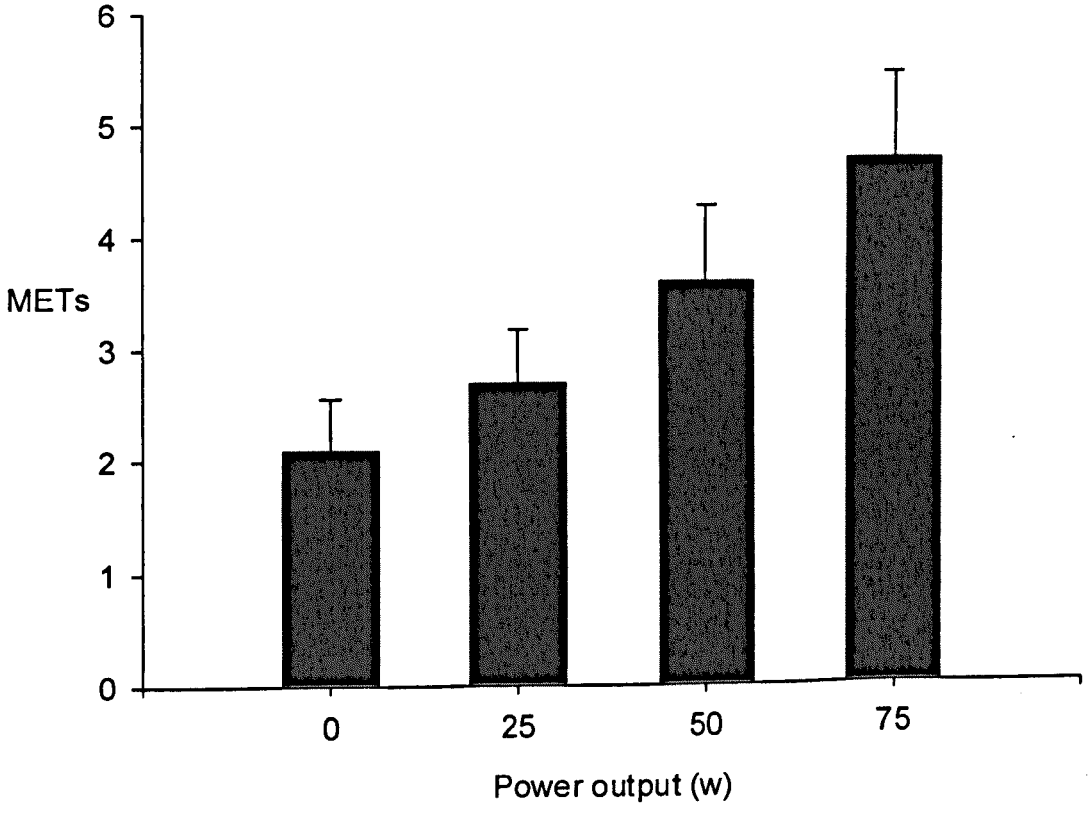
Data are means ± SD.* significant main effect of group ($P < 0.05$) ($n = 26$)

Figure 5. The effect of cancer and chemotherapy on blood lactate production



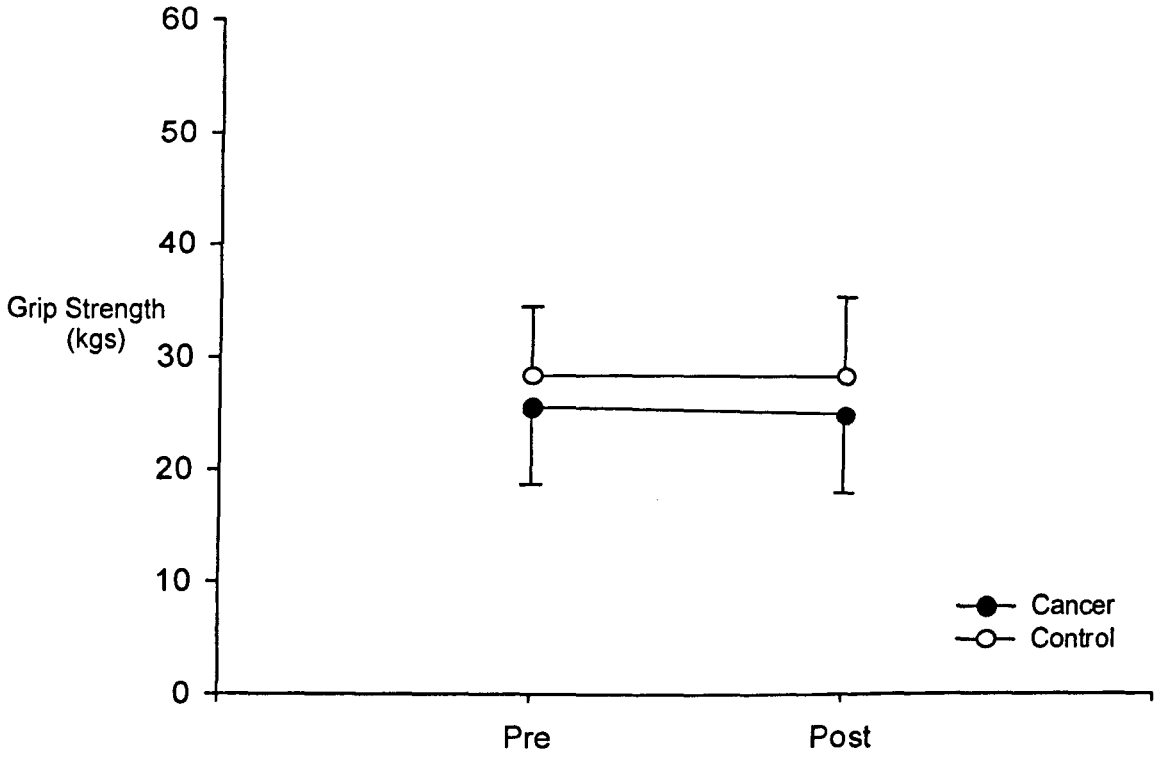
Data are means ± SD. * significant main effect of group (n = 26)

Figure 6. Average power output converted to metabolic equivalents for cancer patients and healthy controls combined



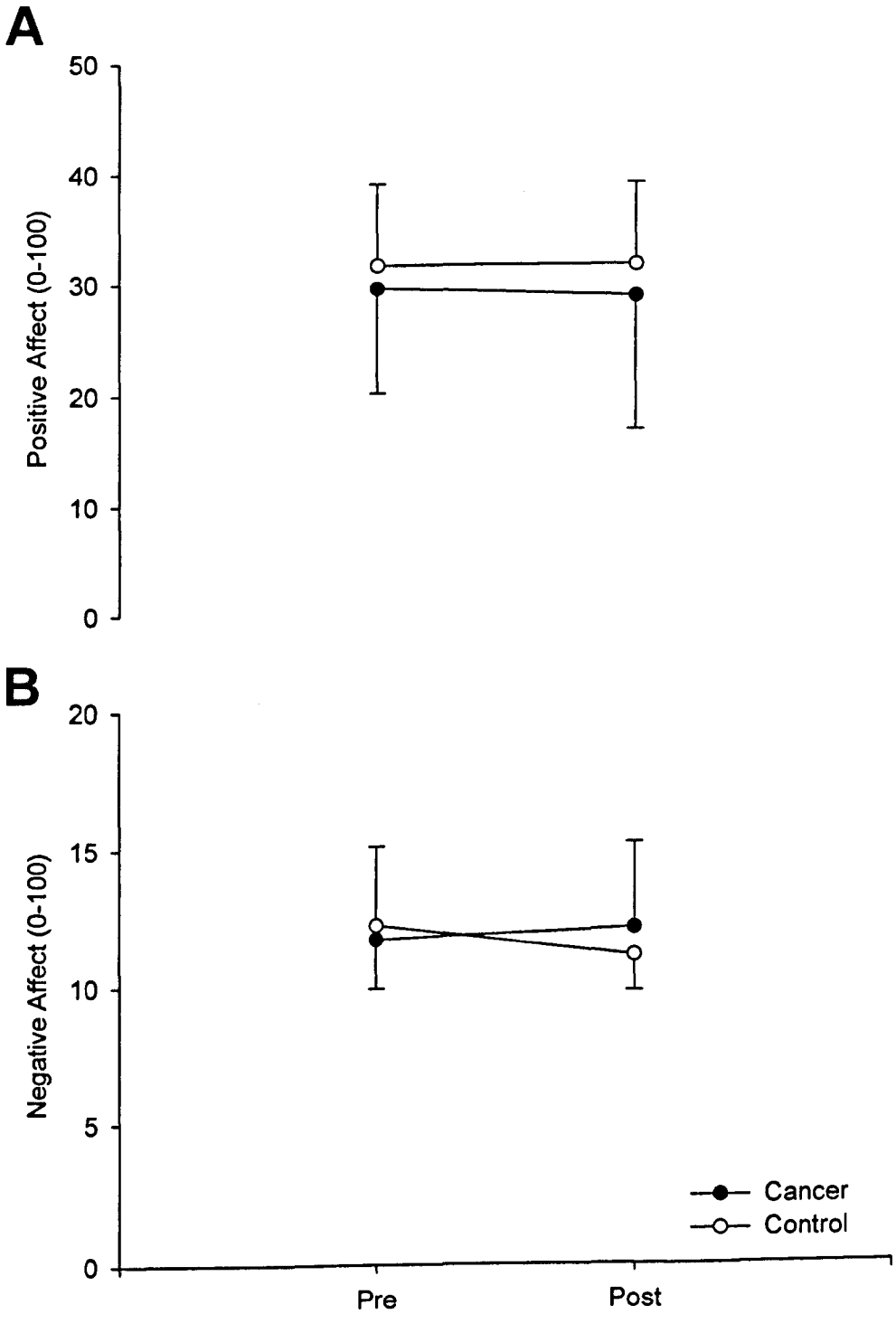
Data are means ± SD. METs, metabolic equivalents; w, watts (n = 26)

Figure 7. The effect of cancer and chemotherapy on grip strength



Data are means ± SD (n = 26)

Figure 8. The effect of cancer and chemotherapy on positive (A) and negative (B) Affect



Data are presented as means ± SD (n = 26)

CHAPTER THREE

THE PSYCHOLOGICAL AND PHYSICAL EFFECTS OF PROGRESSIVE RESISTANCE TRANING IN ELDERLY PROSTATE CANCER PATIENTS RECEIVING ANDROGEN DEPRIVATION THERAPY

Androgen Deprivation Therapy (ADT) is one of the most common forms of adjuvant treatment for prostate cancer. Although ADT is an effective treatment, it is associated with increases in fatigue (Segal *et al.*, 2009), losses in skeletal muscle and strength (Galvao *et al.*, 2009), osteoporosis, skeletal fractures (Smith 2004; Shahinian *et al.*, 2005) and cardiovascular complications (Taylor *et al.*, 2009), which compromise physical function, independence and quality of life (Sharifi *et al.*, 2005).

Psychological side effects of Androgen Deprivation Therapy

The diagnosis, the cancer itself, and ADT treatment can directly impact on psychological well-being. Prostate cancer patients undergoing ADT treatment commonly report fatigue as the primary complaint (Spry *et al.*, 2006). It is unclear whether this fatigue is a result of the cancer itself, ADT or reductions in functional capacity. However, several studies have found significant increases in fatigue, anxiety and depression and reductions in self-esteem in patients receiving ADT (Shahinian *et al.*, 2006). Changes in body composition and reductions in physical function are also likely to have direct effects on QoL, due to a loss of independence (Shepard, 2002). Interventions should aim to improve the quality of life of these patients, through improving physical function, fatigue and psychological well-being through exercise training and lifestyle interventions (Bourke *et al.*, 2011).

Physiological side effects of Androgen Deprivation Therapy

Cross sectional studies have shown lower whole body lean mass and higher whole body fat mass in patients treated with ADT compared to non-ADT patients and healthy matched individuals (Basaria *et al.*, 2002). Longitudinal studies have shown that fat mass increases (9.4-10.4%) and lean mass decreases (2.7-3.5%) over a 12 month period in patients treated with ADT measured by dual energy x-ray absorptiometry (DXA) (Berruti *et al.*, 2002;

Greenspan *et al.*, 2005). A more recent study found that after 36 weeks of ADT treatment, there was a significant increase in whole body and regional fat mass and a decrease in whole body and regional lean mass in elderly men with prostate cancer (Galvao *et al.*, 2008). ADT related bone loss is also a significant problem, with men experiencing more bone loss than early menopausal women (Higano 2003), which leads to an increased risk of skeletal fracture (Preston *et al.*, 2002). These changes in body composition are likely to reduce musculoskeletal fitness, muscular strength, and physical function (Galvao & Newton 2005).

Prostate cancer patients receiving ADT have been shown to have reduced upper and lower body strength compared with controls, using a one repetition maximum (1RM) protocol (Basaria *et al.*, 2002), and reductions in grip strength over a 3 month period (Smith *et al.*, 2007). Patients undergoing ADT experience a high degree of functional impairment (Mohile *et al.*, 2008). More specifically, studies have reported that men on chronic ADT (6 months or more) have significantly reduced lower body physical function performance (reduced chair sit to stands and slower 4m walking speeds) than men on acute ADT (less than 6 months) (Clay *et al.*, 2007; Levy *et al.*, 2008). Such changes will have implications in terms of reducing the age at which an individual falls below the functional capacity threshold, thereby reducing independent living and ultimately QoL.

The effects of resistance training on psychological and physiological and side effects

Of particular interest to this elderly prostate cancer population, is that PRT has been shown to induce health benefits by improving the ability to perform daily tasks (Galvao and Taaffe, 2006). This is likely to improve both fatigue and quality of life. Although the effect of PRT on QoL and fatigue have been investigated, there are still relatively few

studies assessing fatigue in response to high intensity resistance training in these patients, with even less investigating the different aspects of fatigue.

Research into the effects of progressive resistance training in prostate cancer patients has increased over the last 10 years. Early work, such as (Segal *et al.*, 2003) found that PRT significantly increased upper and lower body strength and decreased fat percent (using the sum of skinfolds). Galvao *et al.*, (2006) found that 20 weeks of PRT increased muscle strength and endurance and physical function and preserved whole body lean mass, in patients receiving ADT. However, this was an uncontrolled study. More recently, the effects of PRT on body fat percent using DXA have been investigated (Segal *et al.*, 2009), but there were no data relating to the effects on lean and appendicular lean mass. Marcora *et al.*, (2005) reported increases in lean and appendicular lean mass after 12 weeks of high intensity progressive resistance training in patients undergoing treatments for prostate cancer, however, these data were pilot data. Therefore, there appears to be a lack of randomized controlled studies describing the effects of PRT on body composition using gold standard methods to assess body composition.

There appears to be a lack of randomized controlled studies investigating the effects of a high intensity PRT programme on fatigue, quality of life and body composition (using gold standard techniques) and physical function. Therefore the primary aim of this study was to add to the existing literature by examining the effects of high intensity PRT on fatigue (both physical and mental aspects) in elderly prostate cancer patients receiving ADT. Secondary aims included the effects of PRT on body composition (in particular lean and appendicular lean mass measured by DXA), physical function (using a battery of validated tests), and quality of life.

Methods

Subjects

After ethical approval from the North West Wales NHS Trust, 20 male patients treated for prostate cancer by androgen deprivation therapy were recruited for the study. Recruitment was undertaken by Oncology consultants and researchers at the outpatient's clinic at the local hospital. The inclusion criteria consisted of the following; male patients aged between 60-80 yrs old, with histological confirmed prostate cancer, having received treatment with ADT (anti-androgens e.g. flutamide or LHRH analogies e.g. Zolodex) for at least 3 months; a life expectancy of at least 6 months, and willing to attend a 12 week resistance training program. Patients were excluded if they had any significant cardiovascular (e.g. ischemic heart disease, cerebravascular disease, severe anaemia or uncontrolled hypertension), pulmonary (emphysema or asthma), metabolic (gross obesity or uncontrolled diabetes), renal or neuromuscular disease. Further exclusion criteria included restricted activities of daily living due to uncontrolled disease related pain (i.e. due to bone metastases) and recent resistance training experience.

Experimental design

This was a randomised, controlled experiment. All patients visited the laboratory on two different occasions; week 0 and week 12. The patients were randomly assigned (using a computer generated randomiser: www.randomixer.org) to either a 12 week progressive resistance exercise training programme (PRT) or a control programme (control), where they maintained their habitual physical activity and dietary habits for the same period of time.

Procedures

During week 0, the study and its aims were explained, and a medical and lifestyle questionnaire was administered. Psychological (Hospital Anxiety and Depression Scale (HADS), Bi-dimensional Fatigue Scale (BFS) and the Functional Assessment for Cancer Therapy – Prostate (FACT-P)), and physiological (body composition and physical function) assessments were conducted on both occasions. The patients were allocated to either the PRT or control group by opening a sealed envelope which contained group allocations. This procedure was undertaken after completion of all baseline tests.

Patients were provided with a booklet of validated questionnaires, which were completed at W0 and W12. All questionnaires were completed at the same time of day at the patient's home and not on training days. The control group were provided with self addressed envelopes, whilst the PRT group handed the questionnaires to the researcher at the exercise training sessions.

Fatigue

Fatigue was measured using the bi-dimensional fatigue scale (BFS) (Chalder *et al.*, 1993). The scale consists of 11 items, 7 of which form the physical fatigue sub-scale (BFS-P) and 4 of which form the mental fatigue subscale (BFS-M). The combination of these 2 scores gives a total fatigue score (BFS-T). Each of the items is scored on a 4-point likert scale ranging from 0 being 'better than usual' to 3 being 'worse than usual'. Higher scores indicate greater fatigue. The physical and mental fatigue scales are both reliable and valid (Chalder *et al.*, 1993).

Body composition

For each testing session, patients presented at approximately the same time of day, having fasted and refrained from strenuous exercise for 24 hours. Body mass (kg) (Seca beam balance scales) was measured and subsequently correlated with total body mass by DXA ($r = 0.990, p < 0.001$). Total and regional (head, arms, trunk and legs) lean and fat masses were estimated using a whole-body pencil-beam DXA scanner (QDR1500, software version V5.72; Hologic, Waltham, MA). Appendicular lean mass (total arms + legs lean mass), a proxy measure of total body skeletal muscle mass, was determined and percent body fat was estimated. Immediately following DXA scanning, bioelectrical impedance spectroscopy (BIS) (Hydra 4200; Xitron Technologies, San Diego, CA) was performed on the left hand side of the body to estimate extracellular fluid (ECF), intracellular fluid (ICF) and total body water (TBW). The combination of DXA and BIS data allowed the estimation of total body protein (LBM (g) - (0.2302 x total bone mineral (g) – TBW (g)).

Physical function and activity

Physical function was measured objectively using the senior fitness tests, which is validated in healthy populations (Rickli & Jones, 2001). The tests included 30-second chair sit to stand, 30-second arm curl, chair sit and reach, back scratch, 8-foot up and go and a 6-minute walk and flexibility measures. This battery of tests is designed to encompass all aspects of physical function, fitness and endurance. Patients warmed up for a ten minute period using low intensity aerobic exercise, stretching and mobility exercises. The procedures of each test were explained and demonstrated to the patients whilst they were instructed to 'do their best, but to do so in a safe manner'. All the tests were carried out in accordance with the standardised guidelines. Habitual physical activity was measured using electronic pedometers (Digiwalker DW 200; Yamax, Tokyo, Japan), worn

on the dominant hip during all waking hours of the first (W0) and last (W12) weeks of the study period. For statistical analyses, the average number of daily steps for each of the 2 assessment weeks were used.

Quality of life

Quality of life (QoL) was measured using the FACT-P instrument, which contains 5 subscales related to well-being (physical, social/family, emotional, functional and additional prostate specific). The patients were asked to rate the extent to which each item was true over the last 7 days. Each item is scored on a 5-point likert scale from 0 being 'not at all' to 4 being 'very much'. Higher scores indicate better QoL. The FACT-P has demonstrated high reliability and validity for use in prostate cancer patients (Stone *et al.*, 2000).

Anxiety and depression

Anxiety and depression were measured using the hospital anxiety and depression scale (Zigmond *et al.*, 1983). The HADS is a 14-item screening tool that is used extensively in clinical settings, where it has been shown to be both valid and reliable (Bjellend *et al.*, 2002). The scale consists of 2 separate 7-item subscales, one measuring anxiety and the other depression. The subscales can be combined to calculate a total score. The items are scored on a 4-point likert scale ranging from 0-3. The anchor for each phrase differs, but generally corresponds to 0 'no experience of the situation' to 3 'extensive/intensive experience of the situation', with 6 out of the 11 items being reversed. Total scores can range from 0 (no symptoms) to 21 (severe symptoms), therefore higher scores indicate greater anxiety and depression.

Clinical measures

Prostate specific antigen (PSA) and testosterone were measured at W0 and 12. All intravenous blood samples were performed by a trained phlebotomist at the hospital. The samples were taken at least 24 hrs post exercise in order to avoid any confounding effects of physical activity on testosterone levels (Oremek & Seiffert 1996).

Progressive resistance training protocol

Patients allocated to the PRT group attended a thrice weekly, 12-week resistance training programme designed to induce hypertrophy of muscles (Kraemer *et al.*, 2002). The PRT program consisted of 3 sets of 8 repetitions with a load corresponding to 80% of the 1-repetition maximum (1-RM; i.e. the maximum load lifted for each of the prescribed exercises), with 1–2 minutes of rest between sets, for each of the following machine exercises: leg press, chest press, leg extension, leg curl, calf raise, lat pull down, triceps extension and bicep curl. In week 0, the patients had 2 sessions that acted as a gym induction, with only 1 set performed for each exercise (this allowed the researcher to gain an idea of the patient's ability before performing the 1RM.). The resistance programme was progressive, so that in W1 the patients performed a warm-up set of 12 repetitions, followed by 1 set of 15 repetitions/set at 50 % of 1-RM; during W2 and W3, the training load was increased by adding an additional set each week, so that by W3 the patient performed 1 warm-up set with 3 sets of 15 repetitions/set at 50 % of 1-RM; To further facilitate adaptation, 12 repetitions/set at 70% of 1-RM were performed in weeks 4 and 5, before progressing to 8 repetitions/set at 80% of 1-RM in weeks 6-12. 1RM was reassessed every 4 weeks to ensure correct progression. A similar training programme has been shown to be successful in developing gains in lean mass in rheumatoid arthritis (Lemmey *et al.*, 2009) and prostate cancer patients (Marcora *et al.*, 2005).

Statistical analysis

All data are presented as means ± SD. Differences between groups at baseline were examined using multiple independent samples *t*-test. There were no differences at baseline, therefore treatment effects were assessed using multiple mixed model (group x time) factor analyses of variance (ANOVA) with repeated measures for time. The assumptions of sphericity and normality of distribution were verified by Mauchly's test and the Kolmogorov-Smirnov test, respectively. For all ANOVAs, if a significant group x time interaction was revealed *post hoc* analyses were performed using the bonferroni *t*-test method. After pooling both groups' data, Pearson's correlation coefficient (*r*) was employed to assess the significance of the relationships between changes in arm and leg lean mass and objective measures of physical function. Significance was set at $p < 0.05$ for all analyses, which were conducted using the Statistical Package for the Social Sciences Version 14.0.

Results

A total of 81 patients were approached by the consultant, of whom 72 met all the eligibility criteria. Of these, 52 declined participation due to time and travel concerns and medical complications. After randomisation, 10 patients were allocated to the PRT group and 10 to the control group, with 17 patients completing all the testing procedures. Reasons for not completing all testing procedures included medical complications (n = 2) and time constraints (n = 1). Consequently, the patient's data were removed from any further analysis and post data was collected on 9 exercisers and 8 controls. Comparison of demographic data between the groups is shown in Table 1. There were no significant differences between the groups for age, anthropometric measures, PSA and testosterone, suggesting the groups were well matched. There were no significant differences in any measured variables at baseline (data not shown). Average attendance to the exercise programme was approximately 90 % (with an average of 32/36 sessions), with an overall improvement of 49 % in the average 1RM of the 8 exercises between W0 (44.9 ± 13.0 kg) and W12 (67.1 ± 2.8 kg).

Fatigue

The effects of PRT on fatigue are presented in Table 2. Total fatigue reduced significantly in the PRT group, whilst increasing slightly in the control group ($p = 0.038$). Both physical and mental fatigue scores contributed to the changes in total fatigue, however the reductions in mental fatigue were significant ($p = 0.025$), whereas there was a trend for the reductions in physical fatigue ($p = 0.089$).

Anthropometry and body composition

Total body mass increased significantly by 1.3 kg (± 1.4) in the PRT group and reduced by 1.0 kg (± 2.3) in the control group (interaction; $p = 0.027$). There was a significant interaction for BMI ($p = 0.028$), where BMI increased in the PRT group and decreased in the control group (Table 3).

The effects of the PRT intervention on lean body mass are presented in Table 4. PRT significantly increased both LBM (mean ± SD; 2169 ± 1387 g) and APLM (861 ± 966 g). Conversely, over the same period, the control subjects lost an average of 229 and 221 g in LBM and APLM, respectively. The increase in APLM in the PRT group was due to significant increases ($p = 0.051$) in arm lean mass (PRT: 474 ± 230 g; Control: 163 ± 354 g). There were also increases in leg (387 ± 825; -383 ± 768 g) and trunk lean mass (1237 ± 1474; -21 ± 1132 g), although not significant. Additionally, the number of patients classified as cachectic (calculated using relative skeletal muscle index ≤ 7.26 kg/m^2 (Baumgartner 2000) reduced from 6 to 3 in the PRT group, whereas this did not change in the control group.

Analyses of the bioelectrical impedance spectroscopy data showed there were no significant changes in extracellular water in the PRT group (Table 5). Consistent with this data was a significant increase in estimated total body protein (1,410 ± 1102 g) following PRT, whilst there was a modest increase in the controls (124 ± 761 g). Losses of total fat mass (-722 gm and -587 g for the PRT and control groups, respectively) and trunk fat mass (-776 g and -369 g, respectively) were observed over the intervention period, although these changes were not significant. There was a significant ($p = 0.04$) decrease in percent fat in the PRT group (33.1 to 31.7 %), whilst it did not change in the control group. This

decrease was due to both increases in lean mass and slight reductions in fat mass. Additionally, the number of patients classified as obese reduced in the PRT group, whereas this did not change in the control group (Table 6).

Physical function and activity

The PRT programme improved objectively assessed physical function (Table 7). Relative to baseline, mean performance improved by 24% for the 30-second chair stand test, 18% for the 30-second arm curl test, 55% for the sit and reach test, 13 % for the back scratch test, 15% for the 8 foot up and go test, and 8% for the 6-minute walk test. There were significant interactions for the 30-second chair stand test ($p = 0.022$) and the 8 foot up and go test ($p = 0.026$) and a trend for the 6 minute walk test ($p = 0.090$). These improvements meant that the patients attained or exceeded the respective 25th percentile performance score for healthy, age-matched individuals for all physical function tests, except for the flexibly measures (back scratch and sit and reach). In contrast, there were no changes in performance in control patients. The change in LBM was associated with changes in the scores of the 30 second chair test ($r = 0.480, p = 0.051$). More specifically, the change in legs lean mass was correlated with the change on the 30-second chair test ($r = 0.566, p = 0.018$), whilst the correlation between the change in arms lean mass and arm curl approached significance ($r = 0.451, p = 0.069$). Habitual physical activity, measured using the number of steps per day, did not significantly change in either group, although relative to baseline, the PRT groups steps remained roughly the same (+1.2%), whilst it reduced in the control group (-8%).

Quality of life

The effects of PRT on psychological assessments are presented in Table 8. There was a significant interaction ($p = 0.030$) for FACT-P (total), where the quality of life of the PRT group improved (120-125), but declined in the control group (117-107). The prostate specific variables contributed most to this improvement, with the prostate specific well-being increasing in the PRT group (31.1-37.4), and decreasing in the control group (28.8-27.2) (significant interaction; $p = 0.026$). There were no interactions for either anxiety or depression, although there was a slight increase in anxiety scores in the control group whilst anxiety in the PRT did not increase.

Clinical measures

Testosterone and PSA levels are displayed in Table 9. There were no changes in the PSA and testosterone levels in either group.

Discussion

The purpose of this study was to conduct a randomised controlled study into the physiological and psychological effects of a high intensity progressive resistance training programme in prostate cancer patients receiving ADT. This randomised controlled trial confirmed that high intensity PRT significantly improves fatigue, increases lean mass and restores physical function in prostate patients receiving ADT and also improves aspects of quality of life.

Fatigue

Total fatigue was found to reduce over time in the PRT group, and increase slightly in the control group. These findings are consistent with previous studies that have investigated the effects of exercise on fatigue in cancer patients in general and more specifically, in patients with prostate cancer receiving ADT. Segal *et al.*, (2009) found that in patients with prostate cancer receiving radiotherapy and ADT, resistance training reduced fatigue levels using the FACT-F over a 24 week period, compared with aerobic exercise and usual care. The FACT-F provides a total overall fatigue score however, it is more sensitive to changes in physical fatigue as opposed to mental fatigue. The significant improvements in total fatigue seen in this study were predominately due to the mental component of fatigue, although the improvements in physical fatigue did approach significance. Stone *et al.*, (2000) proposed that physical fatigue is likely to be the most affected component of fatigue in patients with prostate cancer on ADT. However, there appears to be a lack of research into the effects of resistance training on the different aspects of fatigue in this patient population and this study highlights that it is not just the physical component of fatigue that is affected by cancer and ADT.

One reason for the improvement in mental fatigue components is that increases in physical conditioning and muscular endurance could have a direct impact on the mental/cognitive components of fatigue. There is increasing evidence that cognitive function can be impaired in patients undergoing treatment for prostate cancer (Alibhai *et al.*, 2006). Interestingly, this study provides evidence that exercise can improve the mental aspects of fatigue, potentially having an effect on the cognitive aspects of fatigue. This is supported by studies that have looked at the effects of exercise on cognitive function in the elderly and found that it has been improved after exercise intervention (Snowden *et al.*, 2007).

Body composition

The long term reduction in lean mass in patients receiving ADT is widely accepted (Smith 2007; Galvao *et al.*, 2009). Studies have reported losses in total lean mass from 1.4 kg after 36 weeks of ADT treatment (Galvao *et al.*, 2009), to more long term losses of 1.8 kg over a 2 year period (Van Londen *et al.*, 2008). This controlled study is one of few studies that have shown that PRT reverses these losses in lean mass seen in patients receiving ADT. Galvao *et al.* (2006) reported that 20 weeks of resistance training preserved total lean body mass in 10 patients receiving ADT, but no increases in lean mass were seen (Baseline: 52.2 ± 5.6; Week 20: 52.0 ± 5.7 kg). The authors concluded that a control group would have decreased in the study parameters; however, this might not have been the case. In support of this, total lean mass in the control group in this study did not significantly decreases over a 12 week period. Therefore, this randomised controlled study is a much stronger experimental design.

In this randomised study, total lean mass was increased by 2.2kg in the PRT group, with a net difference between the two groups of 2.4kg. These increases in total lean mass are

larger than those reported in the literature. A recent study, showed that in prostate cancer patients who received a 24 week resistance training programme, lean mass was preserved compared to a usual care group (Segal *et al.*, 2009). Although there was a decease of 0.6 kg in lean mass in the resistance training group, there was a net difference of 1.9 kg between the two groups. The discrepancies between this study and those previously published are most likely due to both higher intensity (85 % 1 RM vs. 60-70% 1 RM) and frequency (Galvao *et al.*, 2006) of the training programme used in this randomised study. Segal *et al.*, (2009) used a slightly higher intensity than previous studies (70-75 % 1 RM) in their PRT programme however; they reported body fat percent only, measured by DXA and not lean mass. Although, by calculating the lean mass using the change in total body mass and fat percent, and assuming BMC is constant, it can be estimated that there was a 1.9 kg change in lean mass.

This study was novel, as it was able to show that the significant increase in lean mass was not simply due to increases in extra cellular water, since the estimated hydration of FFM remained constant throughout the study. Moreover, there was an increase of 1.4 kg of estimated total whole body protein in the patients. It can be confirmed that PRT was successful in causing muscular hypertrophy in prostate cancer patients receiving ADT, given that skeletal muscle tissue is the largest reservoir of protein in the body.

Perhaps more important is that PRT increased APLM, with a total of 1 kg net difference between the two groups, as this provides a proxy measure of total of skeletal muscle mass (Kim *et al.*, 2002). There was also an increase in trunk lean mass in the PRT group in this randomised study, although not significant. Therefore, the PRT programme was successful in causing whole body muscular hypertrophy. This is the first fully randomised controlled

study to show more pronounced increases in total lean and appendicular lean mass measured using DXA, in response to a high intensity resistance training programme in patients undergoing treatment for prostate cancer.

Fat mass did not significantly change in response to the PRT; however, fat percent was significantly reduced in the PRT group, due to a significant increase in lean mass and slight reductions in fat mass. This is consistent with other studies that have found significant reductions in fat percent (Segal *et al.*, 2009). It must be noted that although resistance training does not always lead to reductions in fat mass (Galvao *et al.*, 2006), there were significant changes in body fat percent in this study and the number of patients classified as clinically obese reduced in the PRT group after the intervention period. Therefore, overall, the body composition changes were more evident than those described by Galvao *et al.*, (2006) and Segal *et al.*, (2009; 2011).

Physical function

This study resulted in significant improvements in upper and lower body muscle strength (measured using 1RM), in the PRT group, which are consistent with previous studies examining resistance training as an individual exercise mode in patients with prostate cancer (Segal *et al.*, 2003; Galvao *et al.*, 2006).

Perhaps more clinically meaningful, were the improvements in objectively measured physical function in the PRT group (in particular, the sit to stand and the 8-foot up & go tests). These significant improvements in physical function were further reflected by improvements in classification. For example, the PRT group improved from 'below average' to 'normal' in all the upper and lower body physical function tests, apart from the

flexibility tests. The changes in functional performance are similar to those in studies of patients on ADT undertaking resistance training (Galvao *et al.*, 2006).

Numerous cross sectional studies have reported significant correlations between muscle mass and strength (Basaria 2002), and function (Shin *et al.*, 2011). However, significant associations between the change in muscle mass and the change in strength are rarely observed and studies show inconsistent results (Hughes, 2001), suggesting that the increases in strength are most likely to be due other factors, such as neuromuscular adaptations. Interestingly, within this study, although there were associations between regional LBM and some of the physical function tests, the correlations were mostly modest, suggesting that other factors do contribute to the improvements in strength and physical function in these patients.

In terms of quality of life, overall FACT-P scores and prostate specific wellbeing were found to improve significantly in the PRT group, whilst they decreased in the control group. In general, this supports previous research that exercise training improves quality of life in patients with prostate cancer receiving ADT (Galvao *et al.*, 2010; Segal *et al.*, 2003). However, when the overall QoL is broken down into subscales, it is clear that the prostate specific well-being is contributing more to the improvements in overall quality of life, than the general QoL (FACT-G). This is in contrast to Segal (2009), where they found improvements in general cancer related QoL, but not prostate cancer specific well being.

In summary, this high intensity PRT programme successfully reduced total, physical and mental fatigue levels within these patients. The reasons for this are multifactorial, but can

be suggested to be related to improved neuromuscular efficiency, improved cognitive function, and increased prostate specific well being. Also, testosterone and PSA levels did not change in response to the PRT programme, therefore PRT can be considered safe in patients with prostate cancer undergoing ADT.

One of the limitations to this study was the small sample size, as this might account for differences in the effects of PRT between the existing studies within the literature. Consequently, these results would need to be confirmed in a larger study. Although every effort was made not to bias the recruitment process, this cohort of patients with prostate cancer might represent a 'better' population, due to the characteristics of individuals volunteering to take part in exercise programmes. However, if this were true, it could be inferred that PRT might have even larger benefits to those who fall in the lower end of functional and psychological spectrum.

In conclusion, this high intensity 12 week progressive resistance training programme improved fatigue, lean mass and attenuated fat percent to a higher degree than previous published studies. It also improved muscular strength, physical function, and quality of life in patients with prostate cancer receiving ADT. Although resistance training may not have the potential beneficial effects that aerobic exercise has on cardiac health, it appears that resistance training potentially has a more pronounced effect on fatigue, lean and fat mass, strength, and quality of life than aerobic exercise. Progressive resistance training should be encouraged by patients both during and after treatment for prostate cancer. More research is needed to determine the exact mechanisms by which fatigue is reduced during a resistance exercise programme within these patients treated for prostate cancer, with a particular focus on the cognitive aspects of fatigue.

Tables

Table 1. Baseline characteristics of prostate cancer patients receiving treatment

Characteristic	PRT (n = 9)	Control (n = 8)	*p* value
Age (yr)	67.0 ± 6.8	70.1 ± 8.2	0.411
Height (cm)	173 ± 4.5	168 ± 5.6	0.084
Body Mass (kg)	81.0 ± 10.4	82.0 ± 17.0	0.889
BMI (kg/m^2)	27.1 ± 3.5	29.0 ± 6.3	0.455
PSA (ng/ml)	4.0 ± 7.0	2.7 ± 2.2	0.624
Testosterone (mmol/L)	0.5 ± 0.1	0.5 ± 0.1	0.979

Data are means ± standard deviation. Abbreviations: PRT, progressive resistance training; BMI, body mass index; PSA, prostate specific antigen.

Table 2. The effects of 12 weeks high intensity progressive resistance training on fatigue in prostate cancer patients receiving treatment

	W0	W12	*p* value
Total fatigue			
PRT (n = 9)	15.6 ± 5.6	10.1 ± 5.3	0.038*
Control (n = 8)	15.6 ± 2.4	16.7 ± 4.6	
Physical fatigue			
PRT	11.0 ± 5.3	7.1 ± 4.4	0.089
Control	11.1 ± 2.0	11.8 ± 3.9	
Mental fatigue			
PRT	4.6 ± 1.3	3.0 ± 1.2	0.025*
Control	4.4 ± 1.3	4.9 ± 1.7	

Data are means ± standard deviation. * significant interaction *(n* = 17)

Table 3. The effects of 12 weeks high intensity progressive resistance training on body mass in prostate cancer patients receiving treatment

	W0	W12	*p* value
Total body mass (kg)			
PRT (n = 9)	81.0 ± 10.4	82.3 ± 10.8	0.027*
Control (n = 8)	82.0 ± 17.0	81.0 ± 16.4	
BMI (kg/m^2)			
PRT	27.1 ± 3.5	27.5 ± 3.5	0.028*
Control	29.0 ± 6.3	28.5 ± 5.8	

Data are means ± standard deviation. Abbreviations: PRT, progressive resistance training,; BMI, body mass index. * significant interaction *(N* = 17)

Table 4. The effects of 12 weeks high progressive intensity resistance training on body composition in prostate cancer patients receiving treatment

	W0	W12	*p* value
Total lean mass (kg)			
PRT (n = 9)	50.1 ± 5.3	52.3 ± 6.0	0.009*
Control (n = 8)	47.8 ± 8.9	47.6 ± 8.5	
APLM (kg)			
PRT	20.8 ± 3.1	21.6 ± 2.6	0.038*
Control	19.6 ± 4.9	19.4 ± 4.7	
Arms lean mass (kg)			
PRT	5.1 ± 0.8	5.6 ± 0.9	0.051*
Control	4.6 ± 1.2	4.8 ± 1.2	
Legs lean mass (kg)			
PRT	15.7 ± 2.4	16.0 ± 1.9	0.065
Control	15.0 ± 3.7	14.6 ± 3.5	
Trunk lean mass (kg)			
PRT	25.1 ± 2.4	26.3 ± 3.3	0.066
Control	24.0 ± 3.9	24.0 ± 3.9	
Head lean mass (kg)			
PRT	4.2 ± 0.4	4.3 ± 0.4	0.806
Control	4.2 ± 0.6	4.3 ± 0.4	

Data are means ± standard deviation. Abbreviations: PRT, progressive resistance training; APLM, appendicular lean mass. * significant interaction *(n* = 17)

Table 5. The effects of 12 weeks high progressive intensity resistance training on body water in prostate cancer patients receiving treatment

	W0	W12	*P* value
TBW (l)			
PRT	40.1 ± 3.4	40.8 ± 4.1	0.175
Control	37.4 ± 7.9	37.0 ± 7.6	
ICF (l)			
PRT	21.3 ± 2.2	21.8 ± 2.6	0.170
Control	18.9 ± 3.7	18.8 ± 3.9	
ECF (l)			
PRT	18.8 ± 2.7	19.0 ± 2.7	0.277
Control	18.5 ± 4.7	18.2 ± 3.9	
TBW:FFM			
PRT	0.751 ± 0.016	0.742 ± 0.027	0.168
Control	0.759 ± 0.007	0.767 ± 0.022	
Total body protein (kg)			
PRT	9.4 ± 3.0	10.8 ± 3.5	0.013*
Control	9.8 ± 2.4	9.9 ± 2.5	

Data are means ± standard deviation. Abbreviations: PRT, progressive resistance training; TBW, total body water; ICF, intracellular fluid; ECF, extracellular fluid; FFM, fat free mass. * significant interaction *(n* = 17)

Table 6. The effects of 12 weeks high intensity progressive resistance training on fat mass in prostate cancer patients treatment

	W0	W12	*p* value
Total fat (%)			
PRT (n = 9)	33.2 ± 6.4	31.7 ± 6.3	0.044*
Control (n = 8)	36.7 ± 6.0	36.4 ± 5.6	
Total fat mass (kg)			
PRT	27.2 ± 7.8	26.5 ± 7.9	0.821
Control	30.5 ± 10.1	30.0 ± 5.6	
APFM (kg)			
PRT	11.6 ± 3.6	11.6 ± 3.8	0.281
Control	12.7 ± 3.4	12.4 ± 3.1	
Trunk fat mass (kg)			
PRT	14.6 ± 4.7	13.8 ± 4.5	0.400
Control	16.8 ± 7.0	16.4 ± 6.6	
Obese (*n*)$^{\neq}$			
PRT	7	5	
Control	8	8	

Data are means ± standard deviation unless otherwise stated. Abbreviations: PRT, progressive resistance training; APFM, appendicular fat mass. * significant interaction, $^{\neq}$ Percent body fat ≥ 28 % (*n* = 17)

Table 7. The effects of 12 weeks high intensity progressive resistance training on objectively assessed physical function in prostate cancer patients receiving treatment

	W0	W12	*p* value
30-second chair test (reps)			
PRT (n = 9)	10.9 ± 3.3	13.5 ± 4.3	0.022*
Control (n = 8)	9.7 ± 4.2	10.7 ± 4.3	
30-second arm curl test (reps)			
PRT	14.3 ± 4.3	16.8 ± 3.7	0.108
Control	14.0 ± 5.1	14.3 ± 4.6	
Sit and Reach (cm)			
PRT	-10.5 ± 7.0	-4.7 ± 7.8	0.115
Control	-11.3 ± 16.3	-11.8 ± 15.7	
Back scratch (cm)			
PRT	-15.7 ± 10.3	-13.7 ± 10.1	0.181
Control	-12.1 ± 21.9	-13.1 ± 21.3	
8 foot up & go (s)			
PRT	6.2 ± 1.8	5.3 ± 1.5	0.026*
Control	5.4 ± 1.3	5.7 ± 1.9	
6 min walk (m)			
PRT	510 ± 117	551 ± 107	0.090
Control	500 ± 118	479 ± 137	
Physical activity (steps)			
PRT	5836 ± 2547	5909 ± 2693	0.351
Control	4822 ± 2598	4451 ± 2773	

Data are means ± standard deviation. Abbreviations: PRT, progressive resistance training.
* significant interaction *(n* = 17)

Table 8. The effects of 12 weeks high intensity progressive resistance training on quality of life variables in prostate cancer patients receiving treatment

	W0	W12	*p* value
FACT-P (total)			
PRT (n = 9)	120.8 ± 16.9	125.1 ± 14.1	0.030
Control (n = 8)	117.2 ± 17.3	106.7 ± 2.6	
FACT-G (subtotal)			
PRT	89.6 ± 9.3	87.8 ± 14.2	0.236
Control	88.9 ± 10.4	79.0 ± 15.4	
Prostate specific well being			
PRT	31.1 ± 9.3	37.4 ± 3.1	0.026*
Control	28.8 ± 9.8	27.2 ± 10.3	
HADS-Total			
PRT	9.6 ± 6.1	8.3 ± 4.3	0.124
Control	7.9 ± 5.7	11.0 ± 8.6	
HADS-Anxiety			
PRT	6.5 ± 4.7	6.1 ± 3.1	0.128
Control	4.2 ± 4.0	6.7 ± 5.4	
HADS-Depression			
PRT	3.1 ± 2.6	2.1 ± 2.1	0.200
Control	3.7 ± 2.1	4.3 ± 3.2	

Data are means ± standard deviation: Abbreviations: PRT, progressive resistance training; FACT-P, functional assessment for cancer therapy - prostate instrument; FACT-G, functional assessment for cancer therapy – general; HADS, hospital anxiety and depression scale. * significant interaction *(n = 17)*

Table 9. The effects of 12 weeks high intensity progressive resistance training on clinical outcomes in prostate cancer patients receiving treatment

	W0	W12	*p* value
PSA, (ng/ml)			
PRT (n = 9)	4.0 ± 7.0	3.9 ± 6.3	0.209
Control (n = 8)	2.7 ± 2.2	3.4 ± 2.9	
Testosterone, (pmol)			
PRT	0.5 ± 0.1	0.6 ± 0.2	0.598
Control	0.5 ± 0.1	0.5 ± 0.2	

Data are means ± standard deviation. Abbreviations: PRT, progressive resistance training; PSA, prostate specific antigen *(n* = 17)

CHAPTER FOUR

THE RELATIONSHIP BETWEEN PERCEIVED EXERTION, FATIGUE AND BARRIERS TO PHYSICAL ACTIVITY IN BREAST CANCER PATIENTS ON FOLLOW-UP FROM TREATMENT

In cancer patients, physical activity may be important as a means of reversing illness-related declines in physical endurance, increasing capacity for engaging in activities of daily living, improving emotional well-being, enhancing regulation of physiological systems, and prolonging survival (Courneya *et al.*, 2003; Courneya *et al.*, 2006). Despite these well known benefits of physical activity, individuals are not meeting the weekly physical activity levels recommended by the American Cancer Society (150 min per week of moderate to vigorous physical activity). It is estimated that only approximately 30 to 35% of cancer patients post treatment meet these guidelines (Bellizzi 2005; Vallance *et al.*, 2010). Therefore, it is important to gain a further understanding of the barriers and determinants of physical activity for cancer patients.

Previous studies have identified multiple barriers to physical activity for breast cancer patients. These include social, biological and psychological variables (Emery *et al.*, 2009) and also symptoms of disease and treatment related quality of life (Courneya *et al.*, 2009). Biopsychosocial, health belief and self-efficacy models (Bandura *et al.*, 1977) have been used to explain exercise behaviour in healthy populations. However, although these theories should not be disregarded within cancer patients, it appears that disease and treatment-related side effects are also a fundamental part of understanding the barriers to physical activity for breast cancer patients.

The majority of work relating to barriers towards physical activity and adherence to exercise training programmes has been carried out in breast cancer populations. The literature suggests that there are different barriers to physical activity depending on where the patients are in their treatment cycle. For example, Emery *et al.*, (2009) report the importance of emotional health related quality of life (HRQoL) following diagnosis with

breast cancer for increasing and maintaining participation in physical activity in the first 1–2 years following cancer diagnosis. However, depressive symptoms and physical functioning appear to be consistently relevant over time, and family support becomes more important over time (over a 5 year period). Courneya (2009) reports that in breast cancer patients receiving adjuvant chemotherapy, out of 36 different reasons for not adhering to a supervised exercise program, 53 % were disease or treatment related. Nausea (12 %), fatigue (11 %) and loss of interest (9 %) were the most common reasons for missing exercise sessions. This is not surprising as treatment related side effects are more pronounced during treatment as opposed to post treatment.

However, there appears to be discrepancies within the literature regarding the type of barriers amongst the same population of cancer patients. For example, Rogers *et al.*, (2006) found that the most commonly reported barriers to physical activity in patients undergoing therapy for breast cancer were those not associated with treatment (i.e. exercise not being a priority, lack of self-discipline, and lack of time). In contrast, Rogers *et al.*, (2004) also reported that patients undergoing treatment for breast cancer felt that they would engage in exercise if fatigue and time management issues were addressed. They also stated that the most important benefit from engaging in exercise would be reduced fatigue (using qualitative focus groups). Therefore, conflicting conclusions exist as to the reasons why these patients might not engage in physical activity.

There is limited research investigating the treatment related side effects as barriers towards physical activity, however, it does appear that fatigue is one of the most commonly reported barrier in breast cancer patients. For example, Rogers *et al.*, (2006) found that fatigue was the only treatment related barrier towards exercise and it was reported by 40%

of breast cancer patients undergoing treatment. Gho *et al.*, (2009) found that the most common barriers to exercise were self-discipline, procrastination and fatigue in patients with breast cancer.

It is not surprising that fatigue is one of the commonly reported barriers towards physical activity in cancer patients, as it is the most commonly reported disease and treatment-related side effect that occurs in cancer patients (Hoffman *et al.*, 2007). CRF is a complex syndrome that can be defined as a 'persistent sense of tiredness related to cancer and cancer treatment that interferes with usual functioning' (Mock *et al.*, 2005; Watson *et al.*, 2004). It can be characterised by an abnormal whole-body experience of tiredness, decreased capacity of both physical and mental work, and persistent exhaustion that is not related to previous activity or exertion and is not relieved by rest (Glaus *et al.*, 1996; Morrow *et al.*, 2005). Cancer patients repeatedly report activities of daily living, such as chores around the house and walking, as being more effortful when they are fatigued (Curt, *et al.*, 2000). With this in mind, there is a rationale for fatigue acting as a potential barrier to physical activity in patients with cancer.

The discrepancies within the literature between different barriers for physical activity in patients treated for cancer highlight the need for more research in this area. Of particular interest is the relationship between treatment related side effects, more specifically dimensions of fatigue, and physical activity levels. One of the features of fatigue is an increased sense of effort required to accomplish a physical or mental task. Interestingly, in healthy adults, there is evidence (although limited) to suggest a relationship between perceived effort with habitual physical activity (Trost *et al.*, 2002). Patients treated with cancer have an increased perception of effort associated with a task; therefore this

increased perception of effort might be more of an important barrier towards physical activity. With this in mind, the exercise benefits and barriers scale (Schrist *et al.*, 1987) was used in this study as it has a subscale that measures perceived physical exertion as a barrier towards physical activity. Previous studies using this scale have found items related to perceived physical exertion as a barrier to physical activity in healthy individuals (Lovell *et al.*, 2010).

Therefore, the aims of this study were to 1) investigate the perceived benefits and barriers towards physical activity in patients on follow-up from breast cancer treatment and 2) to assess the relationship between fatigue and physical activity level in these patients, in relation to perceived exertion. Based on limited studies in healthy people, it was hypothesised that patients who were fatigued would report more barriers related to physical exertion towards exercise.

Methods

After gaining ethical approval from the North West Wales Research Ethics Committee, female patients attending routine follow-up clinics for stage I-III breast cancer were recruited into the study by specialist breast cancer nurses at the local hospital. Patients were excluded if: they had any metastatic or secondary cancer, were still receiving treatment for breast cancer (expect for Herceptin); and had any significant cardiovascular (e.g. ischemic heart disease, cerebravascular disease, severe anaemia or uncontrolled hypertension), pulmonary (emphysema or asthma), metabolic (gross obesity or uncontrolled diabetes), renal or neuromuscular disease. All participants visited the clinic on one occasion. The study and its aims were explained and the patients were asked to take the information sheet and questionnaires home, complete them with the help of the researcher via the telephone, and post them back to the researcher in a pre-paid self-addressed envelope. The questionnaires took no longer than 30 minutes to complete. A number of demographic characteristics were collected such as age, education, employment status, lifestyle assessment, body mass and height. Patients self-reported disease characteristics using a standard medical questionnaire. These included date of diagnosis, disease location, surgery details, cancer stage, chemotherapy and radiotherapy history, including the dates of last treatment, and any other medical conditions.

Clinical fatigue

Clinical fatigue was assessed using the brief fatigue inventory (BFI) (Mendoza *et al.*, 1999). The BFI includes a 3-item fatigue severity scale and a 6-item interference scale. The first 3-items describe the patient's severity of fatigue, with 0 being "no fatigue" and 10 being "fatigue as bad as you can imagine". The last six items assess how much fatigue symptoms interfered with various aspects of the patient's life during the past 24 hours: general activity,

mood, walking ability, normal work (including housework and work outside the home), relationships with others, and enjoyment of life, with 0 being "does not interfere" and 10 being "completely interferes."

Cancer related symptoms

The MD Anderson Cancer Symptom Inventory (MDASI) (Cleeland 2000) was used to assess cancer symptoms. The MDASI includes a 13-item symptom scale and a 6-item interference scale. The first 13 items describe the patient's symptoms during the last 24 hours, with 0 being "not at all" and 10 being "as bad as you can imagine." Similar to the BFI, the last six items assess how much the symptoms interfered with various aspects of the patient's life during the past 24 hours. Higher scores represented more cancer symptoms. The validity and reliability of the BFI and MDASI have been established (Cleeland 2000).

Physical Activity

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) (Craig *et al.*, 2003). The IPAQ is a validated measurement tool that provides a retrospective account of walking, moderate and vigorous activity in the preceding 7 days. The number of days spent doing each walking, moderate or vigorous activity was multiplied by the duration of time spent for each activity. These scores were then converted to energy expenditure (MET) values, by multiplying time spent in each activity by predefined MET values (3.3 for walking activities, 4.0 for moderate activities and 8.0 for vigorous activities) (Ainsworth *et al.*, 2000). The IPAQ score is reported as a summary of energy expenditure and is presented as total physical activity for the week prior to assessment (MET-minutes per week). The interview based recall was completed by the researcher using a standardised protocol via telephone (Craig *et al.*, 2003). Patients were

categorised into the moderate activity group (MOD) if they reported completing at least five, 30-min exercise sessions per week during their leisure time or if their total physical activity score (a combination of moderate and vigorous walking) was greater than 600 MET-minute per week. Individuals who did not complete at least five, 30-min exercise sessions per week were categorised into the low physical activity group (LOW).

The Exercise Benefits and Barriers Scale (EBBS)

The EBBS (Sechrist *et al.,* 1987) is a validated questionnaire (in healthy adults) which determines the perceptions concerning the benefits and barriers to exercise. The EBBS consists of 29 benefit items in 5 categories: physical performance, preventative health, psychological outlook, social interaction and life enhancement. There are 14 barriers in 3 categories: physical exertion, time expenditure and exercise milieu. Participants rated their agreement with each statement on a 4-point Likert scale ranging from strongly disagree (1) to strongly agree (4). The higher scores indicate a more positive perception of exercise and also a greater perception of barriers to exercise.

Motivational readiness to exercise

Motivation to engage in physical activity was measured by defining moderate lifestyle physical activity of 30 min a day or more on most days of the week, and asking the patients to respond if they were active according to that definition. Patients had the option of responding: (1) "yes, for more than 6 months" (maintenance stage); (2) "yes, for less than 6 months" (adoption stage); (3) "no, but I intend to in the next 30 days" (preparation stage); (4) "no, but I intend to in the next 6 months" (contemplation stage); or (5) "no, and I do not intend to in the next 6 months" (precontemplation). A similar approach has been used by

Marcus *et al.*, (1992). The patients were also asked on a 6-point likert scale how motivated they were to partake in physical activity (with 0 being not at all, to 5 being extremely).

Statistical Analysis

All data are presented as means ± standard deviation (SD), unless otherwise stated. Differences in demographics, fatigue and EBBS scores between physical activity groups (MOD and LOW) were examined using multiple independent samples *t*-test. After pooling both groups' data, Pearson's correlation coefficient (r) was employed to assess the significance of the relationships between physical activity level and fatigue, perceived exertion as a barrier and motivation. Significance was set at $p < 0.05$ for all analyses, which were conducted using the Statistical Package for the Social Sciences Version 14.0.

Results

A total of 118 eligible women treated for breast cancer were approached, of which 78 agreed to take part in the study. Of these, 58 patients were able to be contacted and returned the questionnaires; 8 patients' data were not used in the analyses due to incomplete responses, therefore 50 complete questionnaires were scored and analysed. The mean age of the patients was 51.8 ± 11.3 and mean time since adjuvant treatment cessation was 21 ± 10 months (range: 12 to 38). Treatment history consisted of surgery, chemotherapy and radiotherapy (n = 12), surgery and chemotherapy only (n = 35) and surgery and radiotherapy only (n = 3).

Twenty six of the 50 (52%) patients had a total physical activity score from the IPAQ that was greater than 600 MET-minute per week (1323 ± 594) (MOD), whereas the remaining 24 had a total physical activity score less than 600 MET-minute week (349 ± 151) (LOW). Table 1 provides a comparison of demographic data between the LOW and MOD physical activity groups. There were no significant differences between the groups for age, body mass, cancer stage, and time since treatment cessation. However, the MOD group were significantly taller and therefore a trend for a lower BMI in the MOD group was revealed (p = 0.076). There were no differences between the two groups for self-reported hours of sleep at night (p = 0.556), amount of times waking in the night (p = 0.995), hours of sleep in the day (p = 0.309) and appetite (p = 0.773) (data not shown). Two patients had controlled hypertension. There were no other major co-morbidities reported.

Clinical fatigue

When all patients were combined, a mean global fatigue score of 3.5 ± 2.3 was reported. However, the patients in the LOW physical activity group reported significantly higher global fatigue (4.5 ± 2.3) compared with those in the MOD group (2.6 ± 1.9) ($p = 0.003$).

Cancer related symptoms

Using the MDASI, the symptoms with the highest mean scores were fatigue, drowsiness and feeling sad (Figure 1). Patients who were classified in the LOW physical activity group reported symptoms to be significantly more present compared with those in the MOD group (2.1 ± 1.9 vs. 1.0 ± 1.5, $p = 0.034$). When analysing symptoms individually, the LOW group reported increased feelings of fatigue ($p = 0.040$) and difficulty remembering things ($p = 0.016$) compared with the MOD group. Additionally, there were trends for increased feelings of sadness ($p = 0.061$) and increased shortness of breath ($p = 0.066$) in the LOW physical activity group.

Exercise benefits and barriers

For patients combined, the overall exercise benefits score using the EBBS was 80 ± 11. The MOD physical activity group had a significantly higher exercise benefits score (higher agreement) compared with the LOW group ($p = 0.038$) (Table 2). The highest mean scores (converted to a 4-point likert scale, to allow comparisons between categories) on the exercise benefit items for both the MOD and LOW group were in the physical performance, psychological outlook, and life enhancement categories; these were not significantly different between the groups (data not shown).

The overall exercise barriers score was 32 ± 5. The distribution of responses to the barrier scales are presented in Figure 2. Overall, the most frequently reported barriers to exercise were 'exercise tires me' (72 %), 'I am fatigued by exercise (64%), 'exercise is hard work' (52%) and 'exercise takes too much time from my family relationships' (52%). The highest mean scores (highest agreement) on the barrier items for both the LOW and MOD group were related to physical exertion, time expenditure and access to exercise facilities. Although the highest ranked barriers were similar between the two groups, the LOW group reported significantly higher overall mean barrier scores compared with the MOD group (p = 0.005) (Table 2). The LOW physical activity group scored significantly higher in items relating to both the physical exertion (p = 0.005) and time expenditure (p = 0.024), with a trend for family discouragement (p = 0.071).

The MOD physical activity group rated their motivation to engage in physical activity higher than the LOW group although this was not significant (2.0 ± 0.8 vs. 1.6 ± 0.8, p = 0.068). In the LOW physical activity group 8 patients were in the maintenance stage, 4 were in the adoption stage and 12 were in the pre-contemplation stage, compared with the MOD active group where 20 were in maintenance stage and 6 were in the pre-contemplation stage.

Selected variables that were associated with physical activity levels are shown in Table 3. Global fatigue, using the BFI and cancer symptoms using the MDASI, negatively correlated with physical activity levels (r = -0.561, p = <0.001; r = -0.297, p =0.036 respectively). Scores on the exercise benefits scale were positively correlated with physical activity levels. The only category on the exercise barriers scale that correlated with physical activity was the perceived exertion category (r = -0.267, p = 0.050) thus, the

more physically active patients were, the less they perceived physical exertion as a barrier towards exercise. Motivation to engage in physical activity was also positively correlated with physical activity levels ($r = 0.392$, $p = 0.005$).

Discussion

The purpose of this study was to investigate the perceived benefits and barriers to physical activity in patients on follow-up from treatment from breast cancer. More specifically, to investigate the relationship between fatigue and physical activity levels within this patient population.

A finding of this study was that, based on self reported physical activity levels, approximately half of the breast cancer patients on follow-up from adjuvant treatment engaged in the recommended physical activity levels (150 minutes per week of moderate to vigorous activity). The American Cancer Society estimated that 37.1% of breast cancer patients post treatment meet the physical activity recommendations (Blanchard *et al.*, 2008). Vallance *et al.*, (2010) found 34% of breast cancer survivors (an average of three years post diagnosis) were meeting public health physical activity recommendations, whilst Basen-Engquist (2008) found that 41 % of patients 5 years from cancer diagnosis were meeting the recommended physical activity levels.

Depending which data are used to compare the level of physical activity of patients in this study with the general population, the percentage of patients engaging in physical activity is either approximately the same or a lot higher than the general population. For example, for US women, 46% of those between 45 and 64 yrs engage in leisure time physical activity of moderate to vigorous intensity for 30 minutes on at least 5 days per week (Kugar *et al.*, 2005). For the Canadian population, it is estimated that 48.6% of women between the ages of 45 and 64 are meeting physical activity recommendations (Gilmour, 2007). According to the Health Survey for England (2008), 32 % of women aged 45 – 54 were meeting the recommended physical activity guidelines. Therefore, according to these

figures, and in contrast to previous research, the patients on follow-up for breast cancer are engaging in similar or higher levels of physical activity than the general population.

The discrepancies in these percentages between this study and other breast cancer populations are likely due to different times since diagnosis, and the exclusion of patients with major co-morbidity; therefore the sample is not representative of reference breast cancer populations. However, it might also be that the IPAQ has a tendency to overestimate physical activity levels, and this highlights the need for standardised measures of self-reported physical activity when attempting to compare physical activity levels.

The results of this study suggest that the patients on follow-up from treatment for breast cancer recognise the benefits of exercise. Overall, the patients 'agreed' (mean score of 2.8) with items on the benefits scale, with the highest scores for items related to physical performance, life enhancement, and psychological outlook. This is in agreement with other studies that have used the EBBS, albeit in younger healthy females (Lovell *et al.*, 2010) and in patients with multiple sclerosis (Stroud *et al.*, 2009). The perceived benefits towards exercise were significantly different between the low and moderately active groups, which suggests that the patients who engaged in physical activity perceived the positive benefits of exercise more than those who didn't engage in physical activity. However, overall the LOW active group still 'agreed' with items on the benefits scale, which suggests that other factors may influence intentions to engage physical activity levels.

It is suggested that perceived barriers may influence exercise behaviour more than perceived benefits (Dishman *et al.*, 1995). Overall, the most commonly reported barriers to exercise in this study were items related to perceived exertion. Specifically, the following barriers were reported with both the highest frequency and the highest mean scores: 'exercise tires me', 'I am fatigued by exercise' and 'exercise is hard work'. This is the first study to use the EBBS in patients with breast cancer on follow-up from treatment, so there is little to compare in the literature in relation to physical exertion specifically as a barrier to exercise. However, other studies that have assessed the barriers to exercise using the EBBS in different patients populations have found similar results (Stroud *et al.*, 2009; Passalent *et al.*, 2009). The mean score for physical exertion as a barrier to exercise was similar in patients on follow-up from treatment for breast cancer (3.0 ± 0.7) to other patient populations (ankylosing spondylitis; 3.2 ± 0.7), suggesting that physical exertion plays an important role in the barriers to physical activity in patient with chronic diseases associated with fatigue.

Although items related to perceived exertion are the most commonly reported barrier to exercise amongst healthy populations using the EBBS (Lovell *et al.*, 2010), the scores in this study reflect higher agreement with each item related to physical exertion (2.1 ± 0.6 and 3.0 ± 0.7, respectively). This suggests that physical exertion and feelings of fatigue play a larger role in the barriers towards physical activity in patients on treatment from breast cancer than they do in healthy populations.

In this study the overall fatigue score using the BFI was 3.5 (range 0.1-8.0), which suggests moderate levels of fatigue in these patients. The level of fatigue experienced by patients on follow-up from breast cancer treatment varies depending upon a number of

factors and is reflected in the range of fatigue scores in this study. Bower (2006) found that of 763 women treated for breast cancer, 35% reported fatigue 1-5 years after completion of their treatment. The percentage of patients reporting moderate and severe fatigue was slightly higher in this study (46 %), which is most likely a reflection of the different types of fatigue assessments used, or slightly different patient populations. It is not surprising that the main barrier to physical activity in these patients is related to physical exertion and feelings of fatigue. The patients who did not meet the ACSM guidelines for physical activity had significantly higher fatigue levels and scores related to physical exertion as a barrier compared with those who did meet the recommended levels. This is supported by two very recent studies that found that those patients who did not meet the recommended guidelines for physical activity reported more symptoms associated with fatigue (Rogers *et al.*, 2011; Vallance *et al.*, 2011). However, this study is the first study to assess perception of physical exertion as a barrier to physical activity in this cohort of patients.

The correlation analysis confirmed that there was a strong negative relationship between physical activity levels and fatigue. This is consistent with previous studies that have also found significant relationships between self-reported physical activity levels and symptoms of fatigue (Rogers *et al.*, 2006). The relationship was stronger in the patients in this study compared with previous reports, but this might be explained by the use of different measures of physical activity (IPAQ vs. Goodwin Leisure-Time Questionnaire) and fatigue (BFI vs. FACT-F). Interestingly, there was also a strong relationship between perceived exertion as a barrier towards exercise and physical activity levels in these patients; however, this was not as significant as fatigue and physical activity.

Other factors such as self reported symptoms were associated with physical activity levels, suggesting that those with increased symptom burden do not engage in physical activity as much as those with less symptom burden. Again those who engaged in the recommended physical activity levels had significantly less symptoms associated with cancer, more specifically less difficulty remembering things and a trend for less feeling of sadness and breathlessness. This is consistent with previous literature, where patients who engage in physical activity report less depressive symptoms and also perceived breathlessness to be a barrier towards exercise (Rogers *et al.*, 2006).

This study is in general agreement with previous studies that have reported fatigue, time constraints and treatments related side effects as barriers to exercise in patients with breast cancer (Courneya *et al.*, 2005). Although only a trend, there was a tendency for those in the LOW group to perceive lack of family encouragement as a barrier towards exercise more than those in the MOD group. This is supported by the findings of Cournya *et al.*, (2009) who found that family support becomes an important predictor physical activity behaviour over time (5 years post treatment for breast cancer).

Motivation levels were also associated with physical activity levels, suggesting that those who were more motivated to engage in physical activity had higher levels of physical activity. This can be supported by the fact that the patients who engaged in physical activity also had increased benefit scores, suggesting that they were motivated to exercise due to the rewards of exercise.

Those who met the recommended physical activity levels were also in the maintenance or action stage of the exercise behaviour model compared to those patients that were not

meeting the guidelines. Those who were in these stages reported physical exertion, time expenditure, and family discouragement less frequently as barriers towards exercise. This is also supported by Rogers *et al.*, (2006), who report correlations between exercise stages of change and barriers towards exercise, suggesting that those who are in the maintenance stage are less likely to report barriers towards exercise.

As there appears to be a stronger relationship between fatigue and physical activity than perceived exertion and physical activity, it can be suggested that it is not perceived physical exertion alone that is directly affecting the fatigue and physical activity relationship. To test this hypothesis correctly, mediation analysis could be used to determine whether other factors are influencing the fatigue and physical activity relationship. There is support for this from the self efficacy literature, where Rogers *et al.*, (2006) found that greater perceived barriers has a negative effect on self-efficacy, and is associated with reduced physical activity.

Perceived exertion was measured through the barriers questionnaire and not using real time assessment, such as ratings of perceived exertion. Aadahl *et al.*, (2007) found that perceived exertion was significantly related to self rated fitness and that self rated fitness seems to determine perception of exertion in leisure time, occupation, household and transport activities. As this was the first study to address perceived physical exertion as a barrier towards exercise in patients on follow-up from treatment for breast cancer, future research might follow similar methods as Aadahl *et al.*, (2007), to allow the measurement of perceived exertion during exercise designed to replicate activities of daily living.

In summary, patients on follow-up from adjuvant treatment for breast cancer perceive the benefits of exercise, and those who report higher levels of physical activity, have higher agreement with the positive effects of exercise than those who report low levels of physical activity. The predominant perceived barriers towards exercise were related to fatigue and perceived physical exertion and interestingly those who engaged in physical activity had reduced levels of fatigue and reduced perception of physical fatigue as a barrier towards exercise. Strategies to both educate those on the benefits of exercise and ways to minimise physical exertion as a barrier, particularly following treatment for breast cancer need to be addressed.

Table 1. Patient demographic characteristics

	LOW (n = 24)	MOD (n = 26)	*p* value
Age (yr)	53.3 ± 10.3	50.4 ± 12.2	0.383
Cancer Stage (*n*)			
II	14	12	
III	10	14	
Time since cessation of treatment (months)	23.3 ± 10.5	19.1 ± 8.8	0.447
Co-morbidities (n)	1	1	
Height (cm)	162 ± 4.0	167 ± 4.3	0.000*
Body Mass (kg)	75.9 ± 12.8	74.9 ± 10.4	0.756
BMI (kg/m^2)	28.6 ± 4.1	26.8 ± 3.1	0.076
Physical activity level (MET-minutes per week)	349 ± 151	1323 ± 594	0.000*

Data are means ± standard deviation or no. of subjects (n). LOW, low physical activity level: <600 MET-minutes per week; MOD, moderate physical activity level: >600 MET-minutes per week; METs, metabolic equivalents. * significant difference between the 2 groups

Table 2. Differences in perceptions of exercise benefits and barriers between low and moderately active patients 21 months post breast cancer treatment

	LOW (n = 24)	MOD (n = 26)	*p* value
Total Exercise benefit scores (29-116)	77 ± 8	83 ± 12	0.038*
Exercise barriers score (14-56)	34 ± 6	31 ± 4	0.005*
Exercise milieu	2.1 ± 0.5	2.2 ± 0.4	0.702
Time expenditure	2.6 ± 0.4	2.3 ± 0.5	0.020*
Physical exertion	3.0 ± 0.7	2.5 ± 0.6	0.005*
Family discouragement	2.0 ± 0.6	1.8 ± 0.5	0.071
Motivation to engage in physical activity (0-5)	1.6 ± 0.8	2.0 ± 0.8	0.068

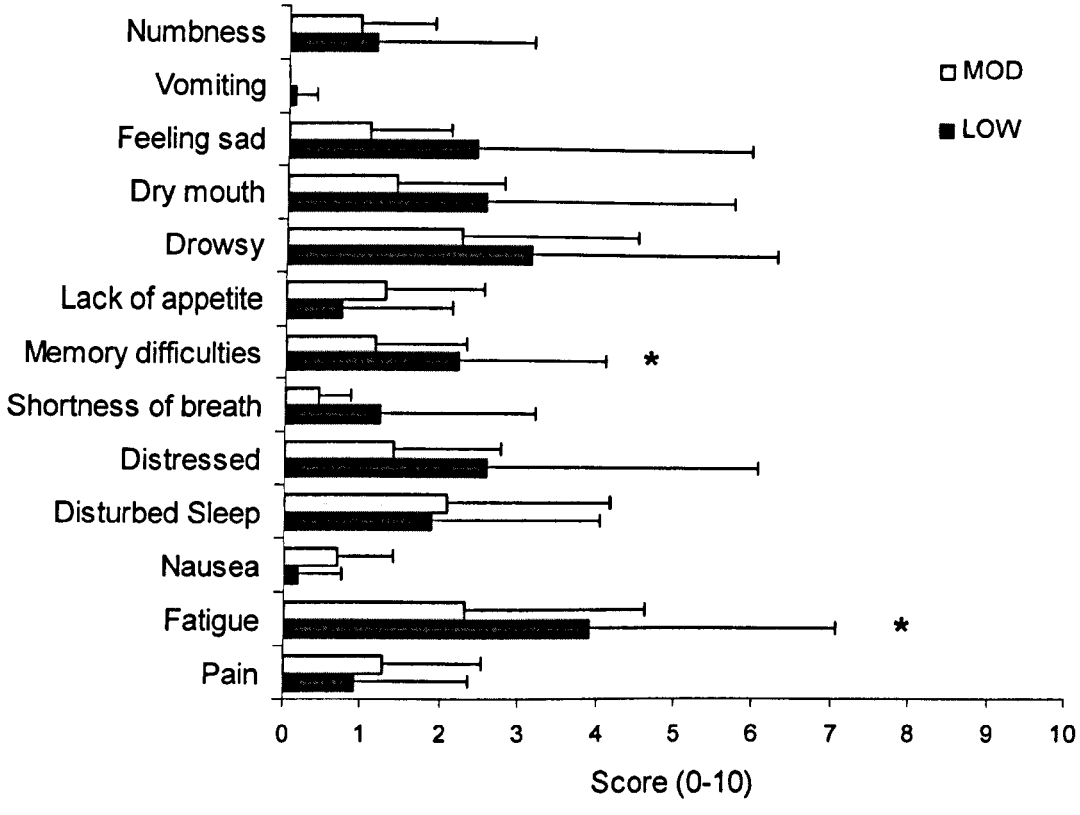
Data are means ± standard deviation. Higher scores indicate a higher agreement with the benefit and barriers towards exercise. LOW, low physical activity level: <600 MET-minutes per week; MOD, moderate physical activity level: >600 MET-minutes per week. * significant difference between groups

Table 3. Correlations between physical activity, fatigue, and exercise benefits and barriers in patients 21 months post breast cancer treatment

	Total physical activity	Fatigue (BFI)
Fatigue (BFI)	-0.561 (<0.001*)	-
Cancer symptoms (MDASI)	-0.297 (0.036*)	0.664 (<0.000*)
Benefits (EBBS)	0.456 (0.001*)	-0.218 (0.128)
Barriers (EBBS)	-0.240 (0.093)	0.151 (0.295)
Physical exertion	-0.276 (0.050)	0.357 (0.001*)
Motivation	0.392 (0.005*)	-0.247 (0.084)

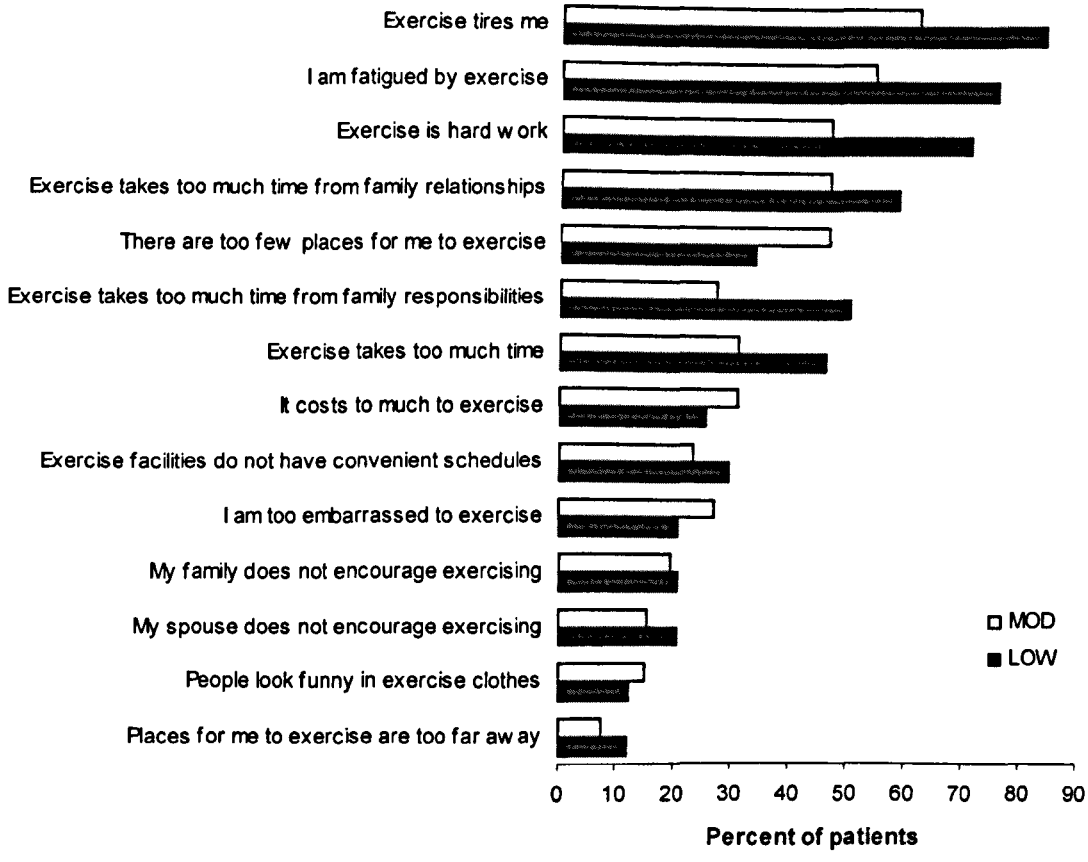
Values are Pearson's correlation coefficient (r) with statistical significance (p) in parentheses. BFI, brief fatigue inventory; EBBS, exercise benefits and barriers scale.
* $p < 0.05$

Figure 1. Reported cancer symptoms using the MD Anderson Symptom Inventory (MDASI)



Data are means ± SD. Severity of symptoms in the preceding 24 hours on a 0-10 scale, with 0 being 'not present' and 10 being 'as bad as you can imagine'. LOW, low physical activity level (n = 24); MOD, moderate physical activity level (n = 26). * significant difference between LOW and MOD physical activity level ($p < 0.05$)

Figure 2. Agreement and high agreement with exercise barrier statements



Data are percentage of patients in agreement or high agreement. LOW, low physical activity level ($n = 24$); MOD, moderate physical activity level ($n = 26$). * significant difference in mean scores (using the 4-point likert scale) between LOW and MOD physical activity level groups ($p < 0.05$)

CHAPTER FIVE

GENERAL DISCUSSION

This chapter presents a summary of the findings from each experimental chapter and relates the main findings to the literature. Also included in the chapter are limitations and future research recommendations and implications for applied practice.

Summary of main findings

Cancer is associated with a number of side-effects related to the disease and its treatments that affect patient quality of life. Among these side effects are cancer related fatigue and disturbed sense of effort. Exercise training has previously been shown to alleviate fatigue in cancer patients, and to improve cardiopulmonary capacity, muscle function and decrease feelings of perceived exertion. Although there are numerous studies investigating the mechanisms of fatigue, little evidence has focussed on specific aspects of fatigue and even less research has focussed on fatigue in relation to perceived exertion.

Chapter Two examined the psychophysiological mediators of physical fatigue in breast cancer patients receiving adjuvant chemotherapy. There are numerous studies investigating the factors contributing to fatigue in patients with cancer, in particular breast cancer. Although fatigue is a multidimensional construct, there is evidence to suggest that different aspects of fatigue could have different pathophysiologies. For this reason, a subtype of fatigue was investigated and defined as the increase in perceived exertion during a physical task. The aim of this study was to provide experimental evidence to investigate the anecdotal reports that chemotherapy increases perception of effort during physical tasks. The secondary aim was to ascertain whether any changes in fatigue and perceived exertion during chemotherapy treatment were associated with changes in the physiological or psychological parameters assessed.

This study provided experimental evidence that breast cancer patients have significantly elevated perception of effort during exercise designed to replicate activities of daily living, compared with healthy matched controls. These baseline differences were associated with reduced exercise capacity, due to reduced physical activity levels and other factors such as reduced haemoglobin levels, and could potentially be due to the more chronic effects of previous surgery and treatment. The most interesting finding was that after one bout of chemotherapy, the breast cancer patients had a significantly elevated perception of effort compared to baseline, with no concomitant changes in any of the measured physiological variables. This study provided novel data, via the direct minute-by-minute monitoring of perceptual and physiological responses during submaximal exercise to suggest that the acute effects of chemotherapy on perceived exertion are not mediated by changes in cardiorespiratory and metabolic function. Therefore, chemotherapy may have a direct effect on the brain, which could explain the increase in perceived exertion.

Chapter three examined the physiological and psychological effects of progressive resistance training in prostate cancer patients receiving androgen deprivation therapy. There is also a paucity of literature examining the effects of resistance exercise upon fatigue in patients with prostate cancer receiving ADT. However, there is considerable evidence to suggest that both aerobic and resistance exercise training programmes improve muscle strength, physical functioning, and body composition within these patients. Also, there are only a handful of studies that have used the gold standard assessment technique of body composition (DXA) and no studies that have attempted to estimate total body protein in these patients.

This study provided further evidence that an intensive progressive resistance exercise programme is safe, effective and well tolerated by elderly prostate cancer patients. In addition, the intensity of the resistance programme was higher than previously published studies, and elicited more pronounced changes in fatigue, strength and body composition. Additionally, it showed that progressive resistance training has a positive affect on quality of life. Of particular interest is that resistance training improved both the mental and physical aspects of fatigue. This study provides valuable practical application, as the appropriate training in elderly prostate cancer patients can improve mental and physical fatigue, muscle strength, physical function, and quality of life, which is vital in the recovery from cancer, particularly in relation to the severe side effects from cancer treatment. A novel aspect identified within this study for future research was the effect of resistance training on cognitive aspects of fatigue in these patients.

Chapter four examined the perceived benefits and barriers towards exercise in patients on follow-up from treatment for breast cancer, with particular focus on treatment related side effects such as fatigue and its relationship with perceived exertion. Previous studies have identified multiple barriers to physical activity within breast cancer patients, which include social, biological and psychological variables and also symptoms of disease and treatment related quality of life. Although psychosocial barriers should not be ignored within these patients, little research has focused on treatment related side affects alone. Although fatigue has been suggested to be a common barrier within cancer patients, there is no research investigating fatigue in relation to perceived exertion as a barrier in these patients. Therefore the aim of this study was to explore the perceived benefits and barriers in patients on follow-up from breast cancer treatment with particular focus on the relationship between physical activity, fatigue and perceived exertion.

This study found that overall the patients generally agreed with the benefits of exercise, in particular, those associated with physical performance and psychological outlook. Those who met the recommended guidelines for physical activity reported higher perceived benefits towards exercise than those who did not. This study also found that those who engaged in the recommended physical activity levels had reduced levels of self reported fatigue, less symptom burden, more motivation to engage in physical activity and perceived fewer barriers towards exercise, in particular those associated with physical exertion. Correlation analyses confirmed these findings, where strong associations were found between physical activity, perceived benefits of exercise, fatigue, motivation and physical exertion as a barrier towards exercise. This is the first study that has investigated physical exertion as a barrier towards exercise in this patient population and it provides a novel understanding for future research into interventions to promote physical activity and exercise in patients on follow-up from treatment for breast cancer.

Fatigue in patients with cancer

The breast cancer patients both during [**chapter two**] and post treatment [**chapter four**] reported prevalence of fatigue consistent with previous studies (Bower *et al.*, 2006). Using the Brief Fatigue Inventory (BFI) those patients during treatment had an average fatigue level of 4.6 (range; 2.0 -7.9), and those post treatment had a slightly lower average fatigue level of 3.5 (range; 0.1 -8.0). Using the BFI cut off points of moderate (3) and severe (7), 54% and 23% of patients reported moderate and severe levels of fatigue during treatment [**chapter two**]. In contrast to this, 36% and 10% of patients reported moderate and severe fatigue during follow-up [**chapter four**]. This is consistent with previous reports, where those on treatment have reported higher prevalence of fatigue compared to those post

treatment (Irvine *et al.*, 2004). The prostate cancer patients [**chapter three**] also had levels of self-reported fatigue comparable to those reported in the literature (Mohile *et al.*, 2007).

Overall, the studies in this thesis support the finding of increased levels of fatigue in patients treated for cancer compared with healthy matched controls; increased prevalence of fatigue in patients during treatment compared to those on follow-up from treatment; provide evidence for increased fatigue across different cancer populations; and provide support for the reduced levels of fatigue in more physically active patients and in response to an exercise intervention.

To gain a better understanding of the mechanisms of fatigue, it is more beneficial to look at particular subtypes of fatigue separately; as different aspects of fatigue could have different pathophysiologies. For this reason, in **chapter two** a particular aspect of fatigue was studied, which was operationally defined as a greater sense of effort required to accomplish a physical task (Ryan *et al.*, 2007). In **chapter three**, fatigue was measured using the BFS, which allowed the physical and mental components of fatigue to be broken down. In **chapter four,** fatigue was related to the patient's perceived physical exertion.

As hypothesised, compared with healthy populations [**chapter two**] patients during treatment for breast cancer reported increased levels of (clinical) fatigue and perceived exertion during a physical task. Also, after one bout of chemotherapy, both fatigue and perceived exertion during a physical task were increased. Interestingly, in **chapter two,** post chemotherapy, the patients rating of perceived exertion (6-20 scale) was 5 points different from the healthy controls. As this is one of the first studies to measure perceived

exertion in patients treated with cancer, comparisons can only be made within the literature with CFS patients, where a difference of approximately 2 points on the RPE scales has been seen between healthy controls and CFS patients (Wallman *et al.*, 2004). Although **chapter four** did not measure perceived exertion directly, patients on follow-up from breast cancer treatment, who reported higher levels of fatigue, were more likely to perceive physical exertion as a barrier towards exercise. In addition, **chapter three** provides evidence that patients reported less fatigue in response to an exercise intervention. As perceived exertion decreases for the same absolute intensity with exercise training, it would be reasonable to suggest that those patients with prostate cancer who reported less fatigue would have had reduced perceived exertion for the same physical tasks.

The novel and consistent findings in the three studies in this thesis support previous anecdotal evidence ('Cancerbackup' leaflet, 2005) that suggests patients find everything 'too much effort' when they are fatigued, and also research that suggest that cancer patients find activities of daily living a lot more effortful when they are fatigued (Hoffman *et al.*, 2007). This thesis provides strong experimental evidence to suggest that one important component of cancer related fatigue is the altered or increased perception of effort in relation to a physical task. The reasons for this increase in perceived exertion are multifactorial and are discussed below in relation to the results of the studies in this thesis, with supporting evidence from the literature.

Contributing factors towards increased perceived exertion

Original work into the ratings of perceived exertion by Borg and Dahlstrom in the 1950's was based on the area of psychophysics (Stevens, 1957), which focuses on the intensities

of sensory perceptions and experiences. The RPE (6-20) scale was designed in order to obtain a strong linear relationship between perceived exertion and exercise intensity and heart rate (Borg *et al.*, 1987). Many studies since have provided evidence to support the fact that the 15-point RPE scale produces a direct linear relationship between subjective ratings and physiological measures such as heart rate and O_2 consumption and several physiological parameters including ventilation, oxygen consumption (VO_2) and metabolic acidosis have been shown to be associated with RPE (Noble & Robertson, 1996). Perception of effort is a complex sensation, with continual debate about the neurophysiological basis of this concept; however, it is beyond the scope of this thesis to enter into an in-depth discussion about where the signals of RPE arise from.

Based on the evidence from the studies in this thesis, the potential reasons why perceived exertion might be increased in patients undergoing or on follow-up for treatment for cancer are discussed. Although other factors could be involved, such as the direct effects of previous treatment on perceived exertion, the main contributing factor to increased perceived exertion measured using the RPE scale [**chapter two**] was the reduction in physical capacity seen in these patients. In **chapter two**, although only retrospective and self-reported, there was a significant reduction in the patient's physical activity levels during treatment compared to at diagnosis, and leisure time activity was significantly reduced compared with the healthy matched controls. This is consistent with previous studies where patients reduce their physical activity levels during treatment for cancer. More importantly, the self-reported reduction in physical activity level was reflected in the cardiovascular and metabolic factors measured in **chapter two.** For example, heart rate and blood lactate production were increased at baseline in those patients who were less physically active compared with healthy matched controls; which is not surprising. Those

individuals who have reduced physical capacity have an increased rating of perceived exertion for the same absolute workload.

Similarly, the main contributing factor towards an increased perception of physical exertion as a barrier towards exercise [**chapter four**] was due to reduced physical capacity. Those patients who were on follow-up for treatment for breast cancer who were less physically activity, reported physical exertion as a barrier towards exercise more than those who were physically active. Again, although only self-reported, it would be reasonable to suggest that those who were less physically active, would have increased ratings of perceived exertion for the same absolute workload. Finally, to support this concept further, in **chapter three**, those patients who underwent the resistance training exercise intervention, reported reduced ratings of perceived exertion after increasing their physical capacity. With this in mind, it is not surprising that those patients who have reduced physical capacity (due to reduced physical activity levels) have an increased perception of effort for the same activities of daily living as those who do not have a reduced physical capacity (healthy controls in **chapter two** and physically active patients in **chapter four**).

However, it must be noted that this reduced physical capacity cannot explain all the differences in perceived exertion and fatigue in these patients. For example, in **chapter two** there was still an increase in perceived exertion after one session of chemotherapy, despite no changes in physical capacity. Also, in **chapter four** there were still moderate to severe fatigued patients who engaged in the recommended levels of physical activity.

Chapter two provides novel experimental evidence to suggest that other mechanisms may contribute to increases in perceived exertion during treatment for cancer. The baseline

differences in perceived exertion are due in part to differences in physical activity levels (as previously discussed), which were reflected by cardiorespiratory and metabolic variables. However, the increases in perceived exertion during a physical task after one session of chemotherapy could not be explained by any changes in these cardiorespiratory or metabolic parameters. This suggests that the increase in perceived exertion could be due to other factors, such as those associated with the brain. More specifically, as there were no differences at baseline in mood (affect) between the patients and healthy controls, and more importantly, no changes after one session of chemotherapy, it can be suggested that the increase in perceived exertion was not associated with psychological factors. It could be that treatment for cancer directly affects the neurobiological process within the brain, which could impact upon perception of effort.

Support for this comes from all three studies where the patients reported difficulties remembering things; often referred to as "chemo brain" (Hoffman *et al.*, 2007). It is suggested that cancer and treatment (in particular chemotherapy and ADT) have an effect on cognitive function; however, no studies have looked at the relationship between cognitive function and perceived exertion in patients treated for cancer. This concept is also supported by **chapter three**, where there was a decrease in the mental aspects of fatigue (with some cognitive components) in response to an exercise programme, with a reduction in the perception of effort for the same absolute workload.

Further support to suggest that cancer treatment has a direct effect on the brain, is that those patients who reported increased perceived exertion also reported more general symptoms associated with cancer. It could be that the sensation of effort is amplified in patients treated for cancer, due to greater attention to physical and mental symptoms. It

has been suggested that those with symptoms of fatigue pay more attention to general signals and symptoms that arise from the body (Wessley *et al.*, 1996).

In support of this, in both **chapter two** and **four** those patients who reported increases in perceived exertion (on the RPE scale and as a barrier towards exercise), also reported more general self-reported subjective symptoms associated with cancer. For example, in **chapter two**, all self-reported symptoms such as pain and nausea were higher in patients compared with healthy controls. Also during treatment, feelings of breathlessness and tiredness were increased in these patients, with a concomitant increase in perceived exertion. In **chapter four,** those patients who reported increased levels of perceived exertion as a barrier towards exercise, also reported increased difficulty remembering things, feelings of sadness and breathlessness. In **chapter three,** patients reported a reduced symptom burden after exercise, with reductions in mental fatigue symptoms associated with anxiety.

In both **chapter two** and **four**, the breast cancer patients reported increased feelings of breathlessness. Although this could be associated with the reduced haemoglobin levels, feelings of breathlessness do often occur in the absence of anaemia. Also, feelings of breathlessness were increased in **chapter two** after one session of chemotherapy, with no increases in haemoglobin levels. The sensation of breathlessness or dyspnea, is a major contributing factor towards perceived exertion (Robert & Nobleson, 1996). Therefore, it is not surprising that as fatigue and perceived exertion increases, so do feelings of breathlessness. However, the mechanism by which these general increased feelings and symptoms are sensed remains unclear and is under continual debate.

Another contributing factor towards the increase in perceived exertion could be the difference in haemoglobin levels measured in **chapter two**. Although probably not anaemic, as this would be identified during clinical screening, those both on treatment [**chapter two and three**] and on follow-up from treatment [**chapter four**] might also have reduced heamoglobin levels compared with the healthy controls. However, as previously discussed in **chapter one** and **two**, although haemoglobin levels are associated with fatigue, they were not the only contributing factor. An argument for this comes from the fact that fatigue and RPE increased after one session of chemotherapy [**chapter two**], with no changes in Hb levels, suggesting that other contributing factors cause the increases in perceived exertion.

In summary, the results from this thesis revealed that fatigue and perceived exertion are increased during and post treatment for cancer. The mechanisms for these increases are complex, but can in part be explained by a reduced physical capacity, which is reflected by cardiovascular and metabolic factors [**chapter two**] and other factors such as Hb. Importantly, this thesis identified other factors which are associated with this increase in perceived exertion such as increased sensation of symptoms and the possible direct effects of treatment on the central nervous system. Additionally, the results from **chapter three**, suggest that resistance exercise had an effect on mental fatigue in patients treated for prostate cancer, again highlighting the cognitive aspects of CRF.

Treatment for cancer related fatigue

Based on the results of the studies in this thesis and previous studies, directions for the treatment of fatigue can be made. Due to the limited understanding of the pathophysiology of this symptom, in many cases fatigue remains undertreated (Sood *et al.*, 2005). It is also

generally untreated because some clinicians do not perceive fatigue being a significant problem (Winningham, 2001), as it is often underreported by patients, who feel it is a normal part of the cancer treatment and/or the recovery process. As discussed in **chapter one,** pharmacological treatment alone have not been effective in the management of CRF, therefore a combination of pharmacological and non-pharmacological treatments are suggested.

The NCCN guidelines for treating fatigue (2011), together with systematic reviews (Wanchai *et al.,* 2011) show that exercise (e.g., home-based and supervised), education and counselling, and sleep therapy are effective nonpharmacologic interventions that improve fatigue and QoL in patients treated for cancer.

As previously discussed [**chapter one**], the strongest evidence for improving fatigue comes from those studies that have looked at the effect of exercise in breast and prostate cancer patients. **Chapter three,** which found reduced levels of fatigue in patients treated for prostate cancer after high intensity progressive resistance training, also supports this recommendation. The rationale for this comes from general exercise physiology concepts, whereby increases in muscle mass, fitness, and physical function [**chapter three**] lead to a reduced perception of effort for the same task. Therefore patients who engage in physical activity or exercise training will perceive daily tasks to be less effortful. However, the main findings of this thesis suggest that there are other factors that contribute to this decrease in perceived exertion associated after exercise training.

The results from **chapter two** and **three** suggest that CRF is associated with the direct effects of treatment on the mental and cognitive aspects of fatigue. Interestingly, there is a beneficial effect of exercise on cognitive function in the elderly, although little research exists investigating the effects of exercise in relation to fatigue and cognitive function in cancer patients. Nevertheless, **chapter three** provides evidence that resistance training can improve the mental aspects of fatigue.

However, when patients are fatigued and perceived exertion is increased during daily tasks, patients often decrease physical activity to maintain effort at an acceptable level, which eventually leads to muscle wasting and reductions in physical capacity. As a consequence, activities of daily living become even more strenuous and fatiguing for these patients. Therefore, the challenge is to encourage those patients who are fatigued to engage in physical activity. This thesis provides experimental evidence to support the anecdotal reports that patients find it hard to commence exercise after treatment from cancer due to an increased perception of effort (Moving Forward, Breast Cancer Care Programme, North Wales, 2011). Based on the results from **chapter four**, treatments for fatigue should also focus on the education of patients in relation to both the benefits of physical activity, and the management of side effects. More importantly, it should address the increased perceived physical exertion in these patients.

Based on the results of this thesis, another potential contributing factor towards the increases in perceived exertion are self-reported disruptions in sleep patterns. Sleep disturbances such as insomnia and hypersomnia, are present in 30 – 75 % of patients treated for cancer (Berger, 2005) and can cause severe distress. Several studies shave

shown that patients on active treatment increase time resting and sleeping in the day and that their pattern of sleep at night is often disrupted (Kuo *et al.*, 2006). The results of **chapter two** support this as the patients on chemotherapy reported increased hours of sleep at night, sleepiness during the day, number of times wakening at night (compared to healthy matched controls), and increased disturbed sleep at night after one bout of chemotherapy. However, this was not reflected in **chapter four,** where self-reported hours of sleep at night, hours of sleep in the day, and disturbed sleep at night were not different between groups with differing levels of fatigue.

This could be explained by the fact that those patients on treatment for cancer would have also been prescribed an antiemetic which causes disruption of sleep; where as the patients on follow-up would not have been on this treatment. This suggests that although increased disturbed sleep maybe associated with increased perceived exertion in patients undergoing chemotherapy, it is not for those on follow-up from treatment. Sleep deprivation studies have shown that RPE is the same in healthy adults during exercise for a lower submaximal workload after 48 hours of sleep deprivation (Oliver *et al.*, 2009). This suggests that sleep deprivation or disturbance could explain some of the increase in RPE in the patients during treatment.

Treatment for disturbed sleep has involved sleep hygiene programmes, counselling and cognitive behavioural therapy. However, there were no differences in the disrupted sleep, and self-reported sleep patterns did not distinguish fatigue levels in those patients on follow-up for treatment [**chapter four**]. This highlights the need for different strategies for different time points in the treatment process.

In summary, as CRF is a multifactorial complex concept, the treatment should be all encompassing. For example, screening and assessing the patients levels of fatigue, treating contributing factors, such as anaemia, pain, and other co-morbidities, enhancing physical activity levels, addressing nutritional considerations, psychosocial interventions, and sleep hygiene (NCCN, 2011). However this thesis has identified target areas for interventions, such as promoting physical activity and addressing increased perceived physical exertion experienced by these patients.

Limitations to the research program

Selection bias may have affected all the studies in this thesis as patients were convenience sampled and self selected. Although some of the individual patients were severely fatigued, the average fatigue levels ranged from 3.5-4.5 in all the studies (i.e. moderate to severe). Therefore, the patients in these studies likely reflected those who were not the most fatigued. This is reflected by the patients who in **chapter two** were unable to return to time point 2 due to being too fatigued (n = 1/17) and unable to complete the exercise protocol due to being too fatigued (n = 1/17). Also, it is likely that those who were interested in physical activity and exercise were more likely to volunteer to take part in the studies. This is reflected in **chapter four,** where the percentage of patients participating in the recommended weekly PA levels was greater (52 %) than that seen in other cancer populations. Every effort was made to ask all patients who were eligible to participate in the studies, but ultimately it was the patient's choice to participate.

Due to the nature of the inclusion and exclusion criteria in the studies, only patients free of other co-morbidities (such as cardiovascular, pulmonary, metabolic, renal or

neuromuscular disease) were eligible for the studies. This ensured that other co-morbidities were not influencing levels of fatigue. However, it is worth noting that the patients in the studies within this thesis were probably not representative of the general breast and prostate cancer populations, as the patients were likely to have less morbidity, fatigue and disability.

In **chapter two** there was not a breast cancer control group, as this was deemed unethical. Had one been included, this would have enabled matching of physical activity levels and other physiological variables, which would have allowed the comparisons between the groups. In turn, this would have given insights into the direct effects of chemotherapy on fatigue *per se*. However, to control for this, a matched healthy control group was used. Thus a repeated measures design with a matched healthy control group allowed the opportunity to i) assess outcome measures at repeated time points and ii) compare with the healthy control group to control for learned effects and natural variations in physiological and psychological variables between time points. Therefore, this allowed the opportunity to investigate both the effects of cancer an previous treatment (breast cancer vs. healthy controls at baseline) on physiological and psychological variables, and also for investigating the acute effects of one chemotherapy bout (pre vs. post test in the breast cancer patients) on physiological and psychological parameters.

Implications for future research

The main findings of this thesis were the increased perceived exertion associated with CRF seen in the patients treated for cancer. In **chapter two**, the increases in fatigue and perceived exertion in patients with breast cancer undergoing treatment were not explained

by physiological parameters measured in this study and in **chapter three**, reductions in fatigue due to exercise training were primarily seen in the mental components of fatigue. Therefore, future research will aim to investigate the direct effects of cancer and/or treatment on the brain in relation to perceived exertion and fatigue. For example, the effects of treatment for cancer on objectively measured cognitive function, using brain imaging techniques, during exercise could be related to fatigue and perceived exertion.

Although this thesis highlights a clear effect of cancer treatment on increased perceived exertion, there is a particular lack of supporting physiological data in patients undergoing treatment for cancer. Monitoring the changes in physiological variables over the period of treatment, in conjunction with perceived exertion, will give a better understanding of the acute versus chronic changes due to cancer therapy. This is highlighted in one of the limitations of **chapter two**, whereby the fact that the patients were not matched for physical activity levels means that it is not possible to tease out the reasons for differences at baseline in perceived exertion between patients and healthy controls. For example, it is not possible to tell whether chemotherapy is having a direct effect on the cardiovascular parameters in a chronic setting, or whether some of the baseline differences in perceived exertion are due to factors associated with the brain, as well as with reductions in physical capacity.

The high intensity progressive resistance exercise intervention prescribed to the patients with prostate cancer was safe and effective in achieving increases in muscle mass in conjunction with reductions in fatigue and improvements in quality of life. This study together with previous research provides evidence for improvements in body composition

with high intensity resistance training in this population. Therefore the rationale is provided for the prescription of high intensity resistance training in this patient group. The current research focuses on the combined effects of aerobic and resistance training programmes in light of the disability of cardiovascular health benefits for this population. However, the next step should involve studies that assess the cost effectiveness of implementing programmes such as this. Importantly, in relation to this thesis, investigations into the effect of exercise on cognitive function and perceived exertion should be carried out in this population.

In **chapter four**, the barriers to physical activity in cancer patients are related to treatment effects, therefore further research should be carried out to educate these patients on the side effects of treatment and in particular the effects of physical activity in alleviating these side effects. In particular, research should focus on the reduction of physical exertion as a barrier towards exercise. To do this, research will need to focus the mechanisms behind reducing perceived exertion in patients with cancer.

Applied focus

This research programme highlights areas of research that need to be addressed. However, it also allows recommendations in relation to the treatment of fatigue. In terms of the applied focus of the thesis, the emphasis should be on providing education and schemes to encourage lifestyle changes in patients with breast and prostate cancer. These programmes should focus on highlighting the benefits of exercise and educating patients on treatment related side effects, such as fatigue and increased perceived exertion. Additionally, there is not only a need to target fatigue and improve QoL in patients treated for cancer, but there

is also a requirement to improve the long-term survival of patients via prevention of disease recurrence. Programmes should educate patients highlighting the benefits of exercise not only in relation to treatment related side effects but also in relation to disease.

Courneya & Friedenreich (2007) identify the rehabilitation period after treatment from cancer as a key focus for future research and intervention programmes. The diagnosis of cancer has been described as a life changing event. The period after treatment, has been described as 'a teachable moment' (Demark-Wahnefried 2005), where in 3-5 months post treatment patients felt that they were fit enough to make behavioural changes at that time, while not yet having lost their motivation to change.

However, many cancer patients find the period after treatment a challenging time, due to a sudden decline in both medical and social support. Educational and supportive programmes that can offer social support to cancer patients during this period could help the transition from the intense levels of support they receive during treatment. The healthcare team play an important role in this, although it has been suggested that due to a lack of awareness, expertise and resources (Stevinson & Fox, 2005), only 20% of them provide health promotion interventions (Demark-Wahnefried 2005). Interestingly, on a recent Breast Cancer Care programme, 19/20 patients on follow-up for treatment from breast cancer said they would take up an exercise and nutrition programme if the right facilities and supervision were available. However, at the present time, there are no routine cancer exercise rehabilitation programmes within the NHS, other than those funded by research programmes or charities (for example Breast Cancer Care; National Association for Cancer Exercise Rehabilitation). There is clearly a need for educating both patients and health care professionals on the benefits of cancer rehabilitation.

Although a cancer rehabilitation programme should try to encompass all aspects of the cancer recovery process, limited funding discourages this. Therefore programmes should target specific interventions. The main findings of this thesis suggest that ways to manage and decrease perception of effort should be a focus of treatment and future research. The evidence is emerging, but possibilities include treatments which have been shown to decrease perception of effort during physical task, such as caffeine (Backhouse *et al.*, 2011). Also, psychostimulants such as modafinil have been studied in healthy populations where increases in time to exhaustion have been reported due to reductions in ratings of perceived exertion (Jacobs & Bell, 2004). Recently, modafinil has reduced severe, but not moderate to mild fatigue in patients treated for cancer (Jean Pierre *et al.*, 2010). However, in general there is little research focussing on the effects of cancer and treatment in relation to perceived exertion and the effects on the brain. Consequently, this should be the focus of future research.

Conclusions

This thesis provides experimental evidence that increased perceived exertion related to a physical task is an important component of fatigue in patients treated for cancer. The increase in perceived exertion in these patients is due in part to reduced physical capacity, reduced haemoglobin levels, and increased symptom burden. Importantly, this thesis provides evidence to suggest that a component of this increased perceived exertion is not associated with cardiorespiratory and metabolic parameters, suggesting that it is related to other factors, such as the effects of chemotherapy on the brain.

Physical activity and exercise is effective in alleviating some of the side effects associated with treatments for cancer. For example, patients who are more physically active experience fewer symptoms associated with cancer, in particular, less fatigue. More specifically, high intensity progressive resistance training is safe and effective at improving fatigue, muscle strength, lean mass, physical function, and quality of life in patients with prostate cancer. Additionally, this thesis provides evidence that PRT has beneficial affects on the cognitive aspects of fatigue in patients with prostate cancer. Therefore resistance training should be promoted by healthcare providers to enhance the rehabilitation process of elderly prostate cancer patients.

Despite the benefits of physical activity and exercise during and after treatment for cancer, not all patients engage in the recommended physical activity levels. The reasons for this are multifactorial, but evidence suggests that perceived physical exertion plays an important role in this. Therefore, patients undergoing treatment or on follow-up for treatment for cancer should be educated as regards to managing the side effects of treatment and how physical activity and/or exercise training can help to alleviate these side effects.

Future research should aim to address the increased perception of effort seen in patients treated for cancer **[chapter two and four]**. Treatment of increased perceived exertion will facilitate patients to initiate activities of daily living, which will in turn reduce the effort associated with commencing an exercise training programme. The benefits associated with exercise training **[chapter three]** such as increased aerobic fitness, improved muscle strength and function, will ultimately reduce perceived exertion for the same absolute

workload and improve perceptions of fatigue. This should lead to prompt recovery from treatment for cancer and eventually improved quality of life.

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APPENDICES

QUESTIONNAIRES

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

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? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

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

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

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

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

Date: _____ Institution: _____

Subject Initials: _____ Hospital Chart #: _____

Study Subject #: _____

M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
1. Your pain at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your fatigue (tiredness) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your nausea at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your disturbed sleep at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being distressed (upset) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your shortness of breath at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with remembering things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with lack of appetite at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling drowsy (sleepy) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a dry mouth at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Date: Institution:

Subject Initials: Hospital Chart #:

Study Subject #:

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
11. Your feeling sad at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your vomiting at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your numbness or tingling at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
14. General activity?	○	○	○	○	○	○	○	○	○	○	○
15. Mood?	○	○	○	○	○	○	○	○	○	○	○
16. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
17. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
18. Walking?	○	○	○	○	○	○	○	○	○	○	○
19. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

Patients I.D number..... **Date...../...../.....** **Time.....**

The PANAS (Watson *et al.*, 1988)

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you feel this way right now, that is, at the present moment. Use the following scale to record your answers:

1	2	3	4	5
very slightly or not at all	a little	moderately	quite a bit	extremely

___P	___ interested	___N	___ irritable
___N	___ distressed	___P	___ alert
___P	___ excited	___N	___ ashamed
___N	___ upset	___P	___ inspired
___P	___ strong	___N	___ nervous
___N determined	___ guilty	___P	___
___N	___ scared	___P	___ attentive
___N	___ hostile	___N	___ jittery
___P	___ enthusiastic	___P	___ active
___P	___ proud	___N	___ afraid

P = _____ N = _____

Bi-dimensional Fatigue Scale (Chalder *et al.*, 1993)

This questionnaire is designed to help us know how you feel. Read each item and underline the reply that comes closest to how you have been feeling in the past two weeks.

Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

1. Do you have problems with tiredness?

   Better than usual

   No more than usual

   Worse than usual

   Much worse than usual

2. Do you need to rest more?

   Better than usual

   No more than usual

   Worse than usual

   Much worse than usual

3. Do you feel sleepy or drowsy?

   Better than usual

   No more than usual

   Worse than usual

   Much worse than usual

4. Do you have any problems starting things?

   Better than usual

   No more than usual

   Worse than usual

   Much worse than usual

5. Are you lacking in energy?

   Better than usual

   No more than usual

   Worse than usual

   Much worse than usual

6. Do you have less strength in your muscles?

   Better than usual

   No more than usual

   Worse than usual

   Much worse than usual

7. Do you feel weak?

   Better than usual

   No more than usual

   Worse than usual

   Much worse than usual

8. Do you have difficulty concentrating?

Better than usual

No more than usual

Worse than usual

Much worse than usual

9. Do you have problems thinking clearly?

Better than usual

No more than usual

Worse than usual

Much worse than usual

10. Do you make slips of the tongue when speaking?

Better than usual

No more than usual

Worse than usual

Much worse than usual

11. How is your memory?

Better than usual

No more than usual

Worse than usual

Much worse than usual

Hospital Anxiety and Depression Scale (Zigmond *et al.*, 1983)

This questionnaire is designed to help us know how you feel. Read each item and underline the reply that comes closest to how you have been feeling in the past two weeks.

Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

1. I feel tense and wound up:

   Most of the time

   A lot of the time

   From time to time, occasionally

   Not at all

2. I still enjoy things I used to enjoy:

   Definitely as much

   Not quite as much

   Only a little

   Hardly at all

3. I get sort of frightened feeling as if something awful is about to happen:

   Very definitely and quite badly

   Yes, but not too badly

   A little, but it doesn't worry me

   Not at all

4. I can laugh and see the funny side of things:

   As much as I always could

   Not quite so much now

   Definitely not so much now

   Not at all

5. Worrying thoughts go through my mind:

   A great deal of the time

   A lot of the time

   From time to time

   Only occasionally

6. I feel cheerful:

   Not at all

   Not often

   Sometimes

   Most of the time

7. I can sit at ease and feel relaxed:

   Definitely

   Usually

   Not often

   Not at all

8. I feel as if I'm slowed down:

   Nearly all the time

   Very often

   Sometimes

   Not at all

9. I get sort of frightened feeling like 'butterflies' in the stomach:

   Not at all

   Occasionally

   Quite often

   Very often

10. I have lost interest in my appearance:

    Definitely

    I don't take so much care as I should

    I may not take quite as much care

    I just take as much care as ever

11. I feel restless as if I have to be on the move:

    Very much indeed

    Quite a lot

    Not very much

    Not at all

12. I look forward with enjoyment to things:

    As much as I ever did

    Rather less than I used to

    Definitely less than I used to

13. I get sudden feelings of panic:

    Very often indeed

    Quite often

    Not very often

    Not at all

14. I can enjoy a good book or radio or TV program:

    Often

    Sometimes

    Not often

    Very Seldom

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy.....	0	1	2	3	4
GP2	I have nausea.....	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
GP4	I have pain.....	0	1	2	3	4
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4
GP6	I feel ill.....	0	1	2	3	4
GP7	I am forced to spend time in bed.....	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little	Some-what	Quite a bit	Very much
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness.....	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	**Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer please tick the box**	☐				
GS7	I am satisfied with my sex life.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

EMOTIONAL WELL-BEING

		Not at all	A little	Some-what	Quite a bit	Very much
GE 1	I feel sad.....	0	1	2	3	4
GE 2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE 3	I am losing hope in the fight against my illness....	0	1	2	3	4
GE 4	I feel nervous.....	0	1	2	3	4
GE 5	I worry about dying.....	0	1	2	3	4
GE 6	I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain areas of my body where I experience significant pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ)

(Craig *et al.*, 2003)

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day?**

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

EXERCISE BENEFITS/BARRIERS SCALE (Sechrist *et al.*, 1987)

DIRECTIONS: Below are statements that relate to ideas about exercise. Please indicate the degree to which you agree or disagree with the statements by circling SA for strongly agree, A for agree, D for disagree, or SD for strongly disagree.

1. I enjoy exercise.	SA A D SD
2. Exercise decreases feelings of stress and tension for me.	SA A D SD
3. Exercise improves my mental health.	SA A D SD
4. Exercising takes too much of my time.	SA A D SD
5. I will prevent heart attacks by exercising.	SA A D SD
6. Exercise tires me.	SA A D SD
7. Exercise increases my muscle strength.	SA A D SD
8. Exercise gives me a sense of personal accomplishment.	SA A D SD
9. Places for me to exercise are too far away.	SA A D SD
10. Exercising makes me feel relaxed.	SA A D SD
11. Exercising lets me have contact with friends and persons I enjoy.	SA A D SD
12. I am too embarrassed to exercise.	SA A D SD
13. Exercising will keep me from having high blood pressure.	SA A D SD
14. It costs too much to exercise.	SA A D SD
15. Exercising increases my level of physical fitness.	SA A D SD
16. Exercise facilities do not have convenient schedules for me.	SA A D SD
17. My muscle tone is improved with exercise.	SA A D SD
18. Exercising improves functioning of my cardiovascular system.	SA A D SD
19. I am fatigued by exercise.	SA A D SD
20. I have improved feelings of well being from exercise.	SA A D SD
21. My spouse (or significant other) does not encourage exercising.	SA A D SD
22. Exercise increases my stamina.	SA A D SD
23. Exercise improves my flexibility.	SA A D SD
24. Exercise takes too much time from family relationships.	SA A D SD
25. My disposition is improved with exercise.	SA A D SD

26. Exercising helps me sleep better at night. SA A D SD

27. I will live longer if I exercise. SA A D SD

28. I think people in exercise clothes look funny. SA A D SD

29. Exercise helps me decrease fatigue. SA A D SD

30. Exercising is a good way for me to meet new people. SA A D SD

31. My physical endurance is improved by exercising. SA A D SD

32. Exercising improves my self-concept. SA A D SD

33. My family members do not encourage me to exercise. SA A D SD

34. Exercising increases my mental alertness. SA A D SD

35. Exercise allows me to carry out normal activities without becoming tired SA A D SD

36. Exercise improves the quality of my work. SA A D SD

37. Exercise takes too much time from my family responsibilities. SA A D SD

38. Exercise is good entertainment for me. SA A D SD

39. Exercising increases my acceptance by others. SA A D SD

40. Exercise is hard work for me. SA A D SD

41. Exercise improves overall body functioning for me. SA A D SD

42. There are too few places for me to exercise. SA A D SD

43. Exercise improves the way my body looks. SA A D SD

RAW DATA

Table 1. Effects of cancer and chemotherapy on ratings of perceived exertion

	Pre				Post			
	0	**25**	**50**	**75**	**0**	**25**	**50**	**75**
Breast cancer	8.8 ± 1.8	10.7 ± 1.8	12.6 ± 1.7	15.0 ± 2.3	9.4 ± 2.1	11.2 ± 1.9	13.5 ± 2.3	16.1 ± 2.6
Healthy control	7.5 ± 1.3	8.7 ± 1.7	10.7 ± 1.9	12.2 ± 2.0	7.4 ± 0.8	8.5 ± 1.2	10.4 ± 1.6	12.3 ± 1.9

Data are means ± standard deviation ($n = 26$).

Table 2. Effects of cancer and chemotherapy on cardiac parameters

	Pre				Post				
	0	25	50	75	0	25	50	75	*P*
HR (bpm)									
Cancer	95 ± 15	102 ± 14	118 ± 12	137 ± 13	99 ± 17	108 ± 16	123 ± 16	141 ± 16	0.050*
Control	85 ± 11	92 ± 13	107 ± 15	125 ± 20	88 ± 13	96 ± 14	112 ± 18	129 ± 22	
SV (ml/min)									
Cancer	77 ± 17	83 ± 16	88 ± 16	90 ± 16	78 ± 17	85 ± 19	85 ± 14	88 ± 15	
Control	87 ± 14	92 ± 16	96 ± 16	98 ± 16	86 ± 11	90 ± 13	93 ± 14	95 ± 15	
CO (L/min)									
Cancer	7.2 ± 1.3	8.4 ± 1.4	10.2 ± 1.3	12.2 ± 1.3	7.5 ± 1.1	8.9 ± 1.4	10.2 ± 1.1	12.4 ± 1.6	
Control	7.5 ± 1.8	8.6 ± 2.1	10.4 ± 2.3	12.3 ± 2.5	7.5 ± 1.6	8.6 ± 1.7	10.3 ± 2.0	12.2 ± 2.4	
Systolic BP									
Cancer	112 ± 20	121 ± 19	133 ± 23	143 ± 30	110 ± 19	118 ± 20	134 ± 20	145 ± 24	0.007*
Control	131 ± 20	140 ± 16	156 ± 17	174 ± 28	135 ± 16	140 ± 17	159 ± 27	172 ± 33	
Diastolic BP									
Cancer	68 ± 6	67 ± 6	67 ± 11	69 ± 10	65 ± 6	65 ± 7	68 ± 9	68 ± 9	0.004*
Control	75 ± 9	76 ± 8	76 ± 9	78 ± 9	74 ± 8	74 ± 7	76 ± 9	77 ± 10	
TPR									
Cancer	12 ± 2	11 ± 2	9 ± 2	8 ± 1	11 ± 2	10 ± 2	9 ± 1	8 ± 1	0.048*
Control	13 ± 3	12 ± 3	10 ± 2	9 ± 2	13 ± 3	12 ± 2	10 ± 2	9 ± 2	

Values are means ± standard deviation.* Main effect of group ($n = 26$)

Table 3. Effects of cancer and chemotherapy on respiratory variables.

	Pre				Post				
	0	25	50	75	0	25	50	75	*P*
VO2 (l/min)									
Cancer	0.46 ± 0.14	0.62 ± 0.18	0.84 ± 0.19	1.07 ± 0.27	0.51 ± 0.15	0.65 ± 0.12	0.87 ± 0.13	1.12 ± 0.17	
Control	0.53 ± 0.17	0.66 ± 0.18	0.90 ± 0.20	1.16 ± 0.20	0.57 ± 0.16	0.70 ± 0.15	0.91 ± 0.19	1.23 ± 0.18	
VCO2 (l/min)									
Cancer	0.40 ± 0.13	0.56 ± 0.15	0.83 ± 0.20	1.17 ± 0.28	0.44 ± 0.14	0.58 ± 0.11	0.87 ± 0.10	1.21 ± 0.13	
Control	0.42 ± 0.14	0.55 ± 0.17	0.78 ± 0.19	1.13 ± 0.25	0.44 ± 0.13	0.58 ± 0.17	0.82 ± 0.22	1.21 ± 0.30	
RER									
Cancer	0.86 ± 0.06	0.90 ± 0.07	1.00 ± 0.09	1.09 ± 0.12	0.84 ± 0.05	0.89 ± 0.08	1.00 ± 0.09	1.09 ± 0.12	0.001*
Control	0.81 ± 0.06	0.82 ± 0.06	0.88 ± 0.06	0.97 ± 0.07	0.80 ± 0.06	0.83 ± 0.07	0.88 ± 0.08	0.98 ± 0.09	
VE (L/min)									
Cancer	13.0 ± 5.2	16.9 ± 5.2	24.5 ± 6.2	33.0 ± 9.5	14.3 ± 4.9	18.5 ± 4.6	26.1 ± 5.1	36.0 ± 7.4	
Control	13.6 ± 4.1	16.5 ± 5.9	21.9 ± 7.3	29.9 ± 9.5	13.8 ± 3.7	17.4 ± 5.3	22.8 ± 7.3	33.5 ± 10.4	
VT (L/min)									
Cancer	0.67 ± 0.25	0.84 ± 0.28	1.11 ± 0.30	1.31 ± 0.33	0.73 ± 0.25	0.92 ± 0.25	1.14 ± 0.19	1.35 ± 0.21	
Control	0.76 ± 0.26	0.84 ± 0.23	1.09 ± 0.21	1.32 ± 0.27	0.76 ± 0.18	0.90 ± 0.20	1.12 ± 0.22	1.42 ± 0.28	
BF									
Cancer	19 ± 5	21 ± 4	23 ± 5	26 ± 6	20 ± 4	22 ± 4	23 ± 5	27 ± 6	
Control	19 ± 3	20 ± 4	21 ± 4	24 ± 7	18 ± 2	20 ± 3	21 ± 5	24 ± 6	

Values are means ± standard deviation).* Main effect of group ($n = 26$)