2006

Resistance exercise in men receiving androgen deprivation therapy for prostate cancer

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RESISTANCE EXERCISE IN MEN RECEIVING ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER

A thesis submitted for the degree of

Doctor of Philosophy

July, 2006

by

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USE OF THESIS

The Use of Thesis statement is not included in this version of the thesis.

ABSTRACTS

This thesis encompasses two literature reviews (chapter 2 & 3) and two experimental chapters (4 and 5) examining the available literature on exercise and cancer, resistance training and its anabolic responses in older men and women, the side effects of Androgen Deprivation Therapy (ADT) for prostate cancer and finally, the role of resistance exercise as a clinical intervention to counteract such changes as an adjuvant therapy.

REVIEW OF LITERATURE ONE

A REVIEW OF EXERCISE INTERVENTION STUDIES UNDERTAKEN IN CANCER PATIENTS

Purpose: To present an overview of exercise interventions in cancer patients during and after treatment and evaluate a dose training response considering type, frequency, volume and intensity of training along with their expected physiological outcomes.

Methods: The review is divided into studies that incorporated cardiovascular training, combination of cardiovascular, resistance and flexibility training and resistance training alone during and after cancer management. The criteria for inclusion were based on studies sourced from electronic and non-electronic databases and which incorporated pre- and post-intervention assessment with statistical analysis of the data.

Results: Twenty-six published studies are summarized**.** The majority of the studies demonstrate physiological and psychological benefits. However, most of these studies suffer limitations because they are not randomized controlled trials and/or use small sample sizes. Predominantly, studies have been conducted with breast cancer patients using cardiovascular training rather than resistance exercise as the exercise modality. Recent evidence supports the use of resistance exercise or "anabolic exercise" during cancer management as an exercise mode to counteract the side effects of the disease and treatment.

Conclusion: Evidence underlines preliminary positive physiological and psychological benefits from exercise when undertaken during or after traditional cancer treatment. As such, other cancer groups in addition to breast cancer should also be included in clinical trials to address more specifically dose response training for this population. Contemporary resistance training designs which provide a strong anabolic effect for muscle and bone may have an impact on counteracting some of the side effects of cancer management assisting patients to improve physical function and quality of life.

REVIEW OF LITERATURE TWO

ANABOLIC RESPONSES TO RESISTANCE TRAINING IN OLDER MEN AND WOMEN: A BRIEF REVIEW

Resistance training has been shown to be the most effective exercise mode to induce anabolic adaptations in older men and women. Advances in imaging techniques and histochemistry have increased the ability to detect such changes confirming the high level of adaptability that remains in aging skeletal muscle. This brief review presents a summary of the resistance training studies which directly compare chronic anabolic responses to training in older (> 60 years) men and women. Sixteen studies are summarized; the majority of these studies indicate similar relative anabolic responses between older men and women following resistance training. Relatively small sample sizes in most of the interventions limited the ability to detect significant sex differences and should be considered when interpreting these studies. Future research should incorporate larger sample sizes with multiple measurement time points for anabolic responses.

EXPERIMENTAL STUDY ONE

CHANGES IN MUSCLE, FAT, AND BONE MASS AFTER 36 WEEKS OF MAXIMAL ANDROGEN BLOCKAGE FOR PROSTATE CANCER

Objective: To assess the effects of androgen deprivation therapy (ADT) on whole body and regional muscle, fat and bone mass in men with prostate cancer without metastatic disease.

Patients and methods: Seventy-two men aged 44 to 88 years underwent spine, hip and whole body dual-energy X-ray absorptiometry (DXA) scans at baseline and following 36 weeks of ADT. Change in whole body and regional lean mass (LM), fat mass (FM), and bone mineral content (BMC) and density (BMD) were determined. In addition, PSA, serum testosterone and hemoglobin were assessed.

Results: Upper limb, lower limb, trunk, and whole body LM decreased by 5.6 ± 0.6%, 3.7 ± 0.5%, 1.4 ± 0.5% and 2.4 ± 0.4% ($p < 0.01$), respectively, while FM increased by 20.7 ± 3.3%, 18.7 ± 2.7%, 12.0 ± 2.5%, and 13.8 ± 2.3% ($p < 0.001$). Hip and spine BMD decreased by 1.5 ± 0.5% and 3.9 ± 0.4% ($p < 0.001$) as did whole body (2.4 ± 0.3%) and upper limb (1.3 ± 0.3%) BMD, but not lower limb BMD. Serum testosterone, PSA and hemoglobin decreased by 93.3% ± 0.4, 98.2% ± 0.5%, and 8.8 ± 0.9 ($p < 0.001$), respectively.

Conclusion: Thirty-six weeks of ADT resulted in a significant decrease in whole body and regional lean mass and bone mass, while whole body and regional fat mass increased in older men with prostate cancer. Strategies to counteract changes in soft tissue and bone mass during ADT should be formulated to minimize risk of sarcopenia, osteoporosis, and obesity.

EXPERIMENTAL STUDY TWO

RESISTANCE TRAINING AND REDUCTION OF PHYSICAL TREATMENT SIDE EFFECTS IN PROSTATE CANCER PATIENTS

Purpose: To examine the effect of progressive resistance training on muscle function, functional performance, balance, body composition and muscle thickness in men receiving androgen deprivation for prostate cancer.

Methods: Ten men aged (59-82 years) on androgen deprivation for localised prostate cancer undertook progressive resistance training for 20 weeks at 6-12 repetition maximum for 12 upper and lower body exercises in a University exercise rehabilitation clinic. Outcome measures included muscle strength and muscle endurance for the upper and lower body, functional performance (repeated chair rise, usual and fast 6-m walk, 6-m backwards walk, stair climb, and 400-m walk time) and balance by sensory organization test. Body composition was measured by dual energy x-ray absorptiometry and muscle thickness at four anatomical sites by B-Mode ultrasound. Blood samples were assessed for PSA, testosterone, growth hormone (GH), cortisol, and hemoglobin.

Results: Muscle strength (chest press, 40.5%; seated row, 41.9%; leg press, 96.3%; $p < 0.001$) and muscle endurance (chest press, 114.9%; leg press, 167.1%; $p < 0.001$) significantly increased following training. Significant improvement ($p < 0.05$) occurred in the 6-m usual walk (14.1%), 6-m backwards walk (22.3%), chair rise (26.8%), stair climbing (10.4%), 400-m walk (7.4%) and balance (7.8%). Muscle thickness increased ($p < 0.05$) by 15.7% at the quadriceps site. Whole body lean mass was preserved with no change in fat mass. There were no significant changes in PSA, GH, testosterone, cortisol, or hemoglobin.

Conclusions: Progressive resistance exercise has beneficial effects on muscle strength, functional performance and balance in older men receiving androgen deprivation for prostate cancer and should be considered to preserve body composition and reduce physical side effects associated with treatment.

DECLARATION

I certify that this thesis does not, to the best of my knowledge and belief:

(i) incorporate without acknowledgement any material previously submitted for a degree or diploma in any institution of higher education;

(ii) contain any material previously published or written by another person except where due reference is made in the text; or

(iii) contain any defamatory material.

I also grant permission for the Library at Edith Cowan University to make duplicate copies of my thesis as required.

ACKNOWLEDGEMENTS

For their contribution toward this thesis and encouragement during the course of this journey I wish to thank:

Professor Robert Newton, for granting me this unique opportunity to undertake my doctoral studies with him at Edith Cowan University, for the conception of the project, and for his supervision, guidance, and support during the project and my time at the University.

Associate Professor Kasunori (Ken) Nosaka for his valuable supervision and important contributions to this research.

Professor Linda Kristjanson and Dr. Michael Mcguigan, for their supervision and assistance on organizing important contacts for the development of this research.

Dr. Dennis Taaffe, The University of Queensland, for continuous inspiration, teaching, supervision, friendship and for showing “step by step” how to conduct research and write scientific papers.

Dr. Nigel Spry, Sir Charles Gairdner Hospital, for his close collaboration and guidance during this research and assistance with subject recruitment.

Dr. Jesse Judge, Joondalup Health Campus Hospital, for his collaboration with subject recruitment.

Dr. Katsuhiko Suzuki, Waseda University Japan and Dr. Kanemitsu Yamaya, Oyokyo Kidney Research Institute Japan for their important contribution with blood sample analyses.

Nadija Vrdoljak for the incredible technical support at all times when needed.

My brilliant family in Brazil: Maria de Lourdes Abido, João Carlos Galvão and João Carlos Galvão Junior for their constant love, friendship, integrity and dedication on providing opportunities to enjoy life and always fight for new challenges.

My friends Renato Abido and Andre Figueiredo for years of friendship and plenty of support even though they are very, very…far away.

My Australian friends: Dr. Sean Muller, Andrews's family and the postgraduate students from Edith Cowan University in particular Warren Andrews, Dr. Tim Doyle and Dale Chapman for their friendship and very important support.

The dedicated group of friends and students from Brazil who constantly provided enormous support while I pursued this dream: Jane Santos, Amanda Klabin, Dan Klabin, Marco Manela, Bebel Klabin, Felipe Calil, Lea Klabin, David Klabin, Gabriel Klabin, Ricardo Manela, Ester Manela, Otávio Koeller, Eder Nunes, Edson Nunes, Rosemar Nunes, Elson Nunes and Monica Torres.

My working colleagues from Rio de Janeiro who provided the first opportunity in the field of exercise science and constant guidance during early years of my work in Brazil: Eduardo Netto, Paulo de Tarso Maciel, Rolando Ceddia and Murilo Nunes.

The outstanding and dedicated group of subjects involved in this research project.

Finally, my wife Roberta for her remarkable support, patience, constant encouragement and love during this journey.

Thank you.

RESEARCH SUPPORT FOR THIS PROJECT

- International Postgraduate Research Scholarship, School of Exercise Biomedical and Health Sciences, Edith Cowan University (2004).

- Australian International Postgraduate Research Scholarship (IPRS), Edith Cowan University (2005-06).

- Life Fitness Academy Michael Pollock Memorial Grant, USA (2005).

- Fitness Technology, Australia (2005).

DEDICATION

This thesis is dedicated to my family

(Parents, brother and wife)

Maria de Lourdes Abido

João Carlos Galvão

João Carlos Galvão Junior

Roberta Peres Fernandes Galvão

PUBLICATIONS AND PRESENTATIONS FROM THE THESIS

Peer Reviewed Medline Journals

Galvão DA & Newton RU. A Review of Exercise Intervention Studies Undertaken in Cancer Patients. **Journal of Clinical Oncology**. 23:899-909, 2005.

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REVISION UNDERTAKEN FOR PEER REVIEW JOURNALS BASED ON THE WORK OF THE THESIS

- **Journal of Clinical Oncology (2006)**
- **Supportive Care in Cancer (2006)**
- **Canadian Medical Association Journal (2005)**
- **Lung Cancer - Journal of the International Association for the Study of Lung Cancer (2005)**
- **Cancer - American Cancer Society (2005)**
- **Scand J Med Science Sports (2005)**
- **Sports Medicine (2005)**
- **International Journal of Sports Medicine (2005)**
- **Journal of Aging and Physical Activity (2005)**

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Chapter 1

INTRODUCTION

Worldwide 15 million new cases and 10 million new deaths from all cancers are expected by the year of 2020 (Parkin, Bray, Ferlay, & Pisani, 2001). In this context, prostate cancer is the sixth most common cancer representing 14.3% of cancers among men in developed countries (Parkin, Pisani, & Ferlay, 1999). Nevertheless, the mortality rate for prostate cancer has declined over the past several years in many developed countries (Baade, Coory, & Aitken, 2004). It has been suggested that the prostate-specific antigen (PSA) screening that was introduced in North America in the late 1980s had a significant role on early detection of the disease contributing to the increased survival rates viewed in the last decade (Oliver, May, & Gunnell, 2001). Given that the life expectancy from prostate cancer patients has increased, clinical interventions aimed at decreasing levels of fatigue, promoting physiological and psychological adaptations, and improving quality of life treatment are relevant.

Recently, Denmeade and Isaacs (2004), in their comprehensive review of the historical development of prostate cancer treatments, reported that although there was a remarkable increase in the number of prostate cancer diagnostics over the last 150 years, understanding related to the specific biology of prostate cancer and its treatments (androgen deprivation treatment (ADT), prostatectomy, radiation, prostatic brachytherapy and systematic therapy) had developed only over the past 30 years. The traditional treatments for prostate cancer that focus on reducing the levels or effects of testosterone by ADT have many undesirable side effects (Diamond, Higano, Smith, Guise, & Singer, 2004; Hedlund, 2000; Holzbeierlein, McLaughlin, & Thrasher, 2004; Pickett, Bruner, Joseph, & Burggraf, 2000; Stege, 2000). Some of these physical side effects include increased fat mass, reduction of muscle and bone mass, altered lipid profiles, anemia and gynecomastia which have negative implications for physiological and psychological function (Cassileth et al., 1992;

Cleary, Morrissey, & Oster, 1995; Diamond, Higano, Smith, Guise, & Singer, 2004; Hedlund, 2000; Holzbeierlein, McLaughlin, & Thrasher, 2004; Michaelson, Marujo, & Smith, 2004; Pickett, Bruner, Joseph, & Burggraf, 2000; Stege, 2000).

Only scant information on alterations to bone mass and soft-tissue following ADT exist (Smith, 2004; Smith et al., 2002; Tayek et al., 1990), and there is no information on changes in bone density levels at various regional sites, regional lean and fat mass (i.e. trunk, upper, and lower limb) during therapy. Abdominal fat has been related to increased risk for the development of cardiovascular complications, thus, if ADT tends to induce greater trunk fat accumulation, alternative or adjuvant therapies should be devised to counteract such conditions. Similarly, are losses in muscle and bone mass greater at weight-bearing sites than non-weight bearing sites and can strategies be incorporated into the patient's management plan to address this? Moreover, these changes in body composition and tissue distribution can be directly related to chronic conditions that result in disability and loss of independence in older adults.

Existing treatments to alleviate these side effects have been predominantly pharmaceutical, however, these treatments are expensive, with the cost benefit ratio questionable and their effects do not translate into improved physical function or decreased levels of fatigue (Smith et al., 2003; Smith et al., 2001).

Considering that the life expectancy for prostate cancer patients has increased, additional information on how bone mass and body composition adapts during ADT seems relevant so that appropriate to counter the physiological side effects can be devised and recommended.

To date, most of the experimental studies examining the role of exercise during cancer treatments have included breast cancer patients (MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Schwartz, Mori, Gao, Nail, & King, 2001; Winningham & MacVicar, 1988; Winningham, M. L., M.G. MacVicar, M. Bondoc, J.I. Anderson, & J.P. Minton, 1989) and other types of cancer (Cunningham, Morris, & Cheney, 1986; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo, Tilman et al., 1997; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999), but have not included prostate cancer patients undertaking ADT. Moreover, most exercise interventions included aerobic exercise (Courneya et al., 2003; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo,

Stieglitz et al., 1997; Dimeo, Tilman et al., 1997; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Schwartz, 1999; Schwartz, 2000; Segal et al., 2001; Winningham, M. L., M. G. MacVicar, M. Bondoc, J. I. Anderson, & J. P. Minton, 1989) rather than resistance exercise. In view of the extensive scientific literature supporting resistance training as being the most effective anabolic exercise method available for improving muscle strength, muscle hypertrophy and bone mineral density (Charette et al., 1991b; Fiatarone et al., 1990; Fiatarone et al., 1994; Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988a; Hakkinen et al., 1998a; Hakkinen et al., 1996; Nelson et al., 1994; Newton et al., 2002; Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996; Taaffe et al., 1994; Wolff, van Croonenborg, Kemper, Kostense, & Twisk, 1999), resistance exercises may have a role to play counteracting the catabolic side effects of ADT by promoting a sufficient anabolic environment which can lead to positive effects on the musculoskeletal system. A preliminary report from Segal and associates (2003) recently examined the effects of a short-term period of resistance exercise on patients diagnosed with prostate cancer undertaking ADT. Although the results support positive psychological and physical outcomes, questions remain as to how specific physical and physiological parameters such as muscle function, functional performance, balance, body composition and bone mineral density would adapt with resistance training in long-term trials. Given the fact that ADT usually occurs over a two to three year period, but can also occur over a 20 year time frame (Schroder, 2000), the role of resistance exercise for prolonged periods of time may be even more relevant for reducing the catabolic conditions produced by ADT. Therefore, the purpose of the present research is to: 1) explore the available literature in the area of exercise interventions during and after cancer therapy and propose possible guidelines for exercise during cancer treatment, 2) review and identify the anabolic effects following resistance training interventions in older adults, 3) examine the effects of ADT in regional body composition, bone mass, bone markers and hemoglobin in a large cohort of men with localized prostate cancer receiving maximal androgen blockage by Luteinizing Hormone-Realizing Hormone Agonist (LRHRa) and antiandrogen during 36 weeks, and 4) investigate the effects of a 20-week high intensity progressive resistance training on muscle function, functional performance, balance, body composition, muscle thickness, bone mineral density, serum hormones and PSA in prostate cancer patients on undergoing established ADT.

SIGNIFICANCE

Considering the notable impact of prostate cancer in the male population world wide and that the life expectancy from prostate cancer patients has increased, clinical interventions aimed to decrease levels of fatigue, promote physical and physiological adaptations and improve quality of life during treatment are necessary. Thus, resistance exercise may have a potential role to counteract the catabolic side effects of ADT promoting a sufficient anabolic environment that can lead to positive effects on the musculoskeletal system. Moreover, because ADT may be continued for as long as 20 years, the role of resistance exercises may be especially relevant in improving physical and physiological parameters and consequently, quality of life. As such, the findings from this study may have important application to exercise prescription in prostate cancer patients undertaking ADT.

PURPOSE

The aims of this project are to test several research questions:

Experiment 1:

1) Is regional body composition affected following maximal androgen blockage in prostate cancer patients?
2) Is regional bone mineral density affected following maximal androgen blockage in prostate cancer patients?
3) Are levels of hemoglobin and bone markers altered following maximal androgen blockage in prostate cancer patients?

Experiment 2:

1) Is muscle function increased following resistance exercise in prostate cancer patients?
2) Is functional performance increased following resistance exercise in prostate cancer patients?
3) Is balance improved following resistance exercise in prostate cancer patients?
4) Is body composition (total lean and fat mass) altered following resistance exercise in prostate cancer patients?

5) Is muscle thickness increased following resistance exercise in prostate cancer patients?
6) Are systemic levels of serum hormones, PSA, and blood cells altered following resistance exercise in prostate cancer patients?

DEFINITIONS OF TERMS

Prostate cancer: "A malignant tumor (carcinoma) of the prostate gland, a common cancer in elderly men. In most men it progresses slowly over many years and the gives symptoms similar to those of benign enlargement of the prostate."(Martin, 2002)

Prostate Specific Antigen (PSA): "An enzyme produced by the glandular epithelium of the prostate. Increased quantities are secreted when the glands enlarge, 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% 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 greater risk of prostate cancer and improve the discrimination between cancer and benign disease in men with PSA in the range 4-10ng/mg. PSA levels tend to be much higher in advanced prostate cancer and the rate of fall on the treatment is a good prognostic indicator of response." (Martin, 2002)

Sarcopenia: The loss of muscle mass with aging (Evans, 1995).

Osteoporosis: "Loss of bony tissue, resulting in bones that are brittle and liable to fracture. Infection, injury and synovitis can cause localised osteoporosis of adjacent bone. Generalised osteoporosis is common in the elderly, and in women often follows menopause. It is also a feature of Cushing's syndrome and prolonged steroid therapy. Osteoporosis can be detected by the quantitative digital radiography and by DEXA scans. A diet with adequate calcium, exercise, and hormone replacement are preventative, and bisphosphonates can be used to reduce or halve further bone loss." (Martin, 2002)

Dual X-ray absorptiometry (DXA): "A method of measuring bone mineral density based on the proportion of a beam of photons that passes through the bone." (Martin, 2002)

Chapter 2

REVIEW OF LITERATURE ONE

A REVIEW OF EXERCISE INTERVENTION STUDIES UNDERTAKEN IN CANCER PATIENTS

Daniel A. Galvão & Robert U. Newton.

Journal of Clinical Oncology. 23:899-909,2005

VOLUME 23 · NUMBER 4 · FEBRUARY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Review of Exercise Intervention Studies in Cancer Patients

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Submitted June 14, 2004; accepted October 14, 2004.

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0732-183X/05/2304-899/$20.00

DOI: 10.1200/JCO.2005.06.085

A B S T R A C T

Purpose
To present an overview of exercise interventions in cancer patients during and after treatment and evaluate dose-training response considering type, frequency, volume, and intensity of training along with expected physiological outcomes.

Methods
The review is divided into studies that incorporated cardiovascular training, combination of cardiovascular, resistance, and flexibility training, and resistance training alone during and after cancer management. Criteria for inclusion were based on studies sourced from electronic and nonelectronic databases and that incorporated preintervention and postintervention assessment with statistical analysis of data.

Results
Twenty-six published studies were summarized. The majority of the studies demonstrate physiological and psychological benefits. However, most of these studies suffer limitations because they are not randomized controlled trials and/or use small sample sizes. Predominantly, studies have been conducted with breast cancer patients using cardiovascular training rather than resistance exercise as the exercise modality. Recent evidence supports use of resistance exercise or "anabolic exercise" during cancer management as an exercise mode to counteract side effects of the disease and treatment.

Conclusion
Evidence underlines the preliminary positive physiological and psychological benefits from exercise when undertaken during or after traditional cancer treatment. As such, other cancer groups, in addition to those with breast cancer, should also be included in clinical trials to address more specifically dose-response training for this population. Contemporary resistance training designs that provide strong anabolic effects for muscle and bone may have an impact on counteracting some of the side effects of cancer management assisting patients to improve physical function and quality of life.

J Clin Oncol 23:899-909. © 2005 by American Society of Clinical Oncology

INTRODUCTION

A progressive increase of cancer burden, with an estimated 15 million new cases and 10 million new deaths, is expected by the year of 2020.[1] In this context, prostate cancer is the sixth most common cancer in the world, representing 14.3% of cancers among men in developed countries with more than 80% of the cases occurring in men older than 65 years.[2] Breast cancer appears as the third most common cancer in the world, and it is ranked as the fifth most prevalent cause of death from cancer overall, being the leading cause of cancer mortality in women.[2] Treatments for cancer include surgery as well as systemic and radiation therapy and have successfully shown reductions in mortality rates. However, for cancer patients, the increased levels of fatigue during treatment remains a concern as it affects the majority of patients during radiotherapy

Introduction

A progressive increase of cancer burden with an estimated 15 million new cases and 10 million new deaths are expected by the year of 2020 (Parkin, Bray, Ferlay, & Pisani, 2001). In this context, prostate cancer is the sixth most common cancer in the world representing 14.3% of cancers among men in developed countries with more than 80% of the cases occurring in men older than 65 years (Parkin, Pisani, & Ferlay, 1999). Breast cancer appears as the third most common cancer in the world and it is ranked as the fifth most prevalent cause of death from cancer overall being the leading cause of cancer mortality in women (Parkin, Pisani, & Ferlay, 1999). Treatments for cancer include surgery, systemic and radiation therapy and have successfully shown reductions in mortality rates. However, for cancer patients, the increased levels of fatigue during treatment remains a concern as it affects the majority of patients during radiotherapy and/or chemotherapy periods compromising their physical function and quality of life (Dimeo, 2002; Dimeo, 2001; Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Irvine, Vincent, Graydon, & Bubela, 1998; Smets, Garssen, Schuster-Uitterhoeve, & de Haes, 1993; Smets, Visser, Willems-Groot, Garssen, Oldenburger et al., 1998; Smets, Visser, Willems-Groot, Garssen, Schuster-Uitterhoeve et al., 1998). Dimeo (2002; , 2001) has proposed that the lack of physical activity during treatment may affect the increased levels of fatigue observed during and after cancer management. As such, several studies examining the role of exercise with cancer patients have linked the increased levels of physical activity during (Adamsen et al., 2003; Courneya et al., 2003; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo et al., 2003; Dimeo, Stieglitz et al., 1997; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; Kolden et al., 2002; MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Na, Kim, Kim, Ha, & Yoon, 2000; Segal et al., 2003; Winningham, M. L., M.G. MacVicar, M. Bondoc, J.I. Anderson, & J.P. Minton, 1989) and after cancer treatment (Dimeo, Tilman et al., 1997; Durak & Lilly, 1998; Durak, Lilly, & Hackworth, 1999; Nieman et al., 1995; Peters, Lotzerich, Niemeier, Schule, & Uhlenbruck, 1994; Peters, Lotzerich, Niemeir, Schule, & Uhlenbruck, 1995; Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000; Segar et al., 1998; Sharkey, Carey, Heise, & Barber, 1993) with

positive effects on decreasing rates of fatigue, enhancing physical performance and quality of life. However, the majority of the exercise interventions undertaken with this population have focused on cardiovascular training (Courneya et al., 2003; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo, Stieglitz et al., 1997; Dimeo, Tilman et al., 1997; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Schwartz, 1999; Schwartz, 2000; Segal et al., 2001; Winningham, M. L., M. G. MacVicar, M. Bondoc, J. I. Anderson, & J. P. Minton, 1989), with few studies using the combination of aerobic and resistance exercises (Adamsen et al., 2003; Durak & Lilly, 1998; Durak, Lilly, & Hackworth, 1999; Kolden et al., 2002; Nieman et al., 1995; Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000) or resistance exercise alone (Cunningham, Morris, & Cheney, 1986; Segal et al., 2003). Therefore, little is known as to the effect of resistance training being a primary exercise choice to counteract some of the physiological conditions accompanied by cancer disease and the traditional treatments. Considering that most of the experimental exercise studies have incorporated breast cancer patients (MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Schwartz, Mori, Gao, Nail, & King, 2001; Winningham & MacVicar, 1988; Winningham, M. L., M.G. MacVicar, M. Bondoc, J.I. Anderson, & J.P. Minton, 1989) and other types of cancer (Cunningham, Morris, & Cheney, 1986; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo, Tilman et al., 1997; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999) but not prostate cancer, there is a particular lack of information on how prostate cancer patients undertaking traditional treatment would respond to an exercise program and yet given the documented effects of androgen deprivation therapy (ADT) (Cassileth et al., 1992; Cleary, Morrissey, & Oster, 1995; Diamond, Higano, Smith, Guise, & Singer, 2004; Hedlund, 2000; Holzbeierlein, McLaughlin, & Thrasher, 2004; Michaelson, Marujo, & Smith, 2004; Pickett, Bruner, Joseph, & Burggraf, 2000; Stege, 2000) these patients should benefit particularly from resistance exercise. To date, only one published paper has examined the effects of a short-term resistance exercise program on patients diagnosed with prostate cancer and undertaking ADT (Segal et al., 2003). Interestingly, they reported quite promising results. In view of the extensive scientific literature supporting resistance training as being the most effective method available for improving muscle strength

and increasing lean tissue mass in different populations ranging from athletes to frail older adults (Charette et al., 1991b; Fiatarone et al., 1990; Fiatarone et al., 1994; Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988a; Hakkinen et al., 1998a; Hakkinen et al., 1996; Kraemer et al., 1999b; Kraemer et al., 2003; Newton et al., 2002; Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996; Taaffe et al., 1994), resistance exercise may also have a great potential to counteract the side effects of prostate cancer during ADT by increasing muscle function, lean tissue mass and bone mineral density with subsequent reduction in levels of fatigue.

There are specific training variables involving resistance exercise prescription which include number of sets and repetitions (volume), intensity of training (load), duration of rest between sets and exercises, frequency of training and repetition velocity (American College of Sports Medicine, 1998b; Kraemer et al., 2002; Kraemer & Ratamess, 2004). Currently, there is no information with regard to such training variables and possible variations with cancer patients undertaking resistance training programs. Interestingly, some of these variables have been examined in untrained older adults (Galvão & Taaffe, 2004; Hunter et al., 2001; Taaffe, Duret, Wheeler, & Marcus, 1999; Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996; Vincent et al., 2002) and favourable responses in strength and function result from a variety of training regimens, even those that involve relatively low intensities (Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996; Vincent et al., 2002; Vincent, Vincent, Braith, Bhatnagar, & Lowenthal, 2003), frequencies (Taaffe, Duret, Wheeler, & Marcus, 1999) and volume (Galvão & Taaffe, 2004; Taaffe & Galvão, 2004). Considering the detrained state and high levels of fatigue of many cancer patients, it may be expected that even a training program consisting of lower intensity, volume and frequency could significantly promote positive physiological and psychological adaptations increasing quality of life in this population.

The purpose of this paper is to present a descriptive overview and chronological perspective of developments of the experimental exercise intervention studies undertaken during and after cancer management. The second aim of this review attempts to establish a dose response of training for this population considering type of exercise, frequency of training, volume of training, intensity of training and expected physiological outcome measures. In addition, we also highlight specific points that should be examined in the future with the goal of obtaining more information on exercise prescription for this population. This review reports 26

published studies appearing in the Medline (electronic version of Index Medicus) database, published by June of 2004 and searched by the terms: exercise; cardiovascular training; resistance training; rehabilitation; and cancer. Secondary searching involved scanning the reference lists from the papers identified above and then locating papers which appeared useful in reviewing the topic. A key criterion throughout this process was identifying studies which incorporated pre- and post-intervention assessment with statistical analysis of the data.

Experimental Exercise Studies during Cancer Treatment

A summary of the published studies examining the effect of exercise on cancer patients undertaking treatment is shown in Table I. Out of the 18 experimental exercise interventions under cancer treatment, 14 had used some type of cardiovascular training (Courneya et al., 2003; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo et al., 2003; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Na, Kim, Kim, Ha, & Yoon, 2000; Schwartz, 1999; Schwartz, 2000; Schwartz, Mori, Gao, Nail, & King, 2001; Segal et al., 2001; Winningham & MacVicar, 1988; Winningham, M. L., M.G. MacVicar, M. Bondoc, J.I. Anderson, & J.P. Minton, 1989), two had used a mixed training program using cardiovascular, resistance and flexibility exercises (Adamsen et al., 2003; Kolden et al., 2002) while the other two studies applied a structured resistance training program (Cunningham, Morris, & Cheney, 1986; Segal et al., 2003). The main outcome measures from these studies include: levels of fatigue (Mock, 2001a; Mock et al., 1997; Schwartz, 1999; Schwartz, Mori, Gao, Nail, & King, 2001; Segal et al., 2003), quality of life, emotional-related distress (Adamsen et al., 2003; Courneya et al., 2003; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; Kolden et al., 2002; Mock et al., 1997; Mock et al., 2001; Schwartz, 1999; Segal et al., 2001), immunological parameters (Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo et al., 2003; Dimeo, Tilman et al., 1997; Na, Kim, Kim, Ha, & Yoon, 2000), aerobic capacity (Adamsen et al., 2003; American College of Sports Medicine, 1998b; Courneya et al., 2003; Dimeo, Fetscher, Lange,

Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo et al., 2003; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; Kolden et al., 2002; MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Schwartz, 1999; Schwartz, Mori, Gao, Nail, & King, 2001; Segal et al., 2001; Winningham, M. L., M.G. MacVicar, M. Bondoc, J.I. Anderson, & J.P. Minton, 1989) and muscle strength (Adamsen et al., 2003; Kolden et al., 2002; Segal et al., 2003).

A. Cardiovascular training

The first study by Winningham and colleagues (1988) examined the effect of a 10-week aerobic program performed three times per week on nausea responses of breast cancer patients undertaking chemotherapy. Subjects were randomly assigned to an exercise, placebo or control group. The exercise group improved significantly more on symptoms of nausea compared to control and placebo ($P < 0.05$). Considering that nausea is a consistent symptom experienced by cancer patients during treatment, this preliminary data showed that cardiovascular training can safely be incorporated during breast cancer traditional treatment and may decrease symptoms of nausea. Winningham and colleagues (1989) also presented data related to a sub-group of their earlier report (Winningham & MacVicar, 1988) which examined the effect of a 10- to 12-week aerobic training program on body composition responses of breast cancer subjects undertaking chemotherapy. Subjects were randomly allocated to an exercise group which trained 3 times per week for 20-30 minutes with intensity set at 60-80% of maximal heart rate or a control group which did not receive the exercise treatment. Although elementary techniques for body composition determination were used in this intervention, the results showed enhanced adaptations for lean tissue mass of the training group compared to the control group. Considering 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.

The effect of a 10-week aerobic interval training program was also investigated by MacVicar and associates (1989). Forty-five women with breast cancer receiving chemotherapy were randomly assigned to an aerobic exercise group (cycling training), a flexibility training group or a control group. Exercise intensity

was set at 60-85% of the maximum heart rate reserve. Results demonstrated differences for maximum oxygen uptake (VO2max) and testing time among groups with the aerobic training group improving significantly more than the flexibility and control group.

Mock and colleagues (1997) examined the effect of a home based exercise program on women with breast cancer undertaking radiotherapy. The exercise program consisted of a 20-30 minute self-paced walking program, 4-5 times per week over 6 weeks. A 12-Minute Walk Test, Symptom Assessment Scales and the Piper scale were used to assess physical function, symptoms experience and fatigue, respectively. Results showed that subjects undertaking the exercise program had a significant improvement in walking distance, symptom experience (anxiety, depression and difficulty sleeping) and fatigue.

The effect of a daily bed cycling program during high-dose chemotherapy treatment in cancer patients followed by autologous peripheral blood cells transplantation was reported by Dimeo and associates (1997). Subjects from the control group experienced significantly higher loss of physical performance levels during hospitalization than the exercise group ($p < 0.05$). Moreover, other physiological parameters such as duration of neutropenia, thrombopenia and severity of diarrhea were significantly reduced after the exercise intervention ($p < 0.05$). Dimeo and colleagues (1998) also reported the response of a 6-week cardiovascular exercise program on fatigue and physical performance in a small sample of cancer patients ($n = 5$) experiencing fatigue during treatment. A progressive walking treadmill program up to 30-35 minutes with intensity set to elicit a blood lactate level of 3 mmol.L in capillary blood was prescribed. At the end of the intervention, walking distance, walking maximal performance, heart rate and lactate concentration were improved ($p < 0.05$) demonstrating once more positive physiological responses accrued with cardiovascular training. In addition, the authors also noted a clear decrease in levels of fatigue at post-test. Subsequently in 1999, the same group of investigators (Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999) also examined a daily exercise protocol consisting of a supine bike program followed by an interval training pattern for 30 minutes in cancer patients receiving high doses of chemotherapy. Outcome measures included psychological distress and levels of fatigue. It was demonstrated at the end of the intervention that subjects undertaking

the exercise program significantly decreased psychological distress with no changes in fatigue levels.

Schwartz and colleagues (2000; , 1999) reported results from a 8-weeks exercise intervention in women with breast cancer undertaking chemotherapy. The exercise program included a home-based walking program with self-paced intensity measured by an accelerometer. Subjects who underwent the exercise program demonstrated greater response in the physical performance assessment (12-minute walk test), as well as decreasing levels of fatigue compared to subjects who did not adopt the training program ($p < 0.05$).

The short-term effect of cardiovascular training on natural killer cell cytotoxic activity (NKCA) in stomach cancer patients were reported by Na and associates (2000). Subjects were assigned to an exercise group which performed 30 minutes of supervised cardiovascular training using arm and cycle ergometer or a non-exercise control group. Blood samples were collected at baseline, day 7 and day 14. At post-test a significantly greater increase in NKCA was noted for the exercise group (27.9%) compared to the control group (13.3%) ($p < 0.05$). Although the training period was short in duration, it is interesting to note that both groups had similar values for NKCA at the midpoint of intervention, with the differences between groups occurring during the second half of the training period.

Schwartz and colleagues (2001) also investigated the relationship of fatigue and exercise through a home-based aerobic exercise program consisting of a 12-minute walk in women undergoing chemotherapy treatment for breast cancer. Functional abilities were assessed through a 12-minute walk test and fatigue levels by a self-reported instrument. The exercise program increased functional ability by 15% whereas the non-exercisers decreased performance by 16%. In addition, decreased levels of fatigue ($p < 0.01$) for the exercise group were observed after the intervention. It is interesting to note that the exercise program was unsupervised with none of the sessions being accompanied by an exercise physiologist. Considering that training program variables were not well controlled during training, the results are somewhat attractive and one would expect even greater adaptations for an exercise program that incorporates a more controlled setting resulting in an enormous impact on the outcome measures with this population.

The effect of a similar home-based walking exercise intervention on breast cancer patients undertaking either radiotherapy or chemotherapy was also examined

by Mock and colleagues (2001). The exercise program consisted of a progressive walking (10-30 minutes) program 5 to 6 days per week with an unspecified training intensity. Similar to Schwartz and colleagues (2001) and their previous report (Mock et al., 1997), physical function was assessed by the 12-Minute Walk Test. In addition fatigue and emotional distress were measured by the Pipe scale and Profile of Mood States (POMS), respectively. Consistent with their previous findings (Mock et al., 1997), the exercise intervention lead to a significant improvement in physical performance by increasing walking distance. Additionally, fatigue and emotional distress were enhanced at post-test indicating once more that positive psychological outcomes may be achieved with a simple home-based walking exercise program.

Segal and colleagues (2001) conducted a randomized controlled trial examining the effect of a supervised and unsupervised walking program on breast cancer patients undertaking treatment (radiotherapy, hormonal therapy or chemotherapy) over 26 weeks. Aerobic capacity, body weight and generic and disease-specific health related quality of life were assessed (MOS SF-36) at baseline and post-test. Results demonstrated that physical function measured by the MOS SF-36 decreased in the control group while it increased in both training groups ($p < 0.05$). At post-test, no differences among groups were detected for quality of life, aerobic capacity or body weight. However, when groups were stratified by type of adjuvant therapy, in this case not receiving chemotherapy, differences in improvement were observed between the supervised and control group for aerobic capacity ($p < 0.01$). It is relevant to point out that the small changes in aerobic capacity (3.5%) may be related to the nonspecific aerobic capacity test protocol (stepping ergometer) utilized by the authors to assess chronic response of a walking program.

The effect of 2-weeks of cardiovascular training on a mixed cancer population undergoing conventional or high-dose chemotherapy during hospitalization was examined by Dimeo and associates (2003). The training program consisted of a daily walking treadmill interval training program with intensity set at 70% of the maximum heart rate. Submaximal stress test results demonstrated that physical performance remained unaltered during treatment with significant reductions in hemoglobin levels at hospital discharge ($p < 0.05$). Although physical performance did not change at post-test, results demonstrated that cardiovascular training may assist on preserving performance status during intensive chemotherapy.

Finally, Courneya and associates (2003) conducted a randomized controlled trial examining the effect of a home based exercise program on quality of life and cardiovascular capacity of colorectal cancer patients undertaking adjuvant therapy. The exercise group was instructed to perform cardiovascular and flexibility activities 3-5 times per week over 16 weeks while the control group advised to not participate in any exercise activity during the study period. No significant differences were observed between groups for quality of life and cardiovascular capacity at the end of the intervention. The failure to detect differences between groups is primarily explained by the fact that 51.6% of the control group did not comply with the study and exercised during the study period. The nature of the exercise itself (home based program) was pointed out by the authors as being one possible reason of the high contamination during the intervention with little effectiveness.

B. Cardiovascular, resistance and flexibility training

Kolden and associates (2002) examined the effect of an exercise training intervention including cardiovascular, resistance and flexibility training over 16 weeks in breast cancer patients undertaking some type of adjuvant therapy (radiotherapy, chemotherapy or hormonal therapy). Subjects were tested for resting blood pressure, body composition, aerobic capacity, flexibility and strength. In addition, numerous psychological outcomes were also examined using the Beck Depression Inventory, State-Trait Anxiety Inventory, Positive and Negative Affect Schedule, Hamilton Scale for Depression, Quality of Life and Global Assessment Scale. At the end of the intervention, there was an observed effect for time for upper and lower body strength, cardiovascular capacity (estimated VO2 maximum), flexibility, and resting systolic blood pressure ($p < 0.05$). Additionally, subjects experienced positive psychological adaptations with training improving some of the Quality of Life measures.

Recently, Adamsen and colleagues (2003), examined the effect of a high intensity supervised exercise program on a mixed cancer population over 6-weeks. The training program included interval training with intensity set at 60 to 100% of

the maximal heart rate, resistance exercises performed at 85 to 95% of 1-RM for 5-8 repetitions and relaxation training. The results demonstrated an increase of 32.5% in maximal strength ($p < 0.0001$) and 16% improvement in VO2max ($p < 0.001$). Several measures of quality of life were also improved however no statistical significant were noted. It is relevant to highlight that this is the first study which incorporates a higher intensity training design, however, the absence of a control group and the short duration of the intervention limited the interpretation of the data.

C. Resistance training

The earliest published study examining the effects of resistance exercise was a short-term intervention involving patients with acute leukemia undertaken by Cunningham and associates (1986). Subjects were randomly assigned to two exercise groups performing the program either three or five times weekly or a non-exercising control group. The training program consisted of several upper and lower body exercises including the chest press, biceps curl, triceps extension, straight leg raises, knee extension, hip extension, hip abduction, shoulder retractors and sit-ups performed with 15 repetitions at an unspecified intensity. Outcome measures included skinfold measures, arm circumference, nitrogen balance and creatinine excretion. Results indicated that groups did not change arm circumference and skinfold measures over the course of the intervention. Although, there were no differences among groups for nitrogen balance during the course of the study, the authors suggested that the exercise program favored both training groups with the control group decreasing levels of creatinine excretion from pre-to post-test ($p < 0.05$).

Recently, Segal and colleagues (2003) reported the results from a 12-week whole body resistance training intervention in prostate cancer patients undergoing ADT. The resistance training program consisted of two sets of eight to 12 repetitions at 60 to 70% of 1RM for six upper body and three lower body exercises performed three times per week. Outcome measures included fatigue, disease-specific quality of life assessment, and muscle strength and body composition. Results showed positive effects of resistance training on decreasing fatigue levels, health-related quality of life and muscle strength with no changes in body composition by the subjects

embarking on the exercise program. The fact that body composition was unaffected by the training program may be related in part to the elementary body composition methods used to assess changes in muscle and fat tissue. In addition, it is well know that strength gains during the first stages of resistance training are predominantly due to neural factors with gains in muscle size becoming dominant as training continues (Sale, 1987, 1988; Sale, MacDougall, Upton, & McComas, 1983). Consequently, the shorter duration of the intervention and the limitations on body composition assessment methods indicated that increases in strength were likely to be related to neural alterations rather than muscle morphological changes. This preliminary data showed optimistic outcomes with a resistance training program which is characterized primarily by anaerobic energy sources rather than aerobic. Taking into consideration that immunological parameters were not assessed in this particular study, it remains to quantify if resistance training may positively alter the immune system of patients under cancer treatment. In addition, it would be interesting to examine how other types of cancer patients would respond with resistance exercises.

Experimental Exercise Studies after Cancer Treatment

Experimental studies examining the effect of exercise on cancer patients after treatment are presented in Table II. Four studies had used cardiovascular exercise programs (Dimeo, Tilman et al., 1997; Peters, Lotzerich, Niemeier, Schule, & Uhlenbruck, 1994; Peters, Lotzerich, Niemeir, Schule, & Uhlenbruck, 1995; Segar et al., 1998; Sharkey, Carey, Heise, & Barber, 1993) while the other four implemented a mixed training program using cardiovascular, resistance and flexibility exercises (Durak & Lilly, 1998; Durak, Lilly, & Hackworth, 1999; Nieman et al., 1995; Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000). Levels of fatigue, muscle strength (Durak & Lilly, 1998; Nieman et al., 1995), cardiovascular function (Dimeo, Tilman et al., 1997; Durak & Lilly, 1998; Durak, Lilly, & Hackworth, 1999; Nieman et al., 1995; Peters, Lotzerich, Niemeier, Schule, & Uhlenbruck, 1994; Peters, Lotzerich, Niemeir, Schule, & Uhlenbruck, 1995; Sharkey, Carey, Heise, & Barber, 1993), immunological parameters (Dimeo, Tilman et al., 1997; Nieman et al., 1995; Peters, Lotzerich, Niemeier, Schule, & Uhlenbruck, 1994; Peters, Lotzerich, Niemeir, Schule, & Uhlenbruck, 1995), symptoms of emotional-related distress and quality of life (Durak & Lilly, 1998; Durak, Lilly, & Hackworth, 1999; Peters,

Lotzerich, Niemeier, Schule, & Uhlenbruck, 1994; Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000; Segar et al., 1998) were the major outcome measures from these studies.

A. Cardiovascular training

Sharkey and associates (1993) conducted the first experimental exercise study examining the chronic response of a 12-week cardiovascular training program on children and young adults with mixed cancer diagnosis who had completed chemotherapy for at least one year. Outcome measures included cardiovascular and pulmonary physiological responses. Although, none of the physiological parameters changed with training, exercise tolerance assessed by exercise time was increased significantly ($p < 0.05$).

The effect of cardiovascular training on NKCA, monocytes and personality was examined in a group of breast cancer survivors by Peters and colleagues (1994; , 1995). Their training program consisted of 30-40 minutes cycling at approximately 60% of maximum heart rate performed five times per week during the first five weeks of training with a subsequent reduction of training frequency for the following six months completing a total 7 months training period. Although NKCA cell numbers were unaltered over the course of the intervention, an increase in the cytotoxic activity was noted at post-test. While the total number of leukocytes was unchanged after the training program, significant changes in leukocyte sub-populations was detected with an increased number of granulocytes and a decreased number of lymphocytes and monocytes ($p < 0.05$). The authors suggested that cardiovascular training would possibly alter the number of specific receptors in the surface membrane on monocytes. Moreover, satisfaction of life increased in the first five weeks of training with a subsequent decrease during the other 6 months of the intervention.

Dimeo and colleagues (1997) examined the effects of a cardiovascular training program on maximal performance and hemoglobin levels of cancer patients directly after hospital discharge. The exercise program consisted of 6-weeks treadmill walking every week day with intensity set to elicit a blood lactate level of 3 mmol.L in capillary blood. Results indicated that subjects that underwent

the exercise program showed a significant increase in maximal performance and hemoglobin concentration compared to controls ($p < 0.05$).

The effects of 10 weeks of cardiovascular exercises on women who had undergone breast cancer treatment were examined by Segar (1998) and associates. Subjects were randomly allocated to an exercise group, exercise plus behavior modification group or a control group in an experimental cross over design. Symptoms of depression, state of anxiety and self-esteem were assessed by the Beck Depression Inventory, the State Anxiety Inventory and the Rosenberg Self-Esteem Inventory, respectively. At post-test, it was observed that the exercise group had significantly less depression and state of anxiety compared to controls with no differences between exercise and exercise plus behavior modification groups. After the crossover, the controls also showed optimistic changes by decreasing depression and state of anxiety showing positive psychological response accrued with cardiovascular training.

B. Cardiovascular, resistance and flexibility training

The effects of an exercise program on breast cancer survivors who had undergone surgery, radiation and chemotherapy were examined by Nieman and colleagues (1995). Subjects were randomly assigned to an exercise or control group. In addition to physical performance measures that included; symptoms-limited exercise testing on the treadmill, 6-minute walk test and lower body strength, immunological training response was also assessed by measuring NKCA and concentrations of circulating immune cells. The training program included 30 minutes walking at 75% of heart rate maximum and seven different resistance exercises performed for 12 repetitions at an unspecified intensity. Results indicated significant improvement for the exercise group on six-minute walk distance test compared to controls ($p < 0.05$). However, differences between groups were neither observed for lower body strength nor natural killer cell cytotoxic activity. It should be noted that the small sample size ($n = 6$ per group) limited the ability to detect significant difference between groups.

Durak and colleagues (1998b) conducted an exercise intervention in a mixed cancer patient population over 10 weeks. The exercise program was performed twice weekly and consisted of cardiovascular training at their own perceived exertion,

resistance training machines using unspecified intensity and flexibility exercises. Outcome measures included quality of life (Modified Rotterdam Quality of Life Survey), endurance capacity and a 4- to 6-repetition maximum strength test. Results demonstrated an average increase of 43% for both upper and lower body strength combined and a 41.4% increase in MET level from the first to the last session of the exercise program. In addition, the quality of life assessment indicated a significant improvement on participants' ability to perform daily functions. The same group of investigators (Durak, Lilly, & Hackworth, 1999) also examined the effect of a 20-week cardiovascular and resistance training program on prostate, carcinoma and leukemia survivors. The exercise protocol was described with little detail in the original manuscript; therefore it is unclear what intensity and volume were applied during the exercise intervention for both cardiovascular and resistance exercises. In addition, neither strength maximum nor cardiovascular capacity tests were implemented at pre-and post test becoming extremely difficult to analyze the authors presented data. At post-test, subjects completed a quality of life survey with the same questionnaire being reassessed in a two year follow-up period. It was reported that the training protocol induced an increase of 38% and 52% for overall strength in the prostate cancer and carcinoma/leukemia group, respectively. No significant change was noted for aerobic capacity. It is interesting to point out the high level of adherence to the exercise program from both groups with subjects from the prostate cancer group having 100% compliance to the training program whereas the carcinoma/leukemia group recorded 65% of adherence over the two year period.

Finally, Porock and associates (2000) investigated the effect of a short-term home based exercise intervention in a mixed population of cancer patients. The training program appears to include both cardiovascular and resistance exercises but lacked an exact description of training program variables (intensity, frequency and volume). Outcome measures included fatigue, anxiety, depression, symptoms of distress and quality of life. Results indicated positive adaptations for depression and anxiety with no change in fatigue levels. It should be noted that the short-term duration of the intervention and the small sample size (n = 9) limited the ability to detect significant changes with training.

Discussion

The primary aim of this paper was to present an overview of published studies undertaken with any cancer population during and after treatment. Unfortunately, most of these studies suffer limitations because they are not randomized controlled trials, use small sample sizes and/or report insufficient scientific methodological criteria. Despite this, it appears that there is a reasonable amount of data in the literature which underline preliminary positive physiological and psychological benefits from exercise when undertaking during or after traditional cancer treatment. It is interesting to point out that the early published report on cancer and exercise by Cunningham and associates (1986) used resistance exercises as the training modality which was based on the original work by Delorme (1948; , 1950) who introduced the model of progressive workload with resistance exercises. Subsequently, the majority of studies examining the effect of exercise on cancer patients undertaking treatment completed from the late 1980's to 2003 implemented the cardiovascular training modality (Courneya et al., 2003; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Na, Kim, Kim, Ha, & Yoon, 2000; Schwartz, 1999; Schwartz, 2000; Schwartz, Mori, Gao, Nail, & King, 2001; Segal et al., 2001; Winningham & MacVicar, 1988; Winningham, M. L., M. G. MacVicar, M. Bondoc, J. I. Anderson, & J. P. Minton, 1989) with only two intervention using the combination of resistance, flexibility and cardiovascular training (Adamsen et al., 2003; Kolden et al., 2002). Therefore, particular attention should be taken of the recent report from Segal and colleagues (2003) who reported positive effects of resistance exercises alone on rates of fatigue, health-related quality of life and muscle strength in prostate cancer patients undertaking ADT. Although these results support positive psychological and physical outcomes, it remains to be examined how specific physiological parameters such as muscle tissue mass and bone mineral density would respond with resistance exercises in this population especially in long term trials. Recently, Smith and associates (2004) reported an increase of 11% of fat mass and a decrease of 3.8% of lean free-bone tissue mass from a year long prospective assessment of the effects of ADT on body composition responses

evaluated by dual energy x-ray absorptiometry. Further, the concern related to the negative effects of ADT on accelerating bone loss has been extensively reported in the literature (Berruti et al., 2002; Daniell, 2001; Daniell et al., 2000; Diamond, Campbell, Bryant, & Lynch, 1998; Diamond, Higano, Smith, Guise, & Singer, 2004; Smith, 2002a; Smith et al., 2003; Smith et al., 2001; Stoch et al., 2001; Wei, J. T. et al., 1999). As an alternative, resistance exercise studies in older adults have consistently shown it to be a safe and effective strategy to counteract sarcopenia (Charette et al., 1991b; Fiatarone et al., 1990; Fiatarone et al., 1994; Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988a; Hakkinen et al., 1998a; McCartney, Hicks, Martin, & Webber, 1996b; Nelson et al., 1994; Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996) and preserve or induce gains in bone mineral density (Kerr, Morton, Dick, & Prince, 1996; Nelson et al., 1994; Pruitt, Taaffe, & Marcus, 1995; Villareal et al., 2003). Recently, Villareal and associates (2003) reported positive effects of a nine months resistance training program on bone mineral density in older women undertaking hormonal replacement. A meta-analysis undertaken by Wolff and colleagues (1999) also proposes that resistance training preserves or reverses bone loss of up to 1% per year in both femoral neck and lumbar spine sites for pre-and post-menopausal women. Taking into consideration the long-term benefits of this exercise modality on bone response, resistance training may have an important role on reducing the effect of bone loss rate in prostate cancer men undertaking ADT. Moreover, considering that traditionally ADT varies from 2-3 years, but can also take up to 20 years (Schroder, 2000), the role of resistance exercise may be even more relevant by improving psychological and physiological parameters and therefore improving quality of life.

In the context of maintaining or increasing lean tissue content in healthy elderly and various patient populations in which muscle and bone loss are problematic, resistance exercise might be more appropriately termed “anabolic exercise”. It is not surprising therefore that the many cardiovascular exercise interventions with cancer patients have produced mixed results as such exercise does not provide a strong anabolic effect for muscle and bone and may not elicit the changes in endocrine status that are desirable in these patients.

It is interesting to note that among the different cancer types, breast cancer has been the most common cancer type examined during exercise trials. Out of the 18 studies undertaken during treatment, nine had used exclusively breast cancer

subjects (Kolden et al., 2002; MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997; Mock et al., 2001; Schwartz, 1999; Schwartz, 2000; Schwartz, Mori, Gao, Nail, & King, 2001; Segal et al., 2001; Winningham & MacVicar, 1988; Winningham, M. L., M.G. MacVicar, M. Bondoc, J.I. Anderson, & J.P. Minton, 1989) with three studies including breast cancer plus a mixed of cancer populations (Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Rumberger, & Keul, 1998; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999) and few other experiments using, leukemia, stomach cancer, prostate, colon rectal and a mix population of cancer types (Adamsen et al., 2003; Courneya et al., 2003; Cunningham, Morris, & Cheney, 1986; Na, Kim, Kim, Ha, & Yoon, 2000; Segal et al., 2003). A similar figure can be observed with the experimental trials undertaken after cancer treatment where three studies were conducted with breast cancer patients (Nieman et al., 1995; Peters, Lotzerich, Niemeier, Schule, & Uhlenbruck, 1994; Peters, Lotzerich, Niemeir, Schule, & Uhlenbruck, 1995; Segar et al., 1998), three in a mixed cancer population including breast cancer (Dimeo, Tilman et al., 1997; Durak & Lilly, 1998; Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000) and two in a mixed cancer population not including breast cancer (Durak, Lilly, & Hackworth, 1999; Sharkey, Carey, Heise, & Barber, 1993). Therefore, future studies aiming to examine the role of exercises in cancer populations should also include other cancer types than breast to reveal possible physiological and psychological benefits from exercise among other cancer groups.

As a secondary purpose of this review we attempted to establish a training dose response with this population based on the existing literature. The importance of scientific exercise principles has been extensively reported (American College of Sports Medicine, 1998a, 1998b; Kraemer et al., 2002; Kraemer & Ratamess, 2004). It is well known that manipulation of the training program variables of frequency of training, intensity of training, specificity of training and rest period between sets and exercise sessions produces clearly differentiated effects on specific physiological adaptations for both cardiovascular and resistance exercise. Nevertheless, long-term trials comparing different training models are rare even in healthy adult populations as reported by the American College of Sports Medicine position stand on the recommended quantity and quality of exercise prescription in healthy adults (American College of Sports Medicine, 1998b). Therefore, most of the studies presented in this review which aim to elucidate training response for cancer patients

during and after treatment, were short in duration (Adamsen et al., 2003; Cunningham, Morris, & Cheney, 1986; Dimeo, Rumberger, & Keul, 1998; Dimeo et al., 2003; Dimeo, Tilman et al., 1997; Durak & Lilly, 1998; MacVicar, Winningham, & Nickel, 1989; Na, Kim, Kim, Ha, & Yoon, 2000; Nieman et al., 1995; Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000; Schwartz, 1999; Schwartz, 2000; Schwartz, Mori, Gao, Nail, & King, 2001; Segal et al., 2003; Segar et al., 1998; Winningham & MacVicar, 1988; Winningham, M. L., M. G. MacVicar, M. Bondoc, J. I. Anderson, & J. P. Minton, 1989) with some interventions still not controlling elementary training variables (Durak & Lilly, 1998; Durak, Lilly, & Hackworth, 1999; Kolden et al., 2002; Mock, 2001b; Porock, Kristjanson, Tinnelly, Duke, & Blight, 2000). The short-term nature of these interventions would likely limit the ability to detect specific physiological responses with training. Moreover, considering that exercise has been endorsed as a crucial component of a healthy lifestyle and is viewed as a lifelong behaviour which may prevent and control various disease conditions (Pate et al., 1995; Thompson et al., 2003; Wei, Gibbons, Kampert, Nichaman, & Blair, 2000; Wei, M. et al., 1999), further studies undertaken for longer periods of time are needed. Additionally, the specific training dose for this population and how it would differentiate from many of the cancer types, treatments modalities and stages of treatment remains an open area for prospective trials. Despite the work by Segal and colleagues (2001) and Cunningham and associates (1986) which compared a home based vs. supervised exercise and five- vs. three times weekly resistance exercises, respectively, none of these studies had actually used more than one training protocol, attempting to compare differences in training response due to various intensities, frequencies, volume and type of training. Consequently, a requirement for future studies on this topic should include randomized controlled trials comparing how various types of cancer undergoing different treatments and stages of the disease would respond to different training stimuli.

Finally, the majority of the studies involving resistance training did not draw on the wealth of scientific research which has been published in regard to resistance training for muscle hypertrophy and strength gain. In all cases excepted one (Adamsen et al., 2003) the intensity of exercise in particular was inferior to the 6-10 RM load that has been deemed optimal for muscle growth and strength enhancement (Kraemer et al., 2002; Kraemer & Ratamess, 2004). One of the better designed

resistance training interventions addressed in this review was by Cunningham and associates (1986) and yet their model was based on research completed around 1950 (Delorme & Watkins, 1948; Delorme, West, & Shriber, 1950). Moreover, the only study which incorporated a better-quality training intensity limited the program to 6-weeks and performed no more than three resistance exercises (Adamsen et al., 2003). Although much more research is required in this important area some guidelines and possible physiological outcomes are provided in Table III. Future research into exercise interventions with cancer patients should involve contemporary resistance training program designs incorporating adequate intensity, periodization, selection of functional exercises involving large muscle groups, and manipulation of rest period and recovery strategies to maximize the anabolic effect on muscle and bone, as well as positive endocrine responses.

Table I. Experimental design exercise studies during cancer treatment.

Study	Duration/ Freq.	n/ sex/ age	Type of cancer	Exercise program	Intensity	Outcome measures
Cunningham et al 1986 (49)	5 weeks 3-5 x week	40, M, W (14-44 y)	Leukemia	Resistance training	Unspecified	↓ Nitrogen balance ↔ Creatinine excretion ↔ AC
Winningham et al. 1988 (50)	12 weeks 3 x week	42, W (45-48 y)	Breast	Cardiovascular Cycling IT 20-30 minutes	60-85% MHR	↓ Nausea
Winningham et al. 1989 (48)	12 weeks 3 x week	24, W (45 y)	Breast	Cardiovascular Cycling IT 20-30 minutes	60-85% MHR	↑ Lean tissue mass ↓ 0.5% Body fat ↓ Skinfold sites
Macvicar et al. 1989 (30)	10 weeks 3 x week	45, W (43-46 y)	Breast	Cardiovascular Cycling IT	60-85% MHR	↑ 42% VO2max
Mock et al. 1997 (23)	6 weeks 4-5 x week	46, W (35-64 y)	Breast	Cardiovascular Walking 20-30 minutes	Self-paced	↑ 4% 12-MWT ↓ Fatigue ↓ Symptom experience

Dimeo et al. 1997 (29)	~ 2 weeks Daily	70, M, W (39-40 y)	Breast, Sarcoma Carcinoma Adenocarcinoma Neuroblastoma	Cardiovascular Cycling IT 30 minutes	50% HRR	↓ 14% MP, ↓ Thro ↓ Neutro, ↓ Hosp
Dimeo et al. 1998 (22)	6 weeks 5 x week	5, M, W (18-55 y)	Hodgkin's lymp. Non-Hodgkin's lymp. Bronchial, Breast Medulloblastoma	Progressive treadmill Walking 30-35 minutes	3 mmol.L (LC) 80% MHR	↓ 100% LC ↓ 18% Heart rate ↑ 101 % TD ↑ 12 % MP
Dimeo et al. 1999 (35)	* Daily	59, M, W (40 y)	Breast, Lung Carcinoma, Seminoma Adenocarcinoma Hodgkin's lymp.	Cardiovascular Cycling IT 30 minutes	50% HRR	↓ Psychologic distress
Schwartz et al. 1999, 2000 (46, 47)	8 weeks 4 x week	27, W (35-57 y)	Breast	Cardiovascular Walking 35 minutes	Self-paced Accelerometers	↑ 10.4% 12-MWT ↓ Fatigue
Na et al. 2000 (25)	2 weeks 5 x week	35, * (28-75 y)	Stomach	Cardiovascular Arms and Cycling Ergometers 30 minutes	60% MHR	↑ 28% NKCA
Schwartz et al. 2001 (52)	8 weeks 3-4 x week	72, W (27-69 y)	Breast	Cardiovascular Walking 12 minutes	Self-paced Accelerometers	↑ 15% 12-MWT ↓ Fatigue

Mock et al. 2001 (31)	6-24 weeks 5-6 x week	52, W (28-75 y)	Breast	Cardiovascular Walking 10-30 minutes	Self-paced	↑ 6% 12-MWT ↓ Fatigue ↓ Emotional distress
Segal et al. 2001 (45)	26 weeks 5 x week	123, W (51.4 y)	Breast	Cardiovascular Walking Home vs. non-home based	50-60% VO2max	↑ Physical functioning ↔ Quality of life ↔ VO2max
Kolden et al. 2002 (24)	16 weeks 3 x week	40, W (45-76 y)	Breast	Cardiovascular Walking, Cycling, Stepping Resistance training Flexibility	Unspecified	↑ 11% Flexibility ↑ 15.4% VO2max ↑ 34.5% UB ↑37% LB ↓ 5% RSBP ↑ Quality of life
Segal et al. 2003 (32)	12 weeks 3 x week	155, M (68.2 y)	Prostate	Resistance training 2 sets 12 repetitions	60-70% 1-RM	↑ 42% UB ↑ 36 % LB ↔ Body composition ↔ PSA, ↓ Fatigue ↑ Quality of life
Dimeo et al. 2003 (26)	~ 2 weeks Daily	66, M, W (20-73 y)	Leukemia, Hodgkin's lymp. Non-Hodgkin's lymp. Myeloma	Cardiovascular Walking	70% MHR	↔ Walking speed ↓ 6.7% HEM

Courneya et al. 2003 (27)	16 weeks 3-5 x week	102, M, W (61.1 y)	Colorectal	Cardiovascular Walking Flexibility	65-75% MHR	↔ Quality of life ↔ Cardiovascular capacity
Adamsen et al. 2003 (28)	6 weeks 4 x week	23, M, W (18-63 y)	Leukemia , Breast Colon, Ovary Testis, Cervix Hodgkin's lymp. Non-Hodgkin's lymp.	Resistance training 3 sets 5-8 repetitions Cardiovascular Cycling Relaxation	60-100% MHR 85-95% 1-RM	↑ 32.5% WB ↑ 16% VO2max ↔ Quality of life

↔ = no change, ↑ = increase, ↓ = decrease, W = women, M = men, * = not described, PSA = Prostate-specific antigen, LC = Lactate concentration, VO2max = VO2 maximum, IT = Interval training, TD = Training distance, MHR = Maximum heart rate, MP = Maximal performance (MET), HEM = Hemoglobin, AC = Arm circumference, UB = Upper body strength, LB= Lower body strength, WB = Whole body strength, RSBP = Resting Systolic Blood Pressure, NKCA = Natural killer cell cytotoxic activity, HRR = Heart rate reserve, Neutro = duration of neutropenia, Thro = duration of thrombopenia, Hosp = duration of hospitalization.

Table II. Experimental design exercise studies after cancer treatment.

Study	Duration/ Freq.	n/ sex/age	Type of cancer	Exercise program	Intensity	Outcome measures
Sharkey et al. 1993 (38)	12 weeks 2 x week	10, M, W (19 y)	Leukemia Ewings Tumor Neuroblastoma Wilms' Tumor Rhabdomyosarcoma	Cardiovascular *	60-80% MHR	10% ET, ↔ AT ↔ Peak OX ↔ Peak HR
Peters et al. 1994, 1995 (39, 40)	28 weeks 2-5 x week	24 ,W (49 y)	Breast	Cardiovascular Cycling	~ 60% MHR	↑↓ Satisfaction of life ↔ NKCA ↔ Leukocytes ↓ 2.1 % Lymphocytes ↓ 1.1% Monocytes ↑ 4.1% Granulocytes
Nieman et al. 1995 (43)	8 weeks 3 x week	12, W (61 y)	Breast	Cardiovascular Resistance raining	75% MHR	↔ NKCA ↔ LB ↑ 6-minute Walk Test
Dimeo et al. 1997 (36)	6 weeks 5 x week	36, M, W (39-42 y)	Non-Hodgkin's lymp. Breast, Sarcoma Seminoma, Lung	Cardiovascular Walking 30 minutes	3 mmol.L (LC)	↑ 32% MP ↑ 30% HEM

Segar et al. 1998 (44)	10 weeks 4 x week	24, W (30-65 y)	Breast	Cardiovascular 30-40 minutes	≥ 60% MHR	↓ Depression ↓ Anxiety
Durak et al. 1998 (41)	10 weeks 2 week	20, M, W (50 y)	Carcinoma, Lymphoma Leukemia	Cardiovascular Resistance training Flexibility	Own RPE	↑ 43% WB, 41.4%↑ MP ↑ Quality of life
Durak et al. 1999 (42)	20 weeks 2 x week	25, M, W (44-71 y)	Prostate Carcinoma Leukemia	Cardiovascular Resistance training	Unspecified	↔ Aerobic capacity ↑ 45% WB
Porock et al. 2000 (37)	4 weeks *	9, M, W (51-77 y)	Bowel, Breast, Oral, Pancreas, Melanoma	Cardiovascular Resistance training	Unspecified	↓ Depression ↓ Anxiety ↔ Fatigue

↔ = no change, ↑ = increase, ↓ = decrease, ↑↓ = increased at week 5 and decreased at post test, * = not described, M = men, W = women, LC = Lactate concentration, MHR = Maximum heart rate, MP = Maximal performance (MET), HEM = Hemoglobin, LB = Lower body strength, WB = Whole body Strength, NKCA = Natural killer cell cytotoxic activity, ET = Exercise tolerance, AT = Anaerobic threshold, Peak OX = Peak oxygen uptake, Peak HR = Peak heart rate.

Table III. Guidelines and possible physiological outcomes from exercise in cancer patients

Exercise Modality	Intensity	Frequency	Volume/ Dosage	Cancer Relevant Expected Outcomes
Cardiovascular Exercises	55-90% MHR 40-85% MHRR	3-5 x per week	20-60 minutes continuous or intermittent	↑ Cardiopulmonary function ↑ Insulin sensitivity*, ↑ HDL*, ↓ LDL* ↓ Fat mass, ↓ Fatigue
Anabolic/Resistance Exercises	50-80% 1-RM 6-12RM	1-3 x per week	1-4 Sets per muscle group	↑ Muscle mass*, ↑ Muscle strength ↑ Muscle power*, ↑ Muscle endurance ↑ BMD*, ↑ FP, ↓ Fatigue ↑ Resting metabolic rate*, ↓ Fat mass*
Flexibility Exercises	?	2-3 x per week	2-4 Sets per muscle group 10-30 seconds	↑ ↔ Range of motion

↑ = increase, ↓ = decrease, ↔ = maintain, MHR =maximum heart rate, MHRR = maximum heart rate reserve, HDL = high-density lipoprotein, LDL = low-density lipoprotein, BMD = bone mineral density, FP = functional performance, RM = repetition maximum
* Data not available with cancer population, recommendation based from studies undertaken with non-cancer population.

Chapter 3

REVIEW OF LITERATURE TWO

ANABOLIC RESPONSES TO RESISTANCE TRAINING IN OLDER MEN AND WOMEN: A BRIEF REVIEW

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Journal of Aging and Physical Activity. 13:343-358, 2005.

Journal of Aging and Physical Activity, 2005, 13, 343-358

Anabolic Responses to Resistance Training in Older Men and Women: A Brief Review

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Resistance training has been shown to be the most effective exercise mode to induce anabolic adaptations in older men and women. Advances in imaging techniques and histochemistry have increased the ability to detect such changes, confirming the high level of adaptability that remains in aging skeletal muscle. This brief review presents a summary of the resistance-training studies that directly compare chronic anabolic responses to training in older (>60 years) men and women. Sixteen studies are summarized, most of which indicate similar relative anabolic responses between older men and women after resistance training. Relatively small sample sizes in most of the interventions limited their ability to detect significant sex differences and should be considered when interpreting these studies. Future research should incorporate larger sample sizes with multiple measurement time points for anabolic responses.

Key Words: weight training, aging, lean mass, strength

Normal aging is characterized by a decline in skeletal-muscle mass and an increase in fat mass (Frontera et al., 2000; Fukagawa, Bandini, & Young, 1990; Lexell, 1995). The reduction in muscle mass, termed sarcopenia, leads to a loss in muscle strength and is associated with a decline in physical function that compromises independent living (Rosenberg, 1997). Numerous studies, however, have shown resistance training to be a safe and effective intervention to counteract sarcopenia, even in the very old—that is, those age 85 years and older (Charette et al., 1991; Fiatarone et al., 1990, 1994; Taaffe, Duret, Wheeler, & Marcus, 1999; Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996).

The landmark study in 1988 by Frontera and colleagues (Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988) using computed tomography scanning of the midthigh and muscle-tissue samples clearly showed the residual capacity that older adults have to increase muscle cross-sectional area (CSA) with an increase in midthigh total muscle area of 11.4% and an increase in Type I and II fiber area of 33.5% and 27.6%, respectively, after 12 weeks of strength training. Subsequently,

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Introduction

Normal aging is characterized by a decline in skeletal muscle mass and an increase in fat mass (Frontera et al., 2000; Fukagawa, Bandini, & Young, 1990; Lexell, 1995). The reduction in muscle mass, termed sarcopenia, leads to a loss in muscle strength and is associated with a decline in physical function that compromises independent living (Rosenberg, 1997). However, numerous studies have shown resistance training to be a safe and effective intervention to counteract sarcopenia, even in very old persons, that is, those aged 85 years and older (Charette et al., 1991a; Fiatarone et al., 1990; Fiatarone et al., 1994; Taaffe, Duret, Wheeler, & Marcus, 1999; Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996).

The landmark study in 1988 by Frontera and colleagues (Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988b)**,** using computed tomography scanning of the mid-thigh and muscle tissue samples, clearly showed the residual capacity that older adults have to increase muscle cross-sectional area (CSA) with an increase in midthigh total muscle area of 11.4% and an increase in type I and II fiber area of 33.5% and 27.6%, respectively, following 12 weeks strength training. Subsequently, numerous studies have reported positive changes in muscle CSA, muscle fiber size, and body composition following resistance training interventions (Charette et al., 1991a; Fiatarone et al., 1990; Fiatarone et al., 1994; McCartney, Hicks, Martin, & Webber, 1996a; Taaffe, Duret, Wheeler, & Marcus, 1999; Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996). Less clear is the effect of age and sex on the anabolic response to resistive exercise.

In studies directly comparing anabolic responses between young and older adults to resistance exercise, older adults retain the ability to adapt in a relatively similar fashion to their younger counterparts (Hakkinen et al., 1998a; Ivey et al., 2000; Lemmer et al., 2000; Roth et al., 2001), although this has not always been reported (Welle, Totterman, & Thornton, 1996). Within young adults, the majority of studies (Abe, DeHoyos, Pollock, & Garzarella, 2000; Cureton, Collins, Hill, & McElhannon, 1988; Hurlbut et al., 2002; Lemmer et al., 2000; Lemmer et al., 2001; O'Hagan, Sale, MacDougall, & Garner, 1995; Roth et al., 2001; Staron et al., 1994) indicate that men and women experience similar relative changes in fat-free mass, muscle CSA and fiber CSA after training, though others (Ivey et al., 2000) have

reported a greater response in men. In older adults (> 60 years), some investigations have demonstrated similar relative strength gains and body composition changes between men and women following training (Fiatarone et al., 1994; Ivey et al., 2000; Lexell, 1995; McCartney, Hicks, Martin, & Webber, 1995, 1996a; Roth et al., 2001; Tracy et al., 1999) while others indicate the presence of sex differences as determined by single muscle fiber contractile function (Trappe et al., 2001), fiber diameter (Bamman et al., 2003; Hakkinen et al., 2002) and muscle CSA (Hakkinen et al., 1998b). It has been suggested that differences in anabolic hormones and the myostatin genotype may contribute to these sex differences (Bamman et al., 2003; Ivey et al., 2000).

Given the increased recognition of sarcopenia in the medical and allied health community, and the recommendation by professional bodies for older adults to undertake resistance exercise (American College of Sports Medicine, 1998b), the effects of training in the older adult need to be clearly delineated, including any differences by sex. Women are more susceptible to falling below the strength thresholds required for daily activities and are subject to longer periods of compromised function than men due to their greater longevity (Ivey et al., 2000). As a result, if sex differences exist in the response to a given exercise stimulus, then this needs to be determined so that the most appropriate exercise programs can be devised. Therefore, the purpose of this paper is to present an overview of studies that have undertaken measures of body composition, muscle and fiber CSA adaptations to resistance training in older men and women who perform the same intervention. In addition, we briefly discuss studies that include only older men or women to provide a more comprehensive overview of the topic. Due to differences in tissue and body composition techniques, this brief review is divided into seven sub-sections: computed tomography, dual energy x-ray absorptiometry, magnetic resonance imaging, compound ultrasound, the BOD POD, muscle biopsy, and myosin heavy chain analysis.

Training Studies by Assessment Technique

An overview in chronological order of the studies directly comparing men and women undertaking the same training intervention is provided in the accompanying

table. Apart from the anabolic response, which is discussed below, the effect of the intervention on body weight and muscle strength is also provided for the reader.

Computed Tomography (CT)

Computed tomography uses multiple x-rays and computers to reconstruct images of the target area and generate quantitative information of muscle area, subcutaneous and intermuscular fat area, and attenuation of the tissue as determined by Hounsfield units (Lee, Wang, & Heymsfield, 2001; Mitsiopoulos et al., 1998; Sipila & Suominen, 1993). McCartney et al. (1995) examined the effect of resistance exercise on muscle CSA assessed by CT in men and women (60 to 80 years) following 10 months training (Table). Subjects were randomly allocated to an exercise or control group and performed the unilateral leg press, ankle plantar flexion, ankle dorsi flexion, as well as several upper body exercises. Similar CSA adaptation of the knee extensor muscles for men (6.2 %) and women (4.7 %) was observed and both percentage changes were significantly greater than controls. In a subsequent report following two years of training (McCartney et al., 1996), CSA of the knee extensors for both men and women continued to increase, although not at the same rate as that in the first year of the study.

Dual Energy X-ray Absorptiometry (DXA)

Dual energy x-ray absorptiometry estimates fat-mass, bone mineral-free lean mass and bone mineral mass using two distinct low-energy x-rays that penetrate the soft tissue and bone areas, and has been demonstrated to be an accurate and precise method of body/tissue composition compared to reference methods such as total body potassium, hydrodensitometry, magnetic resonance imaging (MRI), CT, and four-component models (Haarbo, Gotfredsen, Hassager, & Christiansen, 1991; Kohrt, 1998; Prior et al., 1997; Shih, Wang, Heo, Wang, & Heymsfield, 2000; Visser, Fuerst, Lang, Salamone, & Harris, 1999). Body composition response to resistance training assessed by DXA in older men and women was reported by Martel et al. (1999). Subjects (65 to 73 years) trained three days per week for 24 weeks performing several upper and lower body exercises. There were no significant differences as a result of resistance training in either sex for fat-free mass or body fat.

When men and women were combined, a significant increase was detected for fat-free mass ($p < 0.05$).

Lemmer et al. (2000) reported the effect of a training regimen that incorporated five sets of five repetitions maximum of unilateral leg extension exercise of the dominant leg for nine weeks on strength and body composition in older men and women. There was no significant change in body fat and fat-free mass. Although the aim of the study was primarily designed to detect sex-related changes on muscle strength with training and detraining, results from the body composition changes are limited due to the fact that only the quadriceps muscle group was trained. The same group of investigators (Lemmer et al., 2001) also examined the effect of age and sex following 24 weeks resistance training. Eleven men and 10 women (65 to 75 years) trained three days per week utilizing unilateral leg press, leg curl, leg extension, chest press, lat pull down, military press, upper back, triceps extension and unilateral biceps curl exercises. Men and women significantly increased fat-free mass from baseline to week 24 ($p < 0.05$), with no significant difference by sex.

Hurlbut et al.(2002) examined the effect of resistance training by age, sex and angiotensin I-converting enzyme (ACE) genotype on fasting and glucose-stimulated glucose and insulin response. Twelve men and nine women (65 to 75 years) exercised thrice weekly over 24 weeks. The training routine consisted of three lower body exercises, six upper body exercises and two trunk exercises. Following training, men increased fat-free mass by 1.5 % ($p < 0.05$) and women by 2.2 % which approached statistical significance ($p = 0.06$). There were no significant changes in fat mass for either group.

Recently, Ryan et al. (2004) reported the results from a 24-week whole body resistance training program on body composition in older men and women. There was no significant change in fat-free mass for older women (1.7 %) whereas the increase for older men (1.6 %) reached statistical significance ($p < 0.05$). No changes were observed for body fat in either group. In addition, both men (24.2 %) and women (20.8 %) similarly increased whole body muscle strength ($p < 0.001$), which is the average strength for the exercises/muscle groups examined. Interestingly, while percentage change in these studies (Hurlbut et al., 2002; Ryan et al., 2004) for fat-free mass was similar between men and women, the latter group did not achieve statistical significance perhaps indicating a greater within-group variance. That is,

women may not demonstrate as consistent a change in response to resistance training as men.

Magnetic Resonance Imaging (MRI)

In contrast to CT and DXA which employs ionizing radiation, MRI uses magnetic energy and radio waves to derive images of a target tissue area and has been found to be an accurate method for assessing tissue composition (Lee et al., 2000; Lee, Wang, & Heymsfield, 2001; Mitsiopoulos et al., 1998). The effect of resistance training on muscle volume assessed by MRI has been reported by Ivey et al. (1999) and Tracy et al. (2000). Men and women (65 to 75 years) participated in a resistance training intervention performing unilateral knee extension of the dominant leg three times per week for nine weeks while the opposite leg served as the control. Muscle volume change was similar for both men (11.5 %) and women (12 %), with no change in whole body fat-free or fat mass assessed by DXA. The lack of change in fat-free or fat mass assessed by DXA was not surprising given that only one muscle group was trained.

Roth and colleagues (2001) examined sex differences in thigh muscle volume response after resistance training in subjects aged 65 to 75 years. Nine men and 10 women performed unilateral leg press, unilateral leg curl, unilateral leg extension, chest press, lat pull down, overhead shoulder press, upper back rowing, triceps extension, and unilateral biceps curl exercises thrice weekly for 24 weeks. Both groups demonstrated a significant increase in fat-free mass ($p < 0.05$) but not for percentage of body fat assessed by DXA. MRI results indicated that both men (4.1 %) and women (5.8 %) increased ($p < 0.01$) estimated whole thigh muscle volume with no significant difference between groups. Similarly, men (1.6 %) and women (5.6 %) experienced a significant increase in mid-thigh muscle CSA ($p < 0.01$), although the difference between sexes was not statistically significant.

Compound Ultrasonic Scanner (CUS)

Compound ultrasonic scanner uses acoustic impedance properties of the body's tissues to form an image from which muscle tissue can be separated from bone and fat tissue (Sipila & Suominen, 1993). Hakkinen and colleagues (1998b)

investigated muscle strength, body composition and knee extensor cross-sectional area by CUS of men and women (67 to 72 years) following 24 weeks of resistance training. The program consisted of a combination of heavy resistance and explosive training. Although percentage of body fat assessed by skinfolds did not change during the course of the intervention, muscle CSA of the leg extensors increased by 5.8 % in women ($p < 0.05$) with no significant change for men (2.1 %).

BOD POD

The BOD POD estimates body composition by measuring the volume of air an individual displaces inside an enclosed chamber and has been shown to be a valid technique to estimate body composition (Fields, Goran, & McCrory, 2002; Fields, Hunter, & Goran, 2000). Hunter and associates (2002) used a BOD POD to examine the body composition response in older men and women after 25 weeks of resistance training. Subjects performed five upper body exercises, two lower body exercises and two trunk exercises three times per week during the intervention. Body fat decreased (> 2 %) similarly and significantly for men and women ($p < 0.05$), while the alterations in fat-free mass between men (4.7 %) and women (2.3 %) approached significance ($p = 0.06$).

Muscle Biopsy

Muscle biopsy is a procedure in which muscle samples are extracted by the needle technique, frozen and stored for histochemical analysis (Taaffe, Pruitt, Pyka, Guido, & Marcus, 1996). The effect of resistance training on muscle strength and type I and II muscle fiber CSA for the biceps brachii and the vastus lateralis muscles of men and women (70 to 77 years) was examined by Lexell et al. (Lexell, Downham, Larsson, Bruhn, & Morsing, 1995). Comparable mean gains in biceps brachii type II CSA were found in men (17 %) and women (16 %), respectively. However, this was not statistically significant in men due to the large inter-individual variation. For the vastus lateralis muscle, there was no significant change in type I and II CSA. However, type II CSA for men surprisingly decreased by 14 %.

Hakkinen and colleagues (2002) examined the effects of strength/power training over 24 weeks on muscle fibre distribution and areas of type I, IIa and IIb

CSA of the vastus lateralis in older men and women (60 to 75 years). Type I, IIa, and IIb fiber area significantly increased by 50.6 %, 48.4 %, and 46.2 %, respectively, in men with smaller, yet significant, changes in women of 28.6 % for type I and 33.2 % for type IIa muscle fibers. However, the change in type IIb CSA for women of 18.9 % was not statistically significant. When comparing the results for these two groups, this study demonstrated older men and women had the capacity to significantly increase fiber CSA, with greater adaptations in men.

Bamman and associates (2003) reported the effects of 26 weeks of resistance training on muscle fiber CSA and myosin heavy chain composition in nine men and five women (61 to 77 years). Men and women similarly increased fat-free mass by 4.4 % and 4.2 %, respectively, and decreased body fat by 2.9 % and 3.1 % ($p < 0.05$) as assessed by the BOD POD, with no significant difference by sex. However, results from muscle biopsies indicated that men significantly increased muscle fiber type I, IIa and IIx CSA by 29 %, 41 % and 43 % while women increased by only 6.5 %, 5.7 % and 5 %, respectively, indicating significant differences between the sexes. It is important to note that only five women took part in the study and the number of fibers analyzed was not reported. In addition, it is unclear if the investigators were blinded to sex in the analysis. For clarification purposes, human type IIb fibers have been shown to be homologous to the type IIx in the rat, therefore IIx is commonly used for classification of this fiber type (Smerdu, Karsch-Mizrachi, Campione, Leinwand, & Schiaffino, 1994). Apart from the small number of women taking part in this study, it is possible that fiber size of the vastus lateralis muscle does not reflect changes in other muscles following exercise (Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988b; Narici, Roi, Landoni, Minetti, & Cerretelli, 1989) and sex differences in hypertrophy of other muscle groups could contribute to the similar increase in whole body fat-free mass observed by Bamman et al. (2003).

Myosin Heavy Chain Expression (MHC)

Myosin heavy chain composition is analysed using a muscle sample extracted using the muscle biopsy procedure followed by gel electrophoresis techniques for protein separation (Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988b; Schiaffino et al., 1989). In addition, single muscle fibers may be isolated and the characteristics both in terms of function and diameter. Such analysis has been

completed by Trappe and associates (2001; Trappe et al., 2000) involving older men and women following a resistance training program. In their first report (Trappe et al., 2000), results from a 12-week leg extension program undertaken by older men resulted in an increase ($p < 0.05$) of 20.4 and 12.7 % in the fiber diameter expressed by MHC I and MHC IIa, respectively. Subsequently, the same group of investigators reported the results from an identical training protocol, but on this occasion undertaken by older women (Trappe et al., 2001). The fiber diameter expressed by MHC I and MHC IIa increased in older women by 24.4 % ($p < 0.05$) and 6 %, respectively. When the results from fiber diameter expressed by MHC I and MHC IIa were compared, no sex differences were observed**.** However, single muscle fiber function, expressed by absolute power and maximum shortening velocity, was significantly greater in older men than women ($p < 0.05$). The authors suggested that older men and women respond differently at the muscle cell level when the same training stimulus is applied.

Discussion

As resistance training becomes increasingly recognized as an effective countermeasure to sarcopenia in the medical community, and as more older adults embark in these training regimens, the training responses including possible sex differences need to be clearly identified. Moreover, from a research perspective, if men and women attain similar relative anabolic and muscle strength changes to training, then it is possible to combine both sexes in the same sample in exercise trials to increase statistical power and/or facilitate subject recruitment.

Since the findings by Frontera and colleagues (1988b), which clearly refuted Moritani & de Vries (1980) earlier report of a lack of soft-tissue change in response to training in older men, numerous studies have demonstrated the residual capacity of older adults to increase muscle and fiber cross-sectional area following resistance training. Advances in the assessment of body and muscle composition by MRI, CT, DXA and histochemistry over the past two decades have increased the ability to detect subtle changes that were previously not possible.

Although studies directly comparing older women and men in their anabolic adaptations to resistance training are somewhat limited (e.g., Bamman et al., 2003;

Hakkinen et al., 2001; Lemmer et al., 2001; Roth et al., 2001), numerous studies examined the effect of resistance training on fat-free mass, muscle and fiber area of women and men undertaking different interventions (e.g. Charette et al., 1991; Frontera et al., 1988; Taaffe et al., 1996) supporting the high level of adaptability remaining in aging skeletal muscle.

The only study to date directly comparing muscle area in older men and women by CT reported similar adaptations for the knee extensors of 6.2 % and 4.7 %, respectively (McCartney, Hicks, Martin, & Webber, 1995). The results for older men are in agreement with results reported previously by the same laboratory (Brown, McCartney, & Sale, 1990), where older men increased ($p < 0.01$) knee extensor muscle CSA by 9.9% after 12 weeks of resistance training. Similarly, Frontera et al. (1988b) reported comparable increases in knee extensor CSA in older men assessed by CT (9.3 %) after 12 weeks training and Ferri and associates (2003) reported an increase of 7.4 % in knee extensor muscle CSA following 16 weeks of resistance training. Muscle CSA response to resistance training in older women has been assessed by Sipila & Suominen (1995) using CT, with increases in knee extensor CSA of 4.9 % after 18 weeks exercise, similar to those detected by McCartney and colleagues (1995).

Studies directly comparing fat-free mass and fat mass by DXA (Hurlbut et al., 2002; Ivey et al., 2000; Lemmer et al., 2000; Lemmer et al., 2001; Martel et al., 1999; Roth et al., 2001; Tracy et al., 1999) following resistance training do not support significant sex differences except for the study by Hurlbut and associates (2002). It is important to point out that change in fat-free mass and fat mass were not the main outcomes for these studies. As such, it is not expected that changes in body composition will be detected with only one exercise even in a long-term intervention. In such cases, sub-regional analysis of the DXA scan may have been a more sensitive technique to detect local changes in tissue composition. In addition, the anabolic effect of such isolated interventions is considerably compromised because the endocrine responses favouring muscle hypertrophy will not be produced. For example, elevation of testosterone and growth hormone with resistance training is closely related to the volume of muscle activated (Hakkinen & Pakarinen, 1993; Hakkinen, Pakarinen, Kraemer, Newton, & Alen, 2000; Kraemer et al., 1999a). In contrast, Nichols and colleagues (1993) reported a significant increase in fat-free mass of 3.6 % for older women in response to 24 weeks of whole body exercise. The

percentage changes are comparable with those reported by Lemmer et al. (2001) of 2.1 % and Martel et al. (1999) of 2.4 % in women after the same duration and frequency of training, although the changes observed by Martel et al. (1999) were not statistically significant.

Several studies have compared men and women for muscle fiber CSA adaptations to the same resistance training program. Interestingly, there are conflicting findings among them. Lexell and colleagues (1995) reported similar changes in men and women for the biceps brachii while Bamman and associates (2003) demonstrated substantial increases in men with less magnitude changes in women for the vastus lateralis muscle. Hakkinen et al. (2002) also reported that relative hypertrophy was two-fold higher in type I and IIb fiber CSA for the vastus lateralis muscle in men compared to women.

Comparing these two gender studies with those involving men or women only also reveals conflicting outcomes. For example, the magnitude of change observed in men by Bamman and associates is in agreement with Frontera et al. (1988) who reported a 33.5 % and 27.6 % increase in type I and type II fiber cross-sectional area in men. However, Brown and colleagues (1990) reported substantial increases in both type I (13.7 %) and type II (30 %) biceps brachii muscle fiber CSA in older men similar to Hakkinen and associates (2001) for the vastus lateralis muscle in women (type I, 18 %; type IIa, 27.7 %; type IIb, 38 %) following 21 weeks training. In addition, Charette et al. (1991a) reported an increase of 7.3 % and 20.1 % for type I and II fiber CSA, respectively, after 12 weeks training, while Taaffe and colleagues (1996) reported comparable increases in type I (27.5 %) and type II CSA (22.1 %) following 52 weeks training in women.

The relatively small sample size in most of the studies presented in this review likely limit the ability to detect statistically significant differences between men and women and should be considered when interpreting the results from these experiments. Moreover, large inter-individual variation to identical training protocols increases the standard deviation of the samples and reduces the statistical power to detect a difference if one exists. Some of the studies presented (Hunter, Bryan, Wetzstein, Zuckerman, & Bamman, 2002; Martel et al., 1999; Roth et al., 2001; Trappe et al., 2001) have a two-fold or greater increase in anabolic response between men and women, yet are not significantly different. However, differences of this magnitude may be clinically important. Therefore, clinical/practical versus statistical

significance must be considered. Moreover, numerous studies presented in this review were not specifically designed to examine anabolic differences by sex, having such outcomes only as a secondary endpoint of the intervention. Thus, considering the design limitations and differences in anabolic measurement techniques used in previous studies, future research should incorporate larger sample sizes with multiple measurement time points for anabolic responses.

In summary, the majority of studies directly examining anabolic responses to resistance training in older men and women support comparable adaptations following 9 to 42 weeks of exercise with similar relative increases in muscle strength. However, two recent studies indicate that men may exhibit a greater adaptation than women at the muscle cell level when undertaking the same training program (Bamman et al., 2003; Hakkinen et al., 2002). Although, superior changes in fiber CSA may occur in men, only the study by Bamman et al. (2003) indicates that these anabolic changes translate into greater relative improvements in muscle strength. Therefore, based on the studies conducted to date, it appears appropriate to include older men and women in the same exercise regimen as the anabolic and muscle strength response is relatively similar.

Table. Older men vs. women anabolic response to resistance exercise.

Study	Duration/ Freq./ Sets/ Rep./ Intensity	Subjects (Sex, n, age)	Method	Tissue/ Body Composition % Change	Body Weight % Change	Strength % Change	Sex Difference
Lexell et al. 1995	11 weeks 3 x week 3 sets/ 6 rep 85% 1RM	M (n = 6) 70-77y W (n = 10) 70-77y	Biopsy	(BB) TI 13.0, TII 17.0 (VL) TI - 1.0, TII - 14.0 * (BB) TI 13.0, TII 16.0 * (VL) TI - 8.0, TII 1.0	n.r. n.r.	107.0 WB * 104.0 WB *	M = W
McCartney et al. 1995	42 weeks 2 x week 2-3 sets 10-12 rep 50-80% 1RM	M (n = 39) 60-80y W (n = 37) 60-80y	CT	CSA (QF) 6.2 * CSA (QF) 4.7 *	n.r. n.r.	36.7 WB ♦ * 46.2 WB ♦ *	M = W

Hakkinen et al. 1998	24 weeks 2 x week 3-6 sets 3-15 rep 50-80% 1RM	M (n = 11) 72y W (n = 10) 67y	CUS, S	B.f. - 1.0, CSA (QF) 2.1 B.f. n.c., CSA (QF) 5.8 *	n.c. n.c.	21.3 LB * 30.0 LB *	W > M
Tracy et al. 1999	9 weeks 3 x week 5 sets/5RM	M (n = 12) 65-75y W (n = 11) 65-73y	MRI DXA	B.f. n.c., CSA (QF) 11.5 * B.f. - 0.7, CSA (QF) 12.0 *	0.9 - 0.2	27.0 LB * 29.0 LB *	M = W
Martel et al. 1999	24 weeks 3 x weeks 1-2 sets/ 5RM	M (n = 11) 65-73y W (n = 10) 65-73y	DXA	B.f. - 1.0, F.f.m. n.c. B.f. - 1.0, F.f.m. 2.4	2.4 (n.c)	21.9 WB * 23.9 WB *	M = W
Ivey et al. 2000	9 weeks 3 x week 5 sets/ 5RM	M (n = 12) 65-75y W (n = 11) 65-75y	MRI DXA	B.f. n.c., F.f.m. 0.7 MV (thigh) 11.5 * B.f. - 0.7, F.f.m. -1.8 MV (thigh) 12.0 *	0.9 * - 0.2	n.r. n.r.	M = W

Trappe et al. 2000, 2001	12 weeks 3 x week 3 sets/ 10 rep 80% 1RM	M (n = 7) 74y W (n = 7) 74y	Biopsy	TI 20.4 * ,TIIa 12.7 * TI 24.4 *,TIIa 6.0	(n.r) (n.r)	50.0 LB * 56.0 LB *	M = W
Roth et al. 2001	24 weeks 3 x week 1-2 sets/ 5RM	M (n = 9) 65-75y W (n = 10) 65-75y	DXA MRI	B.f. - 1.0, F.f.m. 1.0 * MV (thigh) 4.1 * B.f. - 0.4, F.f.m. 2.1 * MV (thigh) 5.8 *	- 0.7 1.7	14.5 WB * 21.7 WB *	M = W
Lemmer et al. 2000	9 weeks 3 x week 5 sets/ 5RM	M (n = 12) 65-75y W (n = 11) 65-75y	DXA	B.f. n.c., F.f.m 1.7 B.f. - 1, F.f.m. 2.4	1.2 n.c.	27.0 LB * 29.0 LB *	M = W
Lemmer et al. 2001	24 weeks 3 x week 1-2 sets/ 5RM	M (n = 11) 65-75y W (n = 10) 65-75y	DXA	B.f. - 0.9, F.m. - 2.8 F.f.m. 1.7 * B.f. - 0.4, F.m. 1.0 ** F.f.m. 2.1 *	0.3 1.7	23.0 WB * 22.8 WB *	M = W

Hurlbut et al. 2002	24 weeks 3 x week 1-2 sets 5RM	M (n = 12) 65-75y W (n = 9) 65-75y	DXA	B.f. - 0.8, F.m. - 2.5 F.f.m. 1.5 * B.f. - 0.6, F.m. n.c. F.f.m. 2.1 **	0.1 1.5	23.8 WB * 22.4 WB *	M = W
Hunter et al. 2002	25 weeks 3 x week 2 sets 10RM	M (n = 14) 61-77y W (n = 12) 61-77y	CT, BP	B.f. - 2.7, F.m. - 9.1 * F.f.m. 4.7 * B.f. - 2.1, F.m. - 6.2 * F.f.m. 2.3*	1.0 - 1.0	32.5 WB * 38.5 WB *	M = W
Hakkinen et al. 2002	24 weeks 2 x week 2-4 sets 3-12RM	M (n = 10) 60-75y W (n = 11) 60-75y	Biopsy S	B.f. - 0.9 *, F.f.m. 0.9 * TI 50.6 *†, TIIa 48.4 *†, TIIb 46.2 *† B.f. - 0.8, F.f.m. - 0.4 TI 28.6 * , TIIa 33.2 * , TIIb 18.9	- 0.2 - 1.5	35.0 LB * 38.4 LB *	M > W
Bamman et al. 2003	26 weeks 3 x week 2 sets 10RM 80% 1RM	M (n = 9) 61-77y W (n = 5) 61-77y	Biopsy BP	B.f. - 2.9 *, F.f.m. 4.4 * TI 28.0 *†, TIIa 41.0*†, TIIx 42.0 *† B.f. - 3.1 *, F.f.m. 4.2 * TI 6.5 *, TIIa 5.7 *, TIIx 5.0 *	0.6 - 0.8	82.0 LB *† 52.0 LB *	M > W

Brose et al. 2003	14 weeks 3 x week 1-3 sets 10-12 rep 50-80% 1RM	M (n = 7) 68.3 W (n = 7) 69.9y	DXA Biopsy	B.f. - 0.2, F.f.m. n.c. TI 24.2 *, TIIa 24.6, TIIx 40.6* B.f. - 0.9,F.f.m. 1.6 TI 5.3 *, TIIa 3.1, TIIx 17.0*	- 0.5 n.c.	36.1 WB * 46.0 WB *	M = W
Ryan et al. 2004	24 weeks 3 x week 1-2 sets 12-15RM	M (n = 10) 65-74y W (n = 10) 65-74y	DXA	B.f - 0.8, F.m. - 2.5 F.f.m. 1.6 * B.f - 0.7, F.m. - 0.6 F.f.m. 1.7	0.2 0.7	24.2 WB * 20.8 WB *	M = W

* significantly different from baseline ($P < 0.05$) , ** approached significance compared to baseline ($P = 0.06$), † significantly different between groups ($P < 0.05$), ‡ approached significance between group ($P = 0.06$), DXA = dual energy X-ray absorptiometry, CT = computed tomography, BP = BOD POD, CUS = compound ultrasonic scanner, MRI = magnetic resonance image, S = skinfolds, CSA = cross-sectional area, TI = type I CSA, TII = type II CSA, TIIa = type IIa CSA, TIIb = type IIb CSA, TIIx: = type IIx CSA, F.m.: = fat mass, B.f. = % body fat, F.f.m. = fat free mass, MV = muscle volume, LB = lower body strength, WB = total body strength, QF = quadriceps femoris, H = hamstrings, BB = biceps brachii, VL = vastus lateralis, n.c. = no change, n.r. = not reported, ♦ data taken from graph.

Chapter 4

EXPERIMENTAL STUDY ONE

CHANGES IN MUSCLE, FAT, AND BONE MASS AFTER 36 WEEKS OF MAXIMAL ANDROGEN BLOCKAGE FOR PROSTATE CANCER

Manuscript submitted to British Journal Urology International May 2006

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Introduction

Prostate cancer is the fifth most common cancer representing 19% of cancers among men in developed countries with more than 80% of the cases occurring in men older than 65 years (Parkin, Bray, Ferlay, & Pisani, 2005; Parkin, Pisani, & Ferlay, 1999). Traditional treatments for prostate cancer that focus on reducing the levels of or effects of testosterone by Androgen Deprivation Therapy (ADT) may lead to detrimental side effects in the musculoskeletal system (Diamond, Higano, Smith, Guise, & Singer, 2004; Holzbeierlein, McLaughlin, & Thrasher, 2004; Pickett, Bruner, Joseph, & Burggraf, 2000; Stege, 2000). Some of these side effects are directly related to changes in body composition with an increase in fat mass and reduction in muscle mass that may negatively impact physiological function (Holzbeierlein, McLaughlin, & Thrasher, 2004; Sharifi, Gulley, & Dahut, 2005; Smith, 2004; Smith et al., 2002). Moreover, these treatment side effects would exacerbate the age-related loss of muscle mass, termed sarcopenia, further compromising muscle strength, physical function and dependent living (Rosenberg, 1997). The simultaneous increase in fat mass during ADT can lead to increased levels of total cholesterol and triglycerides (Sharifi, Gulley, & Dahut, 2005; Smith et al., 2002; Tayek et al., 1990) and consequently the possible development of cardiovascular complications (Holzbeierlein, McLaughlin, & Thrasher, 2004; Sharifi, Gulley, & Dahut, 2005). Additionally, ADT has been associated with reduced bone mass which can compromise bone strength and increase fracture risk (Diamond, Higano, Smith, Guise, & Singer, 2004; Shahinian, Kuo, Freeman, & Goodwin, 2005; Smith, 2002b; Smith et al., 2005) compounded by increased risk of falling precipitated by the reduced muscle strength.

Only scant information on alterations to bone mass and soft-tissue following ADT exist (Smith, 2004; Smith et al., 2002; Tayek et al., 1990), and there is no information on changes in the regional distribution of bone, lean and fat mass (i.e. trunk, upper, and lower limb) during therapy. Abdominal fat has been related to increased risk for the development of cardiovascular complication, thus, if ADT tends to induce greater trunk fat accumulation, alternative or adjuvant therapies should be devised to counteract such conditions. Similarly, are losses in muscle and bone mass greater at weight-bearing sites than non-weight bearing sites and can

strategies be incorporated into the patient's management plan to address this? Moreover, these changes in body composition and tissue distribution can be directly related to chronic conditions that result in disability and loss of independence in older adults.

Considering that the life expectancy for prostate cancer patients has increased, additional information on how bone mass and body composition adapts during ADT seems relevant so that strategies to counter the physiological side effects can be devised and recommended. The purpose of the present study was to examine the alterations in whole body and regional bone, lean and fat mass in men that occurs after receiving ADT for prostate cancer.

Methods

Subjects

Seventy-two prostate cancer patients aged 44 to 88 years receiving intermittent androgen blockage had hip, spine and whole body scans by dual-energy x-ray absorptiometry (DXA) performed at baseline and following 36 weeks of treatment. The patients were a sub-group of those participating (n = 250) in a multi-centre trial of ADT from 1999-2004, and were from the one clinical site. Subjects were required to have a histological or cytological diagnosis of adenocarcinoma of the prostate and to have an ECOG performance status of 0, 1 or 2 at baseline. Prior neoadjuvant hormonal therapy did not preclude study entry provided that treatment had been administered more than two years ago and given for no more than six months. Institutional Ethics Committee approval was obtained and each participant provided written consent. ADT was achieved by a maximal androgen deprivation program employing Flutamide (Eulexin®) 250mg tid and Leuprolide (Lucrin®) 22.5mg three monthly depot during the course of 36 weeks. Disease extent was prospectively categorised as: locally advanced disease without evidence of metastatic disease but not considered suitable for or declining radical treatment; recurrent local disease following radical prostatectomy, or radical radiotherapy and associated with a rising PSA ≥ 2ng/mL, measured on three consecutive occasions, at intervals of at least one month or more apart and without evidence of metastatic disease.

Bone Mineral Density and Body composition

Bone mineral density (BMD, g/cm^2) and content (BMC, g) of the total hip, spine and whole body was assessed by DXA (Hologic Discovery W, Waltham, MA). In addition, whole body bone mineral-free lean mass (LM) and fat mass (FM), upper limb lean mass and fat mass (ULLM, ULFM), lower limb lean mass and fat mass (LLLM, LLFM), trunk lean mass and fat mass (TrLM, TrFM) and percent body fat were derived from the whole body scan. Regional analysis was derived by manipulating segmental lines according to specific anatomic landmarks (Taaffe et al., 2001; Taaffe, Lewis, & Marcus, 1994). A vertical line extended between the head of the humerus and the glenoid fossa separated the upper limbs from the trunk, while an oblique line through the femoral neck separated the lower limbs from the pelvis. Upper limb and lower limb lean tissue mass represent the sum of left and right extremities. ULLM and LLLM were then combined to derive appendicular skeletal muscle (ASM) (Heymsfield et al., 1990; Wang et al., 1996).

PSA, Testosterone and Blood Counts

All measurements were performed on samples collect after overnight fasting. PSA and free testosterone was measured by chemiluminescent microparticle immunoassay (Architect I200SR, Abbott Diagnositics). Full blood counts were determined using an automated blood counting (electrical impedance, Beckman Coulter diagnostics).

Bone Markers

Serum osteocalcin was determined using radioimmunassay techniques as previously described (Kent et al., 1990). Urine calcium, urine calcium excretion and urine calcium / creatinine ratio were assessed using a Hitachi 917 chemistry analyser and alkaline phosphatase using a Hitachi modular unit.

Height and Weight

Height and weight were determined by a stadiometer and electronic scale, respectively, and body mass index (BMI, kg/m^2) was calculated from weight divided by the square of height.

Physical activity and Fatigue

The European Organization for Research and Treatment of Cancer EORTC QLQ-C30 version 2.0 core questionnaire quality of life (QOL) were used to assess changes in physical activity and levels of fatigue. The QLQ-C30 core questionnaire incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality of life scale. Several single item symptom measures were also included. All scales are scored from 0 to 100. High scores for a functional scale represented high or healthy levels of functioning, and similarly for global health or quality of life. High scores for a symptom scale or item represented high levels of symptomatology or problem.

Statistical Analyses

Data were analyzed using the SPSS (Version 11.0, SPSS Inc., Chicago, IL) statistical software package. Analyses included standard descriptive statistics and paired two-tailed Student's t-tests. To adjust for multiple comparisons, an alpha level of 0.01 was set as the criterion for statistical significance. Results are given as the mean ± SE.

Results

Subject characteristics are shown in Table 1. The mean age of the participants was 73.5 ± 1 year with a BMI of 27.1 ± 0.4 kg/m^2. Levels of serum testosterone, PSA and hemoglobin decreased ($P < 0.001$) by 93.3% ± 0.4, 98.2% ± 0.5%, and 8.8 ± 0.9, respectively and markers of bone formation and resorption increased following treatment (Table 2). Additionally, following treatment, physical activity levels significantly decreased from 89.5 ± 2.3 to 83.5 ± 2.3 ($P = 0.008$) and fatigue increased from 16.2 ± 2.0 to 26.8 ± 2.5 ($P < 0.001$).

Baseline and week 36 values as well as percent change for whole body and regional lean, fat and bone mass are shown in Table 3. Following treatment, whole body LM (1.4 ± 0.2 kg) and bone mass (61.5 ± 10.3 g) significantly ($P < 0.001$) decreased and FM increased (2.2 ± 0.3 kg). There were significant ($P < 0.01$) declines at all regional sites for LM, with the percent decline in LLLM and ULLM greater than that for the TrLM ($P = 0.004$). Conversely, fat mass increased ($P < 0.001$) at all regional sites with the change in the limbs greater than the trunk ($P < 0.001$). There was a significant ($P < 0.001$) reduction in hip and spine BMD of 1.5 % and 3.9 % respectively, and a decline in upper limb BMD of1.3% ($P < 0.001$) with no significant change for lower limb BMD. The decrease in bone density at the spine was greater than that at the hip site ($P = 0.032$).

Discussion

The results from the present study demonstrate that 36 weeks of ADT in men with non-metastases prostate cancer has a deleterious effect on whole body and regional tissue composition by decreasing muscle and bone mass and increasing fat mass. The change in soft tissue was greater for the limbs than the trunk, and for the older patients may contribute to a decline in their functional performance and loss of independence.

Our findings confirm the changes in whole body composition previously reported by Smith and associates (Smith et al., 2002) where body weight and fat mass increased by 2.4% and 9.4%, respectively, and lean mass decreased by 2.7%

following 48 weeks of ADT. Recently, the same group(Smith, 2004) reported an increase of 11% in fat mass and a decrease of approximately 4% in lean mass after one year of ADT. The present study extends these findings and indicates that the decline in lean mass from the upper and lower limbs is greater than changes occurring in the trunk. This preferential loss from the limbs would be expected given that the trunk includes a large organ mass (which will not be affected by treatment) in addition to skeletal muscle. As reduced muscle mass and function are directly associated with impairments and compromised function in older adults (Bassey et al., 1992; Evans, 1995), our findings would suggest that countermeasures need to be implemented to maintain or even reverse the rate of muscle loss in the most affected areas following ADT. Resistance training has been reliably shown to be a safe and effective strategy to improve muscle mass and function in older adults (Taaffe, 2006) including the very old (Fiatarone et al., 1990) and may play an important role in attenuating or reversing this muscle loss in ADT treated men (Galvao & Newton, 2005).

We also observed an increase in fat accumulation at all regional sites with the upper and lower limbs showing greater changes than for the trunk. The increase in whole body fat is consistent with previous studies (Smith, 2004; Smith et al., 2002), however, we note regional differences in fat distribution with ADT. Increased abdominal fat mass has been associated with a greater risk for developing coronary artery disease, type 2 diabetes, hyperlipidemia and premature death than accretion of fat mass in the extremities (ACSM, 2000). Consequently, although the accumulation of fat was relatively less for the trunk, strategies aimed at minimizing fat accretion during ADT should be explored. In addition, the decline in lean mass would negatively impact basal metabolic rate and hence energy requirement and this would contribute to the increase in fat mass associated with ADT. Therefore, strategies aimed at preserving lean mass will also assist in attenuating the increase in fat mass.

In the present study we also noted a significant decrease in lumbar spine and hip BMD and reduction of whole body BMD following therapy. A number of studies have reported decreases of bone mass following ADT (Diamond, Campbell, Bryant, & Lynch, 1998; Eriksson, Eriksson, Stege, & Carlstrom, 1995; Maillefert et al., 1999; Shahinian, Kuo, Freeman, & Goodwin, 2005) and recent reviews(Diamond, Higano, Smith, Guise, & Singer, 2004; Holzbeierlein, McLaughlin, & Thrasher, 2004) have highlighted the importance of addressing bone loss and osteoporosis in

this group of cancer patients. It is interesting that our analyses showed that although BMD decreased in the upper limbs, these changes were not observed in the lower limbs. The loading that the lower extremities are subject to may have contributed to the preservation of bone density compared to the non-weightbearing upper extremities. Additionally we also noted that BMD for the spine showed greater reductions than at the hip. This may be attributed to the greater trabecular bone composition of the spine compared to the proximal femur, where earlier bone turnover and therefore loss of BMD in the axial skeleton may occur (Marcus, 1991). Maillefert and colleagues (1999) have also reported greater losses in BMD at the lumbar spine than femoral neck in a small group of patients following 18 months of ADT. We observed in addition to the changes in BMD, a marked increase in markers of bone resorption and formation indicating increased bone turnover.

In summary, we found that 36 weeks of ADT has a negative impact on whole body and regional tissue composition in men with non-metastatic prostate cancer. These changes were marked with reductions in lean mass and increases in fat mass occurring at all regional sites (upper limbs, lower limbs and trunk). Additionally, decreases in lumbar spine and hip BMD and whole body and upper limb BMD were observed. We propose that strategies to counteract such changes in soft tissue and bone mineral during ADT in older men should be implemented to minimize the risk of sarcopenia, osteoporosis, and obesity, and subsequent disability.

Table 1. Subjects Characteristics at Baseline (n = 72)

	(Mean ± SE)	Range
Age (yr)	73.5 ± 0.9	(44.4 to 88.4)
Height (cm)	171.2 ± 0.7	(154.5 to 186.8)
Weight (kg)	79.6 ± 1.5	(55 to 116.3)
BMI (kg/m²)	27.1 ± 0.4	(18 to 38)
Body fat (%)	25.5 ± 0.6	(9 to 36)

BMI = body mass index

Table 2. Total testosterone, PSA, haemoglobin and bone markers changes following 36 weeks of Androgen Deprivation Therapy (Mean ± SE).

	Baseline (n = 68)	36 weeks (n = 68)	Percent change (%)	P value
Total Testosterone (pg/ml)	15.1 ± 0.6	0.80 ± 0.03	- 93.3 ± 0.3	< 0.001
PSA (ng/ml)	22.6 ± 3.1	0.23 ± 0.05	-98.2 ± 0.5	< 0.001
Hemoglobin (g/L)	145.2 ± 1.5	131.9 ± 1.5	-8.8 ± 0.9	< 0.001
Bone Markers				
Serum Osteocalcin *	4.7 ± 0.05	7.4 ± 0.7	341.0 ± 111.2	0.002
Alkaline Phosphatase †	89.0 ± 6.1	99.5 ± 7.1	13.5 ± 3.0	0.001
Urine Calcium/Creatinine Ratio †	240.4 ± 24.6	415.3 ± 39.11	101.5 ± 12.2	< 0.001
Urine Calcium Excretion †	21.2 ± 2.4	35.3 ± 3.6	94.0 ± 12.0	< 0.001

PSA = prostate specific antigen, * n = 63, † n = 62.

Table 3. Body composition and bone mass changes following 36 weeks of Androgen Deprivation Therapy (Mean ± SE).

	Baseline (n = 68)	36 weeks (n = 68)	Percent change (%)	P value
Lean tissue mass				
LM (kg)	55.8 ± 0.8	54.4 ± 0.8	-2.4 ± 0.4	< 0.001
ULLM (kg)	6.3 ± 0.1	5.9 ± 0.1	-5.6 ± 0.6	< 0.001
LLLM (kg)	17.1 ± 0.2	16.4 ± 0.2	-3.7 ± 0.5	< 0.001
TrLM (kg)	28.8 ± 0.4	28.3 ± 0.4	-1.4 ± 0.5	0.009
ASM (kg)	23.4 ± 0.3	22.4 ± 0.3	-4.2 ± 0.5	< 0.001
Fat mass				
FM (kg)	20.8 ± 0.7	23.1 ± 0.7	13.8 ± 2.3	< 0.001
ULFM (kg)	2.1 ± 0.1	2.5± 0.1	20.7± 3.3	< 0.001
LLFM (kg)	5.5 ± 0.2	6.4 ± 0.2	18.7 ± 2.7	< 0.001
TrFM (kg)	12.13 ± 0.4	13.1 ± 0.4	12.0 ± 2.5	< 0.001
Body fat (%)	25.8 ± 0.6	28.5 ± 0.7	2.6 ± 0.3	< 0.001
Bone mass				
TBBMD (g/cm^2)	1.164 ± 0.014	1.145 ± 0.014	-2.4 ± 0.3	< 0.001
ULBMD (g/cm^2)	1.732 ± 0.015	1.708 ± 0.015	-1.3 ± 0.3	< 0.001
LLBMD (g/cm^2)	2.576 ± 0.038	2.559 ± 0.041	-0.6 ± 0.4	0.173
Total hip BMD (g/cm^2) *	1.021 ± 0.018	1.001 ± 0.018	-1.5 ± 0.5	< 0.001
Spine BMD (g/cm^2) *	1.123 ± 0.024	1.086 ± 0.023	-3.9 ± 0.4	< 0.001

LM = bone mineral-free lean mass, ASM = appendicular skeletal muscle, TrLM = trunk lean mass, ULLM = upper limb lean mass, LLLM = lower limb lean mass, FM = fat mass, TrFM = trunk fat mass, ULFM = upper limb fat mass, LLFM = lower limb fat mass, TBBMD = total body bone mineral density, ULBMD = upper limb bone mineral density, LLBMD = lower limb bone mineral density, BMD = bone mineral density, * n = 69.

Chapter 5

EXPERIMENTAL STUDY TWO

RESISTANCE TRAINING AND REDUCTION OF PHYSICAL TREATMENT SIDE EFFECTS IN PROSTATE CANCER PATIENTS

Medicine Science in Sports and Exercise, In Press, May 2006

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Introduction

The use of androgen deprivation therapy (ADT) in the form of gonadotropin releasing hormone (GnRH) agonists for prostate carcinoma increased extensively across all stages and histologic grades of prostate cancer in the past decade (Cooperberg, Moul, & Carroll, 2005; Shahinian, Kuo, Freeman, Orihuela, & Goodwin, 2005). However, the reduction in testosterone levels by ADT is accompanied by a number of adverse side effects (Basaria et al., 2002; Basaria, Muller, Carducci, Egan, & Dobs, 2006; Diamond, Higano, Smith, Guise, & Singer, 2004; Shahinian, Kuo, Freeman, & Goodwin, 2005; Sharifi, Gulley, & Dahut, 2005; Smith et al., 2001). Some of these side effects include reduction of muscle strength, lean and bone mass, increased fat mass and risk of fracture, unfavorable lipid profile and depression compromising physical and physiological function (Greenspan et al., 2005; Shahinian, Kuo, Freeman, & Goodwin, 2005; Sharifi, Gulley, & Dahut, 2005; Smith, 2004; Stoch et al., 2001). Importantly, these side effects are closely related to an increased risk of developing other chronic conditions (Basaria, Muller, Carducci, Egan, & Dobs, 2006; Shahinian, Kuo, Freeman, & Goodwin, 2005; Sharifi, Gulley, & Dahut, 2005). Increases of ~7-10% in fat mass and decreases of ~ 2-4% in lean mass after one year of ADT have been reported in recent studies (Greenspan et al., 2005; Lee, McGovern, Finkelstein, & Smith, 2005; Smith, 2004; Smith et al., 2002) as well as reduced muscle strength (Basaria et al., 2002). Additionally, substantial decreases in trabecular and cortical bone mass have been found following administration of ADT with a concomitant increased risk for fracture at multiple skeletal sites (Shahinian, Kuo, Freeman, & Goodwin, 2005; Smith et al., 2005). As a result, strategies to preserve body composition and improve physical function may reduce falls risk, fracture, and subsequent complications.

Existing treatments to alleviate these side effects have been predominantly pharmaceutical, however, these treatments are expensive, and their effects do not translate into improved physical and functional capacity. To date, most of the experimental studies examining the role of exercise during cancer treatments have included breast cancer patients and aerobic exercise rather than resistance exercise (Courneya, 2003; Galvao & Newton, 2005). In view of the extensive scientific literature supporting resistance training as the most effective exercise mode for improving muscle strength, physical function and counteracting sarcopenia in older adults (Fiatarone et al., 1990; Frontera, Meredith, O'Reilly, Knuttgen, & Evans, 1988a; Taaffe, 2006), resistance exercise may have a significant role in preventing the

catabolic effects of ADT by promoting a sufficient anabolic environment which can lead to positive musculoskeletal benefits and enhanced physical function.

Segal and associates (2003) recently reported positive changes in quality of life and fatigue outcomes subsequent to a short-term resistance training program in prostate cancer patients undertaking testosterone suppression. However, questions remain regarding the adaptive response of specific physiological and physical parameters, such as body composition, muscle hypertrophy, bone mineral density, functional performance and balance in a longer-term trial in this population. We therefore designed a non-randomized clinical trial to examine the possible effects of a 20-week high intensity progressive resistance training program on muscle function, functional performance, balance, body composition and muscle thickness in older men receiving ADT for prostate cancer.

Methods

Ninety-one prostate cancer patients, referred by oncologists and urologists or who responded to advertisements via local newspaper and radio in the city of Perth, Western Australia from February through July 2005, were initially screened for participation in the study (Figure 1). Exclusion criteria included: no histologically documented prostate cancer, not receiving ADT in the previous 2 months, not scheduled to receive ADT for the subsequent 6 months, metastatic disease, any musculoskeletal, cardiovascular, or neurological disorder that could inhibit them from exercising, inability to walk 400 m or undertake upper and lower limb exercise, resistance training in the previous 12 months, and unwillingness to undertake 20 weeks of resistance training. Eleven men were eligible and invited for familiarization sessions. One subject withdrew from the study at week seven because of an acute respiratory infection that resulted in several weeks of hospitalization (Figure 1). Prior to participation, all subjects obtained medical clearance from their physician and completed a health history questionnaire. Regarding the activity levels of the subjects prior entering the intervention, seven men were not undertaking any form of structured exercise, one was a regular walker, one a regular walker and jogger, and lastly, one was a recreational bowling player. The study was approved by the university Human Research Ethics Committee and all subjects provided written informed consent.

Training Program

Ten subjects undertook 20 weeks of high-intensity progressive resistance training twice a week for 20 weeks. The initial 10 weeks provided an introductory resistance exercise phase consisting of hydraulic resistance training machines (Isotronic, Fitness Technology, Australia) that are simple and time efficient to use, and provide exclusively concentric muscle contractions likely to facilitate training initiation in this clinical group of men. The exercises included the chest press, seated row, shoulder press, lat pull down, triceps extension, biceps curl, leg press, squat, leg extension, leg curl, abdominal crunch and back extension exercises. In the following 10 weeks, the training program was altered to isotonic resistance which provides concentric and eccentric muscle contractions using similar exercises on different apparatus (Cybex, Strength Equipment, USA). During this period, the lat pull down and shoulder press exercises were alternated with the biceps curl and triceps extension exercises every other session to maintain an exercise session length of 1 hour. In every session, general flexibility exercises as well as one set for the first upper and lower body exercise at a lower training intensity were undertaken to ensure adequate warm-up before the training program. Both training phases were designed to progress from 12 to 6-repetition maximum (RM) for 2 to 4 sets per exercise. Briefly, both training phases were designed as weeks 1-2 (2 sets of 12-RM), weeks 3-4 (3 sets of 10-RM), weeks 5-7 (3 sets of 8-RM) and weeks 8-10 (4 sets of 6-RM) and were based on the American College of Sports Medicine position stand on progression models in resistance training for healthy adults (Kraemer et al., 2002). All sessions were conducted in small groups of 1-4 participants under direct supervision to ensure safety, proper intensity and appropriate exercise technique. Additionally, all participants recorded their training weights, number of repetitions and sets performed in an individual exercise log to ensure adequate progression.

Muscle Function

Measures of muscle function included dynamic isotonic muscle strength and endurance and were assessed at baseline, week 10 and week 20.

Dynamic Isotonic Muscle Strength

Participants underwent two familiarization sessions that included instruction regarding correct exercise technique and practice performing 2 sets of 12 repetitions on all hydraulic resistance machines in addition to the chest press, seated row and leg press isotonic resistance machines before muscle strength was determined. Dynamic isotonic muscle strength for the chest press, seated row and leg press were measured using 1-RM, as described previously (Taaffe, Duret, Wheeler, & Marcus, 1999). The 1-RM is the maximal weight an individual can move through a full range of motion by maintaining proper exercise technique and not changing body position other than that of the specific exercise motion.
The coefficient of variation in our laboratory for repeated 1-RM measures performed approximately 1 week apart is 2.2% to 7.5%.

Dynamic Isotonic Muscle Endurance

Muscle endurance was measured using the maximal number of repetitions performed at 70% of 1-RM for the chest press and leg press exercises (Galvao & Taaffe, 2005). For week 10 and week 20 assessments, the baseline and either the week 10 or final 1-RM value, respectively, was used to determine the resistance. The coefficients of variation performed approximately 1 week apart for the chest press and leg press muscle endurance are 6.3% and 6.8%, respectively.

Physical Performance

A battery of tests was used to assess functional performance at baseline, week 10 and week 20. Tests were performed in triplicate (except for the 400-m walk) with sufficient recovery time between trials (Galvao & Taaffe, 2005). The fastest time recorded was used in the analyses

Chair Rise to Standing

Subjects were seated in a hard-backed chair, with a seat height of 43 cm from the floor, with their arms folded across their chest. They were instructed to rise as fast as possible to a full standing position then return to a full sitting position 5 times(Galvao & Taaffe, 2005; Taaffe, Duret, Wheeler, & Marcus, 1999). The coefficient of variation in our laboratory for the repeated chair rise is 5.6%.

6-Meter Walk

Two measures of gait speed were undertaken: usual pace, in which subjects were instructed to walk at a pace similar to which they may use during common daily events; and a fast pace (Fiatarone et al., 1990). Time taken was determined using 2 timing gates (Swift Performance Equipment, NSW, Australia). The coefficients of variation in our laboratory for usual and fast walk are 5.6% and 6.7%, respectively.

6-Meter Backwards Walk

As a measure of dynamic balance, subjects walked backwards 6 meters placing one foot directly behind the heel of the other with the shoes touching (Fiatarone et al., 1990; Taaffe, Duret, Wheeler, & Marcus, 1999). Time taken was assessed using timing gates. Subjects were spotted by an investigator and if they deviated from the line (lost their balance), they were instructed to move back to the line and continue the test, which increased the time required. The coefficient of variation in our laboratory for the backward walk is 9.4%.

Stair Climb

Subjects were instructed to climb a flight of stairs (13 stairs per flight, 17 cm rise per stair) as rapidly as they could safely manage without use of the handrails (Galvao & Taaffe, 2005). Two subjects required use of the handrails to perform this test. The coefficient of variation in our laboratory for the stair climbing is 4.8%.

400-Meter Walk

For the test of walking endurance, participants were required to walk 400 meters, which consisted of 10 laps out and back over a 20-meter course, as fast as they could at a pace they could maintain over the distance (Galvao & Taaffe, 2005; Taaffe et al., 2003). The coefficient of variation in our laboratory for the 400 meters walk is 2.5%.

Sensory Organization Test

The sensory organization test (SOT) was measured using the Neurocom Smart Balance Master (Neurocom International Inc., USA). SOT consists of averaging three equilibrium scores for six trial conditions. Subjects stood on the Neurocom force plate without socks or any footwear and with a security belt attached (in case of a fall). According

to the manufacturer's protocol and previous studies (Wallmann, 2001) subjects undertook three 20-second trials for each of the following conditions: 1) Eyes open, fixed support surface and surround (visual, vestibular, and somatosensory input); 2) Eyes closed, fixed support surface and surround (absent of visual input); 3) Eyes open, fixed support surface and sway-referenced surround (visual input imprecise); 4) Eyes open, fixed surround and sway referenced support surface (somatosensory inputs imprecise); 5) Eyes closed, fixed surround and sway referenced support surface (somatosensory inputs imprecise and absent of visual input); and 6) Eyes open, sway-referenced support surface and surround (imprecise somatosensory and visual inputs). The Equilibrium score was reported as a value between 0 and 100, with 0 indicating a large sway and loss of balance, and 100 indicating perfect stability. The coefficient of variation for the SOT is 1.5%.

Body Composition and Bone Mineral Density

Bone mineral density (BMD, g/cm^2) of the hip (femoral neck, trochanter and Ward's triangle) and total body bone mineral content (BMC, g) was assessed by dual energy X-ray absorptiometry (DXA, Norland XR-36, Wisconsin, USA). In addition, bone mineral-free lean mass (LM), fat mass (FM), and percent fat were derived from the whole body scan. The whole body scan was performed at baseline, week 10 and week 20, while the hip scan was performed at baseline and week 20. Coefficients of variation in our laboratory (duplicate scans with repositioning) for body composition components are less than 1.0%.

Muscle Thickness

Muscle thickness was assessed using B-mode ultrasound (Aloka, SSD-500, Tokyo, Japan) at four anatomical sites [anterior (biceps brachii) and posterior (triceps brachii) upper arm at 60% distal between the lateral epicondyle of the humerus and the acromial process of the scapula; anterior (vastus lateralis and rectus femoris) and posterior (biceps femoris) thigh at 70% thigh length between the greater trochanter and lateral condyle of the femur] similar to the methods described previously by Abe et al (Abe, DeHoyos, Pollock, & Garzarella, 2000). A 5-MHz scanning probe coated with a water soluble gel was placed on the skin

perpendicular to the tissue interface. The subject was seated during the upper limb measurement with the elbow extended and relaxed and in a standing position during the lower limb measurement with the knee extended and relaxed. The muscle thickness measurement was extracted from the ultrasonic image, with the distance between the subcutaneous adipose tissue muscle-interface to the muscle-bone interface taken as muscle thickness (Abe, DeHoyos, Pollock, & Garzarella, 2000). Two muscle thickness measurements were obtained at each of the four sites and averaged to attain the final value. Great care was taken marking the skin via anthropometric techniques, and printed images of baseline measures were available during the week 10 and 20 repeated measurements to ensure identical sites were assessed.

The coefficient of variation for muscle thickness using repeated ultrasound images in our laboratory is less than 3.5%.

Blood Sampling

Venous blood samples were drawn from a forearm vein at a fixed time (8:30 AM - 10:00 AM) at baseline, week 10, and week 20 into sterile vacutainers containing K_2-EDTA and serum separation tubes (Becton Dickinson,
Franklin Lakes, NJ, USA). The blood corrected by K_2-EDTA tube was used for the measurement of hemoglobin concentration by an automatic full blood counts analyser (Sysmex XE-AlphaN, Sysmex Corporation, Kobe, Japan). The serum separation tubes was left at room temperature for the blood to clot, and centrifuged for 10 min at 3000 rpm at 4^{o}C. The serum samples were stored in 0.7mL aliquots at –80^{o}C until the day of analysis for prostate specific antigen (PSA), free testosterone, growth hormone, and cortisol concentrations.

Analysis of PSA, Serum Hormones and Hemolobin

PSA was measured by an Immurise analyser (Beckman Coulter Inc., Fullerton, CA. USA) using a test kit (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum concentrations of the hormones were determined by RIA using a test kit (free testosterone: DPC free testosterone kit, Diagnostic Products Corporation, Los Angeles, CA, USA; growth

hormone: GH Kit, SRL Co., Tokyo, Japan; cortisol: Cortisol Kit, Immunotech, Beckman Coulter Inc., Praque, Czeck Republic).

Statistical Analyses

Data were analysed using the SPSS (Version 11.0, SPSS Inc, Chicago, IL) statistical software package and included standard descriptive statistics, analysis of variance (ANOVA) and covariance (ANCOVA). Repeated measures ANOVA was used to compare subjects over the three time-points, and ANCOVA was used to compare responses at week 20, adjusted for the baseline value, between acute (< 12 months) and chronic (> 12 months) users of ADT. Where appropriate, the Fisher Protected LSD test was employed to locate the source of significant differences. An alpha level of 0.05 was required for significance and results are given as the mean ± SD. The statistical power to detect change in the primary study outcomes (physical and functional performance) over the 20-week intervention ranged from 0.75 to 1.0.

Results

Subject characteristics are shown in Table 1. All men were receiving ADT before entry to the study with a mean duration of 1135 ± 1360 days. Six men were on GnRH agonists, four men were on maximal blockage therapy (GnRH agonists + antiandrogens), and one was on antiandrogens. Five men were on acute (initiating ADT within the last 12 months, mean 156 ± 97days) and the remaining six were on chronic (receiving ADT for 12 months or longer, mean 1951 ± 1391 days) ADT. All subjects were treated with ADT during the entire course of the study (including pre-, mid- and post-test measures and for all 40 training sessions) over a 6-month period.

Dynamic Muscle Strength and Muscle Endurance

Baseline, week 10, week 20 and percentage change in muscle strength and endurance values are reported in Table 2. There was a significant increase in strength for all three exercises with a continuous improvement for both upper and lower body strength from

baseline to week 10 and week 20 ($p<0.001$). Similarly, upper and lower body muscle endurance (number of repetitions performed) increased ($p<0.001$) when 70% of the1-RM baseline load was used during retesting. Muscle endurance assessed using 70% of the1-RM post-test load also increased ($p =0.024$) for the leg press exercise and approached significance ($p=0.085$) for the chest press.

Physical Performance and Sensory Organization Test

After the 20-week training period, there was a significant improvement ($p<0.05$) in the chair rise, 6-m usual walk speed, backward walk speed, 400-m corridor walk, and stair climbing test (Table 3). Additionally, the change in the chair rise, stair climbing, 6-m usual walk and 400-m walk time was significantly different between baseline and week 10. There was also a significant increase in the SOT equilibrium score ($p=0.042$).

Body Composition and Bone Mineral Density

There was no change for LM, FM, percent body fat, whole body BMC, or hip BMD (Table 4), however, quadriceps muscle thickness increased by 15.7 ± 12.1 % ($p=0.050$). There were no significant differences between acute (< 12 months) and chronic users of ADT for the outcome variables (data not shown).

Serum Hormones and PSA

After the 10- and 20-week training period, there were no changes for free testosterone, total testosterone, GH, cortisol and PSA (Table 5). It should be noted that one subject (Table 1) initiated the study with a relatively high PSA level and experienced a subsequent drop in this marker during the intervention. Excluding this subject from the analyses resulted in PSA values of 0.94 ± 1.4 ng/ml, 0.92 ± 1.2 ng/ml, and 0.86 ± 1.2 ng/ml ($p = 0.945$) at baseline, week 10, and week 20, respectively.

Discussion

This is the first study to comprehensively examine the effects of high intensity progressive resistance training on muscle function, functional performance, balance, body composition and muscle thickness in men receiving ADT for prostate cancer. Substantial improvements in muscle strength and endurance, as well as muscle thickness resulted while body composition and bone mass were preserved during the 20-week intervention. Importantly, these changes were accompanied by enhancement in several measures of functional performance and balance. These results suggest that high intensity resistance exercise can be safely tolerated in this group of men receiving ADT and enhanced muscle and physical function ensues despite a compromised hormonal profile. These findings extend those reported by Segal et al.(Segal et al., 2003) who found an increased quality of life and decreased fatigue in men on ADT following 12 weeks resistance training, and provides a rationale for why these benefits were observed.

In the present study, we found significant increases in muscle strength of 40 to 96%, which are comparable to the effects of this exercise mode in healthy older adults not on ADT (Galvao, Newton, & Taaffe, 2005). These observed changes are likely to be mediated by nonhypertrophy –related factors such as neural adaptations to resistance training as previously described (Sale, 1988). We also assessed the effects of training on muscle endurance, an important neuromuscular parameter that has received only modest attention in exercise studies (Galvao & Taaffe, 2005), and observed considerable improvement for both the upper and lower body, especially when the baseline load was used during retesting. Similar enhancement of muscle endurance using a comparable exercise intervention in community-dwelling healthy older adults not on ADT has been previously reported (Galvao & Taaffe, 2005) and indicates that older adults, including those on ADT, may accomplish daily tasks more easily and with less fatigue following training . The combined results of increased muscle strength and endurance in the present study could partially explain the reduced levels of fatigue observed in the study by Segal et al. (Segal et al., 2003).

Changes in several functional performance measures were also observed in our cohort of men, and these changes are comparable to previous studies in healthy older adults undertaking resistance training (Galvao & Taaffe, 2005; Taaffe, Duret, Wheeler, & Marcus, 1999). Our results are particularly important as it implies a greater reserve capacity, and also that daily activities can be more easily performed by using a lower percentage of maximal

strength and endurance, thereby promoting enhanced independence. In addition, balance was improved following training. The SOT equilibrium score has previously been used to discern fallers from non-fallers in healthy older adults (Wallmann, 2001). Skeletal fracture risk is now recognized as a major side effect from GnRH agonist treatment (Shahinian, Kuo, Freeman, & Goodwin, 2005; Smith et al., 2005) and a relationship between the number of GnRH doses received during the initial twelve months after diagnosis and subsequent risk for fracture has been reported (Shahinian, Kuo, Freeman, & Goodwin, 2005). Our findings of improved functional performance and balance following an exercise program could markedly contribute to a reduction in falls and hence a reduced fracture risk during GnRH administration.

A large reduction in lean and bone mass and an increase in body fat are well established side effects from ADT (Diamond, Higano, Smith, Guise, & Singer, 2004; Greenspan et al., 2005; Lee, McGovern, Finkelstein, & Smith, 2005; Shahinian, Kuo, Freeman, & Goodwin, 2005; Sharifi, Gulley, & Dahut, 2005; Smith et al., 2005). Importantly, it has been suggested that these negative changes in soft tissue are more severe in the first twelve months of ADT (Greenspan et al., 2005). In the present study, whole body lean mass, fat mass and BMC, in addition to hip BMD, were preserved irrespective of acute or chronic ADT exposure. This is an important outcome as these well known detrimental changes in the muscular and skeletal system are closely related to other chronic conditions (Shahinian, Kuo, Freeman, & Goodwin, 2005; Sharifi, Gulley, & Dahut, 2005; Smith et al., 2005) that can compromise independence, possibly affecting mortality. In addition to whole body soft tissue, we also examined local changes in skeletal muscle (targeted by the exercises) assessed by ultrasound. Interestingly, quadriceps thickness increased by 15% despite a severely reduced anabolic hormone environment.

Serum testosterone and PSA did not change during the study indicating that this exercise mode can safely be undertaken in prostate cancer patients on ADT without compromising the therapy purpose of reduced androgen levels. The lack of change in testosterone and PSA is consistent with the only other published study in the area of resistance exercise and prostate cancer (Segal et al., 2003). Further, GH, which could mediate resistance training induced adaptations, did not change as a result of the intervention. Additionally, we found that hemoglobin was also unaltered in our cohort which may also provide a basis for Segal et al. (Segal et al., 2003) findings on reduced levels of fatigue following training. Anaemia has been reported as one ADT-related side effect with reductions in hemoglobin ranging from ~7-30% following therapy (Smith, 2004; Smith et al., 2002; Strum, McDermed, Scholz, Johnson, & Tisman, 1997). The maintenance of hemoglobin levels in our group of

men following 20 weeks of exercise, as well as the enhancement in muscle strength and endurance, provides a likely mechanism for the prevention of fatigue in resistance trained men on ADT.

Several limitations of the trial are worthy of comment. Although all subjects were undertaking ADT during the course of the study, duration of use varied. However, we found similar responses in training adaptations irrespective of acute or chronic ADT exposure, possibly due to the low number of subjects in the sub-analysis. In addition, a randomized controlled trial would have been a stronger experimental design. However, it is likely that a control group after six months on ADT would have decreased in the study parameters and, as such, differences in the exercise group would appear even more substantial. It is important to point out that during the recruitment phase, all men reported that they would not have complied with a 20-week control period if allocated to a control group suggesting that future exercise trials should attempt to use alternative control exercise groups (e.g. cardiovascular, flexibility training) as a strategy to enhance long-term exercise study designs. Nevertheless, our study employed a comprehensive battery of measures to assess muscle and physical function, as well as balance, and DXA and compound ultrasound to study change in soft tissue. Lastly, our subjects were well-functioning individuals mostly motivated to undertake the training program and may not be representative of all older men undertaking ADT for prostate cancer.

In summary, the present study indicates that resistance exercise has beneficial effects on muscle strength, functional performance and balance in older men receiving ADT for prostate cancer and should be considered for preserving body composition and reducing musculoskeletal side effects. Randomized controlled trials are warranted to confirm these findings, and future studies are possible including multi-site. Further, behavioural oncology groups committed to conducting behavioural interventions to assist the recruitment of larger study groups would be desirable. Finally, longer exercise periods (>5 months) and training during intermittent regimens of ADT are yet to be examined.

Figure1. Recruitment and Flow of Participants Through the Exercise Study

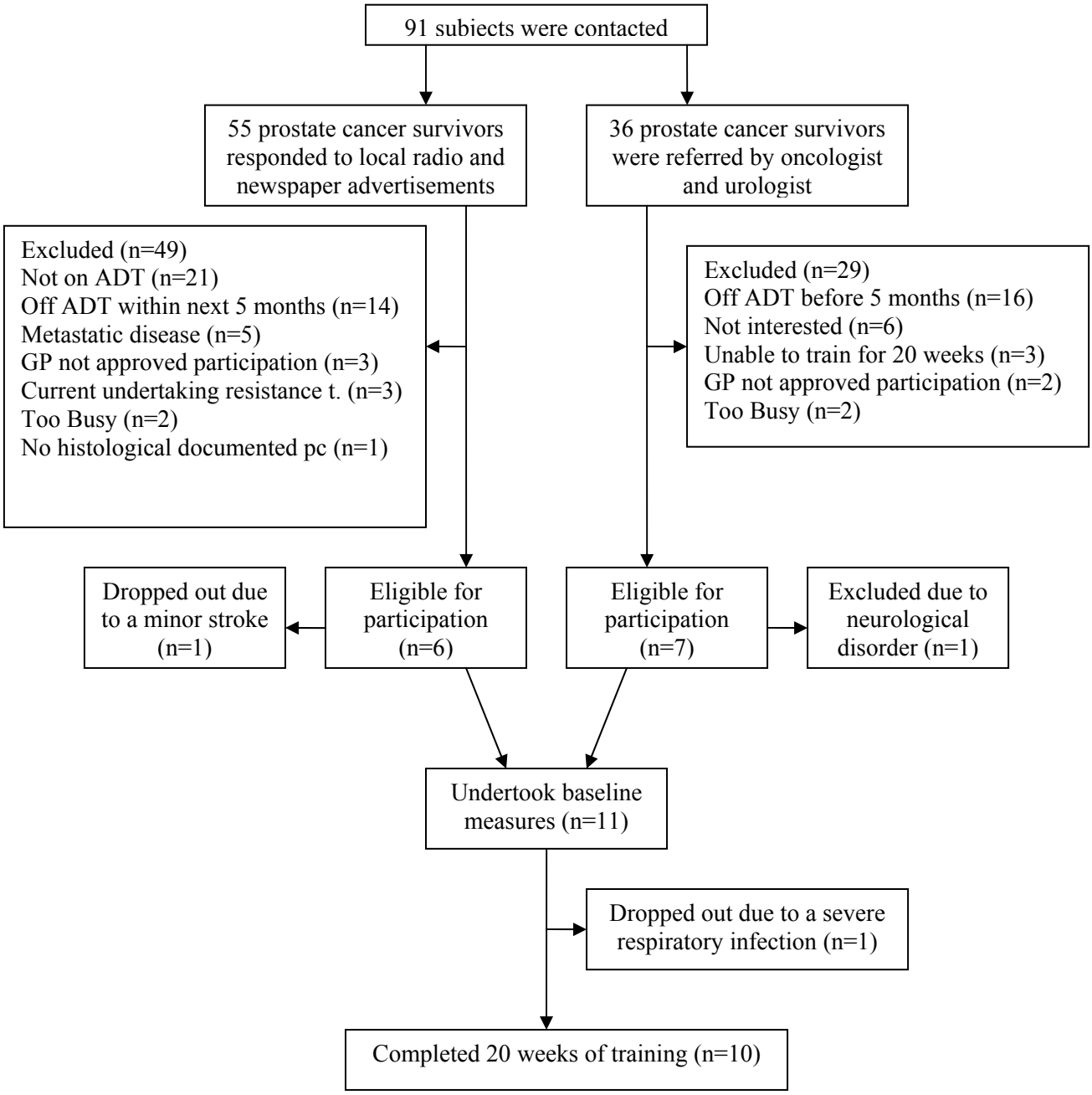

Table 1. Subjects Baseline Characteristic

Subject	Age (years)	Diagnosis (days)	ADT (days)	Free Testosterone (pg/ml)	PSA (ng/ml)	Weight (kg)	BMI (kg/m^2)	Type of ADT
1	79	336	65*	0.79	20.30	66.9	24.3	LHRHa+A
2	65	92	88*	0.26	0.83	73.0	26.8	LHRHa
3	72	184	120*	7.99	1.20	96.7	31.9	LHRHa
4	66	363	210*	0.35	0.04	97.3	32.1	LHRHa
5	59	365	300*	0.15	0.03	68.1	21.2	LHRHa+A
6	72	732	420†	0.87	0.05	75.8	26.2	LHRHa
7	62	2520	720†	9.96	0.04	88.6	29.9	A
8	82	1821	1622†	0.65	2.70	69.9	24.2	LHRHa
9	63	3605	3240†	0.37	3.60	85.6	28.5	LHRHa+A
10	73	3960	3955†	0.35	11.80	76.8	28.0	LHRHa+A
Min	59	92	65	0.15	0.04	66.9	21.2	-
Max	82	3960	3955	9.96	20.30	97.3	32.1	-
Mean	70.3	1397.8	1135.6	2.13	3.09	80.2	27.4	-
SD	8.3	1481.8	1360.4	3.64	6.58	10.9	3.3	-

BMI = body mass index, LHRHa = luteinizing hormone-realizing hormone agonist,
A = antiandrogen, * = acute ADT, † = chronic ADT

Table 2. Muscle Strength and Endurance at Baseline and Following 10 and 20 Weeks Resistance Training (Mean ± SD).

Variable	Baseline	Week 10	Week 20	Percentage change	P value
Chest press 1-RM (kg)	30.9 ± 13.2	39.5 ± 15.4[a]	43.0 ± 16.4[b,c]	40.5 ± 18.5	<0.001
Seated Row 1-RM (kg)	36.4 ± 7.3	44.6 ± 7.3[a]	50.7 ± 7.6[b,c]	41.9 ± 21.4	<0.001
Leg press 1-RM (kg)	81.3 ± 34.2	109.0 ± 37.0[a]	158.0 ± 63.1[b,c]	96.3 ± 25.7	<0.001
Chest press end. (rep)	9.0 ± 2.5	13.8 ± 2.2[a]	20.2 ± 5.5[b,c]	114.9 ± 42.6	<0.001
Chest press end.†(rep)	9.0 ± 2.5	7.3 ± 2.2	9.4 ± 2.0	3.2 ± 31.7	0.085
Leg press end. (rep)	20.3 ± 7.9	35.8 ± 10.8[a]	47.2 ± 10.5[b]	167.1 ± 143.6	<0.001
Leg press end.†(rep)	20.3 ± 7.9	25.0 ± 8.4	27.2 ± 8.6[b]	56.3 ± 94.5	0.024

Significant difference, $P < 0.05$, [a]baseline to week 10, [b]baseline to week 20, [c]week 10 to week 20.
1-RM = one repetition maximal, end. = muscle endurance at baseline test 70% of 1-RM, end. † = muscle endurance at post test 70% of 1-RM, rep = number of repetitions performed.

Table 3. Functional Performance Measures and Sensory Organization Test (SOT) at Baseline and Following 10 and 20 Weeks Resistance Training (Mean ± SD).

Variable	Baseline	Week 10	Week 20	Percentage change	P value
Chair rise (s)	15.4 ± 4.9	11.3 ± 3.5[a]	10.5 ± 2.7[b]	-26.8 ± 7.1	<0.001
6-m backwards walk (s)	23.5 ± 9.3	18.7 ± 10.1	17.7 ± 10.1[b]	-22.3 ± 21.9	0.017
6-m usual walk (s)	5.0 ± 1.0	4.5 ± 0.8[a]	4.3 ± 0.7[b]	-14.1 ± 10.2	0.002
6-m fast walk (s)	3.7 ± 0.7	3.5 ± 0.7	3.5 ± 0.7	-5.5 ± 10.4	0.227
400-m walk (s)	283.1 ± 60.0	255.6 ± 40.8[a]	252.1 ± 46.5[b,c]	-7.4 ± 5.9	0.003
Stair climb (s)	7.0 ± 3.6	6.5 ± 3.9[a]	6.3 ± 2.9[b]	-10.4 ± 9.8	0.014
SOT (0-100)	68.7 ± 8.3	72.7 ± 6.1	75.7 ± 6.9[b]	7.8 ± 6.9	0.042

Significant difference, $P < 0.05$, [a]baseline to week 10, [b]baseline to week 20, [c]week 10 to week 20.

Table 4. Body Composition, Whole Body Bone Mass, Hip BMD and Muscle Thickness at Baseline and Following 10 and 20 Weeks Resistance Training (Mean ± SD).

Variable	Baseline	Week 10	Week 20	Percentage change	p value
Bone mineral-free lean mass (kg)	52.2 ± 5.6	52.2 ± 5.8	52.0 ± 5.7	-0.4 ± 2.2	0.844
Fat mass (kg)	25.7 ± 8.5	25.0 ± 8.5	24.9 ± 8.4	-0.0 ± 6.1	0.823
Percentage body fat	30.7 ± 7.2	30.5 ± 6.7	30.6 ± 6.7	0.3 ± 5.3	0.852
Total BMC (g)	3055.5 ± 396.4	3073.1 ± 430.7	3063.2 ± 410.2	0.2 ± 2.5	0.763
Fem neck BMD (g/cm^2)	0.868 ± 0.123	-	0.880 ± 0.115	1.6 ± 5.3	0.422
Trochanter BMD (g/cm^2)	0.817 ± 0.110	-	0.820 ± 0.124	0.3 ± 4.7	0.806
Wards triangle BMD (g/cm^2)	0.590 ± 0.124	-	0.596 ± 0.145	0.8 ± 7.0	0.751
Biceps thickness (cm)	2.69 ± 0.54	2.83 ± 0.43	2.91 ± 0.57	3.5 ± 6.9	0.621
Triceps thickness (cm)	1.94 ± 0.26	2.22 ± 0.51	2.33 ± 0.49	5.5 ± 17.0	0.875
Quadriceps thickness (cm)	2.15 ± 0.30	2.24 ± 0.42	2.46 ± 0.41[b]	15.7 ± 12.1	0.050
Hamstrings thickness (cm)	4.52 ± 0.74	4.31 ± 0.99	4.53 ± 0.89	0.2 ± 10.0	0.483

[b] Baseline to week 20, $P < 0.05$.

Table 5. Prostate Specific Antigen (PSA), Testosterone, Growth Hormone (GH), Cortisol, and Hemoglobin Following 10 and 20 Weeks of Resistance Training (Mean ± SD).

	Baseline	Week 10	Week 20	* p value
PSA (ng/ml)	3.09 ± 6.58	1.28 ± 1.58	0.90 ± 1.13	0.374
Free Testosterone (pg/ml)	2.13 ± 3.64	2.15 ± 3.61	1.56 ± 3.68	0.532
GH (ng/ml)	0.72 ± 0.75	0.83 ± 0.78	0.48 ± 0.37	0.239
Cortisol (ng/ml)	10.63 ± 3.54	10.35 ± 3.32	10.42 ± 2.67	0.979
Hemoglobin (g/L)	141.3 ± 13.1	142.3 ± 14.4	141.2 ± 13.5	0.913

* ANOVA (baseline, week 10 and 20)

Chapter 6

CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

This chapter summarizes the findings from the literature reviews and experimental studies presented in the previous chapters and highlights future areas of research that are warranted in the field of exercise and prostate cancer.

In literature review 1 (chapter 2), 26 published studies undertaken during and after cancer therapy are summarized. The review provides an outline of exercise studies and benefits derived during and after cancer therapy and is presented by specific exercise modes as cardiovascular, resistance and flexibility training. The majority of studies examined the effect of cardiovascular exercise, and breast cancer was the most common cancer type examined. Only scant information on exercise during prostate cancer therapy exists as just one trial examined the effect of resistance training on rates of fatigue, health-related quality of life and muscle strength in prostate cancer patients undertaking ADT. Although more research is required in this important area we have provided some guidelines and possible physiological outcomes from specific exercise modes. Consequently, future studies should examine the beneficial role that exercise may have in various cancer patient populations, and during various treatments and stages of the disease.

In literature review 2 (chapter 3) resistance exercise induced anabolic adaptations in older men and women were examined by summarizing 16 studies. Comprehensive information regarding resistance training as an exercise modality in an aging non-cancer population is provided with a range of different assessment techniques used among studies examining anabolic adaptations following training. It is clear that resistance training is the most effective exercise mode to reduce the age-related loss of muscle mass and strength and the capacity to adapt with age is preserved. Emphasis on the effects of these adaptations between older men and women responses is discussed. As such, the majority of studies directly examining

anabolic responses to resistance training in older men and women support comparable responses following 9 to 42 weeks of exercise with similar relative increases in muscle strength. A number of specific assessment techniques undertaken in studies with healthy older adults were in our experimental studies (e.g. DXA, Ultrasound, 1-RM).

In experiment 1 (chapter 4) we investigated the effects of 36 weeks of maximal androgen blockage in 72 prostate cancer patients on regional body composition changes, bone mass, hemoglobin and bone markers. Seventy-two prostate cancer patients receiving intermittent androgen blockage undertook hip, spine and whole body scans by DXA performed at baseline and following 36 weeks of treatment. We found that 36 weeks of ADT has a negative impact on whole body and regional tissue composition in men with localized prostate cancer. These changes were marked with reductions in lean mass and increases in fat mass occurring at all regional sites (upper limbs, lower limbs and trunk). Additionally, decreases in lumbar spine and hip BMD and whole body and upper limb BMD were observed. Further, we observed in addition to the changes in BMD, a marked increase in markers of bone resorption and formation indicating increased bone turnover. As such, we suggested that strategies to counteract such changes in soft tissue and bone mineral during ADT in older men are essential to minimize the risk of sarcopenia, osteoporosis, and obesity, and subsequent disability. These findings in addition to other recent studies in the area (Greenspan et al., 2005; Sharifi, Gulley, & Dahut, 2005) creates an important rationale to experiment 2 where the effects of a 20-week progressive resistance exercise program in men on established ADT for prostate cancer is examined.

In experimental study 2 (chapter 5), the effects of a progressive 20-week resistance program on the physical, physiological and morphological responses in prostate cancer patients receiving ADT was investigated. As reviewed in Chapter two (review of literature 1) to date only one study (Segal et al., 2003) has been published in the area of resistance exercise and ADT treated men for prostate cancer. The study by Segal and colleagues (2003) indicated positive effects in terms of decreased levels of fatigue and increased quality of life, however specific physical, functional and physiological outcomes were not determined in their 12-week study. Therefore, the primary aim of experiment 2 was to extend these findings by examining as the effects of resistance exercise on muscle function, function

performance, balance, body composition, muscle thickness and hemoglobin levels in ADT treated men. As such, we conducted a non-randomized clinical trial where 91 potential subjects were initially screened with 11 subjects meeting the criteria to entry the study and 10 subjects completing 40 exercise sessions and study measures during the course of six months. As presented in chapter 5, the results indicated that resistance exercise has beneficial effects on muscle function, functional performance and balance in older men receiving ADT for prostate cancer. Further, body composition was preserved during the 6-month intervention period and quadriceps muscle thickness was increased. These findings extend those reported by Segal et al. (2003) that found an increased quality of life and decreased fatigue in men on ADT following 12 weeks resistance training, and provides a rationale for why these benefits were observed. Moreover, our findings indicate that high intensity resistance training can be safety implemented as part as adjuvant therapy for prostate cancer patients on ADT as markers of the disease (PSA) and the therapy goal of testosterone suppression were unaltered during intervention. These results also support and extends those by Segal and colleagues (2003) who found that PSA and testosterone did not change following a shorter training intervention undertaken at lower intensity and volume.

Although our study employed a comprehensive battery of measures to assess muscle and physical function, and blood markers, a randomized controlled trial would have been a better study design and are warranted to confirm these findings. However, as mentioned in Chapter 5, during the recruitment phase all men reported that they would not have complied with a 5-month control period if allocated to a control group suggesting that future exercise trials should attempt to use alternative control exercise groups (e.g. cardiovascular, flexibility) as a strategy to enhance long-term exercise compliance. Importantly, because we had rigorous inclusion criteria including all participants already on ADT, different to the study by Segal et al. (2003) where subjects were on ADT or were scheduled to initiate ADT for 12 weeks, we are certain that this affected our sample number. Nevertheless, this criterion used ensured that all participants in the study were on ADT at least 2 months before initiating training. This fact not just extends the findings of Segal et al. (2003) but makes our study unique in the way that all men were on least two months on ADT treated prior to baseline measures. In addition, we noted that intermittent regimens of ADT (Bhandari, Crook, & Hussain, 2005) are being

extensively used in major hospitals in the city of Perth, where recruitment was undertaken. Thus, in this specific regimen of therapy patients go “on” and “off” therapy, and most of the time the “on” therapy phase was insufficient to fit with our 20-week exercise intervention and the time for all measures undertaken (6 months study duration) affecting our recruitment.

Future studies are required including multi-site interventions involving behavioural oncology groups committed to conducting behavioural interventions to assist recruitment of larger study groups would be highly desirable. Further, longer exercise periods (>5 months) and training during intermittent regimens of ADT are yet to be examined. Lastly, a requirement for studies examining the impact of different exercise modes, intensities and dosages of training in prostate cancer patients undergoing different treatments and stages of the disease are yet to be determined and should be considered in future clinical trials.

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APPENDIX I - RESISTANCE EXERCISE IN MEN RECEIVING ADT FOR PROSTATE CANCER

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 required to either immediately undertake a resistance training program for 20 weeks or to be part of a delay exercise group that will undertake the exercise program after the first 20 weeks of intervention.
   c. I will be required to have my height, weight, body composition, blood analysis (PSA, hormones, immune system assessment) muscle thickness and bone density taken before, at week 10 and after the study.
   d. I will be required to complete a medical history before the training program commences and a quality of life and fatigue and demographic questionnaire both before and after the training/non-training period.
   e. I understand that my muscle strength will be assessed before, during and after the training period.
   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 and after 10 and the 20-week training/non-training period.
   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 II - MEDICAL DOCTOR CONSENT FORM

Medical Doctor Consent Form for Resistance Training Study

"Resistance Exercise in Men Receiving ADT for Prostate Cancer"

Researchers: Mr. Daniel Galvão, MSc, E-mail: d.galvao@ecu.edu.au Phone: 6304 5073, 6304 5604, 0431636307

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

Professor Linda Kristjanson, PhD E-mail: l.kristjanson@ecu.edu.au

Dr. Michael McGuigan, PhD E-mail: m.mcguigan@ecu.edu.au

Dr. Nigel Spry, MBBS, Radiation Oncologist

School of Biomedical and Sports Science, Edith Cowan University

Dear Doctor,

The School of Biomedical and Sports Science, Edith Cowan University is undertaking a study into the effects of the dosage of resistance training in older adults undertaking ADT (Androgen Deprivation Therapy) for prostate cancer. The intervention program will run for 20 weeks, entailing high-intensity progressive resistance (strength/weight) training for both the upper and lower body. Resistance training has been shown to be a safe and effective method for enhancing muscle strength in older adults, including the very old (*JAMA*, 263(22), 1990). Recently, Segal and colleagues (*J Clin Oncol, 21*(9), 2003) reported positive physiological and psychological benefits from this exercise modality in prostate cancer patients undertaking ADT. We require sixty prostate cancer patients with at least 8 weeks past initiation of ADT with non-bone metastases and no musculo-skeletal or cardiovascular disorder that could inhibit them from exercising. Participants will be randomly assigned to one of three groups: (1) *low dosage group* (1-2 sets of 4-12 repetitions at approximately 60 to 85 % of their maximal strength); (2) *high dosage group (2-4 sets of 4-12 repetitions at* approximately 60 to 85 % of their maximal strength); and (3) a *delay exercise group*, who will undertake testing but not participate in training program during the first 20 weeks period. The exercise and major muscles used in the intervention will be:

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

Exercise sessions will commence with a 10-minute warm-up of aerobic activity and stretching and conclude with a 10-minute cool-down period that includes exercises for the abdominal (e.g. abdominal curls) and lower back area (e.g. single leg raises) and stretching. The exercise sessions will be undertaken in the Conditioning Laboratory in School of Biomedical and Sports Science, Edith Cowan University using hydraulic and traditional resistance training machines to ensure participant safety. All sessions will be conducted in small groups of up to 6 participants under direct supervision by the principal investigators 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, body composition, muscle thickness (non-invasive ultrasound) hip and spine bone density, endocrine responses, immunological responses, PSA levels and functional abilities (e.g. 400-metre walk, balance test, time to rise from a chair), all standard measures in studies of older adults.

Participants must meet the following criteria to participate: (Please, check boxes if applied)

1) Undertaking ADT for at least 8 weeks: □

2) Non-bone metastases: □

3) No musculo-skeletal or cardiovascular disorder that could inhibit them from exercising: □

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.

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 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,

Daniel Galvão and Robert Newton

_____is in sufficient health to participate in the above intervention study.

(Participant)

_____

(Doctor's signature) *(Date)*

APPENDIX III - SUMMARY PARTICIPANTS INFORMATION SHEET

Resistance Exercise Dosage in Men Receiving ADT for Prostate Cancer

Researchers: Mr. Daniel Galvão, MSc E-mail: d.galvao@ecu.edu.au
Professor Robert Newton, PhD E-mail: r.newton@ecu.edu.au
Professor Linda Kristjanson, PhD E-mail: l.kristjanson@ecu.edu.au
Dr. Michael McGuigan, PhD E-mail: m.mcguigan@ecu.edu.au
Dr. Nigel Spry, MBBS, Radiation Oncologist
Contact Telephone number: 6304 5073, 6304 5604
(Mobile) 0431636307

School of Biomedical and Sports Science, Edith Cowan University

Participant Information Sheet

SUMMARY

Purpose of the Study: To examine the effects of resistance training or weight training on weight gain, loss of muscle and bone mass, tiredness, immune system and quality of life in men with prostate cancer.

Subject Involvement: We require 60 prostate cancer patients undertaking treatment to suppress male hormones to participate in this 20-week exercise study. Individuals will be required to have non-bone metastases and no musculo-skeletal or cardiovascular disorder that could prevent them from exercising, and not to have participated in any weight training in the previous 12 months. In addition, volunteers will be required to obtain consent from their doctor before participating in the study.
Intervention: Participants will be placed in one of two groups (by chance): immediate exercise or delayed exercise group. Training groups will undertake twice weekly supervised training sessions for 20 weeks. The delayed exercise group will participate in the tests, and receive all information resulting from them, but not exercise during the first 20 weeks of the intervention. A subsequent training program will be provided for the delayed exercise group.

Test Measures: Before starting the training, after 10 and 20 weeks participants will be asked to take part in some tests to measure their strength, muscle characteristics and abilities to take part in activities (i.e. rise from chair, walk 400 meters). Also samples of blood will be obtained to assess relevant characteristics. In addition, participants will be asked to complete some brief questionnaires about their quality of life and abilities to take part in activities of daily living.

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.

APPENDIX IV - PARTICIPANT INFORMATION SHEET

Resistance Exercise Dosage in Men Receiving ADT for Prostate Cancer

Researchers: Mr. Daniel Galvão, MSc E-mail: d.galvao@ecu.edu.au
Professor Robert Newton, PhD E-mail: r.newton@ecu.edu.au
Professor Linda Kristjanson, PhD E-mail: l.kristjanson@ecu.edu.au
Dr. Michael McGuigan, PhD E-mail: m.mcguigan@ecu.edu.au
Dr. Nigel Spry, MBBS, Radiation Oncologist

Contact Telephone number: Daniel Galvão 6304 5073, 6304 5604
(Mobile) 0431636307

School of Biomedical and Sports Science, Edith Cowan University

Participant Information Sheet

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 effect of resistance exercise on weight gain, muscle and bone mass and the immune system in this cancer group is unknown. Therefore, the purpose of this present study is to examine the effects of resistance training on weight gain, loss of muscle and bone mass, tiredness, immune system and quality of life in men with prostate cancer. The findings from this study will allow health professionals to plan exercise and the correct amount of exercise for men with prostate cancer to help decrease side effects and improve their quality of life

Subject Involvement

We require 60 prostate cancer patients undertaking treatment to suppress male hormones for at least six weeks to participate in this 20-week exercise study. Individuals will be required to have non-bone metastases and no musculo-skeletal or cardiovascular disorder that could inhibit them from exercising, and not to have participated in any weight training in the previous 12 months. In addition, volunteers will be required to obtain consent from their doctor before participating in the study. In study 1, participants will be randomly allocated (by chance) to one of two groups: immediate exercise or delay exercise group. In study 2, subjects from the immediate exercise group (study 1) will be randomly allocated to two different training protocols: low or traditional training dosage while the delay exercise group will remain in a non-exercise condition. Training groups will undertake twice weekly training for 10 weeks (study 1) with subsequent 10 more weeks (study 2) comprising 20 weeks of intervention. The delay exercise group will participate in the tests, and receive all information resulting from them, but not exercise during the first 20 weeks of the intervention. A subsequent training program based from the outcome measures from the first 20 weeks will be provided for the delay exercise group.

Training protocol

Twice weekly exercise sessions will commence with a 10-minute warm-up comprising of low-level activity such as walking and stationary cycling, as well as stretching.

Eight exercises that target the major upper and lower body muscle groups will be performed using hydraulic resistance machines during the first 10 weeks of training (Study 1).The exercises are: Chest Press/Seated Row, Biceps curl/Triceps extension, Leg Press, Shoulder press/ Lat pull down, Squats, Leg Extension/Leg Curls, Upper rower/ Dips, Abdominal/ Back extension.

Ten exercises that target the major upper and lower body muscle groups will be performed using traditional resistance machines in the last 10 weeks of training (study 2). The exercises are: Chest Press, Seated Row, Biceps curl, Triceps extension, Leg Press, Shoulder press, Lat pull down, Leg Extension, Leg Curls, and Abdominal.

Exercise sessions will conclude with a 10-minute cool-down that includes exercises for the abdominal and lower back area and stretching. The exercise sessions will take place in the Strength and Conditioning Laboratory, School of Biomedical and Sports Science, at Edith Cowan University, using hydraulic weight training machines (study

1) and traditional weight training machines (study 2) to ensure participants safety. All sessions will be conducted in small groups of up to 6-8 participants under direct supervision by the principal investigator to ensure proper technique and minimize the risk for injury. The total time to complete the exercise session is less than 60 minutes. All participants will be asked to maintain customary physical activity and dietary patterns over the 20-week period.

The resistance will be set progressively from 12 to 4 repetitions maximum (RM) using repeated lifts before having a rest period. In study 1, the exercise group will perform 2-4 sets of 4-12RM. In study 2, the low dosage training group will perform only 1-2 sets of 4-12RM while the traditional training dosage group will perform 3-5 sets of 4-12RM for each exercise.

To ensure the progressive nature of the training program, both training groups will be encouraged to work past a specific number of repetition-mark. When subjects are able to perform more than the number of repetitions required, during a set the workload will be increased by a 5 - 10% increment for the next set or training session.

All training will take place on Monday and Thursday or Tuesday and Friday.

Test Measures

Prior to the commencement of training, after 10 and 20 weeks a series of tests will be administered. The delay exercise group will only undertake the testing measures before and after the first 20 weeks of intervention and then at 10 and 20 weeks of their exercise intervention.

Body composition and bone density

- 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. Note: height and hip/spine density will not be measured at 6 weeks, only before at week 10 and following the 20-week intervention period.

Muscle thickness

- Muscle thickness of the elbow and knee flexors and extensors will be measured by ultrasound images; this is a safe and non-invasive method to assess soft tissues. The scanning probe will be coated with a water-soluble transmission gel to provide acoustic contact to the surface and some ultrasound images will be recorded from the muscles to determine thickness of the muscles. It will take about 5 minutes to obtain all images, the images will be taken when you sit on a chair or stand. All the testing will take place in the Exercise Physiology Research Laboratory in building 19 on the Joondalup Campus.

PSA, Hormones, Immune system, Bone markers and Beta amyloid (Aβ)

- PSA, Hormones, Immune system markers, Bone markers and Aβ will be determine from blood samples to assess any changes in these physiological markers. All the testing will take place in the Exercise Physiology Research Laboratory in building 19 on the Joondalup Campus.

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. This test will also be performed at week 6 and 18 for the immediate exercise group.
- 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 (only undertaken before at week 10 and after the 20-week period)

- Stair climb

  You will be asked to ascend a flight of stairs (11 stairs) as fast as possible.

- 6-meter backwards walk

  As a test of balance, participants will place one foot will behind the other and will be asked to walk backwards 6 meters.

- 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-meter 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.

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

Lifestyle questionnaires (only undertaken before and after the 20-week period)

- Quality of life will be assessed using a standardized questionnaire (Functional Assessment of Cancer Therapy-Prostate, FACT-P) as well as Levels of Fatigue (Functional Assessment of Cancer Therapy-anemia, FACT-an) that you can complete at home.
- Health history and Demographic information will be also assessed using standardized questionnaires 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 filling 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.

APPENDIX V - EXAMPLE OF UPPER AND LOWER BODY EXERCISES USING THE HYDRAULIC RESISTANCE EXERCISE EQUIPMENT

(Prostate Cancer Study)

Shoulder press/Lat pull down exercise

Leg extension/ leg curl exercise

Biceps curl/ triceps extension

Chest press/ seated row

APPENDIX VI - LETTER TO THE PARTICIPANT

Thank you for your interest in the study "Resistance Exercise in Men Receiving Androgen Deprivation Therapy for Prostate Cancer."

Please find attached:

1. A "Participant Information Sheet" outlining all aspects of the study;
2. A "Summary of Participants Information Sheet";
3. A "Statement of Informed Consent" which you will be required to sign before participating in the study;
4. A "Medical Doctor Consent Form" for your doctor;
5. A sheet titled "Hydraulic Resistance Training Exercises" which contains photographic depictions of several exercises to be undertaken in the study; and
6. 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 and the resistance training exercises sheet 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,

Daniel Galvão MSc (PhD Candidate)
Ph: 63045073, 63045097, 0431636307, Email: d.galvao@ecu.edu.au

APPENDIX VII - HEALTH HISTORY QUESTIONNAIRE

Resistance training in men receiving androgen deprivation 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:

_____

_____

_____

_____

5) Medical condition

(a) When have you been diagnostic with prostate cancer?

_____

_____

_____

(b) Which types of treatments have you undertaken (or are currently undertaking), example: Androgen deprivation therapy, radiation therapy, systematic therapy and/ or surgical castration? Please, specify the duration of treatment?

_____

_____

_____

_____

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

_____

_____

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

_____

_____

_____

_____

_____

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

_____

_____

_____

_____

_____

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:

_____

_____

_____

_____

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

_____

AT THE PRESENT

(a) Do you experience shortness of breath while walking with others of your age?

Yes / No

Do you experience sudden tingling, numbness, or loss of feeling in arms, hands, legs, feet, or face?

Yes / No

(b) 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:

_____

_____

_____

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

APPENDIX VIII - DEMOGRAPHIC QUESTIONNAIRE

Resistance training in men receiving androgen deprivation therapy for prostate cancer

Demographic Questionnaire

To assist us with our research, we would like to know a little about your background. Please circle your response to each of the questions below.

1. How old are you? _____ years, or circle the correct age group

20-30yrs 31-40yrs 41-50yrs 51-60yrs 61-70yrs 71-80yrs >80

2. What is your current marital status?

Single Married Defacto Separated Divorced Widowed

3. What is the highest level of education you completed?

Primary Secondary Trade Certificate/Diploma

Bachelor degree Higher degree Other_____

4. What is your current occupation?

Homemaker Clerical Computing Professional Management

Labourer Trade Retired Other _____

5. What other responsibilities do you have? (Please circle as many as appropriate)

Dependent children Elderly relatives Care of sick/disabled relatives

Study Community volunteering No responsibilities Other _____

6. In which country were you born?

Australia UK Asia Europe America South America Africa

Other_____

APPENDIX IX – ETHICS APPLICATION

CONFIDENTIAL

EDITH COWAN UNIVERSITY

HUMAN RESEARCH ETHICS COMMITTEE

APPLICATION TO UNDERTAKE RESEARCH INVOLVING HUMAN SUBJECTS

THIS FORM IS TO BE COMPLETED FOR ALL RESEARCH INVOLVING HUMAN SUBJECTS

December 2003 (Replacing October 2002)

APPLICATION TO UNDERTAKE RESEARCH INVOLVING HUMAN SUBJECTS
(To be completed for all research involving human subjects)

OFFICE USE ONLY

PROJECT CODE NUMBER:	DATE RECEIVED:	FOR THE MEETING OF:
COMMENTS:		

1. TITLE OF PROJECT:

Resistance Exercise Dosage in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

2. INVESTIGATOR(S)

NAME/S	DESIGNATION Staff OR Student (eg Ma/PhD)	STUDENT NUMBER	FACULTY
Daniel Galvão	PhD Student	2040764	Communications, Health and Science/ Biomedical and Sports Science

CONTACT ADDRESS	PHONE HOME	PHONE BUSINESS
Biomedical and Sports Science Edith Cowan University, Joondalup	92460813	63045152

3. NAME OF SUPERVISOR(S) (students) / HEAD OF SCHOOL (staff)

Principal: Professor Robert Newton
Associates: Professor Linda Kristjanson and Dr. Michael McGuigan

4. EXPECTED DURATION OF RESEARCH PROJECT

COMMENCEMENT DATE:	**COMPLETION DATE:**
February 2005	November 2005

5. FUNDING. ***Is this project the subject of a grant?***

YES:X	**NO:**

If 'yes', what is the Agency or Agencies? ECU Industry Collaborative Grant 2005

Please provide a copy of approval.

6. REVIEW OF ETHICAL CONSIDERATIONS

Has the research proposal previously been submitted to the Human Research Ethics Committee, or to the ethics committee of any other institution?

YES:	**NO: X**

If 'yes', please provide a copy of approval.

7. AIMS OF THE PROJECT

Please give a concise description of the aims of the project using LAY TERMS

The primary aim of the study is to examine the effects of different resistance training protocols in two trials (experiment 1 and 2) with prostate cancer patients undertaking treatment to suppress male hormones. Experiment 1 aims to examine the effects of resistance exercise program over 12 weeks. Experiment 2 will compare a low-dose (LO) or a high-dose training (HI) program aiming to investigate a dose-response of resistance exercises in this cancer population. Outcome measures from both interventions will include changes in: a) muscle function, b) muscle structure, c) fat mass, d) bone mineral density, e) hormone levels, f) immune system, g) Prostate Specific Antigen (PSA), which is a test to detect prostate cancer activity, h) physical performance, i) levels of fatigue and j) quality of life. Further, a cross-over design will be used to examine the effect of timing of the exercise intervention as well as retention of benefits. That is, half the group will commence the exercise intervention immediately, and then return to normal activity after 24 weeks of the exercise program. The other group will delay commencement of the exercise program for 24 weeks and then commence their 24 week exercise intervention.

8. RESEARCH QUESTION

State clearly in lay terms your research question(s).

Experiment 1:

1) Is hydraulic resistance equipment an effective and safe strategy to counteract the side effects of ADT?

More specific questions:

2) Does hydraulic resistance exercise induce muscle anabolic adaptations

assessed by muscle fiber cross-sectional area and MHC expression?
3) Does hydraulic resistance exercise reduce the extent of muscle loss and fat mass gain in patients undertaking ADT?
4) Does hydraulic resistance exercise positively influence PSA levels?
5) Does hydraulic resistance exercise positively induce acute and chronic endocrine adaptations?
6) Does hydraulic resistance exercise positively influence the immunological function in prostate cancer patients undertaking ADT?
7) Does hydraulic resistance exercise enhance functional performance in patients undertaking ADT?
8) Does hydraulic resistance exercise decrease levels of fatigue experienced by prostate cancer patients undertaking ADT?
9) Does hydraulic resistance exercise decrease levels of psychological distress?

Experiment 2:
General questions:
7) Are LO and HI resistance exercise protocols effective and safe strategies to counteract the side effects of ADT?
8) Do LO and HI protocols similarly increase physical performance, physiological nad psychological adaptations in prostate cancer patients?

More specific questions include:
9) Do LO and HI protocols induce muscle anabolic adaptations assessed by muscle fiber cross-sectional area and myosin heavy chain expression?
10) Do LO and HI protocols positively influence PSA levels?
11) Do LO and HI protocols positively induce acute and chronic endocrine adaptations?
12) Do LO and HI protocols positively influence the immunological function in prostate cancer patients undertaking ADT?
13) Do LO and HI protocols decrease levels of fatigue experienced by prostate cancer patients undertaking ADT?
14) Do LO and HI protocols decrease levels of psychological distress?

Experiment 1 and 2 (data combined):
Specific questions include:
1) Does resistance exercise reduce or reverse the rate of bone loss by increasing total body, hip and spine bone mineral density (BMD) sites?
2) Does resistance exercise positively influence levels of beta amyloid?

9. PARTICIPANTS

Please specify any relevant details about the participants, and include the number of participants to be included. Indicate if the research will intentionally involve the following groups of participants:

☐ ***Children and young people***
☐ ***Persons with an intellectual or mental impairment***
X ***Persons highly dependent on medical care***
☐ ***Persons in dependent or unequal relationships***
☐ ***Collectivities***
☐ ***Aboriginal or Torres Strait Islander peoples***

Refer to the National Statement on Ethical Conduct in Research Involving Humans for considerations regarding these groups of participants, and provide further information if appropriate.

The sixty men participating in this study will be undergoing treatment for prostate cancer involving male hormone suppression and so will be receiving some level of medical care. Participants will be required to have no musculo-skeletal or cardiovascular disorder that could inhibit them from exercising. They will however be living independently under self-care and living a relatively normal life.

Please state from where the participants will be recruited and the method of recruitment.

Participants will be recruited by means of direct contact of oncologists and urologists from health care centres in the Perth area to participate in the study. In addition, the study will be advertised in local newspapers as well as by a University press release. Participants will be stratified according to the intention of treatment as curative or palliative. Groups will be balanced based on body composition characteristics, time from diagnosis, time receiving ADT and cancer stage grouping. All participants will be at least six weeks past initiation of ADT. While some participants may have secondary metastases, participants for whom the cancer has spread to the bone will not be included because of concerns regarding bone fragility and interference with markers of bone turnover.

10. INFORMATION LETTER TO PARTICIPANTS AND INFORMED CONSENT DOCUMENT

a. Participants should be provided with an information letter which describes in clear, simple terms, the procedures proposed, the anticipated benefits, and any possible risks of the research project. Written consent from each participant should be obtained to protect the researcher and this institution. Please attach a copy of the information letter to participants and the informed consent document.

b. If you do not intend to obtain written consent, please justify below.

11. DETAILS OF RESEARCH PROCEDURES

Please describe briefly the research procedures which participants will be asked to participant in. Provide details of procedures with possible adverse consequences.

Note: A copy of all forms of data collection instruments (questionnaires, surveys, standardised tests, interview or focus group questions) must be attached to the application.

Indicate if the research will involve any of the following procedures:

- **X** ***Research involving ionising radiation***
- ☐ ***Research involving assisted reproductive technology***
- **X** ***Clinical trials***
- ☐ ***Innovative therapy or intervention***
- ☐ ***Epidemiological research***
- **X** ***Use of human tissue samples***
- ☐ ***Human genetic research***
- ☐ ***Research involving the deception of participants, concealment or covert observation***

Refer to the National Statement on Ethical Conduct in Research Involving Humans for considerations regarding research procedures, and provide further information if appropriate.

This project will involve two experiments with prostate cancer patients undertaking resistance exercises. In experiment 1, subjects will be randomly assigned to an immediate exercise group (IE) or delay exercise group (DE). The IE group will perform twice weekly hydraulic resistance training on 8 different Isotronic machines (Fitness Technology, Australia) which consists of only concentric muscle action over 12 weeks. In experiment 2, the same group of subjects from experiment 1 whom were assigned to the IE group will be randomly allocated to either a LO or HI group. The training program will be undertaken twice weekly by both groups using traditional resistance exercise equipment which involves both concentric and eccentric muscle actions while the DE group will remain as non-exercisers during the first 24 weeks of intervention. A subsequent training program will be provided for the DE group based on best protocol derived from the first 24 weeks of intervention. Subjects will be recruited as described later in the research plan and then randomly assigned to one of the two groups in experiment 1 (IE or DE) and experiment 2 (HI or LO).

Experiment 1

Experiment 1 will be undertaken in 6 phases:

Phase One (Equipment installation and training)

The industry partner (Fitness Technology, Australia) will supply and install the 8 hydraulic machines. They will then train the research personnel in the use and maintenance. The researchers will use and evaluate the novel equipment and then design what they consider an appropriate exercise program which will maximise the anabolic effect on the participants.

Phase Two (Recruitment)

Sixty men undergoing treatment for prostate cancer involving ADT with non-bone metastases and no previous resistance training within the past 12 months, will be recruited by means of direct contact of oncologists from health care centres in the Perth area to participate in the study. Subjects will be stratified to the intention of treatment as curative or palliative. Groups will be balanced based on body composition characteristics, time from diagnosis, time receiving ADT and cancer stage grouping.

Phase Three (Baseline assessment)

The baseline assessment will consist of:

Anthropometric measures

Height will be obtained with the use of stadiometer.

Body weight will be obtained via the use of electronic scales

Muscle fiber cross-sectional area (CSA) and distribution, myosin heavy chain (MHC) expressions

All muscle tissue samples (biopsies) will be taken from the middle and outer portion of the front of the thigh using a needle biopsy technique. This will be performed by a medical practitioner. Subjects will be placed on an examination table lying down on his back (supine) so that the muscles of the leg are relaxed. The skin will be cleaned and

prepared with surgical antiseptic using sterile cotton swabs after which a surgical cover will be placed around the sampling site. A local anaesthetic will be injected into the tissue under the skin around the site to be sampled. A small incision (1 cm) will then be made in the skin overlying the muscle and the biopsy needle inserted into the middle of the muscle (muscle belly) at a depth of 3 cm. Approximately 100 mg (size of a pencil eraser or small finger nail) of skeletal muscle tissue will be removed. All the testing will take place in the Exercise Physiology Research Laboratory in building 19 on the Joondalup Campus. This procedure will be strictly undertaken in accordance with the standards of the Australian Medical Association.

Blood and Urine Sampling
All blood samples will be drawn from the antecubital vein of each subject by a trained and certified phlebotomist under strictly sterile conditions and according to the procedures recommended by the Department of Health.
Urine will be sampled by the participant using a sterile container provided specifically for this purpose to retain total urine volume over a 24 hour period.

Body composition and total body and hip and spine bone mineral density and bone turnover markers

Bone mineral density (BMD, g/cm2) of the hip and spine regions as well as whole body bone mineral content (BMC, g) will be assessed by dual energy X-ray absorptiometry (DXA, Hologic Discovery W, Waltham, MA). In addition, bone mineral-free lean mass (LM), fat mass (FM), and percent fat will be derived from the whole body scan.

DXA scans will be undertaken for body composition which subjects participants to ionizing radiation, however, the dosage to each individual in the study will only be 0.05% of the recommended dose constraint of 5mSv. The total radiation dose to the individual is very low at 2.6 μSv, which compares to 7 μSv for daily natural background exposure, 80 μSv for a return trans-Pacific flight, 100 μSv for a chest x-ray, and 2000 μSv for a lumbar spine x-ray.

Bone turnover (Serum Osteocalcin Concentrations, Free Deoxypridinoline Crosslinks and Creatinine) will be assessed by blood and urine markers of bone (Humphries et al., 2000).

Endocrine system

Blood samples will be drawn three times (prior exercise, directly after exercise and 1 hour post-exercise) from the antecubital vein of each subject. Concentrations of Growth hormones, testosterone and serum cortisol concentration will be determined in duplicate by ELISA (DSL, Webster, Texas).

Immune system

Complete blood counts will be assessed using an automated hematologic analyser (Coulter Corporation, Miami, FL, USA).
Prostate-specific antigen (PSA)

- PSA will be determined from blood samples to assess any changes in the activity

of the prostate cancer cells. PSA assessment will be performed with an immunoenzymetric assay (Tandem-E PSA, Hybritech Inc, San Diego, USA).

Beta amyloid (Aβ)

Levels of Aβ will be determined from blood samples by using monoclonal antibody 6E10, rabbit antiserum R162, and rabbit antiserum 164 in a double-antibody sandwich ELISA

Muscle strength and muscle endurance

Prior to muscle testing, subjects will be familiarized to all assessment procedures. In addition, a warm-up consisting of aerobic activity and stretching will be undertaken. Dynamic concentric muscle strength for several upper and lower body muscle groups will be measured using the one repetition maximum (1-RM) method. The 1-RM is the maximal weight an individual can move through a full range of motion without change in body position other than that dictated by the specific exercise motion.

Physical performance

A battery of tests (repeated chair rise, 6-m backwards walk, stair climb, and 400-m walk) will be used to assess functional performance at baseline and week 12. Tests will be performed in triplicate with recovery time between trials. The fastest time recorded will be used in the analyses.

Balance Assessment

Balance ability will be assessed using the Neurocom Smart Balance Master (Neurocom, Portland, OR) to complete the sensory organisation test (SOT). This test involves the participant standing on a special device which measures movement of the centre of pressure. The subject is placed in a harness to support them should they lose balance. The SOT requires the subject to stand quietly under a series of conditions, eyes open and eyes closed.

Lifestyle

Health-related quality of life will be measured using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale. The Functional Assessment of Cancer Therapy Fatigue will be administrated as well as a Health history and Demographic questionnaire.

Phase Four (Group Selection)

Once baseline testing is completed, subjects will be randomly assigned to one of the two groups: IE (n = 40) or DE (n = 20) group. IE group will undertake hydraulic resistance exercises twice weekly over 12 weeks while the DE group will not exercise during this period.

Phase Five (Intervention Program and Training Protocol)

The resistance training sessions will be undertaken in the Rehabilitation Clinic in the School of Biomedical and Sports Science at Edith Cowan University using hydraulic resistance training machines. Twice weekly exercise sessions will commence with a 10-minute warm up comprising of low-level aerobic activity such as walking and stationary cycling, as well as stretching. Eight resistance exercises that target the major upper and lower body muscle groups (chest press, seated row, biceps curl, triceps extension, leg press, squat, leg extension, leg curl, lat pulldown) will be performed. Exercise sessions will conclude with a 10-minute cool-down that includes exercises for the abdominal area

(e.g. abdominal curls) and lower back area (e.g. single leg raises) and stretching. All sessions will be conducted in small groups of up to 8 participants under direct supervision by the main investigator to ensure proper technique and minimize the risk for injury. The total time to complete the exercise session will be less than 60 minutes. The DE group will not undertake the exercise program. All participants will be asked to maintain customary physical activity and dietary patterns over the 12-week period. The rest period between sets will be 1-2 minutes. To ensure the progressive nature of the training program, the IE group will be encouraged to work past the specific RMs prescribed. When subjects are able to perform more repetitions than the RMs specified during a set the workload will be increased by 5-10% increment for the next set/training session. Intensity will be manipulated in a periodized system raging from 4-12-RM using 1-4 sets per exercise.

Phase Six (week 6, and Post-Intervention Assessment)
After 12 weeks, both groups will undertake all assessment tests that were performed at baseline. In addition, muscle function will be assessed at week 6 for the IE group so strength change over time can be monitored.

Experiment 2
Experiment 2 will be undertaken in 5 phases:

Phase One (Group selection)
Subjects from the IE group (Experiment 1) will be randomly assigned to one of the two training groups: LO (n = 20) or HI (n = 20) group. Both groups, as in experiment 1, will also undertake resistance exercises twice weekly over 12 weeks but on this occasion using traditional resistance training equipment with the DE group remaining maintaining normal daily activity during this period.
Phase Two (Baseline assessment)
Baseline assessment from experiment 2 will correspond to the post-intervention from experiment 1 (phase 6). This phase will contain all tests as outlined above in the section on methodology.

Phase Three (Intervention Program and Training Protocol)
As in experiment 1, the resistance training sessions will also be undertaken in the Rehabilitation Clinic in the School of Biomedical and Sports Science at Edith Cowan University but on this occasion using dynamic resistance training machines. Similar to experiment 1, sessions will be undertaken twice weekly commencing with a 10-minute warm up comprising of low-level aerobic activity such as walking and stationary cycling, as well as stretching. Eight resistance exercises that target the major upper and lower body muscle groups (chest press, seated row, biceps curl, triceps extension, leg press, leg extension, leg curl, lat pulldown) will be performed. Exercise sessions will conclude with a 10-minute cool-down. All sessions will be conducted in small groups of up to 8 participants under direct supervision by the main investigator to ensure proper technique and minimize the risk for injury. The total time to complete the exercise session will be less than 60 minutes. The difference between exercise groups will be in the number of sets performed, that is, 1-2-sets (LO) vs 3-4-sets (HI). The DE group will not undertake the exercise program. Similar to experiment 1, all participants will be asked to maintain customary physical activity and dietary patterns over the 12-week period. The rest period between sets will be 1-2 minutes. To ensure the progressive nature of the training program, both training groups will be encouraged to work past the

specific RMs prescribed. When subjects are able to perform more repetitions than the RMs specified during a set the workload will be increased by 5-10% increment for the next set/training session. Intensity will be manipulated in a similar fashion between training groups by a periodized system raging from 4-12-RM.
Phase Four (week 6, and Post-Intervention Assessment)
After 12 weeks, the two exercise groups and the DE group will undertake all assessment tests that were performed at baseline. In addition, muscle function will be assessed at week 6 for both exercise groups so strength change over time can be monitored.

Phase Five
At the 24 week time point the IE group will commence 24 weeks of "normal" activity. That is, they will not be required to complete any structure exercise intervention but simply adopt the lifestyle that they choose. At this time the DE group will commence whichever program proved most efficacious for the IE group (i.e. concentric only, HI or LO traditional program). The DE group will undergo the same testing protocol over the 24 weeks of training as was completed by the IE group. The IE group will complete the full test battery only at the completion of 24 weeks of "normal" activity.
Statistical Analyses
Data will be analysed using the SPSS Version 11 (SPSS Inc., Chicago, IL) statistical software package. Analyses will include standard descriptive statistics, independent and paired two-tailed Student's t-tests, and two-way repeated measures (group x time) analysis of variance. All tests will be two-tailed and an alpha level of 0.05 set as the criterion for statistical significance.

12. CONFIDENTIALITY OF RECORDS

Confidential records are those which can identify, or potentially identify a participant (or organisation).
Records are required to be preserved for a minimum of five (5) years.

a. How will the confidentiality of records be maintained <u>during</u> the study?
Please indicate if records will be permanently deidentified, and how this will occur.

When the data is collected it will not have any information that could link it with an individual. In other words, the data will be de-identified at the time of collection. A subject ID number will be assigned to each data file and this will be used in all subsequent data analysis. As it is not required to match any results to an individual, no identifying code will be recorded.

***b. How will the confidentiality of the records (primary or original <u>data</u>) be protected during the period of their preservation*?**

All forms, data and participant details will be kept in a locked filling cabinet within the office of the main investigator and the supervisor.

c. How will the original **materials** *be destroyed after the study is completed?*

Following completion of the research project the original documents will be shredded and burned.

d. Who else will have access to confidential materials (e.g. transcribers)? How will these people be included in the assurance of confidentiality?

Only the principal researcher (Daniel Galvao) and immediate supervisors (Prof. Newton, Prof. Kristjanson and Dr. McGuigan) will have access to confidential materials. Only the principal researcher and the principal supervisor will have access to documents at any given time.

13. ETHICAL ISSUES

a. Have you read the ECU Policy on the Ethical Conduct of Research Involving Humans?

YES:X	**NO:**

Please indicate what in your view are the ethical issues involved in this research. The following is a checklist of <u>possible</u> ethical issues.

b. Is any financial remuneration or other reward being offered to participants for participation in the study?

YES:	**NO:X**

If yes, please state how much will be offered and for what purposes, eg. to cover travelling expenses, time spent, etc.

c. Is any information to be withheld from the participants?

YES:	**NO:X**

d. Will material which identifies participants be recorded eg. photographs, video recordings or any sound recordings?

YES:	**NO: X**

e. If interviews are to be conducted will they be tape-recorded?

YES:	**NO:X**

f. Will participants be asked to commit any acts which might diminish self-respect or cause them to experience shame, embarrassment or regret?

YES:	**NO:X**

g. Does the research involve any stimuli, tasks, investigation or procedures which may be experienced by participants as stressful or unpleasant?

YES:X	**NO:**

h. Will the research involve the use of no-treatment or placebo control conditions?

YES:	**NO: X**

i. Will the conduct of the research disturb or influence in a negative way the working relationship of the participants in this research project and other groups of participants in their settings?

YES:	**NO:X**

j. Are there in your opinion any other ethical issues involved in the research?

YES:	**NO:X**

If the answer to any of the questions from 'b' to 'j' is 'yes', please describe below.

g) Progressive resistance training and muscle strength testing has been known to result in mild discomfort, delayed onset muscle soreness (DOMS) and joint stiffness especially in untrained individuals. However, participants will be informed of the possibility of DOMS, symptoms and procedures to alleviate them. Moreover, DOMS is related to the eccentric portion of the lifting and lowering manoeuvre, and resistance in this part of the repetition is the same as that for the concentric phase. For the first 12 weeks of intervention (experiment 1) only concentric contractions will take place which will minimize DOMS. Warm-ups and cool-downs will also be incorporated in each testing session to reduce muscle soreness and return the individual to their resting level before leaving the training facility. There is also the risk of a muscle strain however this risk will be greatly reduced by careful monitoring of each participant, ensuring correct loads are used, checking technique and requiring a warm-up and cool-down period with each exercise session. Further, all sessions will be conducted with one subject each time supervised by the investigators. In addition, the warm-up will consist of submaximal repetitions prior to maximal efforts and will be carefully conducted. Lastly, risk of falling may exist in the performance of the functional tasks, however, participants will be closely supervised and spotted to prevent a fall from occurring.

With the invasive skeletal muscle biopsy technique there is the possibility of a blood related infection (e.g. hepatitis), but the reusable needles will be cleaned and sterilized in accordance with the standards of the Australian Medical Association. Sterile disposable instruments will be used for the preparation of the site and the reusable biopsy needle will be thoroughly sterilized after each operation.

This procedure has been performed on numerous subjects by qualified medical personnel in many institutions worldwide with only slight discomfort being reported. It is common for subjects to experience mild soreness and bruising near the biopsy site, and to feel a strong cramping sensation in the muscle when the biopsy is performed. However, muscle function is not impaired. In fact, subjects have been reported to continue participation in sporting events immediately following a muscle biopsy. In rare instances (2 in 400), some motor nerves may be damaged which may cause local muscle atrophy (decrease in the size of muscle fibers, with a small dimple on the skin). There have been no other major complications reported as a result of taking small tissue samples from the skeletal muscle.

14. POTENTIAL RISKS AND BENEFITS

a. What in your view are the possible* risks *of this research to the participants?

As stated above (13 g), there is a risk of muscle soreness, muscle strain, and mild physical discomfort associated with embarking on a resistance exercise program. With the invasive skeletal muscle biopsy technique there is the possibility of a blood related infection. It is common for subjects to experience mild soreness and bruising near the biopsy site, and to feel a strong cramping sensation in the muscle when the biopsy is performed.

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.

Outline briefly any management plans that have been made to prevent or minimise the likelihood of the event of this risk occurring.

Each session will be progressive with appropriate warm-up and cool-down periods, and close supervision by the main investigator will be provided at all times by careful monitoring of each participant, ensuring correct loads are used and checking exercise technique with each training session.

Reusable needles will be cleaned and sterilized in accordance with the standards of the Australian Medical Association during the biopsy procedure. Sterile disposable instruments will be used for the preparation of the site and the reusable biopsy needle will be thoroughly sterilized after each operation. The incision will be cleaned and sealed using a bandage and the site compressed using a 10 cm strip of sterile elastic surgical stocking for a period of 24 hours. Once the wound has been sealed and bandaged, an ice pack will be placed over the site (10-20 minutes) to minimize bleeding and bruising.

Risk of bruising or infection from the blood draws will be minimized because all blood draws will be performed by a trained phlebotomist 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.

b. What are the possible* benefits *of this research.

(i) To the participants?

Resistance exercise may have a potential role to counteract the catabolic side effects of ADT promoting sufficient anabolic environment that can lead to positive effects on the musculoskeletal system. In addition, considering that traditionally ADT may be continued for up to 20 years, the role of resistance exercises may be even more relevant by improving psychological and physiological parameters and therefore improving quality of life in this cancer population. As such, the participants should experience psychological and physiological benefit from participation and may adopt a more active lifestyle following completion of the study. The result should be increased survivability, wellbeing and quality of life.

(ii) To humanity generally?

Considering the notable impact of prostate cancer in the male population world wide and that the life expectancy from prostate cancer patients has increased, clinical interventions aimed to decrease levels of fatigue and improve quality of life are needed. Existing treatments to alleviate these side effects have been predominantly pharmaceutical however they are expensive with the cost benefit ratio questionable and they do not translate into improved physical function or decreased levels of fatigue. Therefore, a requirement for clinical intervention strategies focusing on counteracting such side effects which are also closely related with the increased risks of developing other diseases (e.g. osteoporosis, sarcopenia, metabolic complications, depression) are necessary. The findings from the present study will increase the knowledge from this relevant and promising area of exercise science and cancer directly impacting prescription of exercise for this cancer group.

APPENDIX X - HYDRAULIC RESISTANCE TRAINING LOG

Name: _____

Date (sessions #)	(1)				(2)				(3)			
SETS	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Chest press Seated Row												
Leg press												
Shoulder p. Lat pull												
Squat												
Upper row dips												
Leg extens. Leg curl												
Biceps curl Triceps ext.												
Abs Back ext.												

APPENDIX XI - ISOTONIC RESISTANCE TRAINING LOG

Name: _____

Date (sessions #)	(1)				(2)				(3)			
SETS	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Chest press												
Leg press												
Lat pull												
Squat												
Leg extension												
Shoulder press												
Leg curl												
Triceps ext.												
Biceps curl												
Abdominal												