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## **Exercise as medicine : reversing treatment toxicities in prostate cancer patients**

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# **EXERCISE AS MEDICINE: REVERSING TREATMENT TOXICITIES IN PROSTATE CANCER PATIENTS**

A thesis submitted for the degree of

**Doctor of Philosophy**

November, 2013

By

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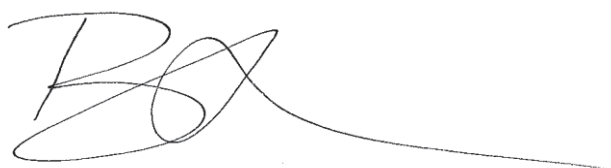
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# **ABSTRACT**

A common treatment for prostate cancer, which is the most common form of cancer after skin cancer in Australian males, is androgen deprivation therapy (ADT). However, ADT is associated with an array of adverse effects including reduced bone and lean mass, loss of muscle strength, negative change in lipid profile, and increased risk of cardiovascular disease (CVD) as well as diabetes, all of which can compromise physical function and quality of life. Physical exercise has been suggested as a key lifestyle intervention for this group of cancer patients as it has enormous potential to limit and even reverse the effects of such treatment toxicities. This thesis is comprised of a review of the literature and three experimental chapters examining the effects of androgen deprivation therapy (ADT) and the role of exercise in ADT treated prostate cancer patients. The review of literature provides a background to cancer, in particular prostate cancer and the commonly reported side effects of treatment. The review identified gaps in the literature that highlighted the need for well controlled and longer term experimental studies to: 1) investigate the impact of androgen deprivation therapy duration on cardiovascular and metabolic outcomes, and 2) investigate the effects of a long term exercise intervention in reversing cardiovascular risk factors and unfavourable alterations in the metabolic profile.

Study 1 examined the feasibility and safety of a maximal treadmill exercise test in ADT treated prostate cancer patients as this was a key assessment of physiological response to the exercise intervention. One hundred and twelve prostate cancer patients

undergoing ADT took part in a physician supervised multistage maximal stress test (Bruce protocol). Of these men, 85% were able to meet the criteria for the attainment of  $\text{VO}_2\text{max}$  whilst three positive tests (3.2%) were observed. The three participants who recorded a positive stress test were sent for further examination and subsequently cleared of any serious issues. Apart from the relatively low  $\text{VO}_2\text{max}$  (10-15<sup>th</sup> percentile), compared to healthy age matched controls, the cardiovascular response to exercise is similar in this cancer population. Maximal exercise testing in this population was demonstrated to be feasible and safe providing a direct assessment of  $\text{VO}_2\text{max}$  whilst treatment duration did not appear to influence the cardiovascular responses to exercise.

Study 2 was a cross-sectional design comparing chronic versus acute ADT treated patients to examine if therapy time exposure leads to additional risk factors for CVD and metabolic toxicities in prostate cancer patients. One hundred and seven men undergoing ADT for treatment of prostate cancer were stratified into two groups, either acute (<3 months) or chronic ( $\geq 3$  months) exposure. Chronic ADT exposure was associated with a 17% reduction maximal aerobic capacity ( $-0.4 \text{ L}\cdot\text{min}^{-1}$ ) and an 8% reduction in resting metabolic rate ( $-147 \text{ kcal}/24\text{hr}$ ). The chronically exposed group also exhibited 8-22% lower maximal strength values (chest press  $-5.9\text{kg}$ , seated row  $-3.9\text{kg}$ , leg press  $-27.5\text{kg}$  and leg extension  $-12.2 \text{ kg}$ ) and a corresponding decrement in physical function variables ranging from 9-16% (400m walk  $+24.9\text{s}$ , chair rise  $+2.0\text{s}$ , and stair climb  $+0.7\text{s}$ ). Whilst not significant, there was also a trend towards a decrease in lean mass of 3.5% ( $-2.1\text{kg}$ ) and an increase in fat mass of 6.5% ( $1.5\text{kg}$ ) in the chronically suppressed group. ADT exposure did in fact have a negative effect on CVD risk factors as well as physical function outcomes.

Whilst the exact mechanisms remain unclear as to why these cardiovascular alterations and physical function variables are further declining as treatment time progresses, it is possible that factors other than those assessed in this study, such as reduced physical activity levels, may have influenced the results.

Study 3 utilised a randomized controlled trial (RCT) study design to examine the long-term effects (6 months) of a combined aerobic and resistance training intervention in reducing or stabilizing CVD and diabetes risk factors in men receiving ADT. Participants were randomly allocated to either an exercise (EX) group (n= 50) or a control (CON) group (n= 48). The combined aerobic and resistance training program consisted of twice weekly clinic based sessions at which the participants completed 20mins of aerobic activity (70-90% maximal intensity) and 6 resistance based exercises targeting the major upper and lower body muscle groups. In addition, participants were prescribed a home based training program consisting of 110 minutes of aerobic activity. The control group were instructed to adhere to their usual lifestyle and care routine. Body composition [lean mass 1.1% (+0.8kg), fat mass -4.2% (-1.1kg) & body fat -3.8% (-1.1kg)], muscular strength [chest press 9.6% (+3.6kg), seated row 7% (+6.0kg), leg press 14.8% (+20kg) & leg extension 19.4% (+10.2kg)], muscular endurance [chest press 49.4% (+5.0 reps) & leg 49.9% (+7.7 reps)] and 400m walk [-4.8% (-13s)] significantly improved ( $p<0.05$ ) following the exercise intervention. There was a trend [5% ( $0.1 \text{ L}\cdot\text{min}^{-1}$ )] towards an increase in maximal cardiorespiratory capacity with no change in other measures of physical function, central blood pressure parameters, resting metabolic rate or hemodynamic profile. This is the first study to demonstrate the effectiveness of a large scale long term multi-centre

RCT exclusively in prostate cancer patients undergoing ADT. The extended duration of the exercise intervention is thought to have led to the favourable adaptation in total fat mass that has not previously been reported in this group of cancer patients. This trial further substantiated the safety and efficacy of a combined aerobic and resistance training intervention and provided support for structured exercise interventions to be considered a key component of the overall course of treatment for men undergoing ADT for the treatment of prostate cancer.

This research has demonstrated that: 1) maximal cardiorespiratory exercise testing is safe and feasible in this population, 2) prolonged exposure to androgen deprivation therapy (>3 months) has a negative impact on a number of cardiovascular, metabolic and physical function outcomes, and 3) a combined aerobic and resistance training program can be safely undertaken in men undergoing ADT and results in an array of benefits for cardiovascular and metabolic outcomes as well physical function. As a result of these findings, patients prescribed ADT for the treatment of prostate cancer should be appropriately counselled as to the negative side effects commonly associated with this form of treatment and be made aware of the safety and beneficial effects an appropriately administered exercise intervention can have on reversing these adverse alterations occurring throughout the course of treatment. Further, these specifically designed exercise interventions should be commenced as soon as practically possible post prostate cancer diagnosis and continue for the course of treatment and ideally beyond.

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# **CHAPTER 1**

## **General Thesis Introduction**

## ***Introduction to prostate cancer***

Prostate cancer is the most common form of invasive cancer in men and is the second most common cause of cancer death in males (Jemal, et al., 2008; Welfare, 2011). Prostate cancer is defined as a malignant tumour (carcinoma) of the prostate gland, a common form of cancer in elderly men. In most men it progresses slowly over many years and gives symptoms similar to those of benign enlargement of the prostate (Martin, 2010). Prostate cancer can be classified into different disease stages such as localised, locally advanced and metastatic disease. Each year ~18,700 Australian men are diagnosed and more than 3,000 die from the disease (Welfare, 2011). Age is the most common risk factor for developing prostate cancer with 63% of cases occurring in men 65 years and older (Ries, et al., 2008).

## ***Testing & treatment options***

The two most common tests for prostate cancer are the prostate specific antigen (PSA) test and the digital rectal examination (DRE). The introduction of the PSA blood test has led to much wider screening taking place resulting in earlier diagnosis and subsequently extended treatment times. Men with prostate cancer are often faced with numerous treatment options including various radiation therapy techniques, surgical approaches, androgen deprivation therapy (ADT) or active surveillance (Nguyen, et al., 2011a). The modality of treatment, particularly during the early stages of prostate cancer remains controversial with a recent study by Wilt, et al. (2012) suggesting that when compared to observation, radical prostatectomy did not reduce all-cause mortality or prostate cancer

mortality in men with clinically localised cancer, diagnosed after PSA testing. This adds to the body of literature supporting active surveillance as the preferred method of treatment in men with localised prostate cancer, in particular those with low PSA or low risk disease (Bill-Axelson, et al., 2011; Thompson, 2010; Wilt, et al., 2008).

As a result of the landmark work by Huggins & Hodges (1972; 1941) demonstrating that testosterone is essential for the growth and development of prostate cancer, treatment options often target the suppression of testosterone through several mechanisms. Previously this was commonly achieved via bilateral orchiectomy although more recent advances have led to the development of less invasive therapeutic castration methods such as ADT in the form of gonadotropin releasing hormone (GNRH) agonists (Leuprolide and Goserline) and antagonists (Abrelax). GNRH is a decapeptide hormone synthesised in the hypothalamus and when GNRH is released it induces the anterior pituitary gland to release luteinising hormone (LH). Luteinising hormone induces Leydig cells in the testes to produce testosterone. GNRH agonists mimic GNRH and shuts down LH production (Choi & Lee, 2011) whilst GNRH antagonists immediately block pituitary GNRH receptors. Despite differing in actions, both GNRH agonists and antagonists result in suppressing testosterone levels to castrated levels.

ADT can be used at different stages of the disease usually in combination with other therapies. Approximately 50% of men with prostate cancer will receive ADT at some point post diagnosis, with most exposed to this treatment for 2-3 years (Bolla, et al., 2002; Heidenreich, et al., 2008; Meng, et al., 2002) as it offers improved efficacy when used with

local therapy such as external beam radiation (Denham, et al., 2005). In the case of localised prostate cancer a single modality treatment is often used although ADT has been used as an adjuvant therapy to improve clinical outcomes (Meng, et al., 2002). Localised advanced prostate cancer usually requires a multimodal approach such as surgery and adjuvant radiotherapy, chemotherapy and ADT or radiotherapy and ADT (Dorff, et al., 2011; Goharderakhshan, et al., 2000; Gravis, et al., 2013; Schulman, et al., 2000). ADT can also be used as a salvage treatment in the case of a recurrence of the disease. In patients with metastatic prostate cancer ADT is usually the first line of treatment (Choi & Lee, 2011).

#### *ADT side effects*

Although ADT has significant benefits for patients with prostate cancer, there are also a number of reported side effects which can be broken into several sub-categories including metabolic, body composition, physical function and quality of life alterations (Alibhai, et al., 2010; Braga-Basaria, Muller, Carducci, Dobs, & Basaria, 2006b; Galvao, et al., 2008b; Smith, et al., 2002a; Smith, et al., 2008). Metabolic complications include insulin resistance, hyperglycemia, increased incidence of diabetes, dislipidemia and the resultant metabolic syndrome (Braga-Basaria, et al., 2006a; Smith, et al., 2008). Closely related to metabolic complications are body composition changes experienced when undergoing ADT. Alterations include an increased abdominal circumference, increased fat mass, reduced lean body mass and reduced bone mineral density (Galvao, et al., 2008b; Smith, et al., 2002a; Smith, et al., 2008). Physical function has been reported to decline in patients undergoing ADT (Alibhai, et al., 2010) largely due to reduced muscular strength



and endurance (Galvao, et al., 2008b). The reduced level of physical function is also closely related to increased reported levels of fatigue (Herr & O'Sullivan, 2000). All side effects act to reduce the patient's quality of life. Recently a number of reviews have explored the association between ADT and risk of cardiovascular disease (CVD). Several large population based studies have reported positive correlations between ADT and both cardiovascular morbidity and mortality (Keating, O'Malley, Freedland, & Smith, 2009; Keating, O'Malley, & Smith, 2006; Levine, et al., 2010; Saigal, et al., 2007), however controversy surrounds this association with Nguyen, et al. (2011b) finding in a pooled analysis of RCT's, that ADT use was not associated with an increased risk of cardiovascular death but was associated with a lower risk of prostate cancer-specific mortality and all-cause mortality. Blankfield (2012), however, has questioned the validity of the Nguyen et al. (2011b) findings due to the possibility of bias in some of the studies reviewed, with the time interval of ADT being less than the duration of the data collection period in 6 of the 8 studies. Blankfield (2012) has suggested that it is problematic to use such studies to detect whether there is an association between ADT and cardiovascular death. Whilst there is still controversy surrounding the association between ADT and cardiovascular disease and mortality, interventions aimed at reducing CVD risk factors and metabolic toxicities should still be explored.

### *Strategies to counter the adverse treatment effects*

Current treatments used to alleviate the side effects of ADT are predominantly pharmaceutical in the form of anti-hypertensive medications, lipid lowering medications and bisphosphonates (Smith, et al., 2011). Although these treatments target specific side effects of ADT, they don't improve physical function, fatigue or quality of life. Further there are substantial costs associated with pharmacological interventions as well as the issue of additional potential side effects of these medications (Smith, et al., 2011). Research has shown positive effects of resistance training for the management of treatment-related toxicities in terms of musculoskeletal health, quality of life, functional performance and balance (Galvao, et al., 2006; Segal, et al., 2003b). Given that cardiorespiratory fitness attenuates overall mortality risk with regard to CVD (Ekelund, et al., 1988), it is thought that the addition of a suitable aerobic component to a resistance training program could have greater effects on treatment-related side effects than resistance training alone. Limited research has explored the role of a combined aerobic and resistance training intervention on cardiovascular health endpoints in ADT treated patients as a countermeasure to reduce cardiovascular and metabolic toxicities.

## Significance of the research

Prostate cancer is now the most common form of cancer after skin cancer in Australian and American males (Jemal, et al., 2008; Sharifi, Gulley, & Dahut, 2005b; Siegel, Naishadham, & Jemal, 2012). The use of ADT for prostate carcinoma has increased extensively across all stages and histologic grades of prostate cancer in the past several years (Cooperberg, Moul, & Carroll, 2005). The work contained within this thesis will establish whether maximal exercise testing is feasible and safe in this population whilst also identifying if the length of ADT exposure predisposes patients to additional CVD risk factors and negative metabolic and physical function alterations. The role of exercise will also be explored as a potential strategy to reduce risk factors associated with cardiovascular and metabolic complications and may also reduce the incidence of co-morbidities associated with androgen suppression (e.g. CVD, obesity, metabolic syndrome and diabetes) as well as improving physical function. Further, the use of physical activity may be a simple and cost effective strategy that provides similar benefits to pharmaceutical interventions (e.g. cholesterol and blood pressure lowering, etc.) without exposing patients to additional potential side effects and financial cost. Finally this work will further refine position statements in the newly established field of exercise oncology (Hayes, Spence, Galvão, & Newton, 2009; Rock, et al., 2012; Schmitz, et al., 2011).

## Purpose of the research

This thesis is comprised of interrelated studies examining the effects of androgen deprivation therapy (ADT) and the role of exercise in ADT treated prostate cancer patients. First, the aim is to investigate the feasibility and safety of maximal exercise testing in this population (study 1). The aim of study 2 is to explore if therapy time exposure leads to additional risk factors for CVD and metabolic toxicities in a cross-sectional study design by comparing chronic versus acute ADT treated patients. The purpose of study 3 is to examine the effects of exercise on reducing or stabilizing CVD and diabetes risk factors in men receiving ADT for their prostate cancer in a randomized controlled trial study design. Specifically, it is aimed to investigate the long-term effects (6 months) of exercise specifically designed to reduce CVD and diabetes disease progression on the following endpoints: 1) cardiorespiratory function and maximal oxygen capacity, 2) vascular function and blood pressure, 3) resting metabolic rate, 4) lipids and glycaemic control, 5) body composition (lean mass and fat mass), and 6) physical and muscle function.

## Hypotheses

Study 1: It is hypothesised that maximal exercise testing will be a feasible and safe testing method which will:

1. provide a useful pre-activity screening tool and a direct assessment of cardiorespiratory capacity; and
2. provide descriptive data to demonstrate ADT treated prostate cancer patients respond to maximal exercise in a similar way to healthy age-matched controls.

Study 2: It is hypothesised that there will be differences between chronic versus acute ADT with chronic ADT exposure being associated with:

1. increased number of risk factors for metabolic syndrome in terms of blood pressure, body composition, lipids and glucose metabolism;
2. decreased vascular compliance in terms of higher brachial and central blood pressure; and
3. decreased overall physical function and muscular strength outcomes.

Study 3: Compared to the control (usual care) group, the effects of a 6-month combined aerobic and resistance exercise program will:

1. increase cardiorespiratory capacity in terms of maximal oxygen capacity ( $\text{VO}_2\text{max}$ );
2. reduce brachial and central systolic and diastolic blood pressure;
3. improve metabolic profile including lipids and glucose metabolism;

4. improve body composition by increasing whole body and regional lean mass and reducing whole body and regional fat mass as well as reducing abdominal obesity (waist circumference) ; and
5. increase overall physical and muscle function.

Overall, these positive effects of the intervention are hypothesised to reduce the risk factors for metabolic syndrome and cardiovascular disease in this population.

## Definitions of Terms

**Prostate Cancer:** a malignant tumour (carcinoma) of the prostate gland, a common form of cancer in elderly men. In most men it progresses slowly over many years and gives symptoms similar to those of benign enlargement of the prostate (Martin, 2010).

**Prostate Specific Antigen:** an enzyme produced by the glandular epithelium of the prostate. Increased quantities are secreted when the gland becomes enlarged or inflamed, and levels of PSA in the blood are significantly elevated in cancer of the prostate. Although there is no clear 'cut-off' level for normality, over 4 ng/ml in the blood is associated with a 20% increased risk of prostate cancer, even in patients with normal-feeling prostates on rectal examination. Newer PSA assays can measure free PSA and compare it to the total PSA in the blood. Low free:total PSA ratios indicate a greater risk of prostate cancer and improve the discrimination between cancer and benign disease in men with a PSA in the range 4–10 ng/ml. PSA levels tend to be much higher in advanced prostate cancer and the rate of fall on treatment (e.g. after radical prostatectomy or radiotherapy) is a good prognostic indicator of response (Martin, 2010).

**Cardiovascular Disease:** A disease affecting the heart or blood vessels. The cardiovascular system includes the heart together with two networks of blood vessels – the systemic circulation and the pulmonary circulation. The cardiovascular system effects the circulation of blood around the body, which brings about transport of nutrients and oxygen to the tissues and the removal of waste products (Martin, 2010).

**Androgen Deprivation Therapy:** A type of hormone therapy that acts to inhibit the action of androgen, in this case testosterone. These act in the hypothalamic pituitary testicular axis to inhibit the production of testosterone and or block testosterone receptors (Smith, 2001).



## List of Abbreviations

**ADT** – Androgen Deprivation Therapy

**CVD** – Cardiovascular Disease

**DBP** – Diastolic Blood Pressure

**GNRH** – Gonadotropin Releasing Hormone

**MAP** – Mean Arterial Pressure

**METS** – Metabolic Equivalents

**PSA** – Prostate Specific Antigen

**PWV** – Pulse Wave Velocity

**QoL** – Quality of Life

**RM** – Repetition Maximum

**SBP** – Systolic Blood Pressure

**VO<sub>2</sub> max** – Maximal Oxygen Consumption

## **CHAPTER 2**

### **Review of Literature**

### ***Cancer introduction and common sites***

Cancer is defined as any malignant tumour which arises from the abnormal, purposeless and uncontrolled division of cells that then invade and destroy the surrounding tissue (Martin, 2010). Cancer cases can be defined by locations that include the oral cavity and pharynx, digestive, respiratory, bones and joints, soft tissue, breast, genital, urinary, eye and orbit, brain and other nervous system, endocrine, lymphoma, myeloma and leukaemia (Siegel, et al., 2012). The spread of cancer cells may occur via the bloodstream or the lymphatic channels or across body cavities such as the pleural or peritoneal spaces, thus setting up secondary tumours at sites distant from the original tumour (Martin, 2010). Cancer is a major public health concern with 108,368 new cancer cases diagnosed in Australia in 2007 and is expected to reach 150, 000 in 2020 (Welfare, 2011). This review will focus on some of the more common forms of diagnosed cancers including breast, colorectal and prostate cancers.

### ***Breast, colorectal and prostate cancers***

Breast cancer is a malignant tumour of the breast, usually a carcinoma and in rare instances a sarcoma (Martin, 2010). It is the most common form of invasive cancer in women with approximately 12,670 cases in Australia in 2007, or 27% of all cancer diagnoses (Welfare, 2011). Prostate cancer was the most commonly diagnosed cancer in Australia in 2007 with 19,403 cases reported. As with breast cancer, prostate cancer is a malignant tumour, although the location of the tumour originates in the prostate gland. Prostate cancer is often a slowly progressing disease that gives symptoms similar to those

of benign enlargement of the prostate. Prior to the introduction of the prostate specific antigen test, many prostate cancer cases were not detected through clinical presentation until the later stages of the disease where the tumour had invaded locally, possibly to regional lymph nodes and metastasized (Martin, 2010). Colorectal cancer, commonly known as bowel cancer includes tumour growth of the colon, rectum or small bowel and was the second highest diagnosed cancer in Australia in 2007 (Welfare, 2011).

## ***Treatment options***

The treatment of cancer is dependent upon several factors including the type of tumour, the site of the primary tumour and the extent of the tumour spread. The most common forms of treatment are active surveillance, surgery, radiotherapy and systemic therapy. Increasingly, combinations of the main cancer treatment modalities listed above are being used in the treatment of cancer with the type and stage of cancer determining the timing and sequence of these treatment combinations (Dorff, et al., 2011; Kelly, et al., 2012).

### ***Active Surveillance***

Due to the concern that prostate cancer screening has led to the diagnosis and treatment of many cancers that would not have become life threatening (Draisma, et al., 2003), active surveillance with curative intent is becoming an increasingly popular alternative to immediate treatment (Soloway, et al., 2008). This form of treatment involves monitoring low risk prostate cancer patients and only providing treatment if higher risk features are detected during this time. This management strategy involves serial PSA assessments, repeat biopsies and other tests intended to identify early forms of progression (Klotz, 2012). This form of treatment has been associated with a prostate cancer mortality rate of less than 3% 10 years post diagnosis, suggesting it as a safe and reasonable option for men with low risk prostate cancer (Klotz, et al., 2010). The benefit of this form of treatment is that patients are not exposed to unnecessary interventions that result in physical and psychological complications.

## *Surgery*

Surgical interventions can be used to diagnose, treat and in some cases prevent certain types of cancer. Surgery often refers to the surgical removal of the tumour and is favoured when the cancer is in its early stages of progression and localised to a specific area. Breast cancer surgery can take the form of either a mastectomy, involving the removal of the entire breast tissue or breast conserving surgery such as a lumpectomy which involves the partial removal of the breast tissue, as well as axillary lymph node dissection and breast reconstructive surgery (McNeely, et al., 2012). In the case of prostate cancer, the surgical intervention is referred to as a radical prostatectomy and involves the removal of the prostate gland. A review of the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) registry has documented surgical rates of approximately 50% in men with newly diagnosed localised disease (Cooperberg, Broering, & Carroll, 2010). Studies have shown radical prostatectomy to provide an excellent long term cancer control outcome in patients with localised disease (Lughezzani, et al., 2012). Prostate cancer surgery may involve a standard radical prostatectomy or nerve-sparing radical prostatectomy which represents the surgery of choice in all men with normal erectile function and confined disease (Heidenreich, et al., 2011). Surgical resection is still the cornerstone of curative therapy in colorectal cancer treatment despite the introduction of non-operative management options. Surgical options include sphincter sparing and non-sphincter sparing procedures depending upon the location and stage of disease, and these can include local excision, radical dissection, bypass operations and laparoscopic procedures (Kosinski, Habr-Gama, Ludwig, & Perez, 2012).

## *Radiotherapy*

Together with surgery and chemotherapy, radiotherapy plays an important role in oncology, both in definitive and palliative aspects of treatment (Teh, Woo, & Butler, 1999). Since the discovery of X-rays in 1895, radiation has developed into a recognised medical specialty with radiation oncology being recognised as a discipline in which health and science professionals work together. The advances in imaging techniques, computerized treatment planning systems, radiation treatment machines as well as improved understanding of the radiobiology of radiation therapy has resulted in rapid progress being made in this field (Baskar, Lee, Yeo, & Yeoh, 2012; Bernier, Hall, & Amato, 2004). Radiotherapy utilises ionizing radiation to control or kill cancerous cells and is used in approximately 50% of all cancer survivors and contributes towards 40% of curative treatment for cancer (Baskar, et al., 2012). Radiotherapy is typically delivered in small doses over a 5 – 8 week period and is designed to damage the DNA of the exposed tissue resulting in apoptosis (Heidenreich, et al., 2011). This therapy can either be external or internal depending upon the chosen course of treatment (Baskar, et al., 2012). External beam radiotherapy is the most common form of radiotherapy and relies upon an external source of high energy x-rays targeted towards a specific region of the body. Internal beam radiotherapy or brachytherapy involves the internal placement of short range radiation sources to more specifically target the desired location and is often used in the treatment of gynaecological and prostate malignancies (Baskar, et al., 2012). Intensity modulated radiation therapy which became available in the late 1990's is now a favourable method to deliver radiation to the tumours as it has the ability to relatively spare the surrounding

non-cancerous tissue through its more precise method of radiation delivery (Teh, et al., 1999). Radiotherapy is often used in combination with other treatment modalities including surgery, chemotherapy or immunotherapy. In the case of breast cancer, post mastectomy radiotherapy reduces the incidence of local and regional recurrences by 50-75% (Hortobagyi, 1998).

### *Systemic Therapy*

Systemic therapy includes two of the most common forms of cancer treatment; chemotherapy and hormone therapy. Chemotherapy is the use of chemicals to prevent or treat cancer and can be administered either intravenously or orally in repeated courses 2-4 weeks apart over a 3-6 month period (Ayanian, et al., 2003; Du & Goodwin, 2001). It is most commonly used in combination with other treatments for numerous types of cancer as either a cure (destruction of cancer cells), to reduce the risk of a reoccurrence, to shrink the cancer to either assist the primary treatment method and or to improve symptoms and prolong life.

Hormonal therapies involve the manipulation of the endocrine system through exogenous administration of specific hormones or pharmacological agents to inhibit the production of certain hormones. Hormonal therapy is well established in the treatment of breast and prostate cancer. Aromatase inhibitors are the standard hormonal therapy for postmenopausal women with both early and late stage hormone sensitive breast cancer. This form of treatment suppresses oestrogen levels in the body and slows the growth of hormone sensitive breast tumours. Currently third generation aromatase inhibitors are



being used by medical practitioners as they have been found to have superior results in terms of disease free survival and time to recurrence when compared to the previous method of treatment (Howell, et al., 2005).

Androgen deprivation therapy (ADT) has become one of the important advances in the treatment of prostate cancer (Quon & Loblaw, 2010) and may be delivered in various forms, all with the aim to block the predominant androgen, testosterone. (Shahinian, Kuo, Freeman, Orihuela, & Goodwin, 2005b). ADT in the form of gonadotropin releasing hormone (GnRH) agonists and antagonists are frequently used in the treatment of prostate cancer with GnRH agonists (Leuprolide and Goserline) acting to gradually down-regulate the pituitary for GnRH resulting in the inhibition of the secretion of gonadotropins whilst the GnRH antagonists (Abiraterone) immediately block pituitary GnRH receptors achieving rapid therapeutic effects (Engel & Schally, 2007). Other hormonal interventions targeting the suppression of androgens include adrenal ablating drugs (Ketoconazole) which act on the adrenal gland to decrease androgen synthesis from steroid precursors through the inhibition of cytochrome P450 enzymes. Androgen receptor antagonists (flutamide, bicalutamide and enzalutamide) act to inhibit androgen receptor ligand-binding domain through competitive binding whilst 5 $\alpha$ -reductase inhibitors (finasteride) decreases the conversion of testosterone to dihydrotestosterone through the inhibition of 5 $\alpha$ -reductase (Sharifi, et al., 2005b).

ADT is used in a variety of settings including primary treatment, as adjuvant therapy to radical therapy and in the setting of biochemical relapse (Alibhai, Gogov, &

Allibhai, 2006). As a result ADT is the most widely used systemic treatment for prostate cancer with almost 50% of men diagnosed with prostate cancer are expected to receive ADT at some point during treatment (Keating, et al., 2009; Meng, et al., 2002).

## ***Treatment associated side effects***

### ***Surgery***

The most common side effects or risks associated with surgical interventions are surgical site infections (SSI). The level of risk for developing a SSI is dependent upon the type of operation, comorbidities of the patient as well as perioperative therapy (Canavese, et al., 1997; Xue, Qian, Yang, & Wang, 2012). Breast cancer surgery side effects are typically related to the operative details (Canavese, et al., 1997; Xue, et al., 2012) including cellulitis, flap necrosis, abscess, dehiscence and hematoma (McNeely, et al., 2012). The rate of surgical site infections can range from 1% to 30% depending upon numerous factors including the definition of a surgery site infection, nature of the operation, follow up times, perioperative therapy and reporting institution (Canavese, et al., 1997). These infections are major sources of postoperative morbidity and mortality. In terms of prostate cancer related surgery side effects, radical prostatectomy is associated with impaired urinary control (incontinence) and sexual complications (Boorjian, et al., 2012; Michaelson, et al., 2008). Urinary incontinence is more common after surgical therapy than after radiation therapy (Mirza, Griebing, & Kazer, 2011). Rates of erectile dysfunction have varied from 10% to 100% (Akbal, Tinay, Simşek, & Turkeri, 2008) with the large variance possibly due to differences in surgical techniques, population demographics, timing of investigation and variations in baseline erectile function amongst others (Mirza, et al., 2011). These side effects have been shown to negatively impact a patient's quality of life (Miller, et al., 2005). Colorectal cancer surgery side effects are often associated with complications arising from the surgery itself and can include

anastomotic complication such as bleeding, leaks, strictures and fistulas (Jung, et al., 2008).

### *Radiotherapy*

Radiotherapy is an important treatment in cancer patients and forms part of the management of 40% of patients cured for their disease (Tubiana, 1992). Whilst significant advances have been made in the past 2 decades due to improvements in engineering and computing, radiotherapy related side effects are still common. These side effects are commonly associated with the anatomical location of the radiotherapy fields (Ahmad, Duke, Jena, Williams, & Burnet, 2012). Radiotherapy related side effects can generally be classified as either early or late side effects with early side effects being reversible. General side effects of radiotherapy, independent of location include; fatigue, gastrointestinal issues, skin problems and loss of appetite. Fatigue is the most common side effect with approximately 80% of patients on radiotherapy experiencing some form of fatigue (Jereczek-Fossa, Marsiglia, & Orecchia, 2002). Whilst generally classified as an early side effect peaking 2 weeks post radiotherapy and improving 4 weeks post treatment, fatigue has been reported as a chronic, or late side effect in 30% of cases (Jereczek-Fossa, et al., 2002).

The likelihood of specific side effects is dictated by the dose fractionation schedule, site treated and any pre-existing comorbidities (Ahmad, et al., 2012). The location specific side effects associated with radiotherapy can include breast oedema, fat necrosis, breast fibrosis, lactation difficulty and in some instance bone fractures in breast

cancer radiotherapy treatment (Yi, et al., 2009) whilst external beam or interstitial radiation therapy in men with localised prostate cancer may lead to bowel, urinary and sexual complications (Akbal, et al., 2008; Michaelson, et al., 2008). These location specific side effects mentioned are all in addition to the general radiotherapy side effects detailed above.

### *Systemic Therapy*

Chemotherapy side effects are typically dependent upon the type of medication used. Regardless of cancer type, fatigue is one of the most commonly reported side effects of all chemotherapy treatments (Jacobsen, et al., 1999) and has the ability to impair health related quality of life (Lindley, et al., 1992). As a result of the nature of chemotherapy the immune system is often suppressed predisposing patients to numerous illnesses and infections (Canavese, et al., 1997). In addition to these symptoms, gastrointestinal issues (nausea and vomiting) have been reported to be experienced in approximately 55% of patients whilst hair loss is another major side effect also experienced by 55% of patients with baldness rates of approximately 3% (Canavese, et al., 1997). Side effects can also be site specific with patients experiencing chemotherapy induced peripheral neuropathy resulting from damage to or dysfunction of peripheral nerves (Stubblefield, McNeely, Alfano, & Mayer, 2012).

Third generation Aromatase Inhibitors (AI) have been associated with an increased risk of osteoporosis and/or fractures in large adjuvant breast cancer trials (Eastell, et al., 2006). Furthermore, approximately 25% of postmenopausal women undergoing AI

treatment report arthralgia, skeletal and muscle pain (Morales, et al., 2007) which can limit the patient's compliance to the treatment as well as negatively impacting their quality of life over a prolonged period of time. Vasomotor symptoms such as hot flashes are the more common side effects with Macquart-Mouline et al., (1997) reporting hot flushes in 58% of patients undergoing a chemotherapy cycle whilst numerous other side effects are also reported such as vaginal discharge, vaginal dryness and dyspareunia that vary in prevalence (Macquart-Mouline, et al., 1997).

ADT has traditionally been used as a treatment during the latter stages of the development of prostate cancer (e.g. the presence of metastases) (Moyad, 2005). However, the development of the PSA blood test has meant that earlier detection of prostate cancer is now possible through better screening, resulting in patients now undergoing ADT in earlier stages of the disease with ADT now recognised as a primary treatment method for prostate cancer (Keating, et al., 2009; Meng, et al., 2002). Although ADT may improve prostate cancer survival, this widely employed treatment option is also associated with a number of adverse effects relating to treatment toxicities (Chen & Petrylak, 2005). The risks of co-morbidity related conditions are increased in this group of cancer patients with side effects including reduced bone and lean mass, loss of muscle strength, negative change in lipid profiles, vasomotor flushing, fatigue, and increased risk of cardiovascular disease as well as numerous metabolic complications all of which can act to compromise physical function and quality of life (Basaria, Muller, Carducci, Egan, & Dobs, 2006; Galvao, et al., 2008b; Greenspan, et al., 2005; Shahinian, Kuo, Freeman, & Goodwin, 2006; Sharifi, Gulley, & Dahut, 2005a; Smith, et al., 2002b). This array of side

effects related to ADT affecting the musculoskeletal system and physiological function has been previously described as “Androgen Deprivation and Sarcopenia-Related Disorders” (Galvao, Taaffe, Spry, & Newton, 2007a).

## ***Cancer Related Cardiovascular Alterations***

### ***Chemotherapy***

The presence of both cancer and cardiovascular disease is becoming more prevalent due to our aging population and overall prevalence of risk factors associated with CVD. This has meant that oncologists must now be aware of cardiovascular risks associated with certain forms of treatment, to either avoid or prevent treatment-related cardiotoxicities. In addition to the pre-existing cardiac risk factors, cardiotoxicities can also be dependent upon the type of drugs used, dose and schedule employed, and the age of patients as well as previous mediastinal irradiation (Serenio, et al., 2008). Specific examples have been reported such as women who have been treated with chemotherapy are reported to be more likely to experience subsequent cardiac disease when compared with those not treated with chemotherapy (Shenoy, et al., 2011). However, these cardiotoxicities associated with chemotherapy are in fact more related to the type of chemotherapeutic chosen and dosage amounts, rather than the type of cancer being treated. For example, certain chemotherapeutic drugs directly damage cardiomyocytes or cause inflammation of the pericardium whilst others can affect the coagulation system which can in turn result in cardiovascular and cerebrovascular ischemia as well as endothelial dysfunction and hypertension (Albini, et al., 2010).

### ***Radiotherapy***

Early reviews, such as that presented by Cuzick et al. (1994) reported a 62% increase in the incidence of cardiac death associated with radiotherapy for the treatment



of breast cancer. However radiation techniques have since been refined and older techniques utilising higher doses of cardiac radiation have been abandoned in favour of computed tomography guided radiation treatment and has resulted in more precise delivery of radiation and individualised treatment plans (Giordano, et al., 2005). As a result, the mortality rate from ischemic heart disease associated with radiation therapy has significantly decreased since the 1980's (Giordano, et al., 2005). A recent report by Darby, et al. (2013) has reported exposure of ionizing radiation to the heart during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease in a linear fashion by 7.4% per gray. Those with pre-existing cardiac risk factors are at a greater risk from radiotherapy when compared to those with no apparent risk factors (Darby, et al., 2013).

### *Combined Chemotherapy and Radiotherapy*

Cancer treatment often takes the form of combination therapy involving a mixture of chemotherapy, radiotherapy or surgery. Although highly successful, combination therapy does predispose the patient to cardiovascular complications such as heart failure, myocardial ischemia, hypertension, thromboembolism and arrhythmias (Yeh & Bickford, 2009). Combination therapy can often amplify cardiotoxicities, one such example is the use of chemotherapy in combination with radiotherapy with this commonly used combination therapy being associated with a higher rate of heart problems when compared to either chemotherapy or radiotherapy alone (Albini, et al., 2010).

## *Hormonal Therapy*

Reviews exploring the association between cardiovascular risks and hormonal therapy, in particular ADT, are becoming more common with reported metabolic complications including increased abdominal circumference and obesity, dislipidemia, insulin resistance and diabetes, hyperglycemia and metabolic syndrome (Alibhai, 2011; Alibhai, et al., 2009; Collier, Ghosh, McGlynn, & Hollins, 2011; Jefferies, et al., 2011; Punnen, Cooperberg, Sadetsky, & Carroll, 2011; Van Poppel & Tombal, 2011) which has led the American Heart Association and American Cancer Society to issue a joint statement acknowledging that ADT negatively affects traditional CVD risk factors and discusses the possibility of an association with overall cardiovascular risk (Levine, et al., 2010).

Recently, several large studies have provided important findings as to additional risks and toxicities related to ADT by increasing risk of CVD and premature death (D'Amico, et al., 2007a; Keating, et al., 2009; Keating, et al., 2006; Saigal, et al., 2007; Tsai, D'Amico, Sadetsky, Chen, & Carroll, 2007; Van Hemelrijck, et al., 2010). Van Hemelrijck et al. (2010) conducted one of the largest population based studies (76, 000 prostate cancer sufferers) utilising a data base for clinical epidemiological prostate cancer research (PcBaSe, Sweden) confirming the increased relative risk of nonfatal and fatal CVD in all men with prostate cancer, specifically those undergoing hormone therapy. Keating et al. (2006) who used the Surveillance, Epidemiology, and End Results (SEER) database found ADT use was associated with higher risks of incident diabetes, coronary heart disease, acute myocardial infarction as well as sudden cardiac death. The authors also go further to

report that short term ADT treatment was significantly associated with greater risks of disease and the elevated risks persisted in men on longer term therapy (Keating, et al., 2006). This raises the question as to how long a patient must be undergoing ADT before experiencing treatment-related toxicities. Saigal and colleagues (2007) also using the SEER database found that the risk of cardiovascular morbidity was increased within 12 months of treatment when compared to similar men who did not receive ADT. Further, another report by D'Amico, Renshaw, Loffredo and Chen (2007b) suggested that even short-term ADT (3 months) was associated with increased risk of prostate cancer-specific mortality and all-cause mortality at a similar rate to that seen at 6 months, suggesting that only 3 months of treatment is sufficient to elicit an adverse cardiovascular profile. Basaria and colleagues (2008) indicate that short-term ADT can increase the risk of insulin resistance, however, the resultant hyperinsulemia acts to maintain glucose within normal ranges and it is not until the duration of ADT is extended (long-term ADT) that this compensatory mechanism fails resulting in hyperglycaemia. A 5-year follow up of patients undergoing hormonal treatment found the treatment was associated with a 20% higher risk of serious cardiovascular morbidity (Saigal, et al., 2007), a finding that stresses that there are also long-term side effects associated with this form of treatment. In more recent work and in light of the work by Keating and colleagues (2009; 2006), Hu, et al. (2012) investigated the risk of peripheral artery disease and venous thromboembolism associated with ADT use and found there was in fact an increased risk of peripheral artery disease (adjusted hazard ratio 1.16: 95% CI 1.12-1.21) and thromboembolism (adjusted hazard ratio 1.10: 95% CI 1.04-1.15) in an ADT treated cohort. A recent study by Jespersen, Nørgaard, and Borre

(2013) has investigated the risk of cardiovascular disease including myocardial infarction and stroke in prostate cancer patients undergoing ADT or orchiectomy and found that ADT was associated with an increased risk of myocardial infarction and stroke. Whilst orchiectomy and ADT result in comparable castration levels, a relationship between orchiectomy and increased risk of cardiovascular disease was not evident. The authors suggest that ADT could lead to a dysfunction in cardiac receptors regulating cardiac contractile function which may play an important role in the cardiac pathology in men receiving ADT. However, this relationship was not evident in men who received orchiectomy treatment as opposed to pharmacological ADT.

The majority of literature supports an earlier report indicating that CVD is the most common form of mortality in men with prostate cancer, and not the actual cancer itself (Lu-Yao, Stukel, & Yao, 2004). As such, it is critical to develop strategies that could ameliorate treatment adverse toxicities, in particular those related to the musculoskeletal and cardiovascular systems (Keating, et al., 2006; Smith, 2002). Such is the importance of these recent findings, a Science Advisory Statement from the American Heart Association, American Cancer Society and American Urological Association has been released which suggests there is a substantial amount of data demonstrating ADT adversely affects traditional cardiovascular risk factors (Levine, et al., 2010). This association does however remain controversial with Nguyen, et al. (2011b) reporting conflicting findings regarding ADT and cardiovascular disease risk factors suggesting ADT is not associated with an increased risk of cardiovascular death. With a large amount of the literature suggesting an association between ADT and cardiovascular disease (D'Amico, et al., 2007b; Hu, et al.,

2012; Keating, et al., 2009; Keating, et al., 2006; Saigal, et al., 2007; Tsai, et al., 2007; Van Hemelrijck, et al., 2010) and Nguyen, et al. (2011b) reporting conflicting findings, it is evident that more research is necessary to definitively establish the relationship between ADT and cardiovascular disease.

## ***Cancer Related Metabolic Alterations***

### ***Breast & Colorectal***

To date, very little research has investigated the metabolic outcomes associated with breast or colorectal cancer treatments. Most research in this area has been concerned with the link between metabolic alterations and the risk of developing cancer rather than the metabolic outcomes associated with the treatment modality (Esposito, Chiodini, Colao, Lenzi, & Giugliano, 2012; Rosato, et al., 2011). Such research has suggested a modest link between impaired glucose metabolism and type 2 diabetes and the rate of breast cancer incidence (Ehrmann-Josko, et al., 2006; Xue & Michels, 2007).

### ***Prostate***

Numerous metabolic complications have been linked to ADT including increased abdominal circumference/obesity, insulin resistance, hyperglycemia, dislipidemia (Ribeiro, Camara, Segre, Srougi, & Serrano Jr, 2010; Saylor & Smith, 2009; Smith, et al., 2002a) and the resultant metabolic syndrome. Metabolic syndrome by definition refers to a clustering of specific CVD risk factors whose pathophysiology appears related to insulin resistance (Michaelson, et al., 2008). Metabolic syndrome is classified when patients meet three of the following five criteria according to the Adult Panel III Criteria ("Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)," 2001); these being fasting plasma glucose level more than 110mg/dL, serum triglyceride levels  $\geq 150$ mg/dL, serum high density lipoprotein less than

40mg/dL, waist circumference greater than 102 cm and blood pressure of  $\geq 135/80$  mmHg. Patients on anti-hypertensive and anti-lipid medications are also considered positive for the respective criterion. This syndrome is most important because of its association with the development of type II diabetes and CVD. In addition to the traditional contributing risk factors, male hypogonadism has also been shown to be an independent risk factor in the development of metabolic syndrome (Muller, Grobbee, den Tonkelaar, Lamberts, & van der Schouw, 2005). An earlier report indicated that 50% of patients undergoing long-term ADT had metabolic syndrome (Braga-Basaria, et al., 2006a) with subsequent analysis demonstrating abdominal obesity and hyperglycemia were responsible for these higher prevalence rates.

Basaria and colleagues (2006) have shown that shorter term ADT patients tend to have significantly higher levels of fasting glucose, insulin and leptin compared to healthy age-matched controls whilst long-term ADT is associated with higher fasting levels of total cholesterol, LDL cholesterol and non-HDL cholesterol than non-ADT prostate cancer men or age-matched healthy controls (Braga-Basaria, et al., 2006b). A large cohort study has demonstrated increased incidence of diabetes, coronary heart disease and sudden cardiac death following ADT (Keating, et al., 2006)(Keating, 2009). Alibhai et al. (2009) have also reported an increased risk of developing diabetes providing a link between glucose and insulin control and ADT. Keating et al. (2006) first reported the increased risk of diabetes in 2006 with more than one third of men receiving GnRH agonist use associated with an increased risk of diabetes. A subsequent follow-up study found a statistically significant increased risk of incident diabetes at a rate of 159.4 events per 1000 person years vs. 87.5

events for prostate cancer patients not receiving ADT (adjusted hazard ratio 1.28) (Keating, et al., 2009). Keating et al. (2009) were also the first to report a possible association between ADT and the incidence of stroke, whilst this association was further corroborated by Van Hemelrijck, et al. (2010) who investigated the absolute and relative risk of cardiovascular disease in a Swedish based prostate cancer register (PCBaSe) and found an increased relative risk of fatal and non-fatal CVD. Whilst the mechanisms surrounding the association between ADT and the risk of stroke are unknown it is postulated that it may result from similar physiological changes that underlie the risk of coronary vascular disease, such as central obesity, lipid alterations and insulin resistance (Keating et al., 2009).

It has been proposed that metabolic changes during ADT are in fact different from those that present during classic metabolic syndrome. Smith et al. (2008) in a prospective study found in contrast to the classic metabolic syndrome ADT treatment increases subcutaneous fat mass, HDL cholesterol and adiponectin, but did not alter the waist: hip ratio, blood pressure or C Reactive protein levels. These results suggest that ADT treatment results in a pattern of metabolic alterations that are distinct from classic metabolic syndrome (Smith, et al., 2008).

### *Body composition*

Body composition alterations relating to cancer treatment are primarily associated with hormonal therapy, in particular ADT for the treatment of prostate cancer. ADT is frequently accompanied by prompt and often marked changes in body composition with patients increasing body mass index and fat mass, reducing lean body mass and muscle



strength and even developing osteoporosis (Galvao, et al., 2008b; Greenspan, et al., 2005; Smith, et al., 2002a). Sarcopenic obesity is a term now used to describe the combination of increased body weight in the form of adipose tissue and reduced muscle mass or strength (Baumgartner, 2000; Zamboni, Mazzali, Fantin, Rossi, & Di Francesco, 2008). Patients undergoing ADT have shown increases in fat mass of 9.4% to 11.0% in one year with a concurrent decrease in lean body mass of 2.7% to 3.8% (Smith, et al., 2002b). Consequently, men on ADT have shown a 5.5-fold increase in risk of being obese compared to controls after adjusting for age (Chen, et al., 2002). The regional distribution of fat in response to ADT has been explored in several studies, with Saylor and Smith (2009) reporting that during ADT, fat accumulation is primarily subcutaneous fat whilst intra-abdominal fat generally does not change significantly. In a recent study it was reported that subcutaneous fat accounted for 94% of the observed 16.5% ( $\pm 2.6\%$ ) increase in abdominal fat area (Smith, et al., 2008). A similar finding was presented by Galvao et al. (2008b) who found increases in fat accumulation at all regional sites following 9 months of androgen deprivation, with greater changes seen for the limbs than the trunk. This highlights one of the more concerning aspects of body composition, being the limited amount of treatment time required to see negative alterations in fat mass. Smith et al. (2001) reported significant increases in fat mass after only 3 months of ADT whilst another study saw a 4.3% ( $\pm 1.3\%$ ) increase in fat mass after only 12 weeks of treatment (Smith, Lee, & Nathan, 2006) highlighting the dramatic changes occurring during the early stages of treatment (Saylor & Smith, 2009).

Insulin resistance is a metabolic abnormality that accompanies diabetes, prediabetes and obesity and is a well-known risk factor associated with diabetes, CVD and sudden death (Keating, et al., 2006; Saylor & Smith, 2009). Impaired insulin response as well as hyperglycaemia have been shown to increase even after short-term ADT (Smith, et al., 2006). Dockery et al. (2003) have observed a 63% increase in fasting serum insulin after 3 months of ADT and Smith et al. (2001) have also reported higher insulin concentrations despite unchanged plasma glucose, suggesting reduced insulin sensitivity after only 3 months of ADT.

## ***Cancer and the Role of Exercise/ Physical Activity***

### *Prevention*

Whilst the terms exercise and physical activity are often used interchangeably in the literature due to the fact they both have common elements, physical activity is defined as any bodily movement produced by skeletal muscle that results in energy expenditure whilst exercise is a sub section of physical activity and refers to planned, structured and repetitive activity with the objective being improvement or maintenance of physical fitness (Caspersen, Powell, & Christenson, 1985). Both exercise and physical activity have been linked to the prevention of certain types of cancer, in particular breast and colorectal cancer with recent evidence suggesting that similar preventative mechanisms may exist for other forms of cancer (Key, Appleby, Barnes, & Reeves, 2002; McTiernan, 2008; Thune & Furberg, 2001). In many cases the dose response relationship of physical activity has been explored with research suggesting that exercise at a greater intensity for longer periods of time produces greater reductions in cancer risks (McTiernan, 2008; Thune & Furberg, 2001). As a result of these findings physical activity is now being included in several health organisations published guidelines regarding modifiable behaviours known to reduce risk of cancer (Kushi, et al., 2012; Lichtenstein, et al., 2006).

Endogenous sex hormones have been found to be closely associated with the aetiology of breast cancer (Key, et al., 2002). The theory behind the role of physical activity and risk reduction is that physical activity may modulate the production,

metabolism and excretion of these endogenous sex hormones thought to be responsible for the development of breast cancer. In a review of approximately 170 observational epidemiologic studies examining physical activity patterns and breast cancer, Friedenreich and Cust (2008) reported that the average risk reduction was approximately 25%-35% with a dose response relationship existing in the majority of studies analysed. The amount required appears to be at least 30-60 minutes per day of moderate to vigorous intensity physical activity to decrease cancer risk (Lee & Lee, 2003).

A meta-analysis by Samad et al. (2005) reported a significant protective effect against colon cancer among physically active males and females, with another study reporting increasing amounts of time spent undertaking recreational physical activity are associated with substantially lower risk of colon cancer (Chao, et al., 2004). Whilst limited research is available regarding the amount of physical activity required to decrease the risk of colon cancer, early work by Lee, Paffenbarger, and Hsieh (1991) reported that men who expended >1000 kcal.wk experienced half the colon cancer rates of their inactive counterparts, with this amount of energy expenditure equivalent to at least 30 minutes of moderate intensity physical activity 5 days per week. Whilst several biological mechanisms have been hypothesised in an attempt to explain the association between physical activity and risk of colorectal cancer, Samad and colleagues (2005) have proposed insulin resistance and hyperinsulemia to be a unifying mechanism by which physical inactivity, as well as other lifestyle factors surrounding insulin resistance, can be attributed to the increased risk of colorectal cancer.

The role of physical activity in reducing the risk of prostate cancer is unclear due to inconsistent findings, with Friedenreich and Orenstein (2002) categorising the association as probable according to the definitions developed and used in the World Cancer Research Fund and American Institute for Cancer Research report on diet and cancer prevention (WCRF/AICR, 2007). A large prospective study by Giovannucci et al. (2005) reported no association between physical activity and overall prostate cancer risk, however men aged 65 years or older who were undertaking vigorous activity for at least 3 hours per week were at the lowest risk of experiencing advanced and fatal cancers. The authors also reported prostate cancer patients with high levels of physical activity were less likely to be diagnosed with poorly differentiated cancers, suggesting that the role of physical activity may only be applicable to advanced forms of cancer. Young- McCaughan (2012) recently reviewed 22 studies published in the last 12 years with 12 of these studies suggesting physical activity reduced the risk of prostate cancer whilst 9 found no association and 1 showed an increased risk of prostate cancer. Overall it was reported that there is a growing body of research suggesting physical activity does exert a protective effect against the development of prostate cancer.

### *Exercise interventions during cancer treatment*

A summary of the exercise intervention studies undertaken during cancer treatment sought to add to the previous reviews of Galvao and Newton (2005) and Baumann, Zopf, and Bloch (2011) and is presented in Table 1. All cancer types were included with the most commonly investigated cancers being of the breast and prostate. Several studies were of mixed cancers and included gynaecological, colorectal, haematological, lung, testicular, Hodgkin's and non-Hodgkin's lymphoma and oesophageal cancers. Of the 39 studies included in Table 1, 24 included an aerobic only intervention, 6 included a resistance only intervention and 8 included a mixed aerobic and resistance exercise intervention. The remaining study compared the effectiveness of an aerobic only or resistance only intervention. Some form of intensity prescription was present in 30 of the studies whilst 11 either reported no specific intensity (n=6) or allowed the participants to self-select their desired intensity (n=5). The most common outcome measures for all studies were physical function/ performance, physical fitness, fatigue, quality of life, strength, body composition and psychological outcomes. To meet the inclusion criteria studies must have employed an exercise intervention during the treatment stages of cancer.

**Table 1.** Exercise intervention studies during treatment

Author (design)	No. of Patients	Cancer Type	Intervention Type	Frequency/ duration/ intensity	Primary Outcomes
Cunningham et al, 1986 (RT)	40	Leukaemia	Resistance	3-5x week/ 5 weeks No specified intensity	↓ nitrogen balance ↔ creatine excretion ↔ Arm circumference
Winningham et al, 1988 (RT)	42	Breast	Aerobic IT (cycling)	3x week, 20-30 mins/ 12 weeks 60-85% Max HR	↓ Nausea*
Winningham et al, 1989 (RT)	24	Breast	Aerobic IT (cycling)	3x week, 20-30mins/ 12 weeks 60-85% Max HR	↑ Lean tissue mass ↓ 0.5% Body Fat ↓ Skinfold sites
MacVicar et al, 1989 (RT)	45	Breast	Aerobic IT (cycling)	3x week/ 10 weeks 60-85% Max HR	↑ VO <sub>2</sub> max 42%*
Mock et al, 1997 (RT)	46	Breast	Aerobic (walking)	4-5x week, 20-30mins /6 weeks Self-paced	↑ 12-MWT 4%* ↓ Fatigue* ↓ symptom experience*
Dimeo et al, 1997 (RT)	70	Breast, sarcoma, carcinoma, adenocarcinoma, neuroblastoma	Aerobic IT (cycling)	Daily, 30 mins / 2 weeks 50% HR reserve	↓ MP (METS) 14%* ↓ Thrombopenia, neutropenia* & hospitalisation duration*

Dimeo et al, 1997 (Non-randomised)	5	Hodgkin's lymph., non-Hodgkin's lymph., bronchial, breast, medullablastoma	Progressive Aerobic (treadmill)	5x week, 30-35mins/ 6 weeks Lactate - 3mmol/L 80% Max HR	↓ Lactate concentration 100% ↓ HR 18% ↑ Training distance 101% ↓ max performance 12%
Dimeo et al, 1999 (RT)	59	Breast, lung carcinoma, seminoma, adenocarcinoma, Hodgkin's lymph.	Aerobic IT (cycling)	Daily/ 6 weeks 50% HR reserve	↓ Psychological distress*
Schwartz et al, 1999, 2000 (RT)	27	Breast	Aerobic (walking)	4x week 35mins/ 8 weeks Self-paced accelerometers	↑ 12-MWT 10.4%* ↓ Fatigue*
Na et al, 2000 (RT)	35	Stomach	Aerobic (arm & cycling ergometer)	5x week 30mins/ 2 weeks 60% Max HR	↑ NKCA 28%
Schwartz et al, 2001 (Non-randomised)	72	Breast	Aerobic (walking)	3-4x week/ 8 weeks Self-paced accelerometers	↑ 12-MWT 15% ↓ Fatigue
Mock et al, 2001(RT)	52	Breast	Aerobic (walking)	5-6x week/ 6-24 weeks Self-paced	↑ 12-MWT 6%* ↓ Fatigue* ↓ Emotional distress*
Segal et al, 2001 (RCT)	123	Breast	Aerobic (walking) Home vs. non home based	5x week/ 26 weeks 50-60% VO <sub>2</sub> max	↑ Physical function * ↔ QoL ↔ VO <sub>2</sub> max



Kolden et al, 2002 (Non-randomised)	40	Breast	Aerobic (walking, cycling, stepping) Resistance Flexibility	3x week/ 16 weeks No specified intensity	↑ flexibility 11%* ↑ VO <sub>2</sub> max 15.4%* ↑ Upper body strength 34.5%* ↑ Lower body strength 37%* ↓ Resting systolic BP 5% ↑ QoL ↑ Upper body strength 42%* ↑ Lower body strength 36%* ↔ Body composition ↔ PSA ↓ Fatigue 7.2%* ↑ QoL 4.4%* ↓ Lean body mass*
Segal et al, 2003 (RCT)	155	Prostate (ADT)	Resistance	3x week/ 12 weeks 2 sets of 12 repetitions 60-70% 1RM	
Coleman et al, 2003 (Non-randomised)	24	Myeloma	Resistance (home based 6 exercises) Aerobic (home based walking)	~6 months Various frequency & intensities	
Dimeo et al, 2003 (Non-randomised)	66	Leukaemia, Hodgkin's lymph., non-Hodgkin's lymph., myeloma	Aerobic (walking)	Daily/ ~2 weeks 70% Max HR	↔ Walking speed ↓ Haemoglobin 6.7%*
Courneya et al, 2003 (RCT)	102	Colorectal	Aerobic (walking) Flexibility	3-5x week/ 16 weeks 65/75% Max HR	↔ QoL ↔ Cardiovascular capacity

Adamsen et al, 2003 (Non-randomised)	23	Leukaemia, breast, colon, ovary, testes, cervix, Hodgkin's lymph, non- Hodgkin's lymph.	Resistance Aerobic (cycling) Relaxation	4x week/ 6 weeks 3 sets of 5-8 repetitions 60-100% Max HR 85-95% 1RM	↑ Whole body strength 32.5%* ↑ VO <sub>2</sub> max 16%* ↔ QoL
Mock et al, 2004 (RT)	119	Breast	Aerobic (home based walking)	5-6x week 15- 30mins/6 weeks to 6 months 50-70% max HR	↓ Fatigue 54%*
Windsor et al, 2004 (RCT)	66	Prostate	Aerobic (home based walking)	3x week 30minutes 60-70% Max HR	↔ in fatigue ↑ fatigue in control group ↑ distance walked in intervention group 13.2%*
Campbell et al, 2005 (RT)	12	Breast	Aerobic (walking, cycling, low level aerobics) Muscle strengthening exercises	2x week /12 weeks Warm up, 10-20min exercise, cool down & relaxation 60-75% Max HR	↑ 12-MWT 32%* ↑ Physical activity 104%* ↑ QoL 16.5% ↔ in fatigue
Fairey et al, 2005 (RT)	53	Breast	Aerobic (cycling)	3x week 15-35 mins/ 15 weeks 70-75% VO <sub>2</sub> max	↑ NKCA 6.8%* ↔ neutrophil function
Pinto et al, 2005 (RT)	86	Breast	Aerobic (home based walking, cycling, swimming)	2-5x week ~10- 30mins/ 12 weeks 55-65% Max HR	↑ Physical activity levels 6.5%* ↑ 1- mile walk test performance 6.4%*

Galvao et al, 2006 (Non-randomised)	10	Prostate (ADT)	Resistance (12 upper and lower body exercises)	2x weeks/ 20 weeks 6-12 RM for 2-4 sets per exercise	<p>↑ Muscle strength &amp; endurance (40.5% - 96.3%)*</p> <p>↑ physical function &amp; balance (7.4% - 26.8%)*</p> <p>↑ Muscle thickness 15.7%*</p> <p>↔ lean body mass or fat mass</p> <p>↑ Muscular strength 41.3%*</p> <p>↑ VO<sub>2</sub>max 14.5%*</p> <p>↑ Body mass 1%*</p> <p>↓ Skinfolds 3%*</p>
Quist et al, 2006 (Non-randomised)	70	Breast, ovary, colon, testes, cervix, lung, oesophagus, sarcoma, rhinopharynx, oral, Hodgkin's lymph, non-Hodgkin's lymph, leukaemia, myelomatosis, myelofibrosis	Resistance (3 exercises) Aerobic (cycling)	<p>High intensity: 3x week 1.5hrs/ 6 weeks</p> <p>Resistance 5-8 reps at 85-95% 1RM</p> <p>Aerobic 10 min 85-95% Max HR</p> <p>Low intensity 4x week 0.5hrs/ 6 weeks</p> <p>Massage 2x week</p> <p>0.5hrs/ 6 weeks</p> <p>Body awareness 1x week 1.6hrs/ 6 weeks</p> <p>Total: 9 hrs/ week</p>	
Monga et al, 2007 (RCT)	21	Prostate	Aerobic (treadmill)	<p>3x week 40mins/ 8 weeks</p> <p>65% Max HR</p>	<p>↓ Fatigue 66.6%*</p> <p>↑ QoL 5.3%*</p> <p>↑ CV fitness 36%*</p> <p>↑ Muscle strength 10.3%*</p>

Schneider et al, 2007 (Non-randomised)	45	Prostate, colon, Hodgkin's, lung, bladder, melanoma, pancreas, rectal, testes, throat	Aerobic Resistance	2-3x week 60mins/ 12 weeks Aerobic: 30-55% HR Reserve Resistance: 2 sets of 10 reps at RPE 3	↔ Cardiopulmonary function during treatment group ↓ resting HR following treatment group 7.4%* ↑ VO <sub>2</sub> max following treatment group 16.4%* ↔ fatigue during treatment group ↓ fatigue following treatment group 33.9% ↑ 12 MWT 14.6%* ↓ fatigue 4.5%*
Chang et al, 2008 (RT)	22	Leukaemia	Aerobic (home based walking)	5x week 12 mins/ 3 weeks Resting HR plus 30bpm	↑ 12 MWT 14.6%* ↓ fatigue 4.5%*
Culos-Reed et al. 2009 (RT)	100	Prostate (ADT)	Aerobic (home based walking) Resistance (light – theraband)	Suggested 3-5x week/ 16 weeks 1x week 60min group session	↑ physical activity 71%* ↓ blood pressure 6% ↓ waist 0.5% & neck 0.9% circumference* ↔ QoL
Hansen et al, 2009 (Non-randomised)	16	Prostate (ADT vs. non ADT)	Resistance (high force eccentric leg cycle ergometer)	3x week 12-15mins / 12 weeks RPE – somewhat hard	↑ quadriceps volume* ↑ isometric knee extension strength* ↑ physical function* ↑ QoL ↑ symptoms of fatigue

Segal et al. 2009 (RCT)	121	Prostate	Aerobic group (cycle, treadmill & elliptical) Resistance group (10 exercises)	3x week/ 24 weeks Resistance – 2 sets of 8-12 repetitions Aerobic – 70-75% VO2peak	Resistance ↑ QoL* ↑ Strength* ↓ Triglycerides* ↓ Body fat* ↑ Aerobic fitness* ↓ Fatigue 0 -24 weeks*
Galvao et al. 2010 (RCT)	57	Prostate (ADT)	Resistance (8 upper and lower body exercises) Aerobic	2x week/ 12 weeks Resistance Exercise – 6-12 RM for 2-4 sets per exercise Cardiovascular exercise – 15-20 min 65-80% Max HR	Aerobic ↔ aerobic fitness* ↓ fatigue 0 -12 weeks* ↑ Muscle mass 1.3%* ↑ Strength 11-31.5%* ↑ Physical function 6.4%* ↑ Balance 3.2%* ↔ Cardiorespiratory fitness
Kapur et al, 2010 (RT)	66	Prostate	Aerobic (home based walking)	3x week 30mins/ 4 weeks	↓ Rectal toxicity 39.6%* ↓ Bladder toxicity 15.5%
Serda et al 2010 (Non-randomised)	33	Prostate	Resistance (10 upper and lower body exercises)	2x week/ 24 weeks 16 weeks – supervised; 8 weeks – unsupervised 8-12 reps 50-70% 8 RM	↑ QoL 8.8%* ↑ Muscle strength 22.8-45.5%* ↑ Muscle endurance 57.7-61.4%* ↓ SBP 6.8%* ↓ BMI 1.6%, WHR 2%, waist 2.5%*

Newton et al, 2011 (Non-randomised)	17	Ovary	Aerobic (home based walking)	Group average 4x week 30minutes Duration dependent upon treatment time	No significance Meaningful improvements in physical function, symptoms, physical well-being & QoL
Noble et al, 2012 (Non-randomised)	575	Breast, colorectal, gynaecological, haematological, lung & prostate	Aerobic Resistance	2x week 1hr/ 12 weeks RPE 11-13	<p>↑ maximum work rate attained 16.8%*</p> <p>↓ Submaximal HR response 3.7%, systolic BP 3.8% and RPE 4.6%*</p>
Quist et al, 2012 (Non-randomised)	25	Lung	Aerobic (cycling) Resistance (group based 6 exercises)	Group based 2x week 1.5hrs/ 6 weeks	<p>↑ VO<sub>2</sub> peak 6%*</p> <p>↑ muscular strength 9-23%*</p> <p>↔ QoL</p>
				<p>Aerobic: 10-15 mins at 85-95% Max HR</p> <p>Resistance: 3 sets of 5-8 repetitions at 70-90%1RM</p> <p>Home based 3x week 20-40mins/ 6 weeks</p> <p>Non reported walking intensity</p>	

Rao et al, 2012 (RT)	10	Breast	Aerobic Resistance (bands and weights up to 2.3kg)	3x week 1hr/ 16 weeks Non specified intensity	↓ BMI 12.5%* ↔ tumour size ↔ C peptide
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Abbreviations: ↑ - increase; ↓ - decrease; ↔ - no change; HR – heart rate; NKCA – natural killer cell cytotoxic activity; QoL – quality of life; BP –blood pressure; RM – repetition maximum; RPE – rating of perceived exertion; BMI – body mass index; IT – interval training; METS – metabolic equivalents; MWT – minute walk test; ADT – androgen deprivation therapy; (RCT) – Randomised Controlled Trial; (RT) – Randomised Trial,\* statistically significant, MP: Maximal Physical Performance

The earliest study published examining the role of exercise in cancer patients was conducted by Cunningham et al. (1986) who initiated a resistance training program in leukaemia patients receiving bone marrow transplant. Patients undertook a supervised resistance training program either 3 times per week, 5 times per week or were assigned to usual care. Body composition and muscle protein were assessed pre and post the 5-week intervention. Body composition was assessed via skinfold and circumference whilst muscle protein status and turnover was assessed via weekly nitrogen balance and creatinine, and 3 methylhistidine excretion. Although no differences were seen in body composition, the two exercise interventions did maintain creatine status whilst the control group significantly decreased, implying that the intervention may have spared muscle protein. Winningham & MacVicar (1988) and Winningham, et al., (1989) were the first to employ an aerobic based exercise intervention in cancer patients. In the first study (Winningham & MacVicar, 1988) breast cancer patients undergoing chemotherapy were allocated for 10 weeks to either an aerobic cycle ergometer group (3x/week), a stretching and flexibility group (1x/ week), or a usual care group. The primary endpoint was self-reported nausea. The cycle ergometer group experienced significantly improved outcomes with regard to symptoms of nausea when compared to the stretching and usual care groups, suggesting that moderate aerobic exercise has the ability to provide an anti- nausea effect in patients undergoing chemotherapy. Winningham et al (1989) and MacVicar, Winningham & Nickel (1989) undertook a secondary analysis of the data examining functional capacity and body composition. Functional capacity ( $VO_2\text{max}$ ) was significantly improved when compared to



the control groups previously described. Body composition was assessed by way of skinfold measurements and as such the specificity of the training program in this study (aerobic exercise only), the relative increase in lean tissue mass may be attributed to the decreased fat tissue. This is likely due to the limitations of this technique not measuring muscle mass directly (Galvao & Newton, 2005).

Mock et al. (1997) had breast cancer patients undergoing chemotherapy complete either a 4-5 day per week unsupervised home based walking program or usual care for 6 weeks. Intensity was self-selected but required participants to complete 20-30 minutes of walking per session. Primary outcome measures were physical function, symptom experience and fatigue. The home based walking group improved significantly in walking distance as well as symptom experience and fatigue when compared to the control group.

The following series of studies conducted by Dimeo et al. (1997a; 1998; 1999) all used mostly breast cancer patients receiving high dose chemotherapy and autologous peripheral blood transplantation. The first of these studies investigated the effects of supervised bed based (supine) interval training 30 mins a day for approximately 2 weeks on physical performance, haematological indices and treatment complications. Compared to the usual care group, the intervention group did not experience decrements in physical performance to the same magnitude, experienced less pain and diarrhoea and shorter periods of neutropenia and thrombopenia. The intervention group also spent on average 1.6 days less in hospital (Dimeo, et al., 1997a). This study suggested that physical activity may partially preserve fitness during high dose chemotherapy. The second of this series

of studies (Dimeo, et al., 1997b) had a similar group of cancer patients undergo supervised treadmill walking 30-35 minutes daily for 6 weeks with a prescribed intensity set to elicit a blood lactate level of 3 mmol/L. Results indicated that supervised treadmill walking led to improvements in physical performance and haemoglobin levels which suggested exercise could not only preserve physical function but actually increase physical function after high dose chemotherapy. The final study of this series applied a similar intervention to that used in the Dimeo et al. (1997b) investigation with the same type of population, however, the key difference was the mode of exercise selected. Dimeo et al. (1999) in this study utilised a supine cycle ergometer once per day that consisted of 30 minutes interval type training to investigate the psychological impact of exercise. The exercise group demonstrated reduced levels of psychological distress with no changes in fatigue levels at the post intervention time point.

Schwartz (1999, 2000) conducted 2 studies to examine the influence of a home based, self-paced walking program on breast cancer patients undergoing chemotherapy. The 8-week intervention required participants to wear an accelerometer whilst walking 4 times per week for 8 weeks. As opposed to the usual care group, the walking group significantly improved their physical performance, as demonstrated by a 10.4% increase in the 12-minute walk test and also reported decreased levels of fatigue.

One of the first studies to employ an exercise intervention in patients with stomach cancer was by Na, Kim, Kim, Ha & Yoon (2000) who employed a combination of arm and cycle ergometers to evaluate the effects of exercise on the natural killer cell

cytotoxic activity (NKCA). Patients exercised at 60% of maximal heart rate twice per day, 5 times per week for 2 weeks with blood samples collected at baseline, and day 7 and 14 of the intervention. Post intervention (day 14) a significantly greater increase in NKCA was observed in the exercise group (28%) compared to the control group (13%).

Schwartz et al. (2001) added to the earlier investigations (Schwartz, 1999, 2000) of a home based self-paced walking program on breast cancer patients undergoing chemotherapy. As a result of the same 8-week intervention used previously, functional ability assessed by the 12-minute walk test increased 15% in the exercise group whilst the control group declined by 16%. Exercise also reduced all four levels of self-reported fatigue with a significant carry over effect of exercise on these fatigue scales. The series of studies conducted by this group of authors all employed self-selected home based exercise interventions. Despite their lack of laboratory based controls or supervision, significant differences were still observed for functional capacity and reported levels of fatigue. This self-selected home based intervention strategy was further explored in a pilot study by Mock et al. (2001). This work expanded on their previous research also using home based self-selected intensities in breast cancer patients (Mock, et al., 1997). Once again, despite the apparent lack of direct supervision or specified intensity, the exercise intervention led to significant improvements in physical performance as demonstrated by increased distance in the 12-minute walk test. Fatigue and emotional distress were also positively influenced as was quality of life. This series of studies, despite utilising relatively simple unsupervised exercise interventions, were able to demonstrate significant improvements in functional performance, fatigue and quality of life, providing

encouraging signs for future researchers to explore the differences between home based interventions and clinic or gym based interventions.

One such study to explore home based vs. non-home based interventions was conducted by Segal et al. (2001) who implemented a randomised controlled trial examining the effects of supervised gym based walking compared to unsupervised home based walking 5 days per week for 26 weeks on breast cancer patients undergoing adjuvant therapy. Results demonstrated an increased perceived physical functioning in the exercising groups whilst the group not exercising at all (control group) reported a decrease in perceived physical functioning, demonstrating a moderately large (and clinically important) difference between the two groups. The authors concluded that exercise has the ability to blunt some of the negative side effects of treatment, with self-directed exercise an effective strategy to improve physical functioning.

One of the first studies to combine cardiovascular and resistance type training into a single exercise intervention was conducted by Kolden et al. (2002). This pilot study also included a flexibility component to the design. A 16-week program was designed for breast cancer patients undergoing adjuvant therapy where they participated in group exercise training delivered in a structure format 3 times per week. The feasibility and health benefits were the primary desired outcomes of this pilot study. Results demonstrated that structured group exercise training was feasible, safe and well tolerated. The health benefits of the program were reported as an observed effect for time for upper and lower body strength, predicted aerobic capacity, flexibility and resting

systolic blood pressure. The authors highlighted the need for physical activity programs to be included in comprehensive, complimentary treatment regimes for breast cancer patients.

The first published study to investigate the effects of a resistance exercise intervention in prostate cancer patients undergoing ADT was conducted by Segal et al. (2003b). For 12 weeks participants underwent 3 days per week of whole body resistance training. The resistance training program was designed to consist of two sets of 8 -12 repetitions at 60-70% of 1RM for 6 upper and 3 lower body exercises. Compared to the control group, the resistance training group demonstrated reduced levels of fatigue as well as improvements in quality of life and muscular fitness. Body composition did not appear to be altered by the intervention. The lack of observed differences in the body composition variables may be accounted for by the elementary assessment of body composition used to measure changes in muscle and fat tissue. Sale (1988) has suggested that the initial adaptations to a resistance training program are usually neural, with gains in hypertrophy developing as the intervention continues. Given this was a 12-week intervention, it is possible that the changes in strength were predominantly due to neural alterations rather than muscle morphology (Galvao & Newton, 2005).

Coleman et al. (2003a; 2003b) had multiple myeloma patients undergoing high dose chemotherapy and autologous peripheral stem cell transplantation undertake an unsupervised home based aerobic and resistance training program for 12 weeks. The resistance training component of the study design was included as it was thought that

cancer patients who have skeletal muscle wasting may not obtain maximal benefit from an aerobic only intervention. As this was only a feasibility study with low subject numbers, the only statistically significant end-point was lean body mass with no differences observed in fatigue levels, aerobic capacity or any other body composition outcomes.

Dimeo et al. (2003) employed a short term aerobic training program on a mixed cancer population undergoing conventional or high dose chemotherapy. The intervention involved daily treadmill walking at 70% of maximum heart rate with the primary endpoint being physical performance. At the conclusion of the 2-week intervention no differences were observed in physical performance, assessed by a sub-maximal stress test. It is likely that the duration of the intervention was too short to elicit a significant alteration in aerobic capacity. Despite the lack of change in physical performance, the authors suggested that aerobic training may preserve performance during intensive chemotherapy.

Courneya et al. (2003) conducted a randomised controlled trial examining the effects of an unsupervised aerobic exercise program on quality of life and cardiovascular capacity in colorectal patients undertaking adjuvant therapy. The exercise intervention involved participants undertaking 3-5 days of cardiovascular and flexibility activities per week for 16 weeks. There were no differences observed between the exercise and control groups for any of the study endpoints which included quality of life, cardiovascular capacity, fatigue levels and body composition. The authors proposed that the lack of

differences between groups may be due to the high levels of exercise in the control group, where 51.6% of the control group exercised during the study period.

Adamsen et al. (2003) was the first study to employ a high intensity supervised training program in a mixed cancer population. Aerobic interval training was prescribed at 60-100% of maximal heart rate whilst resistance exercise was performed at 85-95% of 1RM for 5-8 repetitions. The 6-week program resulted in a 32.5% increase in maximal strength and a 16% increase in VO<sub>2</sub>max providing support for the proposal that cancer patients can tolerate high intensity exercise programs.

As more preliminary studies (Dimeo, et al., 2003; Mock, et al., 1997; Mock, et al., 2001; Schwartz, 1999, 2000; Schwartz, et al., 2001) reported the beneficial effects of walking on physical function, Windsor et al. (2004) sought to strengthen the growing body of literature by conducting a randomised controlled trial on men receiving radical external beam radiotherapy for treatment of localised prostate carcinoma. The home based moderate intensity walking program included 30 minutes of continuous walking, 3 days per week for the duration of their radiotherapy treatment with primary endpoints being fatigue and physical performance. The authors found that men in the control group reported significant increases in fatigue from baseline to end of radiotherapy treatment whilst the exercise group reported no such increases. The control group also reported a slight reduction (although not statistically significant) in distance walked in the physical function test whilst the exercise group significantly increased distance walked. It was also concluded that men instructed to rest if they became fatigued during treatment (control

group) demonstrated a slight deterioration in physical function and a significant increase in fatigue. Although the program was home based and hence lacked direct supervision, the exercise intervention still resulted in significant improvements in physical functioning with no reported increases in fatigue levels.

Campbell et al. (2005) conducted a randomised controlled trial to examine the effects of a supervised group exercise program on physical function, fatigue and quality of life in women with breast cancer receiving adjuvant treatment. A 12-week intervention had participants attend supervised exercise classes twice weekly and consisted of a general warm-up, 10-20 minutes of various exercise (walking, cycling, low level aerobic, muscle strengthening exercises etc.) and a cool-down period. The desired outcome of the intervention was to have participants undertaking exercise at a moderate level for the duration of the session. Although the physical work completed each week was quite low (20-40 mins per week), the study still reported positive outcomes in the exercise group with physical functioning and quality of life both improving as a result of the intervention. There were slight changes in fatigue and satisfaction with life; however the relatively small participant numbers as well as the previously mentioned relatively low dose of exercise resulted in a lack of significant findings.

Fairey et al. (2005) focused their attention on blood immune function responses to exercise on post-menopausal breast cancer patients where patients exercised on cycle ergometers 3 times per week for 15 weeks. The primary endpoint was the change in NCKA while secondary endpoints were the standard haematological variables. Exercise training



did have a significant effect on change in NKCA with no significant changes in the standard haematological variables. The small sample size combined with the use of peripheral blood samples (as opposed to tissue biopsy samples) is thought to have influenced results.

Mock et al. (2004) sought to expand their previous work in breast cancer (Mock, et al., 1997) with a multi-site randomised controlled trial to examine the effectiveness of a home based walking program on fatigue and physical function. This same mode of exercise was chosen as in their earlier work, however, this time participants were instructed to exercise for 30 minutes, 5-6 times per week for the duration of their treatment which was either 6 weeks for radiotherapy or 3-6 months for chemotherapy. Upon initial analysis there were no differences in any of the endpoints, however this was likely due to the fact that 39% of the control group exercised and 28% of the exercise group did not. A secondary analysis considered exercise participation in the analysis and found that moderate intensity home based walking exercise was effective in managing fatigue levels during both radiation and chemotherapy treatments while physical function was maintained during treatment.

Another home based randomised controlled trial was conducted by Pinto et al. (2005) which had breast cancer patients build up to exercising 30 minutes per day, 5 days per week for 12 weeks. Participants were encouraged to exercise at 55%-65% of maximum heart rate, although heart rate was not recorded during the intervention. This study differed to previous home based randomised controlled trials as it was primarily concerned with the efficacy of the delivery of a home based program with the primary

endpoint being physical activity levels during the intervention. The authors found that a 12-week intervention delivered via telephone successfully increased moderate intensity physical activity levels and overall physical activity levels compared to the control group.

Galvao et al. (2006) employed a resistance training program in prostate cancer patients undergoing ADT for the treatment of prostate cancer. The supervised resistance training program consisted of 12 upper and lower body exercises set at an intensity of 6-12 repetition maximum completed twice per week for 20 weeks. Primary endpoints were muscular strength and endurance, functional performance, balance and body composition. As a result of the intervention participants increased muscular strength by between 40% and 96% depending upon the site and muscular endurance was increased 115% for chest press and 167% for the leg press respectively. Significant improvements were also seen in all functional performance tasks including usual walk test (14%), 6m backward walk test (22%); chair rise (27%), stair climb (10%) and 400m walk (7.4%), and balance improved by 7.8%. Whole body lean mass was also preserved whilst no changes were reported in fat mass. This investigation demonstrated that resistance training is an effective intervention strategy in preserving body composition and reducing treatment side effects in men undergoing ADT for prostate cancer.

Quist et al. (2006) explored the role of a 6-week supervised high intensity resistance and cardiovascular training intervention in a single intervention group design, mixed cancer population undergoing chemotherapy. This work sought to expand on the previous research of Adamsen et al. (2003) who also utilised a high intensity exercise

intervention in a mixed cancer population. High intensity exercise training involved participants undertaking a 90 min session 3 times per week involving a warm up, heavy resistance training (3 exercises) and an aerobic fitness component. The aerobic component consisted of 10 minutes of cycling at a workload equivalent to 85-95% of each patient's maximum heart rate. Low intensity training involved participating in 30 minutes of relaxation type massage four times per week. Physical capacity and body composition were the primary endpoints. The average increase in muscular strength was 41.3% whilst aerobic fitness increased by an average of 14.5%. Body mass increased significantly (1%), however, there was also a significant decrease in skin-fold measurements. Although only a short term intervention, results demonstrated the program to be well tolerated with beneficial outcomes for patients undergoing chemotherapy.

Monga et al. (2007) investigated the role of aerobic exercise on fatigue and quality of life in prostate cancer patients undergoing radiotherapy. Participants undertook supervised treadmill walking for 40 minutes 3 times per week for 8 weeks. Intensity was set at 65% of heart rate reserve. Primary outcomes included cardiac fitness, fatigue, functional status and well-being. Although the participant numbers were relatively low in this study (21 participants) and the intervention only lasted 8 weeks, the results still demonstrated a supervised aerobic intervention to be successful at improving cardiovascular fitness ( $p<0.01$ ), muscle strength ( $p<0.001$ ) and quality of life ( $p=0.02$ ) as well as preventing fatigue (significant increase in control group  $p=0.04$ ).

Schneider et al. (2007) employed individualised exercise programs to determine cardiopulmonary and fatigue alterations in male cancer survivors during various forms of treatment, as well as following treatment of numerous forms of cancer. Each individualised program took into account the specific needs of each participant and required participants to attend approximately 60 minutes of supervised exercise 2-3 days per week for 6 months. Results were varied as is expected when employing individualised exercise programs, with the authors suggesting that this is primarily due to where the patient is on the cancer continuum. Regardless of where these patients were on the cancer continuum, exercise appeared to be a safe and effective strategy to maintain or improve physical and mental wellbeing.

Chang et al. (2008) conducted a hospital based randomised controlled trial to examine the effects of a 3-week walking exercise program on fatigue related experiences in leukaemia patients undergoing chemotherapy. Participants were required to walk 12 minutes per day, 5 days per week for 3 weeks. Sessions were supervised and intensity was prescribed as resting heart rate plus 30 beats per minute. Primary outcomes were measures of fatigue, 12-minute walking distance and psychological outcomes. As a result of the intervention, the walking group reported significant time dependant changes in 12-minute walking distance, lower levels of fatigue intensity and interference, symptom distress, anxiety and depressive status when compared to the control group. This study demonstrated that 60 minutes of moderate intensity aerobic exercise per week is effective in not only maintaining patient's energy levels but can also increase their functional capacity by improving 12-minute walking distance.

Culos-Reed et al. (2009) were the first to employ a combined aerobic and light resistance based training program in men undergoing ADT for the treatment of prostate cancer. The study was initiated to explore the effects a physical activity intervention would have on physical activity behaviour, quality of life and fitness measures. The 16-week intervention consisted of a home based aerobic and light resistance training program and weekly group sessions. As the program was home based, participants were encouraged to complete 3-5 sessions per week at a moderate intensity. Theraband's (rubberised bands) were provided for the resistance training component of the study. The weekly group based session included an activity portion that was similar in design to the home based program and included an additional 30 minutes of education/discussion activity. As expected the physical activity group did increase their physical activity behaviour by 71% whilst the control group decreased their activity levels by 13%. There were small reported changes in neck ( $p=0.019$ ) and waist ( $p=0.044$ ) girths as well as blood pressure (systolic  $p=0.004$ ; diastolic  $p=0.0005$ ); however these blood pressure improvements were evident in both groups suggesting this was not a result of the intervention. The high dropout rate (34%) combined with the relative lack of control in specific doses of exercise and limited resistance type exercises meant there were no significant findings for quality of life, fatigue or depression.

Hansen et al. (2009) compared high force eccentric resistance exercise in prostate cancer patients either on or off hormone therapy. All participants underwent 12 weeks of resistance exercise training using a recumbent cycle ergometer 3 times per week at a 'somewhat hard' perceived exertion for 12 – 15 minutes. Groups were based on ADT

usage with quadriceps muscle volume, knee extension strength, functional mobility, quality of life and fatigue compared between groups. The eccentric exercise intervention was well tolerated with both groups deriving some benefits in strength and functional mobility. Although underpowered due to being a pilot study (10 participants completed), the authors reported encouraging signs that despite hormone related muscle function deficits in men undergoing ADT, significant benefits in this group were still seen in strength ( $p=0.01$ ), functional mobility ( $p=0.03$ ) whilst quality of life demonstrated a clinically relevant change that did not meet statistical significance.

Segal et al. (2009) examined the effects of 24 weeks of resistance or aerobic exercise training on fatigue, quality of life, physical fitness and body composition in men with PCa receiving radiation therapy (~60% were also on ADT). The resistance training arm of the study had participants exercise 3 times per week and perform two sets of 8-12 repetitions of 10 different exercises at 60-70% of their 1RM. The aerobic arm consisted of training 3 times per week on a cycle ergometer, treadmill or elliptical trainer at an intensity of 50-60% of their  $VO_{2peak}$  for weeks 1-4 increasing to 70-75% for weeks 5-24. The duration of the aerobic sessions commenced at 15 minutes and progressed 5 minutes every 3 weeks until reaching 45 minutes. The authors found that both resistance and aerobic type exercise mitigated fatigue over the short term with resistance training providing longer term improvements. The resistance training arm reported significant improvements in quality of life ( $p=0.015$ ), muscle strength ( $p<0.01$ ), triglycerides ( $p=0.036$ ) and body fat percentage ( $p=0.049$ ). As expected aerobic training preserved aerobic fitness, however so did resistance training. Whilst the intervention groups did not improve

self-reported fatigue levels, the usual care group did report worsening fatigue during treatment resulting in a significant difference between control and intervention groups. Despite the well-controlled intervention, neither exercise mode prevented weight gain; however resistance training did mitigate the increase in body fat commonly associated with ADT.

Galvao et al. (2010) investigated the effects of a combined resistance and aerobic exercise program in men undergoing ADT for prostate cancer. Participants undertook supervised clinic based training twice per week for 12 weeks with primary endpoints being whole body and regional lean mass with secondary endpoints of muscle strength and function, cardiorespiratory capacity, blood biomarkers and quality of life. The resistance training component of the study consisted of 4 upper body and 3 lower body exercises progressing from 12 – 6 RM for two to four sets per exercise as well as abdominal crunches. The aerobic component of the study consisted of 15-20 minutes of aerobic type exercise at 65-85% of maximal heart rate. Despite a relatively brief exposure to the intervention, participants recorded improvements in muscle mass of 0.8kg ( $p=0.047$ ), muscular strength for the leg press of 31kg ( $p<0.001$ ) and 3kg for the chest press ( $p=0.018$ ), physical function as reported by a 0.3 second improvement in 6m usual walk ( $p=0.024$ ) and a 4.1 second improvement in 6m backwards walk ( $p=0.039$ ) as well as a borderline improvement in balance of 8.7 points ( $p=0.061$ ). The exercise intervention did lead to a borderline improvement in predicted cardiorespiratory capacity as shown by a mean group difference of 7 seconds ( $p=0.018$ ); however the relatively low dose of aerobic

exercise (30-40 minutes per week) likely contributed to the lack of significant difference between groups.

Kapur et al. (2010) retrospectively analysed acute toxicity data from a previous study (Windsor, et al., 2004) to assess the impact of aerobic exercise on acute rectal and bladder morbidity during treatment.. The authors reported a positive association with the severity of radiation induced acute rectal toxicity scores (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer 0-4 point scoring criteria). There was a lack of any beneficial association between exercise and bladder toxicity scores; however it is thought that this could be attributed to the confounding effect of lower urinary tract symptoms reported by patients at the start of treatment. Therefore bladder symptoms could not be solely attributable to radiation therapy.

Serda et al. (2010) explored the role of exercise as a complementary treatment in prostate cancer patients undergoing radiotherapy. The exercise intervention lasted for a total of 24 weeks with the first 16 weeks being supervised whilst the remaining 8 weeks unsupervised. The two 90-minute exercise sessions per week consisted of 1-2 sets of 8-12 repetitions at 50-70% of 8RM for 10 selected exercises. As a result of the intervention there was a significant improvement in muscular endurance which was more evident in the lower limbs. The authors concluded that the improvement in quality of life was likely due to the improvement in functional and physical capacity.

Another walking based intervention was conducted by Newton et al., (2011) who recruited ovarian cancer patients undergoing chemotherapy. The program was home



based and individualised to each participant based on their pre intervention assessment of physical functioning and level of physical activity. Primary outcomes were physical function assessed by the 6-minute walk test, self-reported distress, symptoms and quality of life. This pilot study reported that the majority of the 17 participants completed exercise 4 days per week at a moderate intensity for 30 minutes. Participating in the walking intervention was associated with improvements in physical functioning, physical symptoms and ovarian cancer specific quality of life. The lack of a control group was a limitation to the study, whilst the small sample size also meant that some changes did not reach statistical significance.

The impact of supervised exercise programs on physical capacity and quality of life in mixed cancer populations was recently investigated by Noble et al. (2012). This large scale intervention (305 participants completed pre and post testing) consisted of a 24 session program, completed twice weekly for 12 weeks. Each session consisted of both aerobic and resistance training exercise for a total of 1 hour. Intensity was broadly set at between 11 and 13 on the RPE (6-20) scale for both aerobic and resistance exercises. Primary outcomes assessed were changes in physical function at a sub maximal work rate as well as body mass index and quality of life. The authors reported a significant increase (10.8 Watts,  $p < 0.001$ ) in the maximum work rate attained and significant decrease (4 bpm  $p < 0.001$ ) in the heart rate response, systolic blood pressure (6mmHg,  $p < 0.001$ ) and RPE (1,  $p < 0.001$ ) at a sub-maximal level. Quality of life was also significantly improved following the intervention.

Quist et al. (2012) was the first study to assess the safety and feasibility of a combined aerobic and resistance intervention in inoperable lung cancer patients undergoing chemotherapy. This pilot study employed a 6-week intervention consisting of a supervised structured exercise and relaxation training program. Each supervised session was 90 minutes in duration and consisted of 10 minutes of light stationary cycling (60-90% maximum heart rate), strength training for 3 sets of 5-8 repetitions (70-90% 1RM) and aerobic interval training for 10-15 minutes (85-95% of maximum heart rate). The home based component consisted of walking and relaxation exercises for approximately 20-40 minutes 3 times per week. Primary endpoints were  $VO_2$ peak, muscular strength and physical function. This study showed significant improvements in aerobic capacity, muscle strength, functional capacity and emotional wellbeing. Despite the intervention there was no significant improvement in general quality of life or lung capacity. The authors concluded that this type of combined aerobic and resistance exercise intervention was safe for patients with advanced stage lung cancer.

A pilot study by Rao et al. (2012) employed a 'bootcamp' style exercise intervention which involved breast cancer patients complete both aerobic training and resistance exercises. The type of training employed was a circuit style of training where participants completed activities such as jumping jacks, running in place, arm and leg work using exercise balls, bands and weights up to 2.3kg. Prescribed duration was 48 sessions completed 3 times per week as either one on one or group exercise sessions depending upon personal preference. Primary outcomes were a number of biomarkers including Ki-67 in the actual tumour, insulin-like growth factor 1(IGF-1) and C peptide as well as body

mass index. This supervised exercise program was found to have decreased body mass index which may lead to lower Ki-67 levels and improved survival.

### *Physical activity and Post Cancer Survival*

Studies are emerging to support the link between physical activity and improved survival rates in cancer patients. A recent study by Chen et al. (2011) evaluated the association between exercise post breast cancer diagnosis and total mortality and recurrence. After accounting for quality of life, clinical prognostic factors and other covariates, exercise during the first 36 months post diagnosis did have a beneficial impact on total mortality and recurrence rates. These findings are in addition to several other large scale prospective studies that have also found women who engage in higher levels of physical activity are at a lower risk of dying from breast cancer (Holick, et al., 2008; Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005). Similar findings are also reported for colorectal survivors with several large prospective studies reporting physical activity has improved disease specific survival, in particular for patients with stage II and III colon cancers (Haydon, Macinnis, English, & Giles, 2006; Meyerhardt, et al., 2006). As with both breast and colorectal cancers, physical activity has also resulted in beneficial outcomes for prostate cancer survivors. Kenfield et al. (2011) conducted a prospective study assessing physical activity with total and prostate cancer specific mortality with their findings similar to those presented for other cancer survivors. Men who were physically active, in particular those engaging in 9 MET h/wk or greater of physical activity had a 33% lower risk of death from any cause and a 35% lower risk of prostate cancer specific death, after adjusting for other risk factors for mortality and pre-diagnosis physical activity levels.

Ballard-Barbash, et al. (2012) conducted a systematic review of 45 articles relating to physical activity, cancer survival and biomarkers potentially related to cancer survival. The authors reported there was consistent evidence from 27 observations studies that physical activity is associated with reduced all cause, breast cancer specific and colon cancer specific mortality. Whilst no associations between physical activity and other types of cancers were present, this is likely due to the lack of insufficient evidence in the form of randomised controlled trials in other cancer types.

### ***Background and justification for choice of intervention***

Reduced levels of physical activity and increased levels of fatigue are commonly reported in prostate cancer patients treated with ADT (Galvao, et al., 2008c) which in turn reduces functional capacity. Reductions are seen in cardiorespiratory endurance, upper and lower body strength and endurance, and physical components of quality of life (Alibhai, et al., 2010; Basaria, et al., 2002; Galvao, et al., 2008c) which lead to inhibiting activities of daily living as well as the previously established risks of CVD. Exercise has been shown to be effective for improving surgical outcomes, reducing symptom experience, managing side effects, improving psychological health, maintaining physical function and reducing fat gain and muscle and bone loss in cancer patients (Newton & Galvão, 2008). Studies in the past have used aerobic exercise (Segal, et al., 2009), resistance exercise (Segal, et al., 2003b; Segal, et al., 2009), or a combination of aerobic and resistance exercise (Galvao, et al., 2010). Exercise programs have also differed in method of delivery with some home based (Culos-Reed, et al., 2009) whilst others are group based in a clinic setting (Galvao, et al., 2006; Galvao, et al., 2010).

Resistance exercise improves muscle strength and function and has been shown to be an effective intervention against sarcopenia (Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988). This exercise mode also leads to improvements in functional capacity and quality of life whilst reducing disability in individuals with and without CVD (Hunter, McCarthy, & Bamman, 2004; Williams, et al., 2007). In prostate cancer patients undergoing treatment, studies have shown positive effects of resistance exercise on reducing musculoskeletal treatment side effects, decreasing fatigue, and improving quality

of life, (Galvao, et al., 2006; Segal, et al., 2003a) despite a compromised hormonal profile (Galvao, et al., 2008a). Segal and colleagues (2003b) had patients complete resistance exercises 3 times per week for 12 weeks and reported upper and lower body muscular fitness improvements of 42% and 32%, respectively, whilst Galvao et al. (2006) had patients undergo resistance exercise 2 times per week for 20 weeks and reported significant improvements in upper body muscular strength (chest press 40%, seated row 42%), lower body strength (leg press 96%), functional performance (400m walk 7.4%, stair climb 10.4%, chair rise 27%) and balance (7.8%).

Improvements in muscle mass, such as those seen by Galvao et al. (2010) are important not just in terms of mobility and functional performance but also in assisting glucose disposal (Ferrara, Goldberg, Ortmeyer, & Ryan, 2006). Muscle stimulates insulin sensitivity and accounts for up to 80% of insulin dependent glucose uptake (DeFronzo, et al., 1981). Numerous clinical studies have shown resistance training to lower the percentage of glycosylated haemoglobin and increase glucose disposal as well as favourably impact cardiovascular disease risk factors in elderly individuals (Holten, et al., 2004; Zanuso, Jimenez, Pugliese, Corigliano, & Balducci, 2010). Srikanthan & Karlamangla (2011) conducted a cross-sectional analysis of the National Health and Nutritional Examination Survey III data to investigate the possible correlation between relative muscle mass and insulin resistance and prediabetes. After adjusting for age, ethnicity, sex and generalised and central obesity, the authors found for every 10% increase in skeletal muscle index (skeletal muscle mass relative to total body mass) was associated with an 11% reduction in insulin resistance and a 12% relative reduction in pre-diabetes. This

correlation was stronger in non-diabetic patients (Srikanthan & Karlamangla, 2011) and was not just limited to the lower, sarcopenic end of the muscle mass distribution in the population, suggesting that increases in muscle mass, even above average levels was associated with additional protection against insulin resistance and diabetes.

Studies employing aerobic training only interventions have primarily utilised breast cancer patients, with promising outcomes reported in physical function, fatigue mitigation and quality of life (Campbell, et al., 2005; Mock, et al., 1997; Pinto, et al., 2005). Of the aerobic intervention studies in prostate cancer patients, radiotherapy has been the most common treatment modality (Monga, et al., 2007; Windsor, et al., 2004) with one study utilising ADT treated prostate cancer patients (Segal, et al., 2009). Segal et al. (2009) reported beneficial effects of the aerobic training for both fatigue mitigation and maintenance of aerobic fitness.

With regard to non-cancer patients, it is well established that cardiorespiratory fitness attenuates the mortality risk associated with metabolic syndrome in healthy men, independent of body mass (Katzmarzyk, Church, & Blair, 2004) indicating that cardiorespiratory fitness is of greater importance than body mass per se. High cardiorespiratory fitness levels have also been found to attenuate the increased arterial stiffness in patients with metabolic syndrome (Young Sae et al., 2010). Increases in arterial stiffness, independent of age and blood pressure have been reported in men receiving ADT (Dockery, et al., 2003; Dockery, Rajkumar, Agarwal, Waxman, & Bulpitt, 2000; Smith, et al., 2001) highlighting the need for prescribed aerobic exercise programs focused on

improving cardiorespiratory fitness to offset the metabolic related treatment toxicities in ADT treated patients.

Although there are studies that have investigated the effects that resistance training programs and aerobic training programs have on prostate cancer patients undergoing treatment, very few have utilised a combined aerobic and resistance training intervention with prostate cancer patients undergoing ADT. Culos-Reed et al (2009) was one of the first studies to attempt to employ a combined aerobic and resistance training program in ADT treated prostate cancer patients, however the study was a low intensity home based intervention and hence lacked the control of a laboratory based intervention. This apparent lack of control may have been the reason for a lack of statistically significant differences. Galvao et al. (2010) was the first group to conduct a clinic based supervised randomised controlled study to evaluate the combined effects of a resistance and low volume aerobic exercise program in men undergoing ADT. Galvao et al. (2010) reported favourable changes in total body and regional lean mass as well as improvements in muscular strength and functional performance outcomes. Cardiorespiratory capacity only showed borderline improvement but this was thought to be a result of the low level of aerobic exercise prescribed. Participants undertook 30 – 40 minutes of aerobic exercise per week, which is well below 150 minutes recommended by the American Heart Association for good health. However, the promising aspect of this study was that despite the low dose of aerobic exercise prescribed, borderline changes were still seen in cardiorespiratory capacity.



A combined supervised aerobic and resistance training program was selected to expand upon the original work of Culos-Reed, et al. (2009) and Galvao, et al. (2010) through a clinic based randomised control trial employing a larger aerobic training component than has been previously used in combined aerobic and resistance training programs.

## ***Background of Study Measures***

### ***Cardiorespiratory Fitness Assessment***

Maximal oxygen intake or  $\text{VO}_2\text{max}$  is the maximum amount of oxygen that an individual can utilise during intense or maximal exercise and when measured under maximal exercise is considered the gold standard measurement of cardiorespiratory capacity (Mitchell, Sproule, & Chapman, 1958). This was chosen as a primary outcome measure as it has been shown to be a stronger predictor of overall mortality than self-reported physical activity levels (Byun, et al., 2011) which have been used in previous studies. Blair and colleagues (2001) suggest there is an inverse gradient across categories (medium, low and high) of cardiorespiratory fitness for risk of fatal and non-fatal health outcomes. The authors also reported that the dose response gradient for health-related outcomes is steeper when a direct assessment of cardiorespiratory fitness is used as opposed to self-reported physical activity levels (Blair, et al., 2001). Segal et al. (2009) is one of the very few studies to have utilised a direct assessment of cardiorespiratory capacity in cancer patients, in this case prostate cancer patients undergoing radiotherapy (~60 on ADT). No serious adverse events arose as a result of maximal exercise testing in the Segal, et al. (2009) study. The association between cardiorespiratory fitness and risk of cardiovascular disease is well established (Katzmarzyk, et al., 2004) and given the heightened risk of developing cardiovascular disease as a result of ADT for the treatment of prostate cancer (Collier, et al., 2011; Levine, et al., 2010) it was thought a direct

assessment of cardiorespiratory fitness would be an important component of the testing battery.

### *Resting Metabolic Rate Assessment*

A major side effect of ADT is the loss of skeletal muscle mass due to suppression of testosterone (Galvao, et al., 2008b). This loss of lean mass not only affects functional performance and muscle strength but can also impact resting energy expenditure or resting metabolic rate (RMR). Fat-free mass has been shown to be a major determinant of basal or resting metabolic rate as muscle mass is responsible for approximately 30% of resting energy expenditure and protein turnover as well as 70% of body cell mass (Ravussin, Lillioja, Anderson, Christin, & Bogardus, 1986). This reduction in muscle mass combined with decreased levels of physical activity can reduce total energy expenditure in elderly adults, which can result in other complications such as abdominal fat accumulation and hence increased risk factors for CVD (Cunningham, 1991; Rosito, et al., 2008). Buscemi (2007) has reported that a low resting metabolic rate is associated with metabolic syndrome and given there is a heightened risk of developing metabolic syndrome in prostate cancer patients undergoing ADT, the ability to quantify potential changes in resting metabolic rate may assist in understanding the relationship between exercise, ADT and energy expenditure. Galvão et al. (2008b) reported large reductions in whole body and regional lean mass with concomitant increases in fat mass following 36 weeks of ADT suggesting that reduced lean mass may compromise basal metabolic rate and hence energy expenditure. Although a study by Reis et al. (2009) failed to find any differences in resting energy expenditure in ADT patients, possibly due to their small sample size, they

did identify a significant increase in carbohydrate oxidation and a decrease in lipid oxidation suggesting the way energy is utilised is in fact influenced by ADT. This alteration in lipid oxidation is likely due to the suppression of testosterone as previous studies have shown supplemental testosterone therapy increases lipid oxidation in healthy aging men with low testosterone levels (Frederiksen, Hojlund, Hougaard, Brixen, & Andersen, 2012). Resting metabolic rate testing has been included in the two experimental chapters of this thesis to determine if the preservation of lean mass in patients receiving ADT through resistance training may assist in maintaining resting and total energy expenditure and possibly reduce risk factors associated with CVD.

### *Central Blood Pressure Assessment*

Techniques have now been developed to noninvasively assess central blood pressure, focussing on arterial stiffness and autonomic function (Zhang, et al., 2013). The ability to assess central blood pressure in this population is important as although it is not known exactly how androgens interact with the cardiovascular system, recent studies have shown men undergoing ADT experience decreases in systemic arterial compliance, which is reflected in an increase in aortic stiffness, independent of age and blood pressure (Dockery, et al., 2003; Dockery, et al., 2000; Smith, et al., 2001). This arterial compliance or 'elasticity' is increasingly regarded as a surrogate marker for CVD (Dockery, et al., 2000). Smith et al. (2001) have reported that hypogonadism results in a rise in the augmentation of central arterial pressure suggesting considerable arterial stiffening. The authors suggested that testosterone has a direct role in modulating blood flow and vessel resistance in medium and large arteries which may also contribute to the increased

cardiovascular mortality following temporary ADT. This proposal is further supported by a recent study that used transdermal testosterone replacement in hypogonadal men (unrelated to ADT) to exert a rapid, and partial favourable effect on pulse wave velocity (Yaron, et al., 2009).

### *Body Composition Assessment*

Dual energy X-ray absorptiometry (DEXA) is now a widely used method of assessing fat mass, bone mineral-free lean mass and bone mineral mass in clinical research. DEXA utilises X rays at two energy levels that pass through body tissue providing an accurate and reliable measurement of total body composition whilst also allowing for site specific regional analysis including upper and lower limb and trunk analysis (Shih, Wang, Heo, Wang, & Heymsfield, 2000). Body composition alterations are well established adverse effects of ADT (Galvao, et al., 2008b; Haseen, Murray, Cardwell, O'Sullivan, & Cantwell, 2010) with the term sarcopenic obesity now commonly used to describe the concomitant increases in body weight and reduced muscle mass and strength (Baumgartner, 2000). These body composition changes have the ability to alter resting energy expenditure and metabolic variables as well as contributing to the increased risk of cardiovascular disease. The addition of this outcome will aid in the understanding of ADT associated body composition alterations in response to a combined six month aerobic and resistance training program and seek to explore the related changes in other measured variables.

### *Strength and Endurance Assessments*

One repetition maximum (1RM) strength testing, which is the maximal amount of weight that can be lifted in a single repetition, dates back as far as 1955 and has been found to be a reliable assessment of maximal strength (Hoeger, Hopkins, Barette, & Hale, 1990). 1RM testing has been conducted extensively in our laboratory with similar populations (Galvao, et al., 2006; Galvao, et al., 2010; Galvao, Taaffe, Spry, & Newton, 2007b; Peiffer, et al., 2010) without the presence of any serious adverse events. This view is further supported by Shaw et al. (1995) who has previously reported 1RM testing to be a safe and acceptable tool used to evaluate strength in elderly populations. Muscular endurance, reported as the maximal number of repetitions performed at 70% of 1RM has also been used previously in our laboratory (Galvao, et al., 2006; Galvao, et al., 2008b) with similar populations without the presence of any serious adverse events.

### *Physical Function Assessments*

Tests of physical function were performed to provide objective functional measures of strength and endurance. This battery of tests has been used extensively in our laboratory (Galvao, et al., 2006; Galvao, et al., 2008b; Galvao, et al., 2010; Galvao, et al., 2008c; Peiffer, et al., 2010) and have reported coefficients of variations for the chair rise test, 6 meter backwards walk test and 400 meter walk test of 5.6%-6.7%, 9.4% and 2.5% respectively (Galvao, et al., 2006). In addition to providing objective functional measures of strength and endurance, lower extremity function, assessed in the current series of studies by the sit to stand test and stair climb have been previously shown to be highly predictive of subsequent disability in older individuals (Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995).

## ***Implications of literature review - Conclusion***

It is becoming increasingly evident that physical activity and exercise play a key role in the various stages of cancer. Physical activity has been shown to reduce the likelihood of several types of cancer, in particular breast and colorectal cancer (Key, et al., 2002; Thune & Furberg, 2001). This review has extensively explored the role of exercise during treatment for cancer as a method of reducing certain toxicities of the treatment including fatigue, quality of life and psychological distress whilst also exerting positive influences on muscular strength and endurance, physical function and body composition. Research is also emerging in support of the link between physical activity and improved survival rates in cancer patients demonstrating the far reaching effects of physical activity and exercise across the entire cancer continuum.

Exercise interventions during cancer treatment date back to 1986 (Cunningham, et al., 1986) and since then have involved different cancer populations including breast, colorectal, prostate and mixed populations whilst the interventions have included aerobic exercise, resistance training or a combination of both. The interventions have also varied in terms of settings with some being gym or laboratory based whilst others have been home based. Numerous psychological and physiological endpoints have been used with the most common being fatigue, quality of life, physical fitness and function, muscular strength and endurance and body composition. Investigators have most commonly used breast cancer patients with study results varying due to the differences in settings and psychological and physiological endpoints.



Whilst exercise interventions in breast cancer patients during treatment have been numerous, there are only limited studies that have attempted to explore the role of exercise in prostate cancer patients undergoing ADT. Of the six interventions conducted whilst patients were undergoing ADT, three were resistance only interventions (Galvao, et al., 2006; Hansen, et al., 2009; Segal, et al., 2003b), two were combined aerobic and resistance interventions (Culos-Reed, et al., 2009; Galvao, et al., 2010) whilst the remaining study compared aerobic and resistance exercise interventions (Segal, et al., 2009). Of the two combined aerobic and resistance interventions, one of these was a home based intervention (Culos-Reed, et al., 2009) and the other was a short term (12 weeks) intervention (Galvao, et al., 2010). The majority of previous studies investigating the effects of exercise on cancer patients during therapy have been either 12 weeks duration or less and whilst several have lasted 16 weeks very few have extended beyond this. This has been predominantly due to the nature of the treatments lasting 12 weeks or less (Baskar, et al., 2012; Heidenreich, et al., 2011). However, as ADT treatment may last several months up to several years, little is known about the long term effects of exercise during longer duration ADT. There are currently no long- term randomised controlled trials investigating the effects of a combined aerobic and resistance training intervention during ADT for the treatment of prostate cancer. Baumann, et al. (2011) in a recent review have highlighted the need for further randomised controlled trials with high methodological quality to be conducted to establish evidenced-based recommendations for prostate cancer patients.

## *Conclusion*

A complex relationship exists between prostate cancer, ADT, metabolic factors, physical fitness and the subsequent risk of cardiovascular disease. There is now an abundance of literature suggesting ADT does in fact adversely affect traditional CVD risk factors; however the timing of the onset of these risk factors and other related side effects still needs to be explored. The timing of the onset of these risk factors has implications on the scheduling of exercise interventions and associated time course responses to exercise during ADT treatment. Long term clinical trials are required to investigate interventional strategies that not only reduce the CVD risk factors associated with ADT but also other treatment related toxicities such as fatigue and quality of life. Although current research supports the positive psychological outcomes (e.g. improvements in quality of life), questions remain how specific physiological outcomes such as cardiorespiratory function, vascular function, blood pressure, lipids and glycemic control would adapt following a combined aerobic and resistance training exercise intervention. Based on current recommendations from the American College of Sports Medicine (1998) to incorporate both aerobic and resistance exercise to enhance cardiovascular and musculoskeletal function in healthy older adults and more recently in cancer survivors (ACSM, 2010), a similar approach should be tested in a long term randomised controlled trial in prostate cancer patients on ADT.

## **CHAPTER 3**

### **Feasibility and safety of maximal exercise testing in men receiving androgen deprivation therapy for prostate cancer**

## INTRODUCTION

Exercise is being increasingly established as a key adjuvant therapy in clinical oncology with a growing body of literature providing strong evidence that exercise is well tolerated, safe, and can mitigate several common treatment related side-effects (Jones & Alfano, 2013). As a growing number of cancer patients begin to undertake structured exercise programs (Baumann, et al., 2011; Jones & Alfano, 2013) it is necessary to determine the safety and feasibility of formal exercise testing in clinical settings as it is becoming increasingly used as a screening tool and for exercise prescription purposes (Jones, et al., 2007a). Given that many cancer patients are older (Yancik, 2005), combined with the potential adverse cardiovascular effects of certain cancer treatments (Albini, et al., 2010), the risk of cardiovascular disease is often elevated in these populations (Albini, et al., 2010; Jones, et al., 2007b; Keating, et al., 2009) highlighting the need for thorough screening prior to commencing an exercise program.

Pre-exercise screening will often include a series of questions designed to identify individuals with signs or symptoms of underlying disease. These questionnaires may be used in addition to detailed medical history and physical examination (Balady, et al., 1998). Further screening often involves cardiopulmonary exercise testing which provides an objective determination of an individual's cardiorespiratory fitness and baseline parameters for training intensities as well as accurate screening for cardiac, pulmonary and physical limitations (Balady, et al., 1998).

When cardiopulmonary testing is used during incremental exercise with continuous gas exchange it provides the only way of assessing maximal oxygen consumption directly. Maximal oxygen uptake as assessed in a graded exercise test is the greatest amount of oxygen that can be consumed while performing dynamic exercise involving large muscle groups and is considered to be the gold standard in assessing cardiopulmonary fitness and exercise capacity (Fletcher, et al., 2001). Whilst the assessment of peak exercise during a graded exercise test may be subjective due to the motivation of the patient, the collection of expired gas can provide an objective measure of maximal exercise capacity (Cohn, 1999). The inclusion of electrocardiography (ECG) can be applied as both a diagnostic and screening tool (Steins Bisschop, et al., 2012). The use of ECG monitoring during a graded exercise test allows for the non-invasive measurement of the heart's ability to respond to stress in a controlled environment and aids in the diagnosis of coronary artery disease and estimating prognosis for cardiac outcomes (Sharma, Kohli, & Gulati, 2012). Whilst traditional exercise stress tests are primarily concerned with ST segment changes indicative of myocardial ischemia, the addition of exercise capacity, heart rate and blood pressure responses all enhance the diagnostic and prognostic value of the exercise test (Sharma, et al., 2012).

Given that androgen deprivation therapy (ADT) for the treatment of prostate cancer has been associated with an increased risk of cardiovascular disease (Keating, et al., 2009; Levine, et al., 2010; Saigal, et al., 2007), a comprehensive cardiovascular screening battery, including clinical exercise testing, may be necessary prior to the commencement of an exercise program, particularly if the patient is sedentary or has

identified risk factors. To date, no study has investigated the safety and feasibility of maximal exercise testing, including ECG, expired gas, heart rate and blood pressure responses in men undergoing ADT for the treatment of prostate cancer. As such, this study seeks to determine the feasibility and safety of maximal exercise testing in prostate cancer patients by reporting descriptive data from maximal exercise tests as well as reporting any adverse events and exercise abnormalities. From this it may be determined if ADT treated prostate cancer patients respond differently to maximal exercise when compared to the available data from healthy age-matched controls. Further, this study will examine if maximal exercise testing with expired gas and ECG monitoring is a necessary screening tool in this population.

## METHODS

Subjects were recruited by invitation of their attending specialist physician. One hundred and twelve prostate cancer patients (age 42 – 89 years) receiving ADT for their treatment (duration  $4.3 \pm 4.9$  months) underwent a physician supervised multistage maximal stress test utilising the Bruce protocol (Bruce, 1971) on a motorised treadmill. The Bruce protocol is a widely used incremental exercise testing protocol consisting of three minute stages commencing at 2.7km/h and a 10% incline. The speed and incline increase with each stage with participants encouraged to continue until volitional exhaustion (Bruce, 1971). Participants in this study were recruited for the purposes of undertaking a large scale exercise intervention study (Newton, et al., 2009), and as such the exclusion criteria applied to the intervention study (Chapter 5) also applied to the current study. The exclusion criteria included the presence of an acute illness or any musculoskeletal, cardiovascular or neurological disorder that could inhibit exercise response or adaptation or put the participant at risk from exercising. All participants obtained medical clearance from their general practitioner and completed a detailed health history questionnaire. This study protocol was approved by the University Human Research Ethics Committee and all participants signed informed consent documentation prior to any data collection.

Participants were continuously monitored with a 12-lead ECG system (CardioDirect 12S, Irvine, CA) at rest, during the maximal exercise test and during recovery. During the maximal exercise test the subject's expired gases were collected (Parvo Metabolic Measuring System, Sandy, UT) to measure their maximal oxygen uptake ( $\text{VO}_{2\text{max}}$ ).

$\text{VO}_2\text{max}$  was determined to be the point at which the highest  $\text{VO}_2$  value was recorded over an averaged 30s period. All subjects were instructed to exercise until volitional exhaustion or they experienced signs or symptoms necessitating the termination of the test which included: 1) chest pain, 2) ischemic ECG changes, or 3) an abnormal blood pressure response. A plateau in oxygen consumption was used as qualification for achieving  $\text{VO}_2\text{max}$ . In the absence of a plateau, a secondary criteria was a Respiratory Exchange Ratio (RER)  $>1.1$ . If the subject was unable to achieve a plateau or RER values  $>1.1$  their data were excluded from the presentation of maximal values. The coefficient of variation for  $\text{VO}_2\text{max}$  (repeated maximal exercise tests) is approximately 4% (Howley, Bassett, & Welch, 1995).  $\text{VO}_2\text{max}$  is presented as an absolute value and relative to body mass as well as metabolic equivalent of task (METs), where 1 MET is equivalent to  $3.5 \text{ ml O}_2\cdot\text{kg}\cdot\text{min}^{-1}$ . The duration of the maximal exercise test is presented as minutes: seconds.

Systolic and diastolic blood pressure was assessed via manual auscultation using a mercury column sphygmomanometer and appropriate-sized cuff pre-test whilst in the standing position on the treadmill, during the last minute of each stage and 3 minutes post cessation of exercise.

### *Positive Test Criteria*

A positive (abnormal) test was defined as 1) any significant ECG change indicative of ischemia during exercise or recovery, or 2) the development of exercise induced bundle branch block. A significant ECG change was defined as  $\geq 0.1\text{mV}$  of horizontal or down-sloping ST-segment depression  $\geq 80$  milliseconds after the J-point (as compared to the



level of the PQ interval) (Gibbons, et al., 1997). ST segment changes toward the isoelectric line were not considered positive, regardless of the magnitude of change. If the baseline ECG revealed a J-ST segment depression of  $>0.05\text{mV}$ , then 'double criteria' (an additional  $0.2\text{mV}$ ) of ST depression was required with the appropriate horizontal or down-sloping morphology to qualify as a positive test (Jones, et al., 2007a). All cases were interpreted by the same supervising physician.

For further analysis, participants were stratified into two groups: 1) patients receiving ADT  $<3$  months (acute ADT) or 2) patients receiving ADT  $\geq 3$  months (chronic ADT) to determine if additional ADT exposure does influence the physiological responses to maximal exercise. Several studies have reported negative metabolic changes after short-term (3 months) ADT (Dockery, et al., 2003; Smith, et al., 2001; Smith, et al., 2006), suggesting an acute exposure to ADT may be sufficient to elicit an adverse cardiovascular profile and hence alter the physiological response to exercise.

Body weight and height were measured using standard anthropometric measures. Body weight was measured to the nearest  $0.1\text{kg}$  using a digital scale (AND TB: 200), whilst height was measured to the nearest millimetre using a wall mounted stadiometer (SECA 700, Brooklyn, NY). Body mass index (BMI,  $\text{kg}/\text{m}^2$ ) was calculated as body mass (kg) divided by height (m) squared. Whole body fat was assessed by dual energy X-ray absorptiometry (DEXA, Hologic Discovery A, Waltham, MA).

### *Statistical Analysis*

Data analyses were performed using the Statistical Package for Social Sciences version 18.0 software (PASW, Chicago, IL). Standard descriptive statistics were used to describe subject characteristics. Differences between groups  $\text{VO}_2\text{max}$  were examined using Student's independent t test while blood pressure and heart rate responses were examined using 2 x 4 mixed model analysis of variance procedures. All tests were two-tailed and an alpha level of 0.05 was applied as the criterion for statistical significance. Data were assessed for normality using the Kolmogorov-Smirnov test. Results are reported as the mean  $\pm$  standard deviation.

## RESULTS

### *Subject characteristics*

One hundred and twelve participants were tested for the purposes of this study. Of the one hundred and twelve, ninety five participants (85%) met the criteria for attainment of VO<sub>2</sub>max. The characteristics for the one hundred and twelve participants are presented in Table 2. Mean ADT duration was 2.0 ± 0 months and 7.1 ± 6.2 months for the acute and chronic groups, respectively. There were no significant differences between groups for any descriptive characteristics. A borderline difference was observed (p=0.053) for body fat %.

**Table 2.** Subject characteristics including age, testosterone, height, body mass, body mass index and aerobic fitness (n=112).

Variable	Mean ± SD	Acute ADT	Chronic ADT	Mean Difference (95% CI)	P Value
		Mean ± SD	Mean ± SD		
		n=60	n=52		
Age (years)	68.8 ± 9.3	67.6 ± 9.0	69.9 ± 9.6	-2.3 (-6.1, 1.6)	0.254
Testosterone (mmol/L)	1.4 ± 2.6	1.3 ± 1.5	1.5 ± 3.4	-0.2 (-1.2, 0.8)	0.651
Height (cm)	172.4 ± 6.5	172.1 ± 6.6	172.9 ± 6.4	-0.8 (-3.7, 2.1)	0.589
Body Mass (kg)	84.0 ± 13.6	84.3 ± 13.2	83.7 ± 14.2	0.7 (-5.1, 6.4)	0.822
Body Mass Index (kg.m <sup>2</sup> )	28.0 ± 3.9	28.2 ± 3.8	27.8 ± 4.0	0.4 (-1.4, 2.1)	0.678
Body Fat %	27.3 ± 5.2	26.4 ± 5.1	28.3 ± 5.2	-1.9 (-4.0, 0.1)	0.053

### *Adverse events and abnormal ECG responses.*

Of the ninety-five participants who achieved VO<sub>2</sub>max, three positive tests (3.2%) and ninety-two negative tests (96.8%) were observed. Two positive tests were due to ST segment depression while the remaining positive test was due to right bundle branch blockage. There were no positive events in the seventeen participants who failed to meet the criteria for VO<sub>2</sub>max. The three participants who recorded a positive stress test were sent for further examination. All three participants were cleared of any serious issues precluding them from participating in an exercise intervention. One participant had their maximal exercise test postponed due to poorly controlled blood pressure (>200mmHg systolic or 110mmHg diastolic) but returned at a later date to safely complete the test.

### *Cardiorespiratory fitness*

The cardiorespiratory fitness data are presented in Table 3. Combined relative VO<sub>2</sub>max for all participants was  $24.7 \pm 6.0$  ml.kg.min<sup>-1</sup> (range 13.7 – 45.2 ml.kg.min<sup>-1</sup>). There was a significant difference in cardiorespiratory fitness between the acute and chronic groups with a significantly higher value in the acute group relative to body mass (P=0.020), as an absolute value (p=0.035) or in corresponding metabolic equivalents (P=0.020). Whilst not statistically significant (P=0.080), the acute group was able to complete an additional 59 seconds of the exercise stress test.

### *Heart rate and blood pressure response to exercise*

Heart rate increased significantly (P<0.001) from baseline (93±13 bpm) to the end of stage one (119±17 bpm), stage two (136±18 bpm) and VO<sub>2</sub>max (155±18 bpm). There

was no time by group interaction ( $P=0.378$ ) between acute and chronic groups during the test with acute and chronic groups increasing heart rate by  $76\pm 17$  bpm and  $73\pm 12$  bpm, respectively. There were also no significant difference observed between groups for heart rate recovery after 3 minutes of low intensity active recovery with values of  $46\pm 13$  bpm and  $43\pm 19$  bpm for the acute and chronic groups, respectively.

Systolic blood pressure increased significantly ( $P<0.001$ ) from baseline ( $145\pm 18$  mmHg) to the end of stage one ( $188\pm 28$  mmHg) and stage two ( $205\pm 28$  mmHg). There was no time by group interaction ( $P=0.941$ ) between acute and chronic groups during the test with acute and chronic groups increasing systolic blood pressure by  $62\pm 24$  mmHg and  $63\pm 27$  mmHg, respectively. Combined diastolic blood pressure did not increase significantly ( $p=0.857$ ) from baseline during the graded exercise test nor did mean arterial pressure ( $p=0.344$ ). Further, there was no time by group interaction ( $p=0.492$ ) between acute and chronic groups for either diastolic blood pressure or mean arterial pressure during the test.

**Table 3.** Maximal Exercise Testing Data

Variable	All Participants n=112	Acute ADT Mean $\pm$ SD n=60	Chronic ADT Mean $\pm$ SD n=52	Mean Difference Between Groups (95% CI)	P Value
<b>Resting Data</b>					
Heart Rate	83 $\pm$ 13	82 $\pm$ 11	84 $\pm$ 16	-2 (-8, 3)	0.819
SBP (mmHg)	145 $\pm$ 18	144 $\pm$ 19	146 $\pm$ 16	-2 (-9, 5)	0.609
DBP (mmHg)	87 $\pm$ 10	86 $\pm$ 10	85 $\pm$ 11	1 (-3, 6)	0.547
MAP (mmHg)	106 $\pm$ 11	105 $\pm$ 11	105 $\pm$ 12	0 (-5, 5)	0.940
<b>Submaximal Data</b>					
<i>Stage 1</i>					
Heart Rate	119 $\pm$ 17	118 $\pm$ 17	121 $\pm$ 16	-3 (-11, 3)	0.873
SBP (mmHg)	188 $\pm$ 28	188 $\pm$ 28	188 $\pm$ 30	0 (12,12)	0.991
DBP (mmHg)	87 $\pm$ 11	86 $\pm$ 11	86 $\pm$ 14	0 (-5, 5)	0.974
MAP (mmHg)	120 $\pm$ 14	118 $\pm$ 22	118 $\pm$ 25	0 (-10, 10)	0.967
<i>Stage 2</i>					
Heart Rate	136 $\pm$ 18	135 $\pm$ 18	137 $\pm$ 19	2 (-11, 6)	0.869
SBP (mmHg)	205 $\pm$ 28	205 $\pm$ 29	205 $\pm$ 29	0 (14, 14)	0.999
DBP (mmHg)	89 $\pm$ 12	87 $\pm$ 11	90 $\pm$ 13	-4 (-9, 2)	0.226
MAP (mmHg)	127 $\pm$ 15	123 $\pm$ 25	128 $\pm$ 17	-5 (-15, 5)	0.302

<b>Maximal Data</b>					
Heart Rate	155 ± 18	157 ± 17	152 ± 18	5 (-2, 13)	0.158
SBP (mmHg)	208 ± 30	206 ± 30	209 ± 30	-3 (-15, 10)	0.684
DBP (mmHg)	88 ± 12	87 ± 11	90 ± 13	-3 (-8, 2)	0.214
MAP(mmHg)	128 ± 15	126 ± 14	129 ± 17	-3 (-9, 4)	0.377
RER	1.18 ± 0.09	1.17 0.09	1.19 0.07	-0.02 (-0.06, 0.01)	0.131
VO <sub>2</sub> max (ml.kg.min <sup>-1</sup> )	24.7 ± 6.0	26.1 6.0	23.2 5.8	2.9 (0.5, 5.3)	0.020
VO <sub>2</sub> max (L.min <sup>-1</sup> )	2.1 ± 0.9	2.3 1.1	1.9 0.6	0.4 (0.1, 0.7)	0.035
VO <sub>2</sub> (METS)	7.1 ± 1.7	7.5 1.7	6.6 1.6	0.8 (0.1, 1.5)	0.020
Maximal Test Duration (min)	8:06 ± 2:43	8:33 2:46	7:34 2:36	0:59 (-0:07, 2:05)	0.080
<b>Recovery Data (3min post)</b>					
Heart Rate	111 ± 17	113 ± 18	108 ± 17	5 (-4, 13)	0.303
SBP (mmHg)	178 ± 31	177 ± 31	179 ± 32	-2 (16, 12)	0.785
DBP (mmHg)	83 ± 11	81 ± 11	84 ± 14	-3 (-9, 2)	0.218
MAP(mmHg)	114 ± 16	113 ± 15	116 ± 18	-3 (-10, 4)	0.415

Note: SBP; Systolic blood pressure, DBP: Diastolic blood pressure, MAP; Mean arterial pressure, RER; respiratory exchange ratio, METS; metabolic equivalent

## DISCUSSION

This study examined the feasibility and safety of maximal treadmill exercise in prostate cancer patients undergoing ADT. This study demonstrated that 85% of the participants were able to meet the criteria established for the achievement of  $\text{VO}_2\text{max}$ . In terms of participant safety, three positive tests (3.2%) were observed while one test was postponed due to poorly controlled blood pressure. Although three positive tests were observed, further examination revealed no underlying issues that would preclude the individual from commencing an exercise program. The test postponed due to poorly controlled blood pressure was conducted at a later date without issue. This demonstrates that maximal exercise testing in this population appears to be a relatively safe and feasible assessment tool to be used for both screening and exercise prescription purposes.

In this study, ADT treated prostate cancer participants  $\text{VO}_2\text{max}$  of  $24.7 \pm 6.0$   $\text{ml.kg.min}^{-1}$  fell within the 10<sup>th</sup> – 15<sup>th</sup> percentile for age-matched (60-69y) men according to the American College of Sports Medicine Guidelines for Exercise Testing and Prescription (Thompson, Gordon, & Pescatello, 2010), however, peak blood pressure response of  $208 \pm 30 / 88 \pm 12$  mmHg closely corresponded to the age- and sex-predicted maximal mean blood pressure response of  $197 \pm 24 / 84 \pm 12$  mmHg reported by Daida, Allison, Squires, Miller, and Gau (1996) using the Bruce treadmill protocol. The maximal heart rate value of  $155 \pm 18$  bpm falls between the two most common maximal heart rate formulas of  $220 - \text{age}$  (151 bpm) (Fox, Naughton, & Haskell, 1971) and  $208 - 0.7 \times \text{age}$  (159 bpm) (Tanaka, Monahan, & Seals, 2001). This suggests that aside from the relatively low



VO<sub>2</sub>max values recorded in this study (10 -15<sup>th</sup> percentile), the cardiovascular response to exercise is similar in this cancer population to that of healthy age-matched individuals.

#### *Acute vs. chronic ADT exposure*

When comparing acute and chronically suppressed ADT participants' physiological responses to the maximal exercise test, VO<sub>2</sub>max was the only variable significantly differentiating the groups with a mean difference of 0.4 L.min<sup>-1</sup> (95% CI 0.1, 0.7). The difference in VO<sub>2</sub>max remained significant even when reporting relative to body mass with a mean difference of 2.9 ml.kg.min<sup>-1</sup> (95% CI 0.5, 5.3). It is not known why these differences occurred between the two groups. One possible reason may be due to the reduction of physical activity levels after cancer diagnosis. While not measured in the present study, physical activity has been shown to decline from pre-diagnosis levels in cancer patients (Courneya & Friedenreich, 2007; Irwin, et al., 2003) and could result in a reduction of cardiac output and oxidative capacity (Jones, Eves, Haykowsky, Freedland, & Mackey, 2009; Steins Bisschop, et al., 2012). Both heart rate and blood pressure responded similarly pre, during and post-test regardless of the duration of ADT exposure, as did heart rate recovery. With regard to the ECG responses, all three positive tests were in the acute ADT exposure group, however, due to the small number of positive tests no conclusion can be drawn as to the likelihood of a positive test being related to duration of ADT exposure.

In a recent review, Steins Bisschop, et al. (2012) examined the safety and feasibility of cardiopulmonary exercise testing in cancer patients which included one prostate cancer

study. Twenty studies describing 1158 patients were deemed to meet the review eligibility criteria and of the twenty studies only eleven reported whether adverse events occurred. Of the eleven studies it was reported that adverse events only occurred in 1% of all tests, however the low incidence may be due to the fact that only 55% of the studies reviewed utilised ECG monitoring procedures. The relatively low rate of positive tests in the current study is also similar to previous work in clinical non-cancer populations (ATS/ACCP, 2003). In an extensive review conducted by Fletcher, et al. (1995) the risk of death and life threatening complications during maximal exercise testing was reported to be 0.5 per 100,000 tests in healthy individuals while in patients with cardiovascular disease this rate rises to 2-5 per 100,000 tests. As a result of these findings it appears that the risk of an adverse event in maximal exercise testing appears to be dependent upon the extent of underlying disease (Jones, et al., 2007a).

Given ADT has been associated with an increased risk of cardiovascular disease (Keating, et al., 2009; Levine, et al., 2010; Saigal, et al., 2007) it is recommended that prostate cancer patients undergo a thorough screening process prior to commencing an exercise intervention. Further, maximal exercise testing with gas exchange provides an objective measure of maximal aerobic capacity which can form the basis of aerobic exercise prescription and accurately assess the effectiveness of the exercise intervention. Given the relatively low number of positive tests and subsequent clearance of any serious cardiac complications in this study, this early evidence suggests that risk of adverse events is relatively low in this population and certainly no higher than age-matched apparently healthy individuals.

As the priority is to get more men with prostate cancer to exercise and not to create barriers to participation as a result of expensive equipment and additional staffing requirements, an exercise stress test is strongly recommended but should not be a requirement prior to commencing an exercise program.

Whilst the findings of this study are promising, several limitations need to be considered when interpreting the results of this study. The sample size of this study is relatively low making it difficult to detect group differences in acute and chronic ADT responses. Selection bias does exist in this study due to the nature of recruitment. All participants who underwent the maximal exercise test were recruited for the purposes of participating in a randomised controlled trial investigating the effects of an exercise intervention on reducing treatment-related side effects in men receiving therapy for prostate cancer (Newton, et al., 2009). As such the exclusion criteria applied to the intervention study was required to be met in order to complete the maximal exercise test. The small amount of positive tests observed, although promising from a safety aspect, does make it difficult to detect group differences. Larger sample size studies are required to definitively determine if ECG monitoring is a necessary part of screening prior to participating in exercise in this population.

### *Conclusion*

Maximal treadmill exercise testing in prostate cancer patients undergoing ADT was demonstrated to be feasible and safe with 85% of participants able to achieve the criteria established for achievement of VO<sub>2</sub>max and only 3.2% of participants recording a positive

test. ADT treated prostate cancer patients responded similarly to a maximal graded exercise test regardless of ADT time exposure. This study provides preliminary evidence to suggest a relatively low risk of adverse events exists when ADT treated prostate cancer patients undergo maximal exercise. Whilst an exercise stress test provides a valuable screening tool and is useful for exercise prescription purposes, it should not create an additional barrier to participation in an exercise program.

## **CHAPTER 4**

**Cardiovascular capacity, resting metabolic rate, vascular function,  
body composition and physical function in men undergoing acute  
and chronic androgen deprivation: a cross-sectional investigation**

## **INTRODUCTION**

Androgen deprivation therapy (ADT) has become a widely used treatment for prostate cancer (Heidenreich, et al., 2011). Previously, ADT was reserved for patients with bone metastases (advanced stages), however, since the early 1990's ADT has become more prevalent in locally advanced prostate cancer with improved disease free and overall survival rates reported (Bolla, et al., 2002; Shahinian, Kuo, Freeman, Orihuela, & Goodwin, 2005a). Although ADT has been highly successful in terms of improving prostate cancer survival rate, there are an increasing number of studies reporting associations between ADT and treatment related toxicities, such as reduced bone and lean mass, loss of muscle strength, negative changes in lipid profiles, and increased risk of cardiovascular disease (CVD) as well as numerous metabolic complications all of which can act to compromise physical function and quality of life (Basaria, et al., 2006; Galvao, et al., 2008b; Greenspan, et al., 2005; Shahinian, et al., 2006; Sharifi, et al., 2005a; Smith, et al., 2002b). Given the successful outcomes of this treatment, ADT is often commenced in men with early stage prostate cancer (Chodak, 1998) with treatment at times extended over several years (Michaelson, et al., 2008).

Treatment time can affect the likelihood and severity of certain treatment-related toxicities. For example, early work by Smith, et al. (2001) reported that increased arterial stiffness and adverse body compositional changes were associated with increasing insulin concentrations after only 6 months of ADT treatment which suggested a reduced insulin sensitivity. In terms of metabolic adaptations, Dockery, et al. (2003) reported an increase in serum insulin levels after only 3 months of ADT exposure. Alibhai et al. (2010) recently

investigated physical function and quality of life changes in men undergoing ADT at various time points. The authors reported declines in physical function, grip strength and self-reported physical function when compared with controls; secondary findings indicated ADT users had worsening role physical function, bodily pain and vitality. The key finding of this study was that these reductions in physical function and quality of life were apparent within the first 3 months of ADT initiation.

Basaria et al., (2006) have investigated the metabolic implications of long-term ADT and found men receiving >12 months ADT developed insulin resistance and hyperglycaemia, independent of age and BMI. Long term ADT has also been associated with frank diabetes and metabolic syndrome (Basaria, 2008) whilst Saigal and colleagues (2007) found 24% of men undergoing ADT experienced a cardiovascular event within 1-4 years of starting treatment versus 18% in a matched group of men not receiving ADT.

The current study was initiated to determine if risk factors for CVD are associated with subsequent cycles of therapy providing further support for lifestyle interventions to be part of the treatment plan for men undergoing ADT. In addition to CVD risk factors, muscle function and physical performance measures were determined given the impact of ADT on age-related loss of muscle strength and function and the paucity of research in this area. Therefore, the aim of this cross-sectional study was to investigate if therapy time exposure is associated with additional risk factors for CVD, metabolic treatment related-toxicities and physical function by comparing acute versus chronic ADT-treated patients.

## **METHODS**

### *Participants*

Subjects were recruited by invitation of their attending specialist physician. One hundred and seven men undergoing treatment for prostate cancer involving ADT with no formal regular exercise training (undertaking structured aerobic or resistance training less than two times per week) within the previous 3 months were recruited for this study. All participants had been hypogonadal for a period of at least 2 months prior to testing. Exclusion criteria included the presence of an acute illness or any musculoskeletal, cardiovascular or neurological disorder that could inhibit or put them at risk from exercising. As this cohort were also recruited for the purposes of partaking in an exercise intervention (Chapter 5), the participants were informed that they were required to be able to walk 400 m and to undertake upper- and lower-body exercises. All participants obtained medical clearance from their general practitioner and completed a detailed health history questionnaire. This study protocol was approved by the University Human Research Ethics Committee and all participants signed informed consent documentation prior to any data collection.

### *Protocol*

Participants were stratified into two groups: 1) patients receiving ADT <3 months (acute ADT) or 2) patients receiving ADT ≥3 months (chronic ADT), based upon recent findings of Alibhai, et al. (2010) and Smith, et al. (2006). Alibhai, et al. (2010) indirectly assessed cardiorespiratory endurance and upper extremity strength and reported these



outcomes were negatively affected within 3 months of starting ADT whilst Smith, et al. (2006) have previously investigated insulin sensitivity during ADT and have reported that 3 months of treatment significantly increased fat mass and decreased insulin sensitivity. Given that inclusion criteria required participants to be hypogonadal for a period of 2 months prior to the commencement of testing, the acute group were tested within 8-12 weeks of initiating androgen deprivation therapy. Subjects performed a familiarisation session to reduce any learning effect gained throughout baseline testing. The battery of tests were completed over a 2-day period and included cardiorespiratory capacity, body composition, blood pressure and arterial stiffness, blood collection, muscle strength and endurance, and physical function.

#### *Cardiorespiratory Capacity:*

Participants performed a standardised progressive maximal walking test (Bruce Protocol) on a motorized treadmill supervised by a physician. During this test, the subject's expired gases were collected (Parvo Metabolic Measuring System, Sandy, UT) to measure their maximal oxygen uptake ( $\dot{V}O_{2max}$ ).  $\dot{V}O_{2max}$  was determined to be the point at which the highest  $\dot{V}O_2$  value was recorded over an averaged 30s period. All subjects were encouraged to achieve maximal exertion. A plateau in oxygen consumption was used as qualification for achieving  $VO_{2max}$ , in the absence of a plateau, a secondary criteria was a Respiratory Exchange Ratio (RER)  $\geq 1.1$ . If the subject was unable to achieve plateau or an RER value  $>1.1$  their data were excluded from the analysis. Although not measured in this laboratory the coefficient of variation for repeated maximal exercise tests is

approximately 4% (Howley, et al., 1995).  $\dot{V}O_{2\max}$  is presented as an absolute value and relative to body mass as well as metabolic equivalent of task (METs). The average time of the test is also reported.

The electrocardiogram (ECG) was recorded using a 12-lead monitoring system (CardioDirect 12S, Irvine, CA) and blood pressure was measured during the last minute of each 3-minute stage via manual auscultatory technique. The coefficient of variation for the measurement of systolic and diastolic blood pressure is 5.7% and 5.3%, respectively (Marshall, 2004).

#### *Body Composition:*

Body weight and height were measured using standard anthropometric measures. Body weight was measured to the nearest 0.1kg using a digital scale (AND TB: 200), whilst height was measured to the nearest millimetre using a wall mounted stadiometer (SECA 700, Brooklyn, NY). Body mass index (BMI,  $\text{kg/m}^2$ ) was calculated as body mass (kg) divided by height (m) squared. Whole body as well as regional fat and lean tissue mass was assessed by dual energy X-ray absorptiometry (DEXA, Hologic Discovery A, Waltham, MA). Measurements of whole body, upper limb, lower limb, and trunk lean and fat mass and percentage body fat were derived from the whole body scan. Appendicular skeletal muscle (ASM) was calculated by combining upper extremity lean mass and lower extremity lean mass. In our laboratory, the coefficient of variation involving duplicate scans with repositioning are less than 1% for body composition variables (Galvao, et al., 2006). Circumference measures were taken at standardised sites (Thompson, et al., 2010)

including the waist, hip, arm and calf and reported to the nearest 0.1 mm.

### *Resting Metabolic Rate*

On the same day following the DEXA scan, resting metabolic rate (RMR) was measured via respiratory gas analysis over a period of 20 minutes with a 5-minute period used for analysis. The period selected was based upon the analysis of oxygen consumption with a coefficient of variation of <10%. Using standardised procedures, the subject was completely rested in a darkened room for 10 minutes prior to the mouthpiece being fitted for the 20 minute collection period (Compher, Frankenfield, Keim, & Roth-Yousey, 2006). Resting metabolic rate was presented as kcals per 24hrs as well as kcals/ 24hrs relative to total body mass (kcals/kg/24hr) and total lean mass (kcals/lean kg/24hrs). A previous study investigating the intra-individual variations in resting metabolic rates have reported a coefficient of variation of 2.9% (Soares & Shetty, 1986).

### *Blood Pressure and Arterial Stiffness:*

A validated oscillometric device (HEM-705CP, Omron Corporation, Japan) was used to record brachial blood pressure at the dominant arm in triplicate (O'Brien, Mee, Atkins, & Thomas, 1996). This is presented as peripheral diastolic blood pressure, peripheral systolic blood pressure and peripheral mean arterial pressure. Central (ascending aortic) blood pressure and indices of arterial stiffness were determined by pulse wave analysis using the SphygmoCor version 6.1 software (AtCor Medical, Sydney, Australia). This is presented as central diastolic blood pressure, central systolic blood pressure and central mean arterial pressure. Radial artery pressure waveforms were captured at the right arm

by applanation tonometry using a high fidelity micromanometer (SPC-301, Millar Instruments, Houston, Texas, USA). A generalised transfer function was applied to the radial artery waveform in order to obtain the central pressure waveform at the ascending aorta. This method has been validated against invasive techniques for determination of central blood pressure (Karamanoglu, O'Rourke, Avolio, & Kelly, 1993; Pauca, O'Rourke, & Kon, 2001) whilst the augmentation index (AIx) is a marker of systemic arterial stiffness and presented as the ratio of augmentation to central pulse pressure, expressed as a percentage (Safar & London, 2000; Williams, et al., 2006). Variability has been previously reported as 0.3 mmHg for central systolic pressure and 1.5% for augmentation index.

Carotid to radial pulse wave velocity was measured by collecting arterial pressure waves at both the carotid and radial locations. The surface distance between the two locations was measured and the pressure wave transit time was calculated using a foot of the wave to foot of the wave method. The reported coefficient of variation for forearm (radial) pulse wave velocity is 2.9% whilst the brachial pulse wave velocity coefficient of variation is 7.7% (Nottin, et al., 2006).

Participants were instructed to undertake no strenuous physical activity for 24 hrs and fast for 12 hours prior to the test. Participants were completely rested for 30 minutes prior to the test (RMR testing was conducted immediately prior). Participants were also asked to maintain similar dietary patterns in the 2 days prior and any medications were recorded.

### *Metabolic Profile:*

Venous blood samples (2 x 8.5 ml) were drawn from the antecubital vein to assess markers of cardiovascular disease and diabetes. Full blood analysed for haemoglobin A1C whilst the remaining blood was separated and the serum and plasma analysed for testosterone, insulin, PSA, triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, and glucose. Participants were asked to maintain similar dietary patterns prior to the blood tests. All blood variables were analysed commercially by accredited Australian National Association of Testing Authorities laboratories (Pathwest Laboratory Medicine, WA).

### *Muscle Strength and Endurance:*

As mentioned above, subjects were familiarized to all assessment procedures during their familiarisation session. Dynamic concentric muscle strength for the chest press, seated row, leg press and leg extension exercises was measured using the one-repetition maximum (1-RM) method as previously used with a similar population (Galvao, et al., 2006). The coefficient of variation in our laboratory for 1RM measures performed approximately 1 week apart is 2.2-7.5% (Peiffer, et al., 2010). Muscular endurance was assessed using the maximal number of repetitions performed at 70% of 1-RM for the chest press and leg press exercises representing upper and lower body muscle endurance, respectively (Galvao & Taaffe, 2005). Reported coefficients of variation for the chest and leg press muscular endurance are 6.3% and 6.8%, respectively (Galvao, et al., 2006; Peiffer, et al., 2010).

### *Physical Function:*

A battery of tests were used to assess functional performance and are similar to those used previously with a similar population (Galvao, et al., 2006). The tests were performed in triplicate (except for the 400-m walk which was performed once) with sufficient recovery time between trials. The best performance on each test was used in the analyses.

*Repeated chair rise* - participants were seated with their arms folded across their chest and rose to a standing position without using their hands for support and then returned to a seated position as fast as possible, with the outcome being the time taken to perform this task 5 times. Timing was started from the command 'go' and the total time required to complete all 5 cycles was recorded with a handheld stopwatch. The coefficient of variation for the repeated chair rise in our laboratory is 5.6%-6.7% (Galvao, et al., 2006).

*Stair climb* - participants were instructed to climb a flight of stairs (11 steps at 16 cm height per step) as fast as possible, without using the handrail. Time to complete the stair climb was recorded using a handheld stopwatch with the tester standing at the top of the flight of stairs. The coefficient of variation in our laboratory for the stair climb is 4.8% (Galvao, et al., 2006).

*6-meter backward tandem walk* - as a test of dynamic balance, participants covered a 6 meter distance walking backwards with one foot being placed directly behind the other so the heel of one foot and the toes of the other foot were touching. Time to complete the task was determined using electronic timing gates positioned at 0 and 6

meters (Kinematic Measurement System, Fitness Technology, SA Australia). The coefficient of variation for the 6-meter backwards walk test is 9.4% (Galvao, et al., 2006).

*6-meter usual and fast walk-* Participants were assessed for their usual walking pace explained to them as the pace they would usually walk whilst carrying out everyday activities. The fast paced walk required participants to cover the 6 meters at their maximal walking pace. Times were recorded using the same method as the 6-meter backwards tandem walk (Kinematic Measurement System, Fitness Technology, SA Australia). The coefficients of variation in our laboratory for the usual and fast walk are 5.6% and 6.7%, respectively (Peiffer, et al., 2010).

*400 meter walk –* Participants were required to walk 400 meters, consisting of 10 laps out and back over a 20 meter straight path at a pace as fast as they could maintain for the distance of the test. Time taken to complete the test was recorded via a handheld stopwatch, reported to the nearest second. The coefficient of variation for the 400 meter walk test is 2.5% (Galvao, et al., 2006).

### *Statistical Analysis:*

Data analyses were performed using the Statistical Package for Social Sciences version 18.0 software (PASW, Chicago, IL). Normality of the data were assessed using the Kolomogorov-Smirnov test. The analyses included standard descriptive statistics and Student's independent sample t tests. A chi square test was used to determine differences in metabolic syndrome variables between groups. All tests were two-tailed and an alpha level of 0.05 was applied as the criterion for statistical significance. Results are reported as the mean  $\pm$  standard deviation.



## RESULTS

### *Subject Characteristics*

One hundred and seven participants were tested for the purposes of this study. Combined participant characteristics are presented in Table 4. Subject characteristics separated for the acute and chronic ADT exposure groups are presented in Table 5.

**Table 4.** Subject characteristics including age, height and body composition variables (n=107).

Variable	Mean $\pm$ SD	Range
Age (years)	68.6 $\pm$ 8.8	42.0 – 89.0
Height (cm)	172.4 $\pm$ 6.3	156.0 – 186.0
Body Mass (kg)	84.0 $\pm$ 13.7	59.0 – 146.2
Body Mass Index (kg.m <sup>2</sup> )	28.5 $\pm$ 4.15	20.2 – 43.2
Waist Circumference (cm)	99.5 $\pm$ 12.5	64.0 – 151.0
Waist to Hip Ratio	1.00 $\pm$ 0.1	0.62 – 1.25

There were no significant differences in any of the subject characteristics between the acute and chronic ADT exposure groups.

**Table 5.** Subject characteristics including age, height and body composition variables for the acute and chronic ADT exposure groups.

Variable	Acute ADT Mean $\pm$ SD n=57	Chronic ADT Mean $\pm$ SD N=50	Mean Difference (95% CI)	P Value
Age (years)	67.6 $\pm$ 8.9	69.9 $\pm$ 9.7	-2.3 (-5.9, 1.3)	0.395
Height (cm)	172.2 $\pm$ 6.4	172.7 $\pm$ 6.3	-0.5 (-3.2, 2.1)	0.648
Body Mass (kg)	85.7 $\pm$ 13.6	83.4 $\pm$ 14.0	2.3 (-3.1, 7.8)	0.105
Body Mass Index (kg.m <sup>2</sup> )	28.9 $\pm$ 4.3	28.0 $\pm$ 3.9	0.9 (-0.7, 2.4)	0.215
Waist Circumference (cm)	99.2 $\pm$ 12.1	100.3 $\pm$ 12.9	-0.9 (-5.5, 3.9)	0.737

### *Body Composition*

Body composition variables for the two groups are provided in Table 6. No differences were observed in lean tissue mass or fat mass between the two groups.

**Table 6.** Body composition and bone mass variables for acute and chronic androgen deprivation groups

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	Mean Difference (95% CI)	P Value
<b>Lean tissue mass</b>				
<b>(kg)</b>				
Lean Mass	60.1 $\pm$ 7.5	58.0 $\pm$ 8.6	2.1 (-1.0, 5.2)	0.184
Upper Limb	6.7 $\pm$ 1.6	6.5 $\pm$ 1.3	0.2 (-0.4, 0.7)	0.484
Lower Limb	18.7 $\pm$ 2.4	18.0 $\pm$ 2.7	0.7 (-0.3, 1.6)	0.173
Trunk	30.2 $\pm$ 4.2	29.3 $\pm$ 4.8	0.9 (0.8, 2.6)	0.316
Appendicular Skeletal Muscle	25.6 $\pm$ 3.3	24.5 $\pm$ 3.9	1.1 (-0.3, 2.5)	0.112
<b>Fat mass (kg)</b>				
Fat Mass	23.1 $\pm$ 7.3	24.6 $\pm$ 8.3	-1.5 (-4.5, 1.4)	0.307
Upper Limb	2.6 $\pm$ 0.8	2.7 $\pm$ 0.8	-0.1 (-0.4, 0.2)	0.653
Lower Limb	6.8 $\pm$ 2.3	7.7 $\pm$ 2.3	-0.9 (1.7, 0.3)	0.058
Trunk	12.4 $\pm$ 4.5	12.9 $\pm$ 5.8	-0.5 (-2.5, 1.5)	0.627
<b>Body fat %</b>	26.4 5.1	28.3 5.2	-1.9 (-4.0, 0.1)	0.053

No differences were observed in any of the girth values measured between the acute and chronic groups (Table 7.).

**Table 7.** Girth values for selected regions for acute and chronic androgen deprivation groups

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	Mean Difference (95% CI)	P Value
Waist Circumference	99.2 $\pm$ 12.1	100.3 $\pm$ 12.9	-0.9 (-5.5, 3.9)	0.737
Hip Circumference	99.8 $\pm$ 7.6	100.4 $\pm$ 7.2	-0.5 (-3.4, 2.3)	0.702
Arm Circumference	29.9 $\pm$ 3.2	29.6 $\pm$ 3.0	0.3 (-0.9, 1.4)	0.659
Calf Circumference	36.5 $\pm$ 2.8	36.1 $\pm$ 2.7	0.4 (-0.7, 1.4)	0.508

### *Cardiorespiratory Capacity*

There was a significant difference in cardiorespiratory fitness between the two groups (Table 8). Maximal oxygen consumption was significantly higher in the acute group when presented in absolute terms ( $\text{L}\cdot\text{min}^{-1}$ ) ( $p=0.035$ ) and relative terms ( $\text{ml}\cdot\text{kg}\cdot\text{min}^{-1}$ ) ( $p=0.020$ ). Corresponding metabolic equivalents were also significantly higher in the acute group ( $p=0.02$ ). Whilst test duration was not statistically significant, the acute group exercised for an additional 54 seconds.

**Table 8.** Maximal exercise capacity values as determined from the exercise stress test for acute and chronic androgen deprivation groups

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	Mean Difference (95% CI)	P Value
$\text{VO}_2\text{max}$ ( $\text{L}\cdot\text{min}^{-1}$ )*	$2.3 \pm 1.0$	$1.9 \pm 0.6$	0.4 (0.1, 0.7)	0.035
$\text{VO}_2\text{max}$ ( $\text{ml}\cdot\text{kg}\cdot\text{min}^{-1}$ )*	$26.1 \pm 6.0$	$23.2 \pm 5.8$	2.9 (0.5, 5.3)	0.020
$\text{VO}_2$ (METS)*	$7.5 \pm 1.7$	$6.6 \pm 1.6$	0.9 (0.1, 1.5)	0.020
Test duration (mins)	$8.5 \pm 2.8$	$7.6 \pm 2.6$	0.9 (-0.1, 2.1)	0.080

### *Resting Metabolic Rate*

There was a significant difference observed in resting metabolic rate between the two groups with the acute group recording a significantly higher ( $p=0.005$ ) resting metabolic rate and relative to body mass resting metabolic rate ( $p=0.017$ ) then the chronic group (Table 9). Whilst not statistically significant ( $p=0.079$ ) resting metabolic rate relative to lean body mass was 1.3 kcal/lean kg/24hr higher in the acute group.

**Table 9.** Resting metabolic rate for acute and chronic androgen deprivation groups.

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	Mean Difference (95% CI)	P Value
Resting Metabolic Rate (kcal/24hr)	1795 $\pm$ 256	1647 $\pm$ 236	147 (46, 249)	0.005
Relative Total Body Mass Resting Metabolic Rate (kcal/kg/24hr)	21.5 $\pm$ 3.0	20.0 $\pm$ 2.6	1.5 (0.3, 2.7)	0.017
Relative Lean Body Mass Resting Metabolic Rate (kcal/lean kg/24hr)	30.5 $\pm$ 3.2	29.2 $\pm$ 4.1	1.3 (-0.2, 2.9)	0.079

### Central Blood Pressure

No differences were observed between groups in any of the central or peripheral blood pressure variables. Further, there were no differences observed between groups in central augmentation pressure (Table 10).

**Table 10.** Hemodynamic and pulse wave analysis parameters for acute and chronic androgen deprivation groups

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	Mean Difference (95% CI)	P Value
Peripheral SBP (mmHg)	150.9 $\pm$ 19.9	149.0 $\pm$ 19.4	1.9 (-5.8, 9.6)	0.624
Peripheral DBP (mmHg)	85.6 $\pm$ 12.1	84.5 $\pm$ 10.4	1.1 (-3.4, 5.6)	0.626
Peripheral MAP (mmHg)	108.4 $\pm$ 15.0	107.2 $\pm$ 12.8	1.2 (-4.3, 6.7)	0.669
Central SBP (mmHg)	139.1 $\pm$ 21.1	138.7 $\pm$ 20.2	0.4 (-7.7, 8.5)	0.922
Central DBP (mmHg)	86.8 $\pm$ 12.3	85.5 $\pm$ 10.6	1.3 (-3.2, 5.8)	0.571
Central MAP (mmHg)	108.9 $\pm$ 16.1	107.2 $\pm$ 12.8	1.7 (-4.1, 7.5)	0.557
Peripheral Augmentation Index (%)	83.5 $\pm$ 13.0	86.5 $\pm$ 13.9	-3.0 (-8.3, 2.3)	0.261
Central Augmentation Pressure (mmHg)	15.4 $\pm$ 8.2	16.7 $\pm$ 9.6	-1.3 (4.8, 2.1)	0.445

Augmentation Load	14.3 ± 5.0	14.6 ± 4.9	-0.3 (-2.3, 1.6)	0.732
Central	140.4 ±	144.4 ± 19.6	-4.0 (-11.3, 3.3)	0.281
Augmentation Index	17.8			
Pulse Wave Velocity	10.0 ± 1.4	10.0 ± 1.8	0.0 (-0.6, 0.7)	0.983



### *Muscular Strength & Endurance*

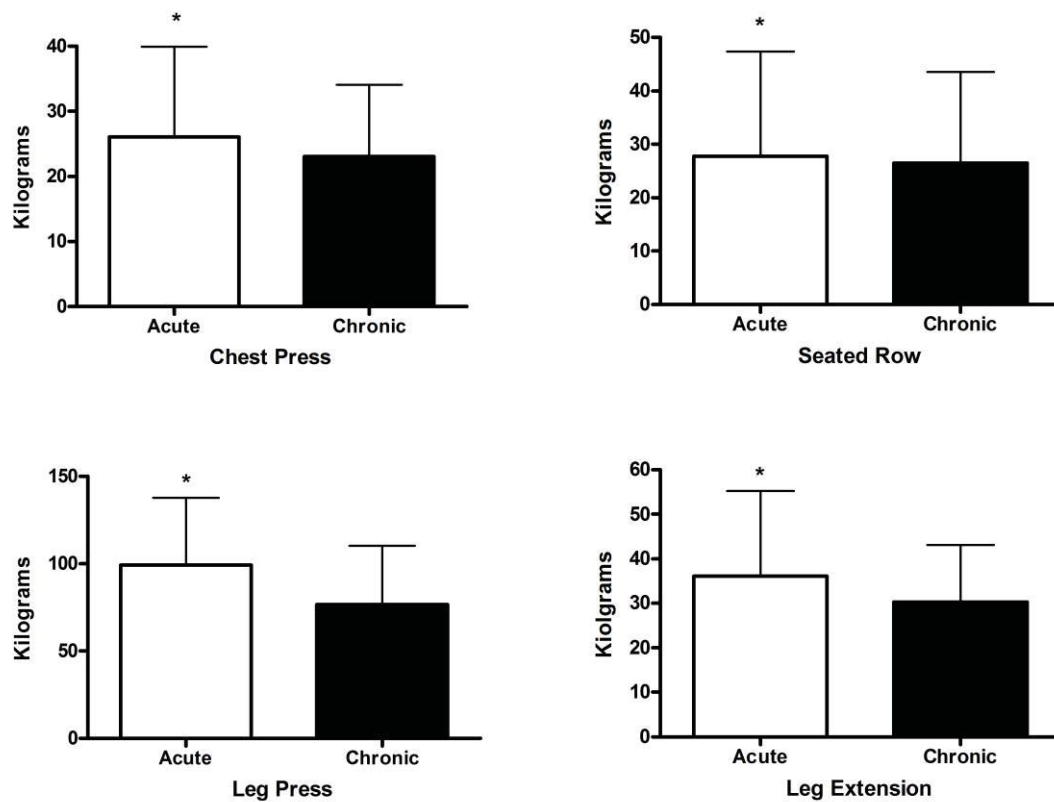
The chest press ( $p=0.013$ ), seated row ( $p=0.022$ ), leg press ( $p=0.007$ ) and leg extension ( $p<0.001$ ) were all significantly higher in the acute group compared to the chronic group (Table 11, Figure 1). There were no significant differences observed for upper or lower body muscular endurance.

**Table 11.** Maximal strength and endurance values for acute and chronic androgen deprivation groups

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	Mean Difference (95% CI)	P Value
Chest Press 1RM (kg)*	39.9 $\pm$ 12.2	34.1 $\pm$ 12.0	5.9 (1.3, 10.5)	0.013
Seated Row 1RM (kg)*	47.4 $\pm$ 8.1	43.5 $\pm$ 9.4	3.9 (0.6, 7.2)	0.022
Leg Press 1RM (kg)*	137.8 $\pm$ 60.6	110.3 $\pm$ 42.7	27.5 (7.8, 47.3)	0.007
Leg Extension (kg)*	55.3 $\pm$ 16.9	43.1 $\pm$ 17.4	12.2 (5.6, 18.7)	<0.001
Chest Press 70% 1RM (reps)	10.0 $\pm$ 3.0	9.3 $\pm$ 3.7	0.7 (-7.4, 2.2)	0.326
Leg Press 70%1RM (reps)	16.5 $\pm$ 7.6	16.0 $\pm$ 7.4	0.5 (-3.3, 4.3)	0.794

\*Note: 1RM = one repetition maximum; reps = number of repetitions

**Figure 1.** Maximal strength and endurance values for acute and chronic androgen deprivation groups



\* Denotes significant different between acute vs. chronic ADT exposure,  $p < 0.05$ .

## Physical Function

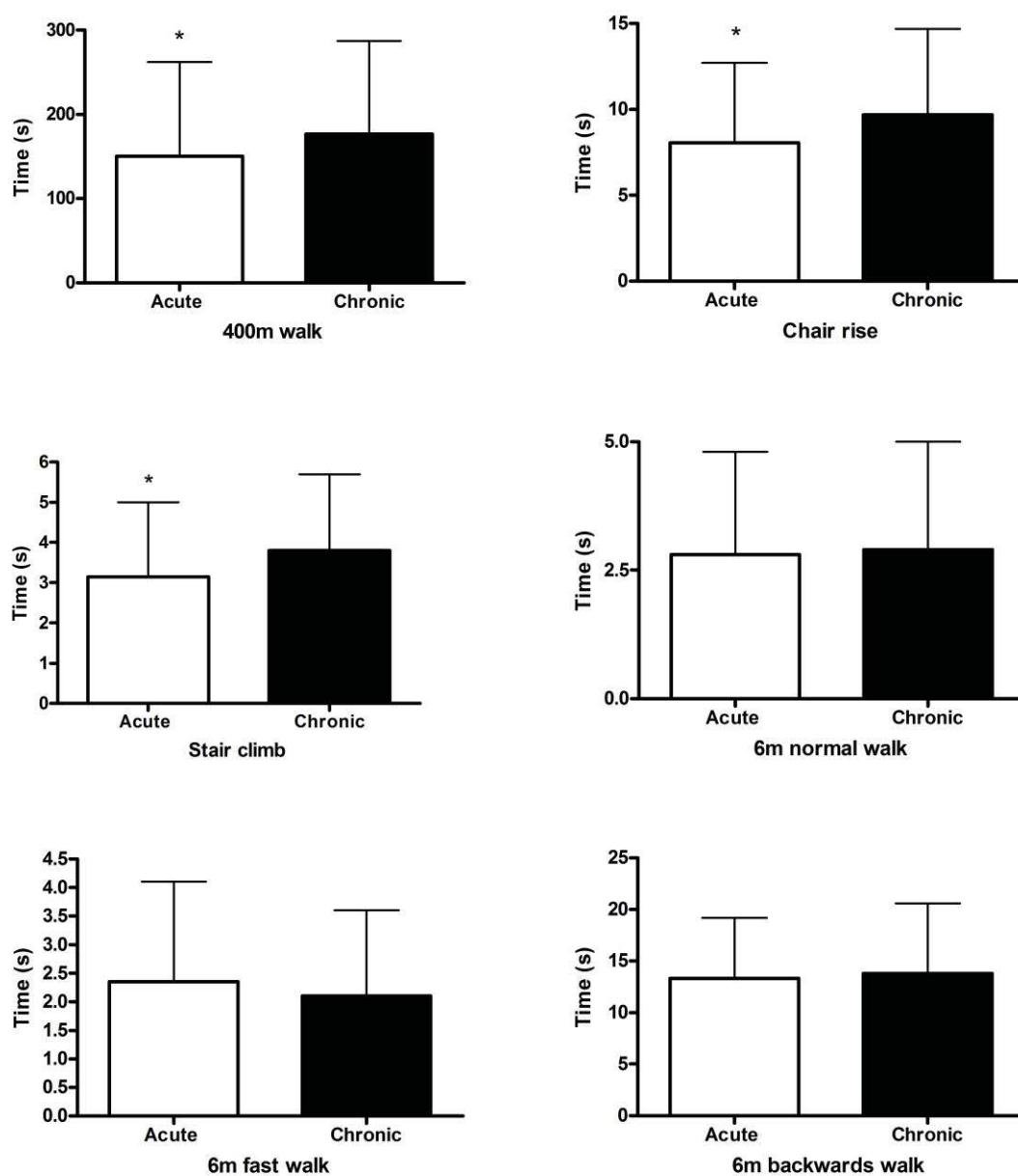
The acute group performed the 400m walk significantly ( $p=0.023$ ) faster than the chronic group (Table 12, Figure 2). The acute group also performed the chair rise ( $p=0.014$ ) and stair climb ( $p=0.016$ ) significantly faster than the chronic group. No significant differences were observed in any of the 6m walk times.

**Table 12.** Physical Function values for acute and chronic androgen deprivation groups

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	Mean Difference (95% CI)	P Value
400m walk (s)*	261.9 $\pm$ 38.3	286.8 $\pm$ 66.2	-24.9 (-46.3, -3.5)	0.023
Chair rise (s)*	12.7 $\pm$ 3.4	14.7 $\pm$ 4.7	-2.0 (-3.6, -0.4)	0.014
Stair climb (s)*	5.0 $\pm$ 1.3	5.7 $\pm$ 1.9	-0.7 (-1.4, -0.1)	0.016
6m normal pace walk	4.8 $\pm$ 0.8	5.0 $\pm$ 0.8	-0.2 (0.6, 0.1)	0.121
6m fast pace walk	4.1 $\pm$ 0.6	3.6 $\pm$ 0.6	0.5 (-0.8, 1.8)	0.481
6m backwards walk	19.2 $\pm$ 7.4	20.6 $\pm$ 7.0	-1.4 (-4.2, 1.4)	0.316

\*Denotes significant difference ( $p<0.05$ )

**Figure 2.** Physical Function values for acute and chronic androgen deprivation groups



\* Denotes significant difference between acute vs. chronic ADT exposure,  $p < 0.05$ .

### *Metabolic Profile*

No differences were observed between the acute and chronic ADT groups in any of the blood markers analysed (Table 13).

**Table 13.** Blood markers for acute and chronic androgen deprivation groups

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	Mean Difference (95% CI)	P Value
HbA1C (%)	6.4 $\pm$ 3.7	6.1 $\pm$ 1.0	0.3 (-0.8, 1.3)	0.638
Testosterone (pg.mL <sup>-1</sup> )	1.3 $\pm$ 1.5	1.5 $\pm$ 3.4	-0.2 (-1.2, 0.8)	0.651
Prostate Specific Antigen (ng.mL <sup>-1</sup> )	1.2 $\pm$ 1.7	1.4 $\pm$ 2.6	-0.2 (-1.1, 0.7)	0.659
Insulin (mU/L)	11.2 $\pm$ 6.7	9.2 $\pm$ 4.3	2.0 (-0.3, 4.2)	0.085
Triglycerides (mmol/L)	1.3 $\pm$ 0.6	1.4 $\pm$ 0.7	-0.1 (-0.3, 0.1)	0.393
LDL cholesterol (mmol/L)	2.8 $\pm$ 0.9	2.9 $\pm$ 1.0	-0.1 (-0.5, 0.3)	0.575
HDL cholesterol (mmol/L)	1.3 $\pm$ 0.4	1.4 $\pm$ 0.4	-0.1 (-0.3, 0.1)	0.269
Total cholesterol (mmol/L)	4.7 $\pm$ 1.1	4.9 $\pm$ 1.0	-0.2 (-0.6, 0.2)	0.287
Glucose (mmol/L)	5.5 $\pm$ 1.1	5.9 $\pm$ 1.9	-0.4, (-1.0, 0.2)	0.216
C Reactive Protein (mg/L)	2.9 $\pm$ 3.3	2.5 $\pm$ 2.0	0.4 (-0.7, 1.5)	0.469

### *Metabolic Syndrome Variables*

According to National Cholesterol Education Program Adult Treatment Panel III, 20.3% of the acute group and 13.5% of the chronic group were classified as having metabolic syndrome (Table 14). There were no differences observed between groups for any of the metabolic syndrome criteria.

**Table 14.** Percentage of acute and chronic androgen deprivation groups that met the individual metabolic syndrome criteria and overall metabolic syndrome criteria.

Variable	Acute ADT Mean $\pm$ SD	Chronic ADT Mean $\pm$ SD	P value
Fasting plasma glucose	16.9%	17.3%	0.998
Serum triglyceride	20%	21.3%	0.874
Serum HDL	20.3%	17.3%	0.815
Waist circumference	39.0%	39.2%	0.994
Hypertension	86.4%	75%	0.093
Meeting $\leq 3/5$ criteria	20.3%	13.5%	0.337

## ***DISCUSSION***

This study examined the difference between acute (<3 months) and chronic ( $\geq 3$  months) androgen deprivation exposure with a variety of cardiovascular, musculoskeletal and metabolic parameters with the aim of determining if additional therapy time exposure results in additional cardiovascular disease risk factors or metabolic treatment related toxicities. This study further sought to explore the effects of therapy time exposure on physical function. Following post screening and baseline testing participants were divided into two groups according to time on ADT. A 3-month cut-off for acute and chronic exposure was defined based upon recent work by Alibhai (2010) as well as several other studies that have attempted to explore similar outcomes (Dockery, et al., 2003; Smith, et al., 2006).

Both groups were similar in terms of age, height and body mass. Although not statistically significant, the chronic androgen deprivation group did have on average 2.1kg less lean body mass and 1.5kg more fat mass. Whilst neither of these body composition alterations were significant, it is thought that the combined effect of less lean mass and more fat mass may be a clinically meaningful difference with regard to functional performance and metabolic risk factors. In a recent review, Haseen et al. (2010) described the changes in body composition including body weight, BMI, body fat % and declines in lean muscle mass in response to ADT. Using pooled data, Haseen et al. (2010) reported relative mean changes in fat mass of 7.7% (95% CI 4.3%, 11.2%) and fat free mass of -2.8% (CI -3.6%, 2.0%) in prostate cancer patients undergoing ADT regardless of treatment time

(3-24 months). Whilst in the present study there was a trend towards greater fat mass accumulation and reduction in lean mass in the chronically suppressed group when compared to the acute group, the lack of significant differences is likely due to the negative alterations in body composition occurring earlier in treatment. Smith (2001) has reported significant reductions in lean mass after only 1 month of ADT with a follow-up study revealing 80% of the observed changes in fat and lean mass were evident at 6 months (Smith, et al., 2008). Negative body composition alterations appear to occur after only a relatively brief exposure to ADT, with longer duration treatment resulting in a greater amount of fat mass accumulation and loss of lean mass.

To date, no study has used a maximal exercise protocol to directly assess cardiorespiratory fitness in men undergoing ADT for the treatment of prostate cancer. Our findings demonstrate there are differences in cardiorespiratory capacity between short and long term androgen deprivation with the acute group exhibiting significantly higher maximal oxygen consumption values compared to the chronic group, even when expressed relative to body mass. The acute group  $VO_{2max}$  was 21% higher than the chronically exposed group, which has important implications when considering low levels of cardiorespiratory fitness have been associated with a markedly increased risk of premature death from all causes and in particular, cardiovascular disease in all populations (Laukkanen, et al., 2010). Conversely, an increase in cardiorespiratory fitness is associated with a reduced risk of cardiovascular disease (Barlow, et al., 2012). Whilst not significant, the acute group was able to complete an additional 54 seconds of exercise when compared to the chronically suppressed group, reflecting the significantly higher



VO<sub>2</sub>max values. No differences were observed in any of the blood pressure parameters between the acute and chronic groups.

Therapy time exposure does appear to influence resting energy expenditure with the acutely suppressed group reporting a significantly greater resting metabolic rate when compared to the chronically suppressed group. The majority of studies indicate that fat free mass plays a major role in the variance in resting metabolic rate amongst individuals (Cunningham, 1991; Weinsier, Schutz, & Bracco, 1992), with more recent research suggesting that both fat free mass and fat mass are significant contributors to resting metabolic rate (Johnstone, Murison, Duncan, Rance, & Speakman, 2005). Whilst no significant differences in any body composition values were reported between the acute and chronically suppressed groups, it is likely that the combined effects of the non-significant differences in lean body mass (2kg) and fat mass (1.5kg) contributed to this significant reduction in resting energy expenditure in the chronically suppressed group.

Therapy time exposure does appear to affect muscular strength with the acutely suppressed group reporting significantly higher strength values than the chronically suppressed group. This was the case for both upper (chest press and seated row) and lower (leg press and leg extension) body strength. The greater strength reported in the acutely suppressed group as accompanied by a greater level of physical function with the 400m walk, chair rise and stair climb all being performed significantly faster compared to the chronically suppressed group. Whilst Alibhai et al. (2010) have previously observed declines in physical function in this group of men, the declines generally occurred within 3

months of initiation of ADT and then remained stable. In contrast, our current findings indicate that further physical function declines are associated with longer duration ADT.

When exploring cardiovascular disease risk factors, metabolic syndrome has been widely used as a surrogate marker for cardiovascular disease. In our study, 20.3% of the acute group and 13.5% of the chronic group met the National Cholesterol Education Program Adult Treatment Panel III criteria for metabolic syndrome. These values are lower than the 55% of ADT treated prostate cancer patients previously reported by Braga-Basaria (2006a) to have metabolic syndrome but similar to non-ADT treated prostate cancer patients (22%) and control group (20%) reported in the same study (Braga-Basaria, et al., 2006a). Whilst on average, neither group met three of the necessary five criteria, increased waist circumference and hypertension did appear to be the two most common cardiovascular risk factors present in both groups, demonstrating these risk factors are present irrespective of treatment duration.

Whilst not measured in the present study, physical activity levels are known to exert large influences on aerobic fitness and functional performance. Previous research in breast cancer patients has demonstrated that physical activity levels are significantly reduced following cancer diagnosis and during treatment (Demark-Wahnefried, et al., 1997; Irwin, et al., 2003) and that these reductions in physical activity negatively alter energy balance. It is possible that in the current study physical activity levels were reduced following diagnosis and either continued to decline as treatment time progressed or the side effects associated with declining physical activity levels did not present until later in

treatment which may have contributed to the differences observed in aerobic fitness, resting metabolic rate and potentially physical function outcomes.

### *Conclusion*

In summary, we found that chronic ADT exposure ( $\geq 3$  months) was associated with reduced cardiorespiratory capacity, resting metabolic rate, muscular strength and physical function when compared to those only exposed to ADT for a relatively short amount of time ( $< 3$  months). The exact mechanisms remain unclear as to why these cardiovascular alterations and physical function variables are further declining as treatment time progresses although it is thought that physical activity levels, which were not measured in this study, may have influenced the results. Although there was a trend towards alterations in lean body mass and fat mass, the lack of significant differences seen in body composition variables may be attributed to the fact that these negative alterations were occurring after only a relatively brief exposure to ADT treatment. These findings suggest that prolonged exposure to ADT for the treatment of prostate cancer is associated with negative alterations to numerous cardiovascular and physical function outcomes. Resistance training programs should be designed to offset the potential loss of lean muscle mass and muscular strength whilst aerobic training should target preserving, or even increasing cardiorespiratory fitness given the association between aerobic fitness and cardiovascular disease risk. These interventions should remain a priority for the entirety of the expected treatment duration.

## **CHAPTER 5**

**A 6-month randomized controlled trial of exercise in prostate cancer patients receiving treatment: effects on cardiorespiratory capacity, physical function, vascular function and resting metabolic rate.**

## **INTRODUCTION**

Exercise interventions are increasingly being used in cancer survivor programs given their effectiveness in maintaining or even reversing toxicities relating to the treatment being undertaken. In the case of patients undergoing ADT for the treatment of prostate cancer a number of adverse side effects are directly attributable to the treatment, due to the lack of testosterone (Galvao, et al., 2008b). Side effects include reduced bone and lean mass, loss of muscle strength, negative change in lipid profiles, and increased risk of cardiovascular disease (CVD) as well as numerous metabolic complications (Basaria, et al., 2006; Galvao, et al., 2008b; Greenspan, et al., 2005; Shahinian, et al., 2006; Sharifi, et al., 2005a; Smith, et al., 2002b). Although exercise is being increasingly used in prostate cancer patients (Baumann, et al., 2011), very few RCT's exist that have attempted to assess the effectiveness of a prescribed exercise program aimed at targeting the negative side effects associated with ADT. Further, no long term RCT's have used a combination of resistance exercises and appropriate dosage of aerobic activity prescribed for overall health and improving aerobic fitness set down by the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) (Nelson, et al., 2007; Schmitz, et al., 2011).

The recent ACSM roundtable discussion paper on exercise guidelines for cancer survivors (Schmitz, et al., 2011) utilised evidence categories set down by the National Heart, Lung, and Blood Institute (NHLBI, 1998) to categorise the strength of previous research studies. When categorising the strength of studies reporting aerobic benefits in

prostate cancer studies, only 3 'evidence category A' (overwhelming data from randomised controlled trials) studies have used ADT only populations. Of these three studies, one was a home based intervention consisting of walking, stretching and light theraband exercises at a non-specified intensity (Culos-Reed, et al., 2009) whilst the other two studies were primarily strength oriented (Galvao, et al., 2006) or used a low level of aerobic exercise prescription (Galvao, et al., 2010). The promising aspects of the latter two studies (Galvao, et al., 2006; Galvao, et al., 2010) was that beneficial aerobic outcomes were observed despite not specifically adhering to a targeted aerobic training program. Consequently, this raises the question as to what gains can be made when specifically targeting aerobic fitness concurrently with resistance training?

Both of the primary muscle strength based studies by Galvao et al. (2006; 2010) were also categorised as evidence category A by the ACSM roundtable as was the work of Segal (Segal, et al., 2003b) who also used a primarily resistance based training program. This research provided further rationale to adopt a similar resistance training program in the present study whilst adding an aerobic component to the study design. Of the remaining outcomes assessed in the present study, the ACSM has classified body composition and physical function as category B evidence (few RCT's exist or they are small and inconsistent), suggesting randomised clinical trials are required to clarify the effects of an exercise program in this population.

The current study sought to expand the original work of Galvao and colleagues (2010) who have previously used a similar protocol to that presented, albeit over a shorter

time period (12 weeks). Despite only being exposed to a relatively brief exercise program, Galvao et al. (2010) found significant improvements in muscle mass, strength, physical function and balance in hypogonadal men when compared to the usual care group. This previous study found no improvements in aerobic capacity, although this is likely due to the relatively low dose of aerobic exercise prescribed. Given the increased incidence of cardiovascular and metabolic diseases associated with ADT, it was important in the current study to implement an intervention that focussed on attempting to improve the maximal aerobic capacity of the participants. The protective effect provided by increasing levels of maximal aerobic power has been highlighted in large population based studies (Blair, et al., 1995; Ekelund, et al., 1988; Erikssen, 1986). Therefore, the present study would be strengthened by supplementing the original aerobic training prescribed in the Galvao et al. (2010) investigation with additional aerobic training sessions. The weekly accumulated aerobic volume was prescribed to meet the 150 min/wk guideline as set down by numerous health organisations, namely the American College Sports Medicine and American Heart Association recommendation (Haskell, et al., 2007). The intervention was expanded to six months duration as opposed to the 12 weeks used by Galvao et al. (2010) to investigate what further adaptations would occur with an additional 3 months exposure to the intervention, as well as to assess the adherence to a longer, multi-centre based exercise program.

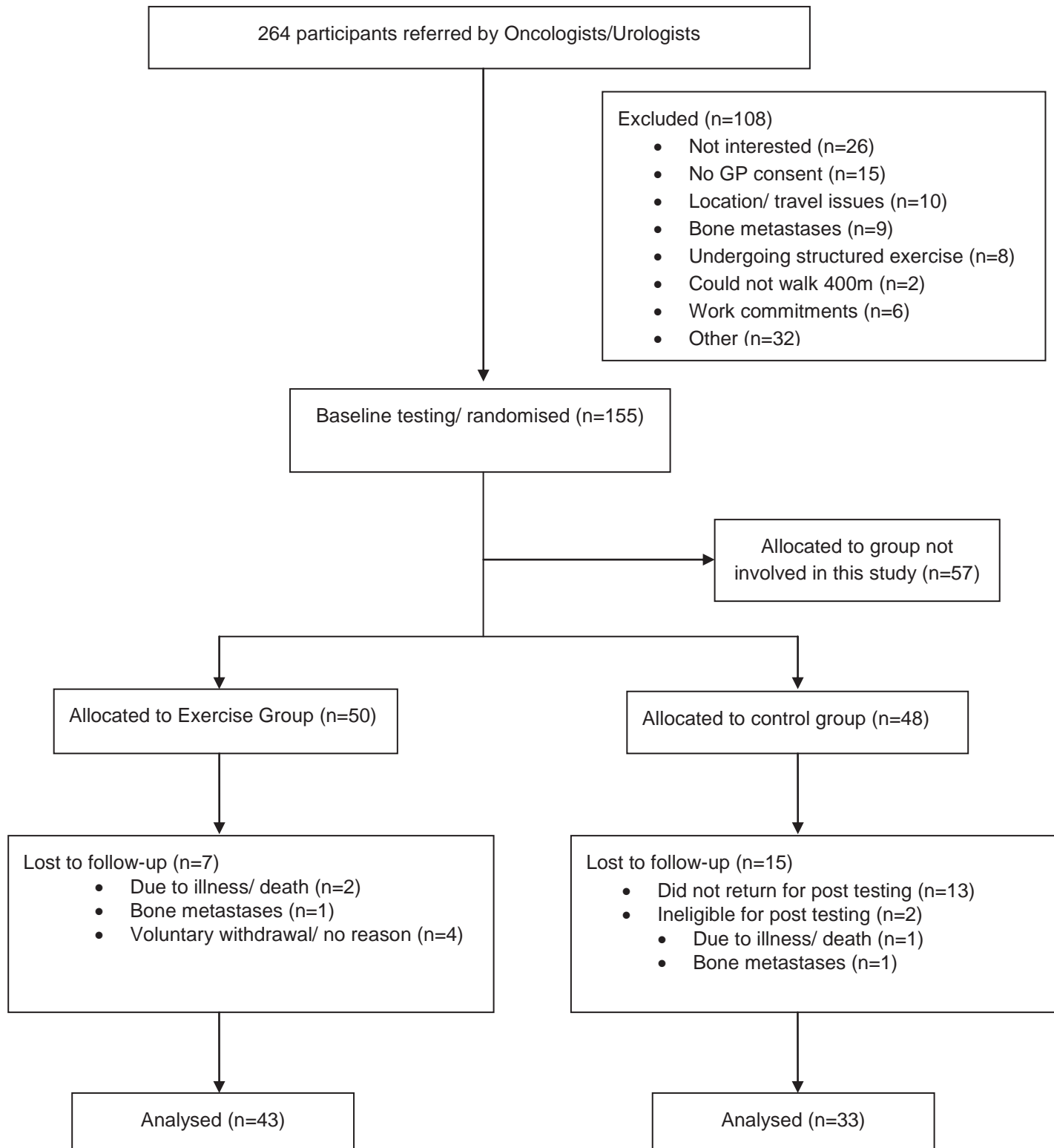
## **METHODS**

### *Participants*

This study was a parallel group randomised control trial comparing a combined aerobic and resistance training program to a usual care (control) program. One hundred and fifty five men undergoing treatment for prostate cancer involving ADT with no formal regular exercise (undertaking structured aerobic or resistance training less than two times per week) within the previous 3 months were recruited by invitation of their attending specialist for this study. All participants had been hypogonadal for a period of at least 2 months prior to testing and expected to remain hypogonadal for the period of the intervention. Exclusion criteria included the presence of an acute illness or any musculoskeletal, cardiovascular or neurological disorder that could inhibit or put them at risk from exercising. The participants were informed that they were required to be able to walk 400 m and to undertake upper- and lower-body exercises. Those entering the study undertook a series of familiarisation sessions and baseline measurements prior to randomization to either 1) aerobic and resistance exercise group or 2) usual care (control group) for 6 months. The study protocol received human ethics approval from the Edith Cowan University Ethics Committee. All participants obtained medical clearance from their general practitioner and completed a detailed health history questionnaire in addition to written informed consent. The participant flow through the trial is presented in Figure 1.



**Figure 3.** Consort Flow diagram of participant randomisation including enrolment, intervention, allocation, follow-up and data analysis



### *Exercise Intervention:*

The combined aerobic and resistance (EX) training participants took part in a combination of clinic and home based training for 6 months. The clinic based component consisted of twice weekly sessions to undertake the resistance training component of the intervention and included 40 minutes of the weekly aerobic intervention component. The additional 110 minutes of aerobic training to make up the required weekly 150 minutes of aerobic activity was completed at home each week and documented in their training log. The usual care control group (CON) was instructed to maintain their normal physical activity and dietary routine.

The clinic based sessions were approximately 60 – 75 minutes in duration (including the warm-up and cool-down periods) and were conducted at 5 different sites across the Perth metropolitan area in Western Australia depending on the participant's location of residence (Joondalup, Mt Lawley, Nedlands, South Lake & Mandurah). Sessions commenced with a 5-minute warm-up comprising various low-level aerobic activities using a treadmill, cycle ergometer or elliptical trainer, as well as static stretching. Participants were instructed to perform an equal number of warm-up sessions on each ergometer.

The resistance training regime included 6 exercises that targeted the major upper and lower body muscle groups which were the chest press, seated row, lat pull-down, leg press, leg extension and leg curls. These exercises have been previously utilised in a number of exercise intervention studies (Galvao, et al., 2006; Galvao & Taaffe, 2005; Newton, et al., 2002; Taaffe, Duret, Wheeler, & Marcus, 1999). The rest period between

sets was 1-2 minutes. To ensure the progressive nature of the training program, participants were encouraged to work past the specific repetition maximums (RMs) prescribed. The resistance was increased by a 5-10% increment for the next set or training session if the participants were able to perform more repetitions than the RMs specified during a set. Intensity was systematically manipulated on a 4-week cycle from 6-12 RM (e.g. the maximal weight that can be lifted 6 to 12 times) using 1-4 sets per exercise (Table 15).

**Table 15.** Resistance training progression overview

Weeks	Sets	Repetitions
1-4	2	12
5-8	3	10
9-12	3	8
13-16	4	6

Each clinic based session included 20 minutes of aerobic exercise completed prior to the resistance training component using an equal amount of various modes including walking or jogging on a treadmill, cycling and rowing on a stationary ergometer, as well as exercising on an elliptical trainer. The target intensity was set at 70%-90% of each participant's individualised heart rate at VO<sub>2</sub>max which was monitored with individual heart rate monitors (Polar F3, Polar Electra Oy, Finland) provided for each participant and recorded at the completion of the session. The same intensity (70%-90%) was also used for the prescription of the 110 minutes of home based aerobic activity to meet the required 150 min/wk.

The criterion for the clinic based exercise program was to design optimal stimulus to the cardiorespiratory and neuromuscular systems whilst maximizing compliance and retention. All exercise sessions were conducted in small groups of up to 10 participants, with participants exercising under direct supervision of an Accredited Exercise Physiologist to ensure correct technique and to minimize the risk for injury. Each session concluded with a 5-minute cool-down period of lower intensity aerobic and stretching activities.

### *Measurements:*

Primary and secondary endpoints were identical to those in the previous cross sectional study (Chapter 4) and took place at baseline and 6 months (end of intervention). Briefly, these measurements included cardiorespiratory capacity as assessed by maximal oxygen uptake ( $\text{VO}_2\text{max}$ ), lean tissue mass and fat mass by DXA, selected girth measurements by anthropometry, resting metabolic rate via respiratory gas analysis with fat and carbohydrate oxidation determined from measurements of oxygen consumption, blood pressure by a validated oscillometric device (HEM-705CP, Omron Corporation, Japan) and reported as both central and peripheral systolic, diastolic and mean arterial blood pressure values along with central and peripheral augmentation pressures. The metabolic profile was externally analysed utilising standardised industry techniques for haemoglobin A1C, testosterone, insulin, PSA, LDL cholesterol, HDL cholesterol, total cholesterol, and glucose. Muscular strength was assessed using the one- repetition maximum (1-RM) method while muscular endurance was reported as the maximum number of repetitions performed at 70% of 1-RM for the chest press and leg press exercises with an additional variable presented as muscular endurance relative to baseline 1RM. This required the participant to complete as many repetitions as possible for the original baseline 1RM and the more recently established post intervention 1RM. Physical function was assessed using a battery of tests that included the repeated chair rise, stair climb, 6-meter walks and the 400 meter walk.

### *Statistical Analysis:*

Data analyses were performed using the Statistical Package for Social Sciences version 18.0 software (PASW, Chicago, IL). Normality of the data were assessed using the Kolomogorov-Smirnov test. The per protocol analyses included standard descriptive statistics and independent samples t tests. Between group differences for the variables collected pre and post intervention were examined using a 2 x 2 mixed model analysis of variance. The differences between the change scores for the independent variables between groups pre and post intervention are reported as treatment effects. All tests were two-tailed and an alpha level of 0.05 applied as the criterion for statistical significance. Results are reported as the mean  $\pm$  standard deviation.

## RESULTS

Ninety-seven participants undertook baseline testing. Combined mean age was  $69 \pm 9$  years and a mean ADT treatment duration of  $4.3 \pm 4.7$  months. Forty-eight participants were randomly assigned to the CON group whilst 50 participants were randomised to the EX group. Baseline subject characteristics are shown in Table 16.

There were no differences for age, height, body mass, waist circumference or ADT treatment duration between the EX and CON groups.

**Table 16.** Subject baseline characteristics

Variable	Control (n=47)	Exercise (n=50)
Age (years)	$69.4 \pm 8.9$	$69.3 \pm 9.4$
Height (cm)	$170.0 \pm 11.9$	$172.8 \pm 6.7$
Body Mass (kg)	$89.3 \pm 15.5$	$84.8 \pm 16.1$
Waist Circumference (cm)	$103.7 \pm 12.0$	$102.8 \pm 15.8$
ADT duration (months)	$3.9 \pm 3.9$	$4.8 \pm 5.4$

### *Attrition Rate*

At the 6-month time point 33 out of the original 48 participants remained in the CON group whilst 43 of the original 50 participants remained in the EX group. As presented in Figure 3, 7 participants in the EX group discontinued the intervention, due to voluntary withdrawal (n=4), bone metastases (n=1) and illness/death (n=2). The CON group had 15 participants not complete post testing. Of these withdrawals, 13 did not return for follow-up testing whilst 2 were ineligible for testing due to bone metastases (n=1) and illness (n=1). The attrition rate for the CON group was 31% whilst the attrition rate for the EX group was 14%. Overall attrition rate for the study was 22%.



## Body Composition

There was a significant group by time interaction present for total lean mass ( $p=0.050$ ), total fat mass ( $p=0.043$ ), trunk fat ( $p=0.003$ ) and body fat percentage ( $p=0.006$ ) (Table 17). The differences occurred in EX for total lean mass while fat mass, trunk fat and body fat percentage increased in CON with no change in EX. No significant interaction was observed for upper lean mass, lower lean mass, appendicular skeletal muscle mass or whole body mass. A time effect was present for lower limb lean mass ( $p=0.040$ ) and whole body mass ( $p<0.001$ ).

**Table 17.** Body composition variables for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
<b>Lean tissue mass (kg)</b>				
Total Lean Mass*				0.050
Pre	58.7 ± 6.1	59.4 ± 8.6		
Post	58.6 ± 5.9	60.1 ± 8.6		
Difference Score	-0.1 ± 1.4	0.7 ± 1.9	0.8 (0.4, 1.6)	
Upper Limb				0.245
Pre	6.7 ± 1.0	6.8 ± 1.2		
Post	6.7 ± 1.0	6.9 ± 1.3		
Difference Score	0.0 ± 0.2	0.1 ± 0.5	0.1 (-0.9, 3.4)	
Lower Limb				0.996
Pre	18.2 ± 2.2	18.8 ± 3.0		
Post	18.3 ± 2.3	19.0 ± 2.9		
Difference Score	0.1 ± 0.7	0.2 ± 0.7	0.1 (-0.3, 0.3)	
Appendicular Skeletal Muscle				0.603
Pre	24.9 ± 3.1	25.7 ± 4.0		
Post	25.0 ± 3.2	26.0 ± 4.1		
Difference Score	0.1 ± 0.9	0.3 ± 1.0	-0.2 (-0.3, 0.6)	

<b>Fat mass (kg)</b>					
Total Fat Mass*					0.043
	Pre	25.7 ± 6.0	24.1 ± 9.9		
	Post	27.2 ± 6.5	24.5 ± 9.0		
	Difference Score	1.5 ± 1.7	0.4 ± 2.5	-1.1 (-2.1, -0.3)	
Trunk*		14.2 ± 3.8	13.2 ± 6.6		0.003
	Pre	14.9 ± 3.9	13.0 ± 5.9		
	Post	0.7 ± 0.9	-0.2 ± 1.6	-0.9 (-1.6, -0.3)	
	Difference Score				
Whole body mass (kg)					0.097
	Pre	86.5 ± 12.3	85.7 ± 17.0		
	Post	88.4 ± 12.3	86.5 ± 16.4		
	Difference Score	1.9 ± 2.7	0.8 ± 2.6	-1.1 (-2.3, 0.2)	
Body Fat %*					0.006
	Pre	29.2 ± 3.6	27.2 ± 6.0		
	Post	30.3 ± 3.8	27.2 ± 5.9		
	Difference Score	1.1 ± 1.3	0.0 ± 1.8	-1.1 (-1.9, -0.3)	

\* denotes significant group x time interaction

There were no significant group by time interactions for waist, hip, arm, or calf circumferences (Table 18).

**Table 18.** Circumference measurements for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
Waist Circumference				0.673
Pre	103.7 ± 10.2	99.7 ± 13.2		
Post	104.3 ± 10.5	99.7 ± 12.9		
Difference Score	0.6 ± 3.15	0.0 ± 3.3	-0.6 (-2.1, 0.8)	
Hip Circumference				0.452
Pre	101.5 ± 6.4	99.0 ± 8.1		
Post	102.7 ± 6.3	100.3 ± 9.0		
Difference Score	1.2 ± 4.8	1.3 ± 4.75	0.1 (-2.1, 2.3)	
Arm circumference				0.065
Pre	30.3 ± 2.8	29.4 ± 2.8		
Post	30.4 ± 2.7	30.1 ± 2.7		
Difference Score	0.1 ± 1.4	0.7 ± 1.4	0.6 (-0.1, 1.3)	
Calf Circumference				0.396
Pre	36.8 ± 2.6	36.3 ± 2.5		
Post	36.8 ± 2.6	36.5 ± 2.6		
Difference Score	0.0 ± 1.0	0.2 ± 1.0	0.2 (-0, 0.7)	

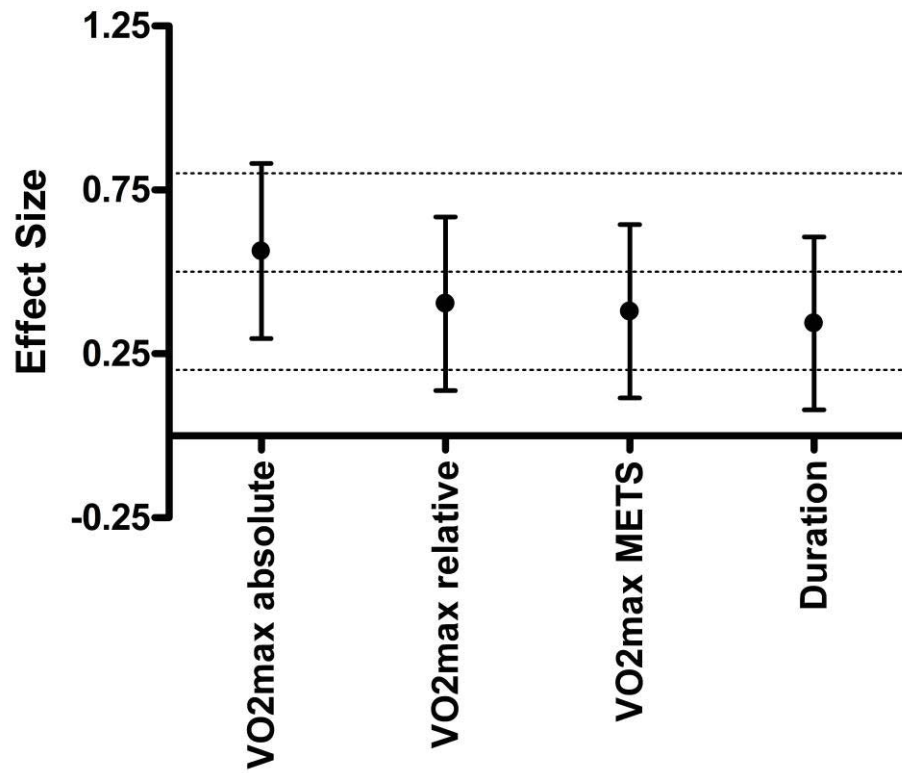
### Cardiorespiratory Capacity

There was no significant group by time interactions present for any of the cardiorespiratory capacity variables measured. Although not significant ( $p=0.095$ ), absolute  $VO_2\text{max}$  ( $\text{L}\cdot\text{min}^{-1}$ ) increased by 5% with a moderate effect size of 0.6 (Cohen, 1988) in the EX group whilst the CON group did not change (Table 19, Figure 4).

**Table 19.** Maximal exercise capacity values as determined from the exercise stress test for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
$VO_2\text{max}$ ( $\text{L}\cdot\text{min}^{-1}$ )				0.095
Pre	$1.95 \pm 0.35$	$2.05 \pm 0.56$		
Post	$1.94 \pm 0.35$	$2.16 \pm 0.55$		
Difference Score	$-0.01 \pm 0.20$	$0.11 \pm 0.22$	$0.10 (-0.1, 0.2)$	
$VO_2\text{max}$ ( $\text{ml}\cdot\text{kg}\cdot\text{min}^{-1}$ )				0.169
Pre	$23.0 \pm 4.5$	$24.7 \pm 6.2$		
Post	$22.6 \pm 4.9$	$25.4 \pm 5.7$		
Difference Score	$-0.4 \pm 2.1$	$0.7 \pm 3.1$	$-1.1 (-0.5, 2.9)$	
$VO_2\text{max}$ (METS)				0.171
Pre	$6.6 \pm 1.3$	$7.1 \pm 1.8$		
Post	$6.5 \pm 1.4$	$7.3 \pm 1.6$		
Difference Score	$-0.1 \pm 0.6$	$0.2 \pm 0.9$	$0.3 (-0.1, 0.8)$	
$VO_2\text{max}$ duration (mins)				0.239
Pre	$7.7 \pm 2.6$	$8.3 \pm 2.3$		
Post	$8.4 \pm 2.7$	$9.6 \pm 2.1$		
Difference Score	$0.7 \pm 1.9$	$1.3 \pm 1.6$	$0.6 (-0.5, 1.8)$	

**Figure 4.** Maximal exercise capacity variables effect size



Note: 0.2 Small effect, 0.5 moderate effect, 0.8 large effect (Cohen, 1988)

### Resting Metabolic Rate

There was no significant group by time interactions present for resting metabolic rate when presented as kilocalories per day or fat oxidation or carbohydrate oxidation (Table 20).

**Table 20.** Resting metabolic rate for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
Resting Metabolic Rate (kcal/24hr)				0.655
Pre	1743 ± 235	1753 ± 266		
Post	1735 ± 299	1776 ± 295		
Difference Score	-8 ± 228	23 ± 257	31 (-1.7, 168)	
Fat Oxidation (mg/min)				0.512
Pre	59.4 ± 19.6	58.6 ± 16.9		
Post	59.4 ± 21.7	70.8 ± 23.7		
Difference Score	-0.0 ± 26.6	12.2 ± 24.8	12.2 (-5.3, 29.7)	
Carbohydrate Oxidation (mg/min)				0.329
Pre	158.6 ± 47.7	159.0 ± 47.8		
Post	157.6 ± 64.8	138.3 ± 47.2		
Difference Score	-0.9 ± 66.9	-21.6 ± 49.6	-19.7 (-59.9, 20.6)	

### Central Blood Pressure

There were no significant group by time interactions present in any of the peripheral blood pressure responses. Further, no group by time interactions were observed in any of the central blood pressure measurements including augmentation index, augmentation pressure or augmentation load. No group by time interactions were observed for pulse wave velocity (Table 21).

**Table 21.** Haemodynamic and pulse wave analysis parameters for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
Peripheral SBP (mmHg)				0.629
Pre	150 ± 23	151 ± 20		
Post	145 ± 22	148 ± 18		
Difference Score	-5 ± 18	-3 ± 19	2 (-9, 15)	
Peripheral DBP (mmHg)				0.851
Pre	87 ± 14	87 ± 10		
Post	83 ± 11	83 ± 10		
Difference Score	-4 ± 9	-4 ± 13	0 (-8, 7)	
Peripheral MAP (mmHg)				0.960
Pre	108 ± 17	109 ± 13		
Post	105 ± 16	106 ± 11		
Difference Score	-3 ± 11	-3 ± 14	0 (-9, 8)	
Central SBP (mmHg)				0.907
Pre	139 ± 25	140 ± 19		
Post	135 ± 23	137 ± 18		
Difference Score	-4 ± 17	-3 ± 20	1 (-12, 13)	
Central DBP (mmHg)				0.923
Pre	87 ± 14	88 ± 10		
Post	84 ± 12	84 ± 10		
Difference Score	-3 ± 9	-4 ± 13	-1 (-8, 7)	

Central MAP (mmHg)					0.993
Pre	108 ± 17	109 ± 13			
Post	105 ± 16	106 ± 11			
Difference Score	-3 ± 11	-3 ± 14	0 (-9, 9)		
Peripheral Augmentation Index (%)					0.916
Pre	86.6 ± 17.0	86.9 ± 12.2			
Post	84.7 ± 11.3	84.5 ± 12.8			
Difference Score	-1.9 ± 12.5	-2.4 ± 14.4	-0.5 (-9.3, 8.4)		
Central Augmentation Pressure (mmHg)					0.842
Pre	16 ± 10	16 ± 8			
Post	16 ± 8	16 ± 9			
Difference Score	0 ± 9	0 ± 9	0 (-5, 6)		
Augmentation Load					0.544
Pre	15 ± 5	13 ± 4			
Post	15 ± 6	15 ± 4			
Difference Score	0 ± 6	2 ± 4	2 (-2, 5)		
Central Augmentation Index (%)					0.397
Pre	145 ± 23	142 ± 17			
Post	141 ± 18	141 ± 17			
Difference Score	-4 ± 18	-1 ± 19	3 (-9, 16)		
Pulse Wave Velocity					0.510
Pre	9.9 ± 1.9	10.3 ± 1.6			
Post	9.2 ± 1.4	10.0 ± 1.4			
Difference Score	-0.7 ± 1.9	-0.3 ± 1.6	0.4 (-0.8, 1.3)		



### *Muscular Strength & Endurance*

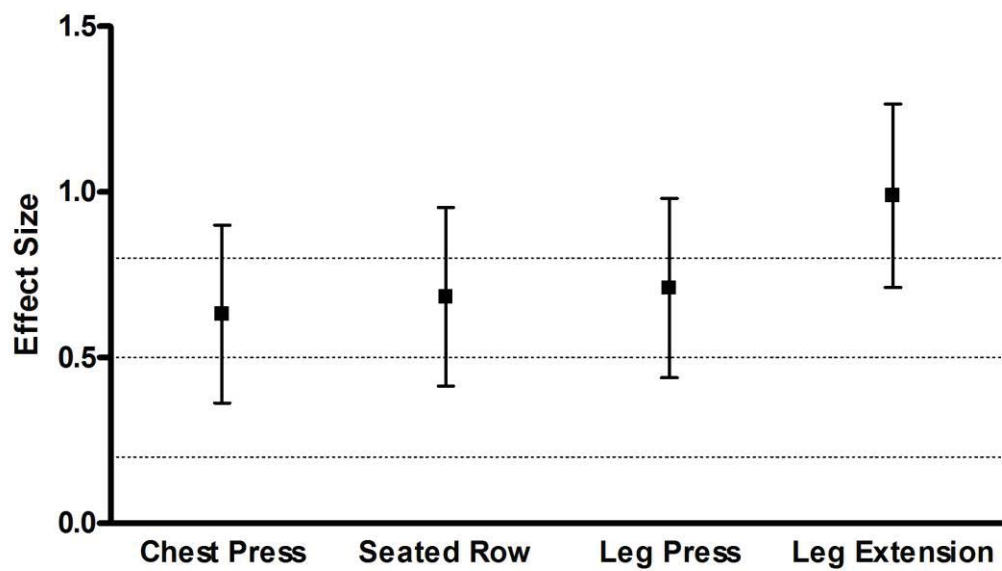
There was a significant group by time interaction present for all 1-RMmaximal strength variables (Table 22, Figure 5). This included the significant increases in chest press ( $p=0.008$ ), seated row ( $p=0.004$ ), leg press ( $p=0.003$ ) and leg extension ( $p<0.001$ ) for EX group with no change in CON. This resulted in a moderate effect size for chest press (0.6), leg press (0.7) and seated row (0.7) and a large effect size for leg extension (1.0).

**Table 22.** Maximal strength values for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
Chest Press 1RM (kg)*				0.008
Pre	36.7 ± 12.4	37.1 ± 11.1		
Post	35.8 ± 11.7	39.8 ± 10.8		
Difference Score	-0.9 ± 4.1	2.7 ± 6.6	3.6 (-1.0, -6.2)	
Seated Row 1RM (kg)*				0.004
Pre	67.7 ± 13.5	69.7 ± 13.4		
Post	65.6 ± 11.6	73.8 ± 13.6		
Difference Score	-2.1 ± 9.4	4.1 ± 8.7	6.2 (-2.0, -10.3)	
Leg Press 1RM (kg)*				0.003
Pre	130.8 ± 57.1	134.5 ± 48.2		
Post	134.1 ± 52.1	157.8 ± 58.9		
Difference Score	3.3 ± 22.0	23.3 ± 31.8	-0.0 (-7.0, -32.9)	
Leg Extension 1RM (kg)*				<0.001
Pre	48.9 ± 16.0	52.4 ± 16.9		
Post	48.7 ± 15.8	62.4 ± 17.7		
Difference Score	-0.2 ± 10.8	10.0 ± 9.8	10.2 (-5.4, -15.0)	

Note: 1RM = one repetition maximum; \* denotes significant time x group interaction

**Figure 5. Muscular Strength Effect Size**



Note: 0.2 Small effect, 0.5 moderate effect, 0.8 large effect (Cohen, 1988)

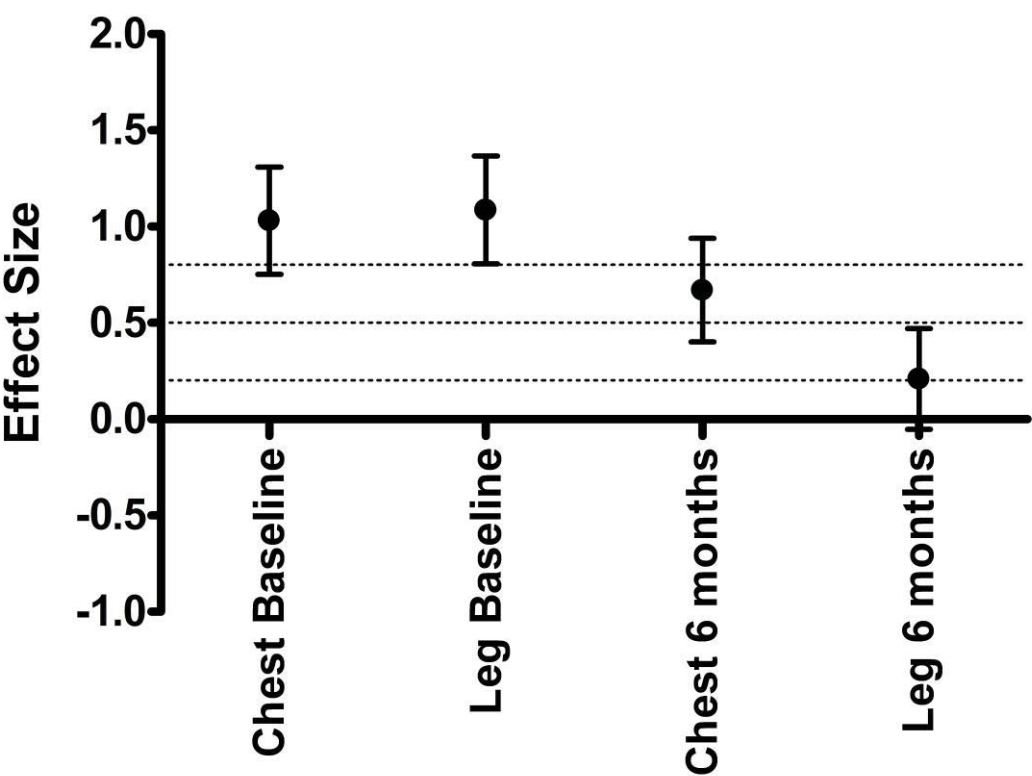
There was a significant group by time interaction present for the muscular endurance variables assessed (Table 23, Figure 6) which included chest press endurance ( $p < 0.001$ ) and leg press endurance ( $p = 0.001$ ) with both endurance measures significantly increasing in the EX vs. CON condition. An independent samples t-test did reveal a significant difference between the CON and EX groups for chest press endurance when using the 6-month 1RM value ( $p = 0.032$ ) with no difference was observed for the leg press.

**Table 23.** Muscular endurance values for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
Chest Press 70% Baseline 1RM reps*				<0.001
Pre	9.6 ± 3.3	10.3 ± 4.0		
Post	8.4 ± 3.8	14.1 ± 5.3		
Difference Score	-1.2 ± 4.1	3.8 ± 5.3	5.0 (-2.4, -7.7)	
Leg Press 70% Baseline 1RM reps *				0.001
Pre	15.6 ± 5.2	15.2 ± 6.7		
Post	14.9 ± 4.9	22.1 ± 8.5		
Difference Score	-0.7 ± 5.8	6.9 ± 7.7	7.7 (-3.4, -12.0)	
Chest Press 70% 6 month 1RM reps ^				
Pre	n/a	n/a		
Post	8.1 ± 4.3	11.0 ± 4.3 <sup>#</sup>		
Leg Press 70% 6 month 1RM reps ^				
Pre	n/a	n/a		
Post	14.4 ± 4.6	15.6 ± 6.4		

Reps = number of repetitions; \* denotes significant time x group interaction; N/A not applicable as 6 month 1RM required for test; ^ significant difference CON vs. EX

**Figure 6.** Muscular Endurance Effect Size



Note: 0.2 Small effect, 0.5 moderate effect, 0.8 large effect (Cohen, 1988)

### Physical Function

There was a significant group by time interaction for the time taken to complete the 400m walk ( $p=0.010$ ), indicating an improvement in the EX group (Table 24). No significant differences were observed for the chair rise, stair climb or any of the 6m walk tests.

**Table 24.** Physical Function values for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
400m walk (s)*				0.010
Pre	272 ± 40	269 ± 47		
Post	270 ± 44	254 ± 41		
Difference Score	-2 ± 19	-15 ± 22	13 (3, 23)	
Chair Rise (s)				0.410
Pre	14.0 ± 3.5	12.9 ± 2.5		
Post	13.3 ± 2.7	11.8 ± 2.5		
Difference Score	-0.7 ± 2.4	-1.1 ± 2.0	0.4 (-0.6, 1.4)	
Stair Climb (s)				0.304
Pre	5.5 ± 1.3	5.0 ± 1.3		
Post	5.6 ± 1.4	5.0 ± 1.1		
Difference Score	0.1 ± 0.6	0.0 ± 0.6	0.1 (-0.1, 0.4)	
6m normal pace walk (s)				0.124
Pre	5.0 ± 0.7	4.9 ± 0.8		
Post	4.6 ± 0.6	4.7 ± 0.7		
Difference Score	-0.4 ± 0.6	-0.2 ± 0.6	-0.2 (-0.5, 0.1)	
6m fast pace walk (s)				0.629
Pre	3.6 ± 0.5	3.5 ± 0.6		
Post	3.5 ± 0.4	3.4 ± 0.5		
Difference Score	0.1 ± 0.3	-0.1 ± 0.6	0.0 (-0.2, 0.1)	
6m backwards walk (s)				0.331
Pre	19.8 ± 7.5	18.8 ± 4.7		
Post	18.6 ± 9.5	16.6 ± 4.4		
Difference Score	-1.2 ± 4.3	-2.2 ± 4.5	1.0 (-1.1, 3.1)	

\* denotes significant time x group interaction

## Metabolic Profile

There were no significant group by time interactions present in any of the blood biomarkers measured (Table 25).

**Table 25.** Blood markers for the CON and EX group pre and post intervention

Variable	Control	Exercise	Treatment effect (95% CI)	P Value
HbA1C (%)				0.457
Pre	6.0 ± 0.5	5.9 ± 0.6		
Post	6.0 ± 0.7	5.8 ± 0.5		
Difference Score	0.0 ± 0.3	-0.1 ± 0.4	0.1 (-0.1, 0.2)	
Testosterone (pg.mL <sup>-1</sup> )				0.221
Pre	0.6 ± 1.0	1.5 ± 2.9		
Post	1.8 ± 2.6	1.6 ± 2.1		
Difference Score	1.2 ± 2.8	0.1 ± 3.7	1.1 (-0.7 , 3.0)	
Prostate Specific Antigen (ng.mL <sup>-1</sup> )				0.551
Pre	0.8 ± 1.4	0.8 ± 1.3		
Post	0.2 ± 0.4	0.4 ± 1.4		
Difference Score	-0.6 ± 1.1	-0.4 ± 1.8	-0.2 (-1.0, 0.5)	
Insulin (mU/L)				0.845
Pre	10.7 ± 5.3	8.8 ± 3.8		
Post	10.9 ± 4.9	9.1 ± 3.9		
Difference Score	0.2 ± 4.8	0.3 ± 2.3	-0.2 (-2.0, 1.7)	
Triglycerides (mmol/L)				0.131
Pre	1.2 ± 0.3	1.2 ± 0.5		
Post	1.5 ± 0.5	1.3 ± 0.5		
Difference Score	0.3 ± 0.4	0.1 ± 0.5	0.2 (-0.1, 0.5)	
LDL Cholesterol (mmol/L)				0.641
Pre	2.8 ± 0.9	2.9 ± 0.8		
Post	2.9 ± 0.7	2.9 ± 0.8		
Difference Score	0.1 ± 0.5	0.0 ± 0.5	0.1 (-0.2, 0.3)	

HDL cholesterol		1.2 ± 0.4	1.3 ± 0.4		0.897
(mmol/L)		1.3 ± 0.2	1.3 ± 0.3		
	Pre	0.1 ± 0.3	0.0 ± 0.2	0.1 (-1.3, 0.2)	
	Post				
	Difference Score				
Total cholesterol					0.444
(mmol/L)		4.6 ± 0.9	4.7 ± 1.2		
	Pre	4.9 ± 1.2	4.9 ± 1.0		
	Post	0.3 ± 1.0	0.2 ± 1.0	0.2 (-0.3, 0.6)	
	Difference Score				
Glucose (mmol/L)					0.073
	Pre	5.3 ± 0.6	5.5 ± 1.1		
	Post	5.5 ± 0.8	5.3 ± 0.6		
	Difference Score	0.2 ± 0.6	-0.2 ± 0.6	0.4 (0.0, 0.6)	
C Reactive Protein					0.202
(mg/L)		1.6 ± 1.7	1.8 ± 2.2		
	Pre	2.1 ± 1.7	1.6 ± 2.2		
	Post	0.5 ± 1.3	-0.2 ± 2.5	0.7 (-0.4, 1.8)	
	Difference Score				

## ***DISCUSSION***

This is the first study to utilise a 6-month, multi-centre, randomised controlled trial to examine the influences of a combined aerobic and resistance training program on body composition, cardiorespiratory capacity, resting metabolic rate, central blood pressure, muscular strength and endurance, physical function and blood biomarkers in men undergoing ADT for the treatment of prostate cancer. As a result of the intervention, improvements were made in body composition, muscular strength and endurance and a trend towards an increase in cardiorespiratory capacity.

Increases in fat mass and reductions in lean mass are common side effects of ADT (Galvao, et al., 2008b; Smith, 2004; Smith, et al., 2002a; Smith, et al., 2006). In the present study the EX intervention had a positive effect of significantly increasing lean mass (treatment effect 0.8kg) and reducing total fat mass (treatment effect -1.1kg) with further analysis revealing that specifically, trunk fat was favourably impacted (treatment effect -0.9kg) as well as overall percentage body fat (treatment effect 1.1%). Galvao et al. (2010) have previously reported changes in lean body mass (0.8kg) in a 12-week combined aerobic and resistance training intervention, however no changes were seen in whole body fat, trunk fat or body fat percentage. It is thought the addition of a more substantial aerobic training component (150 minutes/wk vs. 30-40 minutes/wk) combined with the longer intervention (26 weeks vs. 12 weeks) brought about these previously unreported changes. Galvao and colleagues (2011) have reported that longer term ADT (> 6 months) patients may respond differently to an exercise program when compared to short term



ADT (< 6 months). The authors reported that the shorter term ADT group increased total body fat during the 12 week exercise intervention (0.9kg,  $p=0.018$ ) when compared to the longer term therapy group suggesting that the length of ADT duration may have impacted the results in the current study.

Both upper body and lower body muscular strength were significantly improved as a result of the EX intervention. Upper body strength improvements were represented by an increase in chest press (treatment effect 3.6kg) and seated row (treatment effect 6kg) whilst the lower body strength was represented by an increase in leg press (treatment effect 20kg) and leg extension (treatment effect 10.2kg). These changes in strength were supported by similar significant increases in upper body muscular endurance (treatment effect 5 repetitions) and lower body muscular endurance (treatment effect 8 repetitions) when compared to baseline load used post intervention. The changes observed in muscular strength and endurance are similar to those seen by Galvao and colleagues (2006) who employed a similar resistance training intervention in 10 men undergoing ADT. Importantly, these muscular strength and endurance responses are also similar to those seen in healthy men undertaking similar exercise interventions (Galvao, Newton, & Taaffe, 2005). Muscular strength has been demonstrated to contribute to the already established protective effects of cardiorespiratory fitness against the risk of death in men (Ruiz, et al., 2008), providing further justification for a combined aerobic and resistance training intervention in this population.

Whilst not statistically significant, maximal aerobic capacity did increase 5% in the EX group with no change in the CON group. This is an important finding as no study has previously utilised a direct assessment of maximal aerobic capacity in prostate cancer patients undergoing ADT. Segal and colleagues (2009) have previously explored the effects of either a resistance or aerobic exercise intervention for radiotherapy patients utilising  $VO_{2peak}$  as an outcome measure. They also reported a 5% advantage to either resistance or aerobic training groups as a result of a 24-week intervention period, compared to a usual care group. An interesting outcome of this study was that their resistance training group also increased  $VO_{2peak}$  with the authors reporting that although resistance training is not generally considered a primary means for developing  $VO_{2peak}$ , studies have shown circuit weight training to increase  $VO_{2peak}$  by 6% (Segal, et al., 2009; Thompson, et al., 2007). Therefore, it is possible in this current study that the combined effects of aerobic and resistance training led to greater improvements in  $VO_{2max}$  than an exclusive aerobic training intervention would have.

Aerobic functional walking capacity, as assessed by the long distance corridor walk was significantly improved in the EX group following the 6-month intervention, demonstrated by a reduced time to complete the given distance in the EX group when compared to pre intervention values (treatment effect 13s). This is a significant outcome given the long distance corridor walk has been shown to be a strong predictor of mortality, cardiovascular disease and mobility limitations in older adults (Simonsick, Fan, & Fleg, 2006). This current study demonstrates that walking endurance can be improved in this population through appropriate exercise prescription.

To date, no other study has investigated the impact of an exercise intervention on resting metabolic rate (RMR) in men receiving ADT for the treatment of prostate cancer, with only one study examining the effect that prostate cancer treatment has on RMR (Reis, et al., 2009). In the current study, no differences were observed for RMR as a result of the intervention. The secondary finding was that there was also no change in the CON group suggesting ADT did not have an impact on RMR over the 6-month period. The findings of the current study concur with the only other RMR related study conducted by Reis et al. (2009) who found no differences in resting energy expenditure after 12 months of ADT. Reis (2009) suggested the lack of differences may be a result of the small sample size ( $n = 16$ ), however, we employed a larger sample size ( $n = 76$ ) in the current study and the findings did not change. Reis et al. (2009) also identified a significant increase in carbohydrate oxidation and a decrease in lipid oxidation although this was not the case in our control group over the 6-month period. The exercise intervention did result in an increase in fat oxidation rates by 21%; however, the large variation within our cohort meant the change was not statistically significant. Similarly, carbohydrate oxidation rates decreased by 14%, however, a similar variation amongst the participants led to a non-significant finding.

Serum testosterone and PSA did not change over the course of the intervention, as has already been demonstrated by Galvao et al. (2006), providing further evidence that exercise can be safely undertaken without compromising the purpose of reduced androgen levels (Galvao, et al., 2006). Blood glucose levels, although statistically not significant, did respond positively to the intervention with the EX group reducing blood

glucose levels by approximately 0.2 mmol/L whilst the CON group had an increase of 0.2 mmol/L, a treatment effect of 0.4 mmol/L. Basaria et al. (2008) have previously described that insulin resistance usually develops within a few months of ADT commencement, however the resulting hyperinsulemia maintains glucose levels in the normal range until such time that this compensatory mechanism fails during prolonged treatment resulting in hyperglycemia. Our study found no such changes in insulin during the 6-month control period or during the intervention; however the trend towards improved glucose control as a result of the intervention is a positive outcome that has the potential to reduce the likelihood of developing hyperglycemia during treatment, the defining characteristic of diabetes mellitus.

## *Conclusion*

This study has shown that a 6-month combined aerobic and resistance exercise program has a favourable impact on body composition, muscular strength and endurance, physical function and a trend towards an increase in cardiorespiratory fitness. Of major significance was the fact that total fat mass, trunk fat and body fat percentage can be reduced in men undergoing ADT for the treatment of prostate cancer. Although previous studies have found alterations in lean body mass (Galvao, et al., 2010) and total fat mass when adjusting for ADT duration (Galvão, et al., 2011), this is the first study to report favourable adaptations in overall fat mass in prostate cancer patients regardless of ADT treatment time. The muscular strength and endurance outcomes combined with the trend towards an increase in maximal aerobic capacity are of considerable significance in reducing mortality (Ruiz, et al., 2008). The authors reported the age-adjusted death rate in men with high levels of both muscular strength and cardiorespiratory fitness was 60% lower than the death rate in the group of unfit men with the lowest levels of muscular fitness. This study provides further justification that exercise, in particular combined aerobic and resistance training, should be considered a key component of the course of treatment in men undergoing ADT for the treatment of prostate cancer.

## **CHAPTER 6**

### **Concluding discussion and implications for clinical guidelines and future research**

This chapter provides a generalised summary of the outcomes resulting from the literature review and the results of the experimental chapters of this thesis. This chapter also identifies the future research required in this field.

The literature review initially provided a background to cancer and identified the most common forms of cancer which included breast, colorectal and prostate cancer. The review explored the various cancer treatment options available which included active surveillance, surgery, radiotherapy and systemic therapy (chemotherapy and hormonal therapy) and the side effects associated with each form of treatment. It was identified that the most common side effects of surgery were related to the actual surgical procedure itself, comorbidities of the patients as well as preoperative therapy. Radiotherapy side effects were dependent upon the location of the cancer whilst common non site-specific side effects included fatigue, gastrointestinal issues and loss of appetite. Systemic therapy included both chemotherapy and hormonal therapy with fatigue being the most commonly reported side effect associated with chemotherapy. As hormonal therapy takes numerous forms, the side effects are related to the actual type of hormonal therapy employed. Side effects for third generation aromatase inhibitors used in the treatment of breast cancer include osteoporosis and/or fracture as well as arthralgia, skeletal and muscle pain whilst side effects associated with ADT for the treatment of prostate cancer were categorised into cardiovascular and metabolic alterations. Cardiovascular alterations were concerned with the increased risk of cardiovascular disease found to be present in ADT treated patients whilst metabolic alterations were

reported as increased abdominal circumference, obesity, insulin resistance, hyperglycemia and dislipidemia.

The role of physical activity throughout the cancer continuum was explored with research presented that supports the hypothesis that exercise may exert a protective effect against the development of certain types of cancer, in particular breast and colorectal cancer. Studies were also presented that support the link between physical activity and improved survival rates in cancer patients. The majority of research has focused on breast cancer patients with promising findings suggesting increased levels of physical activity are associated with lower overall mortality rates and cancer recurrence. The review of exercise and cancer studies focused on exercise interventions during cancer treatment. Thirty-nine studies were reviewed in Table 1 (pages 40 - 48) that investigated the role of an exercise intervention during cancer treatment. All cancer types were included in the review with the most commonly investigated cancer being of the breast, with others including prostate, leukaemia and mixed cancer populations. With regard to the type of intervention, of the 39 studies reviewed, 24 were aerobic only, 6 were resistance only, 8 were combined resistance and aerobic whilst the remaining study compared the effectiveness of either a resistance or aerobic intervention. The most common endpoints were physical function/ performance, physical fitness, fatigue, quality of life, strength, body composition and psychological outcomes. Despite a variety of intensities being prescribed, including self-selected intensities and an apparent lack of experimental control in a number of the home based exercise interventions, the majority of studies demonstrated positive outcomes as a result of exercise during cancer



treatment. Exercise was determined to be a safe, effective and feasible strategy to employ during cancer treatment to target the various side effects arising from treatments.

The first experimental chapter was undertaken to assess the feasibility and safety of maximal exercise testing in ADT treated prostate cancer patients. One hundred and twelve prostate cancer patients underwent a physician supervised multistage maximal stress test (Bruce protocol) (Bruce, 1971) on a motorised treadmill. 85% of the participants were able to meet the criteria established for the achievement of  $VO_{2max}$  and only 3 positive tests (3.2%) were observed during the testing period. Apart from the comparatively low cardiorespiratory capacity, when compared to healthy age-matched controls the cardiovascular response to exercise was similar in this cancer population. Overall, these results demonstrated that maximal exercise testing in prostate cancer individuals was feasible and safe and provided a direct assessment of  $VO_{2max}$  that can be used as a screening tool, for exercise prescription purposes and to track the effectiveness of exercise interventions.

In the second experimental chapter a cross-sectional study was undertaken to determine if the length of ADT treatment was linked to the development of additional risk factors for cardiovascular disease and metabolic related toxicities. One hundred and seven men undergoing ADT for the treatment of prostate cancer were stratified into two groups, the acutely suppressed group ( $n= 57$ ) had been exposed to ADT for less than 3 months whilst the chronically suppressed group ( $n= 50$ ) had been exposed to ADT for 3 months or more. We found the chronically suppressed group to have a lower aerobic capacity and

resting metabolic rate. The chronically suppressed group also possessed lower maximal strength values and a corresponding decline in physical function. Whilst not statistically significant, there was a trend towards a decrease in lean mass and an increase in fat mass in the chronically suppressed group. It is thought that the combination of decreasing lean mass and increasing fat mass would be a clinically meaningful body composition alteration that resulted in a lower resting metabolic rate in the chronically suppressed group. Whilst not measured in this study it is possible that physical activity levels may have declined as treatment time progressed. The reduction in physical activity in cancer patients has been previously demonstrated in breast cancer patients (Demark-Wahnefried, et al., 1997; Irwin, et al., 2003) and this may have contributed to the difference observed in maximal aerobic capacity and physical function outcomes.

In the third experimental chapter, a randomised controlled trial was conducted to investigate the effects of a long term (6 months) combined aerobic and resistance training intervention in patients receiving ADT for the treatment of prostate cancer. Participants were randomly allocated to either an exercise group (n= 50) or a control group (n= 48). The combined aerobic and resistance training program consisted of twice weekly clinic based sessions as well as home based aerobic training. Primary endpoints assessed were cardiorespiratory capacity, body composition, resting metabolic rate, central blood pressure, metabolic profile and muscular strength and endurance. As a result of the exercise intervention, there were significant improvements in body composition, muscular strength and endurance and a trend towards an increase in cardiorespiratory capacity. Whilst similar findings have been reported in smaller studies, this was the first study to

demonstrate the effectiveness of a large scale, long term (6 month), multi-centre randomised controlled trial. The extended duration of the exercise intervention is thought to have led to the favourable adaptation in total fat mass that has not previously been reported in this group of cancer patients. This trial further reiterated that exercise, in particular combined aerobic and resistance training, is a safe and effective intervention that should be considered a key component of the overall course of treatment for men undergoing ADT for the treatment of prostate cancer.

This research has demonstrated that maximal exercise testing in ADT treated prostate cancer patients is a feasible and safe method of testing. This research has also demonstrated that additional therapy time exposure is associated with a number of adverse cardiovascular and metabolic outcomes. Patients prescribed ADT for the treatment of prostate cancer should be appropriately counselled as to the negative side effects commonly associated with this form of treatment and be made aware of the beneficial effects an appropriately administered exercise intervention can have on reversing these negative alterations occurring throughout the course of treatment. Further, these specifically designed exercise interventions should be commenced as soon as practically possible post prostate cancer diagnosis and continue for the course of treatment and ideally beyond.

Additional follow-up studies are required to determine if a supervised 6-month exercise intervention does change physical activity behaviours in this population once the supervised exercise sessions are concluded. These studies should focus on cardiovascular,

metabolic and physical function outcomes whilst also considering post cancer survivorship and quality of life outcomes. A potential limitation to this study was the inability to report physical activity levels immediately post cancer diagnosis. This data would have provided a clearer understanding of the causes of some of the declines in physical fitness and the development of cardiovascular disease risk factors and treatment related toxicities. Whilst specific intensities and dosages of the resistance training program used in this randomised controlled trial have been well established, the aerobic training component of the study requires further investigation. More research is required to examine the effects of different aerobic exercise modes, durations and intensities required to significantly influence cardiorespiratory fitness in this ADT treated prostate cancer population. The role of high intensity interval training may be a more effective use of time and provide a more optimal stimulus to elicit the desired changes in this population.

The effects of a combined diet and exercise program in prostate cancer patients undergoing ADT is also yet to be examined in a large scale trial. It is thought that the addition of a dietary intervention in this population would complement the existing body of literature that focuses predominantly on physical activity prescription. Given that common side effects of ADT include increased abdominal fat, loss of muscle mass, increased risk of diabetes and cardiovascular disease, a dietary intervention that specifically targets certain side effects (such as increases in body fat) would supplement the physical activity interventions currently prescribed. The addition of a dietary intervention may possibly result in even more favourable adaptations to those already

seen though physical activity focused interventions, in particular body composition alterations and diabetes related risk factors.

The field of exercise oncology despite being relatively young has experienced significant growth in recent times. The studies presented in this thesis seek to add to the body of knowledge and provide practical applications in the field of exercise oncology. In particular this thesis expands the field of exercise and prostate cancer and provides justification for oncologists and other health care professionals to encourage exercise to be considered as a key component of the treatment process. The successfulness of the multi-site exercise intervention utilised in this thesis should encourage prostate cancer support networks to consider promoting and utilising community based exercise oncology programs.

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## APPENDICES

### ***Appendix A Participant Letter***

Dear Mr

Thank you for your interest in the study “A randomized controlled trial of exercise to reduce treatment side-effects in men receiving therapy for prostate cancer.”

Please find attached:

1. A “Participant Information Sheet” outlining all aspects of the study;
2. A “Statement of Informed Consent” which you will be required to sign before participating in the study;
3. A “Medical Doctor Consent Form” for your doctor; and
4. A map of the Joondalup Campus.

As previously mentioned, all volunteers are required to obtain their doctor’s approval prior to participation – please take the Medical Doctor form to your doctor (GP) and have them complete and sign the consent form (you may also want to show them the Participant Information sheet). Following approval from your doctor, please contact me to arrange a meeting where an orientation to the study will be provided and baseline measurements will commence. At this meeting, please bring with you the “Medical Doctor Consent Form” and “Statement of Informed Consent.”

If you have any questions, please don’t hesitate to contact me.

I look forward to hearing from you.

Best regards,



## ***Appendix B Participant Information Sheet***

### **“A RANDOMIZED CONTROLLED TRIAL OF EXERCISE TO REDUCE TREATMENT SIDE-EFFECTS IN MEN RECEIVING THERAPY FOR PROSTATE CANCER”**

Researchers:

Professor Robert Newton, PhD, E-mail: r.newton@ecu.edu.au Phone: 08 6304-5711

Dr. Dennis Taaffe, PhD, E-mail: dtaaffe@hms.uq.edu.au Phone: 07 3346-7904

Dr. Daniel Galvão, PhD, E-mail: d.galvao@ecu.edu.au Phone: 08 6304-3420

Professor Nigel Spry, MBBS, Radiation Oncologist

Professor Frank Gardiner, MBBS, Urologist, E-mail: f.gardiner@uq.edu.au Phone: 07 3365-5237

### ***Purpose of the Study***

The usual treatments for prostate cancer may have side effects. Some of these side effects include weight gain, loss of muscle and bone mass, tiredness which may affect a person's quality of life. However, exercise has been shown to be a safe and effective method for strength development in older adults. Recently, resistance exercise has also been shown to safely increase muscle strength, quality of life and decrease tiredness in men with prostate cancer. However, the effects of combining weight bearing/impact loading activities and resistance and aerobic exercise on bone strength, weight gain, muscle and physical function in prostate cancer patients undergoing hormone therapy is unknown. Therefore, the purpose of this present study is to examine the effects of different exercise modes (weight bearing/ impact loading, resistance and aerobic) on weight gain, loss of muscle and bone mass, tiredness, physical function and quality of life in men with prostate cancer. The findings from this study will allow health professionals to plan exercise programs for men with prostate cancer to help decrease side effects and improve their quality of life.

### ***Participants Involvement***

We require one hundred and ninety-five men undergoing treatment for prostate cancer to suppress male hormones for at least 2 months to participate in this 12 months exercise study. Participants are required to not have bone metastases because of concerns regarding bone fragility and no musculo-skeletal, neurological or cardiovascular disorder that could inhibit them from exercising, and to not have participated in regular (e.g. 2 to 3 times per week) resistance training in the previous 12 months. In addition, volunteers will be required to obtain consent from their doctor (GP) before participating in the study.

Participants will be randomly assigned into three groups:

- (1) resistance/impact-loading exercise group
- (2) usual care/delay exercise group
- (3) resistance/cardiovascular exercise group

## Exercise Training Program

*Resistance/impact-loading exercise program (group 1)* - Sessions will take approximately 60 minutes (this includes the warm-up and cool-down periods) and will be conducted in the Exercise and Sport Centre at Edith Cowan University (ECU) in Perth, and Bunbury and at the University of Queensland (UQ) in Brisbane. Further, training sites in exercise clinics in Nedlands, Murdoch and Mandurah will be available to participants. Twice weekly exercise sessions will commence with a 5-minute warm up comprising of low-level aerobic activity such as walking and stationary cycling, as well as stretching. Six resistance exercises that target the major upper and lower body muscle groups (chest press, seated row, leg press, leg extension, leg curl, lat pulldown) will be performed. The rest period between sets will be 1-2 minutes. To ensure the progressive nature of the training program, subjects will be encouraged to work past the specific RMs prescribed. The workload will be increased by 5-10% increment for the next set/training session if subjects are able to perform more repetitions than the RMs specified during a set. Intensity will be manipulated ranging from 6-12-RM using 1-4 sets per exercise.

The impact-loading regime involves several activities which we have previously used in a yearlong training study in postmenopausal women. For the first 12 weeks, 2 rotations will be performed of skipping (30 sec), bounding over soft hurdles (13-16 cm), and drop jumping (10-15 cm). In the second 12 weeks, hopping on one leg (10 times) will be added, and 3 rotations of all activities will be performed. In the third 12-week period, leaping (10 times) will replace skipping, and for the remainder of the program 4 rotations will be performed of bounding (19-25 cm), drop jumping (20-25 cm), hopping, and leaping. All exercise sessions will be conducted in small groups of up to 10 participants, with participants exercising in pairs or under direct supervision to ensure correct technique and minimize the risk for injury. Each session will conclude with a 5-minute cool-down period of stretching activities.

In addition to the clinic training, twice weekly home-based training will take place. As with the clinic impact-loading program, the home exercise program will also follow a circuit routine and comprise, in a progressive fashion, 2 to 4 rotations of skipping, hopping, leaping, and drop jumping.

*Usual care/delay exercise group (group 2)* - This group will receive a printed booklet with information about exercise but will not receive exercise training in the initial 6 months of the study. In the second half of the study (month 7 to month 12) participants will undertake cycling sessions twice a week. Further participants in this group will also be offered a 3-month resistance training program following the 12-month intervention period. These sessions will be supervised by an exercise leader and take place on campus at ECU and at UQ. Subjects will be monitored during these sessions using the ratings of perceived exertion scale (RPE), and by heart rate response.

*Resistance/cardiovascular exercise group (group 3)* - This group will undertake the same resistance training regime as described above for group (1) that will include 6 exercises that target the major

upper and lower body muscle groups for the initial 6 months with a follow up home based program for the remaining 6 months of the program. In addition, each clinic session will include 20 minutes of aerobic exercise using various modes such as walking or jogging on a treadmill, cycling or rowing a stationary ergometer, or exercising on a cross training machine. Target intensity will be 60%-85% estimated maximum heart (220 – age) with individual heart rate monitors (Polar Electra Oy, Finland) provided for each participant. In addition to the clinic training, patients from this group will be encouraged to undertake twice weekly home-based training incorporating aerobic activity (e.g. walking, cycling) for the duration of the study.

All training will take place on Monday and Thursday or Tuesday and Friday at Edith Cowan University Mount Lawley, Joondalup and Bunbury Campus or in Exercise Clinics in Nedlands, Murdoch and Mandurah in WA, and The University of Queensland St Lucia Campus in Brisbane.

### ***TEST MEASURES***

Assessment at baseline, month 6 and month 12 (end of intervention) will contain all tests as outlined below.

#### **Body composition and bone density**

- Height and body weight.
- Body composition (fat mass and lean mass) and bone density of the hip and spine sites will be measured by dual x-ray absorptiometry (DXA), a routine technique for the measurement of bone density. You will lie on a specially designed table for approximately 10 minutes and a scanning arm will move above your total body and above your hip and spine (separate scans for your whole body, hip and spine). A low-dosage x-ray will pass from underneath the table to the scanning arm. The total radiation dose for all scans undertaken during the study is very low only a little more than normal background radiation and much less than, for example, an international flight.

#### ***Blood Pressure and Arterial Stiffness***

- The stiffness of your blood vessels and the blood pressure at the heart will be measured by a procedure known as pulse wave analysis. This is a painless procedure that requires a small pen like device to be placed on your wrist. Before and during the measurement you will be required to lie on a bed in a semi recumbent position. The overall measure takes approximately 15 minutes and also includes a normal blood pressure measure on the upper arm.

#### ***Cardiorespiratory Capacity***

- Maximum oxygen uptake (measure of aerobic capacity) will be measured by expired air analysis during a staged walking test on a motorized treadmill. Exercise capacity will be determined on the basis of the speed and grade of the treadmill as well as direct expired air gas analysis. Electrocardiogram will be recorded using a 4-lead monitoring system and blood

pressure will be measured each testing minute by sphygmomanometer. You will be asked to walk in a staged progressive walking test on a motorized treadmill under direct supervision of a medical doctor and an exercise physiologist.

### ***Muscle performance***

- Maximal muscle strength will be determined for each of the several upper and lower body muscle exercises to be undertaken in the training program using weight-training machines. The maximal strength is the most weight that can be lifted one time using correct technique.
- To determine muscle endurance of the upper and lower body, the number of times you can lift a weight that is 70% of your 1RM will be determined.

### ***Functional performance***

- Stair climb: You will be asked to ascend a flight of stairs (11 stairs) as fast as possible.
- 6 metres backwards walk: As a test of balance, participants will place one foot behind the other and will be asked to walk backwards 6 metres.
- Chair rise: You will be seated in a chair and asked to rise and sit 5 consecutive times, without the use of your arms for support, as fast as possible.
- 400 metres corridor walk: You will be asked to walk 20 meters in a corridor, turn and return to the starting position and repeat another 9 times.
- Balance test: You will be asked to stand on a special platform under conditions of eyes open and eyes closed. The platform will tilt slightly back and forth and the surrounding walls will also move. You will be wearing a harness which will support your body weight if you lose balance.

Note: before muscle performance and physical function tests are performed, demonstrations, practice time, sufficient warm-up and stretching will be undertaken.

### ***PSA, hormones and markers of cardiovascular disease and diabetes***

- PSA, hormones, and markers of cardiovascular disease and diabetes will be determined from blood samples to assess any changes in these physiological markers. All the testing will take place in the Exercise Physiology Research Laboratory at both ECU and UQ.

### ***Lifestyle questionnaires***

- Quality of life will be assessed using a standardized questionnaire for prostate cancer patients (EORTC QLQ-C30 and EORTC QLQ-PR25) that you can complete at home.
- Psychological distress (e.g. Anxiety, Depression) will be assessed using a standardized questionnaire (Brief Symptom Inventory 18).
- Health history and Demographic information will be also assessed using standardized questionnaires that you can complete at home. Self-reported physical activity will be also assessed by the leisure score index from the Godin Leisure-Time Exercise Questionnaire that you can complete at home.

## ***Risks***

Resistance training may result in mild discomfort and muscle soreness, however, this will be minimised by all sessions being supervised and commencing with a warm-up and concluding with a cool-down period of mild stretching activities. It is also possible that some muscle soreness may result from baseline performance testing, however, all participants will undertake a warm-up period of stretching before beginning the full exercise program. The risk of discomfort and muscle soreness will also be minimised by a gradual increase in exercise intensity. Lastly, risk of falling may exist in the performance of some tasks, however, participants will be closely supervised and spotted to prevent a fall from occurring. In the event that an emergency occurs, medical assistance will be obtained from the University Health Service according to our established emergency procedures.

Lastly, the discomforts associated with the blood drawing procedures are minimal. There is a risk that sometimes bruising and infection may occur and that the arm might become sore. Risk of bruising or infection from the blood draws will be minimized because all blood draws will be performed by a trained phlebotomist (lab technician) with extensive experience in both research and clinical settings. The total amount of blood drawn during each testing session will not exceed 10 ml. No syringes, lancets, needles or other devices capable of transmitting infection from one person to another shall be reused. All of these items, which are disposable, will be destroyed after each use. As an additional safeguard in preventing contamination new disposable gloves will be required for all blood draws. All contaminated items will be disposed of promptly in sharps containers.

All information will be strictly confidential and kept safely locked in a filing cabinet in the primary investigators office. Should publications result from this study, no reference will be made to any individuals.

On completion of the intervention and measurements, a summary of study and individual results will be made available to all participants.

## **PARTICIPATION IS VOLUNTARY AND SUBJECTS ARE FREE TO WITHDRAW FROM THIS STUDY AT ANY TIME.**

The study has been approved by Human Research Ethics Committee at Edith Cowan University subjects will be free to withdraw from the study at any time. Contact number, should there be any concerns relating to the project, is (08) 6304 2170 or Email: [research.ethics@ecu.edu.au](mailto:research.ethics@ecu.edu.au).

## ***Appendix C Statement of Informed Consent***

### **A RANDOMIZED CONTROLLED TRIAL OF EXERCISE TO REDUCE TREATMENT SIDE-EFFECTS IN MEN RECEIVING THERAPY FOR PROSTATE CANCER**

#### **STATEMENT OF INFORMED CONSENT**

1. I have read and understood the 'Information Sheet' for this study.
2. The nature and possible effects of the study have been explained to me.
3. I understand that the study involves the following procedures:
  - a. I will be required to obtain my doctors approval to undertake the study before any measures or training can take place.
  - b. I will be randomly assigned to undertake one of the following three exercise programs for 12 months: (1) resistance/impact-loading exercise, (2) usual care/delay exercise group, or (3) resistance/cardiovascular exercise.
  - c. I will be required to have my height, weight, body composition, blood analysis (PSA, hormones, cholesterol), blood pressure, cardiorespiratory capacity, and bone density taken before, at 6 months and after the study (month 12).
  - d. I will be required to complete a medical history before the training program commences and a quality of life and fatigue questionnaire before, at 6 months and after the study period (12 months).
  - e. I understand that my muscle strength will be assessed before, at 6 months and after the study period (12 months).
  - f. I understand that the following measures of physical function: the time to climb a flight of stairs, the time it takes to walk backwards 6 meters, the time it takes to

rise from a chair and to walk 400 meters and my balance ability will be assessed before, at 6 months and after the study period (12 months).

- 4 I understand that all research data will be treated as confidential.
- 5 Any questions that I have asked have been answered to my satisfaction.
- 6 I agree to participate in this study and understand that I can withdraw at any time without prejudice.
- 7 I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.

This study has been approved by Human Research Ethics Committee at Edith Cowan University contact number, should there be any concerns relating to the project, is (08) 6304 2170 or Email: research.ethics@ecu.edu.au.

**Name of subject (please Print)** \_\_\_\_\_

Signed \_\_\_\_\_ Date \_\_\_\_\_

Contact Phone Number

\_\_\_\_\_

**Witness (Name, please print)** \_\_\_\_\_

Signed \_\_\_\_\_ Date \_\_\_\_\_

## ***Appendix D Medical Doctor Consent Form***

### **MEDICAL DOCTOR CONSENT FORM FOR EXERCISE STUDY**

#### **“A RANDOMIZED CONTROLLED TRIAL OF EXERCISE TO REDUCE TREATMENT**

#### **SIDE-EFFECTS IN MEN RECEIVING THERAPY FOR PROSTATE CANCER”**

##### Researchers

Professor Robert Newton, PhD	E-mail: r.newton@ecu.edu.au	Phone: 08 6304- 5711
Dr. Dennis Taaffe, PhD	E-mail: dtaaffe@hms.uq.edu.au	Phone: 07 3346-7904
Dr. Daniel Galvão, PhD	E-mail: d.galvao@ecu.edu.au	Phone: 08 6304-3420
Assoc/Professor Nigel Spry, MBBS, Radiation Oncologist	E-mail: Nigel.Spry@health.wa.gov.au	
Professor Frank Gardiner, MBBS, Medical Urologist	E-mail: f.gardiner@uq.edu.au	

#### **School of Exercise, Biomedical and Health Sciences, Edith Cowan University and School of Human Movement Studies, The University of Queensland**

Dear Doctor,

The School of Exercise, Biomedical and Health Sciences, Edith Cowan University and School of Human Movement Studies, The University of Queensland are undertaking a study into the effects of exercise in older adults undertaking ADT (Androgen Deprivation Therapy) for prostate cancer. The intervention program will run for 12 months, entailing various combinations of progressive resistance (strength/weight) training, weight bearing/impact loading, stretching and aerobic exercises. Resistance exercise has been shown to be a safe and effective method for enhancing muscle strength in older adults. Preliminary studies have reported benefits from resistance exercise in prostate cancer patients undertaking ADT. However, the combined effects of both aerobic and resistance exercises and the inclusion of weight bearing/impact loading activities for this group of patients are yet to be examined. Such strategies could counteract the musculoskeletal treatment-related side effects (e.g. osteoporosis) and the newly reported adverse effects from ADT on cardiovascular and glucose metabolism. We require one hundred and ninety-five prostate cancer patients with at least 2 months past initiation of ADT and anticipated to remain hypogonadal for the duration of the study. Participants are required to not have bone metastases, musculo-skeletal, neurological or cardiovascular disorder that could inhibit them from exercising and to not have participated in regular (e.g. 2 to 3 times per week) resistance training in the previous 12 months. Participants will be randomly assigned to one of three groups: (1) resistance/impact-loading exercise, (2) usual



care/delay exercise group, and (3) resistance/cardiovascular exercise groups. The resistance exercise and major muscles used in the intervention will be:

1. *Chest Press: Pectorals, Deltoid, Triceps Brachii*
2. *Seated Rows: Rhomboids, Latissimus Dorsi, Biceps Brachii*
3. *Biceps curl: Biceps Brachii, Brachialis*
4. *Triceps extension: Triceps Brachii*
5. *Leg Press: Quadriceps, Gluteals, Hamstrings*
6. *Leg Curls: Hamstrings*
7. *Leg Extensions: Quadriceps*

Exercise sessions will commence with a 5-minute warm-up of aerobic activity and stretching and conclude with a 5-minute cool-down period that includes exercises for the abdominal and stretching. The exercise sessions will be undertaken at Edith Cowan University Sports and Exercise Centre (Mount Lawley, Joondalup, or Bunbury Campus) and at The University of Queensland (School of Human Movement Studies), using traditional resistance training machines to ensure participant safety. The impact-loading regime involves several activities shown to be safe and effective to maintain bone in older women, such as bounding and hopping. The aerobic component of the training session will incorporate 20-30 minutes of aerobic exercise at an intensity of 60-85% of heart rate maximum (a heart rate monitor will be worn). Exercise mode will alternate between rowing, cycle and treadmill ergometers. All sessions will be conducted in small groups of up to 10 participants under direct supervision to ensure proper technique and minimize the risk for injury. The total time to complete the exercise session will be less than 60 minutes.

Outcome measures in the study include muscle strength and endurance, cardiorespiratory capacity, blood pressure, body composition, hip and spine bone density, and functional abilities (e.g. 400-metre walk, balance test, time to rise from a chair), which are all standard measures in studies of older adults, as well as testosterone, PSA, cholesterol, insulin, glucose and quality of life.

Participants must meet all the following criteria to participate:

- (1) Undertaking ADT for at least 2 months
- (2) Non-bone metastases
- (3) No established osteoporosis or undertaking medication known to affect bone metabolism, such as bisphosphonates
- (4) No musculo-skeletal, cardiovascular or neurological disorder that could inhibit them from exercising

The study has been approved by Human Research Ethics Committee at Edith Cowan University and subjects will be free to withdraw from the study at any time. The concern of the principle investigators are of past and/or present medical conditions that may compromise the individual's ability to participate in the intervention, whether they be musculo-skeletal, neurological, cardiovascular, etc. in origin. For these reasons all potential participants have been asked to seek their medical doctor's approval prior to involvement in the study.

Should you require further information, please feel free to contact us by phone or by e-mail.

Sincerely,

Robert Newton, Dennis Taaffe, Daniel Galvão, Nigel Spry and Frank Gardiner

\_\_\_\_\_ is in sufficient health to participate in the above intervention study.

*(Participant)*

\_\_\_\_\_  
*(Doctor's signature)*

\_\_\_\_\_  
*(Date)*

\_\_\_\_\_  
*(Doctor's name)*

## ***Appendix E Urologist Letter***

### **“A RANDOMIZED CONTROLLED TRIAL OF EXERCISE TO REDUCE TREATMENT SIDE-EFFECTS IN MEN RECEIVING THERAPY FOR PROSTATE CANCER”**

Dear Urologist,

This letter is to advise you that your patient is currently an active participant in a NHMRC funded research study being conducted jointly by the School of Exercise, Biomedical and Health Sciences, Edith Cowan University and the School of Human Movement Studies, The University of Queensland. Your patient has been referred to us by our collaborative researchers, Prof Nigel Spry and Prof David Joseph from Sir Charles Gardiner Hospital.

We are currently undertaking a study into the effects of exercise in older adults undertaking ADT (Androgen Deprivation Therapy) for prostate cancer. The intervention program runs for 12 months, entailing various combinations of progressive resistance (strength/weight) training, weight bearing/impact loading, stretching and aerobic exercises. Resistance exercise has been shown to be a safe and effective method for enhancing muscle strength in older adults and previous work within our institutions has reported benefits from resistance exercise and combined resistance and aerobic exercise in prostate cancer patients undertaking ADT. Findings from our latest research, currently in press in the Journal of Clinical Oncology, showed a significant decrease in typical side effects associated with ADT such as reduced levels of fatigue, increased lean muscle mass, and improved overall quality of life.

However, the combined effects of resistance exercises and the inclusion of weight bearing/impact loading activities for this group of patients are yet to be examined. Such strategies could counteract the musculoskeletal treatment-related side effects (e.g. osteoporosis and premature sarcopenia). Furthermore, increased research into aerobic the adaptations is necessary with new evidence that this can reduce adverse effects from ADT on cardiovascular and glucose metabolism.

The concern of the principle investigators are of past and/or present medical conditions that may compromise the individual's ability to participate in the intervention, whether they be musculo-skeletal, neurological, cardiovascular, etc. in origin. For these reasons all potential participants have been asked to seek their medical doctor's approval prior to involvement in the study.

Should you require further information or wish to refer other existing patients, please feel free to contact our research assistant and exercise physiologist Greg Levin by email (g.levin@ecu.edu.au) or on our dedicated phone line (6304 2329).

Sincerely,

Robert Newton, Dennis Taaffe, Daniel Galvão, Nigel Spry and Frank Gardiner

## ***Appendix F Health History Questionnaire and Demographics***

### **“A RANDOMIZED CONTROLLED TRIAL OF EXERCISE TO REDUCE TREATMENT SIDE-EFFECTS IN MEN RECEIVING THERAPY FOR PROSTATE CANCER”**

#### **Medical History and Medications Questionnaire**

Last Name	First Name	Middle Initial
Date of Birth (Age)	Sex	Home Phone
Address	City, state	Post code
Family Physician		
Emergency Contact (Name)	Phone	Relationship

### **MEDICAL HISTORY**

#### **GENERAL**

##### **1) Smoking**

(a) Are you or have you ever been a smoker? Yes / No.

(b) Past / Current smoker? \_\_\_\_\_

(c) Age you started smoking: \_\_\_\_\_

(d) Age you quit smoking (for past smokers only): \_\_\_\_\_

(e) Average number of cigarettes smoked per day: \_\_\_\_\_

##### **2) Drinking (alcohol)**

(a) How many drinks do you usually have per week? \_\_\_\_\_

##### **3) Body weight**

(a) Has your weight fluctuated more than a few kilos in the last 12 months? Yes / No.

(b) If ‘Yes’, approximately how many kilograms? \_\_\_\_\_

**4) Physical activity**

(a) What is your current level of physical activity? Active/ Inactive. Details:

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**5) Medical condition**

(a) When were you diagnosed with prostate cancer?

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(b) Which types of treatments have you undertaken (or are currently undertaking), example: Androgen deprivation therapy or hormonal therapy, radiation therapy, and/or surgery? Please, specify the start date of each treatment and the duration treatment?

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(c) Do you know your PSA levels? When was the last time that your PSA levels were assessed?

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(d) Do you have any other medical conditions? (chronic or serious illness) Yes /No. Details:

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(e) Have you ever had any medical surgery? Yes /No. Details:

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**6) Bones**

(a) Have you been tested for osteoporosis before (DXA scan)? Yes / No

(b) What were the results? Normal bone density / Osteopenia / Osteoporosis

(c) Have you been placed on any medications to help strengthen your bones?  
(i.e Fosamax, Actonel, Calcitriol) Yes / No (Include details of medications in  
Medications Questionnaire.): \_\_\_\_\_

(d) Has your doctor recommended you do anything else to improve your bone density?  
(i.e. weight bearing exercise, calcium supplements) Yes /No. Details:

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(e) Have you ever broken a bone as a result of minor trauma? (including vertebral crush fractures) Yes / No. Details:

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**AT THE PRESENT**

(a) Do you experience shortness of breath while walking with others of your age?  
Yes / No

(b) Do you experience sudden tingling, numbness, or loss of feeling in arms, hands, legs,  
feet, or face?  
Yes / No

(c) Do you experience swelling of your feet and ankles?

Yes / No

(d) Do you get pains or cramps in your legs?

Yes / No

(e) Do you experience any discomfort in your chest?

Yes / No

(f) Have you ever been told that your blood pressure was abnormal? (If yes, do you currently take any medication?)

Yes / No

(g) Have you ever been told that your serum cholesterol or triglyceride level was high?

Yes / No

(h) Do you have diabetes? (If yes, how is controlled?)

Yes / No. Details:

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### MEDICATIONS

Please list below medications you are currently taking. Fill out every column for each medication you list.

MEDICATION	DURATION (in months and years)	Reason for taking (which medical condition) and other comments

**A randomized control trial of exercise to reduce treatment side-effects in men receiving therapy for prostate cancer**

**Demographic and Supplementary Medical Questionnaire**

**1. What is your current marital status?**

Single	Married	Defacto
Separated	Divorced	Widowed

**2. What is the highest level of education you have completed?**

Primary	Secondary	Trade
Certificate/Diploma	Bachelor degree	Higher degree
Other _____		

**3. Are you currently employed?**

Yes / No

**3b. If Yes:**

Full Time / Part Time

What is your occupation? \_\_\_\_\_

**4. Have you previously been treated for Prostate Cancer?**

Yes / No

**4b. If Yes, which of these treatment options did you previously receive?  
(please mark all appropriate options)**

Radiation	Brachytherapy	Chemotherapy
Surgery		
<input type="checkbox"/> Radical Prostatectomy		Hormone Therapy
<input type="checkbox"/> Orchiectomy		<input type="checkbox"/> Injection
		<input type="checkbox"/> Tablet

**5. Do you know what your Gleason Score (prostate biopsy) is?**

2      3      4      5      6      7      8      9      10



### Appendix G Training Day Log

Session		1	2	3	4	5	6	7	8	9	10
Day											
Date											
<b>Upper body</b>		<b>Reps/Wt</b>									
Chest Press											
Seated Row											
Shoulder Press											
Lat Pull											
Triceps extension											
Biceps curl											
<b>Lower Body</b>		<b>Reps/Wt</b>									
Incline Leg Press											
Leg Curl											
Leg Extension											
Seated Calf Raise											
<b>Trunk</b>		<b>Reps/Wt</b>									
Abdominal Crunch											
<b>Other</b>											
Stretches											
Warm-up											
Cool-down											
<b>Aerobic</b>											
Bike											
Heart Rate/RPE											
Rowing											
Heart Rate/RPE											
Treadmill											
Heart Rate/RPE											

Training heart rate:

Observations: