THE PHYSIOLOGICAL AND PSYCHOSOCIAL EFFECTS OF A 16-WEEK COMBINED AEROBIC AND RESISTANCE EXERCISE PROGRAM IN MEN RECEIVING ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER

by

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Signature of Author

Dedicated to

My mom Brenda

&

Nick

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ABSTRACT

Objectives: Men who receive androgen deprivation therapy (ADT) for prostate cancer (PCa) are at risk of several adverse effects that can be detrimental to both their physical and mental health. Common adverse effects include weight gain, muscle wasting, cardiovascular morbidity, fatigue and impaired quality of life (QOL). This study tested whether a combined aerobic and resistance exercise program can alleviate some of these symptoms in men receiving ADT.

Design: Men with PCa, aged 50-80 years, receiving ADT were recruited to participate in this prospective randomized controlled trial. Subjects were assigned to a usual care group (UCG) or an exercise intervention group (EIG). The EIG completed a 16 week combined aerobic and resistance exercise program. Outcomes measures were assessed at baseline, 16 weeks, and 24 weeks and included: cardio-respiratory fitness; muscle strength and endurance; body composition; and reports of QOL, fatigue, mood, partner relations, and exercise behaviour.

Results: Fifteen men were recruited to this study, but two participants in the EIG did not finish the study leaving the EIG with an $n = 6$ and the UCG with an $n = 7$. The exercise program did not lead to changes in weight, BMI or body fat. There was a small, close to significant, increase in muscle mass in the EIG over the intervention period ($p = 0.052$). This is encouraging as it demonstrates that exercise can counteract the catabolic effects of ADT. Interestingly, cardio-respiratory fitness improved over the course of the study for both groups. Muscular fitness, however, improved only for the EIG. There was a significant difference in chest press strength ($p = 0.041$) and leg press strength was bordering significance ($p = 0.058$). Unexpectedly, QOL declined for both groups during the intervention ($p = 0.029$). Participants in both groups also reported increased levels of fatigue from baseline to 24 weeks, although these changes were not significant ($p = 0.586$). Mood worsened over the study period for both groups from baseline to 16 weeks, but this increase in anxiety and depression was reduced at the follow-up period. These changes, too, were not significant ($p = 0.364$). Reports of partner relationships trended towards lower scores from baseline to 16 weeks. The men's report in both groups and the women's report in the EIG improved at the 24 week mark, but women in the UCG experienced further decline. Surprisingly, participants in both groups reported increases in exercise behaviour from baseline to 24 weeks. This could account for the lack of difference found in many of the measures. The power of this study was 0.22.

Conclusion: Although this was a small study, it showed that a combined aerobic and resistance exercise program can have some positive benefits for men with PCa who are receiving ADT. Larger trials are needed to further examine the role of exercise in ameliorating the side effects of ADT, particularly in the areas of mood and partner relationships.

LIST OF ABBREVIATIONS USED

ACSM	American College of Sports Medicine
ADL	activities of daily living
ADT	androgen deprivation therapy
BMI	body mass index
BMD	bone mineral density
Ca	cancer
CAB	combined androgen blockade
CV	cardiovascular
CVD	cardiovascular disease
CHD	Coronary heart disease
DAS	Dyadic Adjustment Scale
DHT	dihydrotestosterone
DM	diabetes mellitus
EBRT	external beam radiation therapy
ED	erectile dysfunction
EF	erectile function
EIG	exercise intervention group
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-B	Functional Assessment of Cancer Therapy-Breast
FACT-F	Functional Assessment of Cancer Therapy-Fatigue
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FFA	fatty free acids
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression Scale
HDL	high density lipoprotein
HTN	hypertension
HR_{peak}	peak heart rate

HSL	hormone-sensitive lipase
IIEF	International Index of Erection Function
kg	kilograms
lbs	pounds
LDL	low density lipoprotein
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LSI	Leisure Score Index
m	metres
MAB	maximum androgen blockade
MET	metabolic equivalent
MetS	metabolic syndrome
MI	myocardial infarction
PA	physical activity
PCa	prostate cancer
PDE5i	phosphodiesterase type 5 inhibitors
PKA	protein kinase A
PSA	prostate-specific antigen
QOL	quality of life
RCT	randomized controlled trial
RP	radical prostatectomy
SF-36	Short Form-36 Health Survey
SPPB	Short Physical Performance Battery
TG	triglycerides
UCG	usual care group
VO_{2max}	maximum oxygen consumption
1-RM	one repetition maximum

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Hope you enjoy my work!

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CHAPTER 1
Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy in North American men[7,8] and is highly prevalent around the world.[9] Globally 782,600 men were diagnosed with PCa in 2007.[10] In Canada, one in six men is diagnosed with PCa during their lifetime[8,11] with over 900 new cases being diagnosed each year in Nova Scotia.[7] Because of advances in medical and surgical treatment methods, over 90% of men with PCa will live beyond a decade after diagnosis.[12-14] While this improvement in treatment efficacy is promising, there is growing evidence regarding the potential adverse effects of such treatments, with particular attention on androgen deprivation therapy (ADT).[15-18]

Androgen deprivation therapy, more commonly called hormone therapy, is used to treat approximately one half of all PCa cases.[19] The complications associated with ADT and disease-related symptoms can have devastating consequences on a man's quality of life (QOL),[20-23] physical function,[24-27] and emotional well-being.[28,29] These changes may limit a man's ability to complete activities of daily living (ADL) or maintain his independence. This is particularly important given that the majority of men with PCa are aged 65 years or older [9,30,31] and are already at risk for functional decline. There is a clear need for management strategies targeted at maximizing the health and wellness of men living with PCa who are undergoing ADT.

At present, men undergoing ADT are not routinely prescribed exercise programs of any kind. Some physicians may encourage physical activity (PA), but the standard of care does not include specific exercise guidelines or referrals to exercise specialists. However, many of the problems that are associated with ADT have been effectively managed with exercise interventions in other patient populations. Exercise reduces CVD risk,[32-35] enhances QOL,[36-39] reduces fatigue levels,[40,41] and even improves mood.[42-47]

In recent years there has been an increased focus on exercise or PA as a means of managing the side effects specific to ADT.[48-54] Currently, the most commonly studied exercise for men receiving ADT is resistance training. Resistance training can lead to large improvements in muscular fitness,[48-50,54] which is encouraging as it demonstrates that the catabolic effects of ADT can be reversed or diminished. Aerobic exercise has been shown to improve aerobic capacity and prevent increased fatigue.[52] Studies are needed to determine whether this type of exercise will decrease the incidence of CVD as it has been shown to do in people without cancer (Ca). One study that investigated a PA program found improvements in aerobic capacity, QOL, and fatigue[52] while another study looking at the same PA program protocol found few positive observations.[53] The latest exercise intervention for men on ADT involved a combined resistance and aerobic program.[54] The authors reported large gains in lean mass and strength and enhanced QOL.[54] Enhanced health-related QOL and reduction of fatigue has been reported in a few exercise studies,[48,49,51] which could have direct implication on daily functioning for men receiving ADT. Other benefits of exercise for men receiving ADT include improvement in walking speed, functional tasks and dynamic balance.[50,54]

This study is novel for two reasons. First, it is unknown which type of exercise or PA program is optimal for the health of men on ADT. Since resistance training is geared towards muscular fitness and aerobic exercise targets the cardiovascular (CV) system it is reasonable to assume that both are crucial. Secondly, although some studies have looked at QOL, to my knowledge, this will be the first study that examines the role of exercise specifically in mood or partner relationships for men on ADT.

1.1 Research Objectives and Hypothesis

1.1.1 Primary Objective

- To determine whether a combined aerobic exercise and strength training program can influence cardio-respiratory fitness, muscle strength and endurance, body

composition, and QOL in men aged 50-80 years with any stage of PCa who are receiving ADT.

1.1.2 Secondary Objectives

- To determine if a combined aerobic exercise and strength training program can alter fatigue, depression, and anxiety in men undergoing ADT.
- To provide preliminary data on whether exercise can influence relationship adjustment between men on ADT and their partners.

The role of exercise in managing the adverse effects experienced by men undergoing ADT is not fully understood. This study aims to support or refute known findings and advance current knowledge in this field, specifically in the role of a combined aerobic and resistance exercise program for this population. Results of this study will help guide clinicians in designing exercise programs for men on ADT that are both safe and effective.

1.1.3 Hypotheses

1. Significant differences will be observed between the exercise and control groups in all outcomes of interest over the study period including: increased cardio-respiratory fitness, increased muscle strength and endurance, decreased body fat, increased muscle mass and enhanced QOL.
2. Exercise training will reduce fatigue, depression, and anxiety.
3. Relationship adjustment between men on ADT and their partners will improve because of his participation in a regular exercise program.

CHAPTER 2

Background and Literature Review

PCa occurs when the cells of the prostate gland mutate and multiply beyond control.[55] The prostate gland is an exocrine gland of the male reproductive system that is responsible for storing and secreting semen, spermatozoa, and seminal vesicle fluid.[56] Slightly larger than a walnut in size, the prostate gland is located below the bladder, surrounding the urethra.[56] The etiology of PCa is largely unknown, but established risk factors include age (50 years and older), presence of family history, ethnicity (e.g. increased risk for black men), and elevated insulin growth factor.[31] Symptoms include burning or pain during urination, difficulty urinating, urinary urgency, sexual dysfunction, and blood in the urine or semen.[55] Early PCa may not be accompanied by symptoms and often detected through routine screening of prostate-specific antigen (PSA), which is a protein produced by the prostate gland. Once a man has been diagnosed with PCa, treatment decision making is ultimately guided by his PSA levels, the stage of the disease, and the grade of the tumour. Treatment options for PCa include active surveillance, radical prostatectomy (RP), external beam radiation therapy (EBRT), brachytherapy, chemotherapy, high intensity focused ultrasound, cryotherapy and ADT.[57]

Androgen deprivation therapy aims to prevent PCa cell growth through suppression of testosterone. As early as 1941, Huggins and Hodges recognized the dramatic effects of suppressing testosterone in men with advanced PCa.[58] Hormone therapy is widely used in the treatment of metastatic PCa (Stage IV), but has been used as well for locally advanced disease.[14,15] For men with localized disease undergoing radiation therapy, neoadjuvant, ADT improves disease-specific and overall survival.[59,60] Although hormone therapy has the potential to improve survival in certain cases, controversy remains as to when to initiate treatment due to the many adverse effects reported in men on ADT.[15] Interestingly, urologist's individual preferences accounts for 21% of the variation in the decision to use ADT.[61]

2.1 ANDROGEN DEPRIVATION THERAPY

Prostate Ca is an androgen-dependant disease, meaning that the cells of the prostate gland, including the malignant cells, rely on the presence of androgens to grow and proliferate. Androgens are steroid hormones that are secreted by the testes in men and by the ovaries in women.[56] In men, the adrenal cortex is also responsible for a small percentage of androgen production (< 5 – 10%)[17,56] and the main androgen is testosterone.[9] Once testosterone enters the blood, 95% of the hormone is bound to proteins while 5% circulates freely.[17] Testosterone can be converted to its more potent derivative dihydrotestosterone (DHT) through the enzyme action of 5α-reductase.[9,56] The ratio of testosterone to DHT in serum is 10:1, but this ratio is reversed in the prostate gland.[9] It is DHT that is mostly responsible for prostate development and growth by binding to androgen receptors in the prostate cells.[9,17]

Testosterone production is initiated through neuroendocrine regulation in the brain. Luteinizing hormone releasing hormone (LHRH), also called gonadotropin releasing hormone, is released in pulses from the hypothalamus.[17,56] LHRH travels to the anterior pituitary gland and stimulates the synthesis and release of two gonadotropins: leutinizing hormone (LH) and follicle stimulating hormone.[17,56] In response to LH stimulation, testosterone is produced in the leydig cells of the testes, which are embedded in the interstitial tissues.[56] Testosterone levels are then maintained through a negative feedback loop. The inhibitory effect of testosterone on LH release is mediated predominantly by a locally produced metabolite of testosterone aromatization namely 17β-estradiol.[56] Estradiol can inhibit LH release indirectly at the level of the hypothalamus through inhibition of LHRH release or directly on the pituitary gland.[56]

There are several types of hormone therapies that are aimed at disrupting this pathway and reducing the amount of testosterone and DHT in the prostate gland. Length of treatment can generally be defined as short-term ADT (< 6 months), long-term ADT (≥ 6 months), intermittent ADT (e.g. 9 months “on”, 3 months “off”), continuous, or permanent (orchiectomy).

Approximately 90% of men undergoing ADT for PCa use a class of drugs called LHRH agonists to achieve castrate levels of testosterone.[62] The use of LHRH agonists to reduce testosterone seems counter-intuitive. Initially LHRH agonists will lead to a surge in serum testosterone levels called the "flare" phenomenon, which is potentially life threatening for men with high-volume metastatic disease.[15] Anti-androgens, discussed below, are often used in the initial phase of LHRH agonist administration to prevent testosterone from acting on androgen receptors.[15] Continued exposure to LHRH agonists, however, will lead to the down regulation of LHRH receptors causing inhibition of LH and decreased testosterone levels. LHRH agonists can be administered via intramuscular injection, subcutaneous injection, or subcutaneous implant.[15] Commercially available LHRH agonists in the United States and Canada include: Leuprolide, Goserelin, Triptorelin, and Histrelin.[15]

Anti-androgen medications can be steroidal or non-steroidal and are usually only taken in conjunction with another form of ADT.[62] The terms maximum androgen blockade (MAB), most commonly used in Europe or combined androgen blockade (CAB), more commonly used in the United States, refer to the addition of an anti-androgen to surgical or medical castration.[62] Examples of anti-androgen drugs include: Flutamide, Bicalutamide, Nilutamide.[15,62]

Estrogens act at the level of the hypothalamus to suppress the release of LHRH resulting in reduced testosterone production.[15] Huggins and Hodges used a synthetic estrogen called Diethylstilbesterol to treat men with PCa which resulted in dramatic improvements in physical symptoms and QOL.[15,58] The pair was awarded a Nobel Prize in 1966 for this work.[15]

An orchiectomy is the surgical removal of the testes. The testes are responsible for 95% of the body's testosterone production,[56] therefore this method of castration is highly effective. Unlike drug therapies, however, this form of hormone suppression is

irreversible. Also, men may be reluctant to undergo this type of procedure due to the resulting physical appearance.

2.2 Adverse Effects of Androgen Deprivation Therapy

ADT is aimed at decreasing testosterone levels in the body with the goal of preventing PCa cell growth and disease relapse.[57] Testosterone and its derivative DHT are responsible for PCa progression through androgen receptor-mediated signaling.[9] Medical or surgical castration is used to interrupt this pathway, leading to low levels of male hormones and associated side effects. Acute changes that can be seen as early as the first few weeks of treatment include erectile dysfunction (ED), hot flashes, and loss of libido.[15] Several additional physical problems discussed below have been reported in men who undergo prolonged androgen suppression.[15,16,18,63,64]

2.2.1 Body Composition

It is known that testosterone has an overall anabolic effect in muscle leading to increased protein synthesis and decreased protein breakdown.[56] In one study, participants on ADT lost 2.7 ± 0.5% of their lean body mass after 48 weeks of treatment.[65] After only 36 weeks of ADT, loss of lean mass was observed in all body regions.[66] These included the upper limb, lower limb, trunk and whole body with the loss ranging from 1.4 to 5.6%.[66] van Londen et al. found that lean body mass decreased after 12 months of ADT and further decreased after 24 months of treatment.[67]

Testosterone has also been shown to inhibit triglyceride uptake and slow fat accumulation.[56,68] The decreased levels of testosterone in men undergoing ADT likely explain the reported changes in body composition. Smith et al. studied the effects of a LHRH agonist in 40 men at baseline and after 48 weeks of treatment.[65] Body mass index (BMI) rose by 2.4 ± 0.8 % ($p = 0.005$) with a 9.4 ± 1.7% ($p < 0.001$) rise in body fat mass measured using dual-energy x-ray absorptiometry.[65] Significant declines in the

percentage of lean body mass of 2.7 ± 0.5% ($p < 0.001$) were also observed.[65] Although there were substantial increases in the cross-sectional area of the abdominal subcutaneous fat and of the abdomen of 11.1 ± 3.4% ($p = 0.003$) and 3.9 ± 1.2 % ($p = 0.003$) respectively, intra-abdominal fat did not change significantly.[65] The results of a prospective cohort study by Galvão et al. with 72 men undergoing MAB were consistent with the previous study, but reported larger changes in fat mass and lean mass.[66] They described dramatic increases in percentage fat mass ranging from 12.0% ($p < 0.001$) in the trunk to 20.7% ($p < 0.001$) in the upper limbs which resulted in an overall increase in body fat of 2.6% ($p < 0.001$).[66]

A cross-sectional study by Clay et al. with 102 participants found that men on long-term ADT had a significantly higher percentage body fat (4.3 – 4.9 %) and lower percentage lean body mass (4.4 – 4.5 %) compared to men on short-term ADT, men with PCa not on ADT, and healthy controls.[25] Results from a second cross-sectional study (n = 48) by Basaria et al. also showed that men on ADT had significantly higher percentage fat mass in the arm, leg, trunk, and total body compared to men with PCa not receiving ADT and to healthy controls.[69] Interestingly, the PCa group also showed increased percentage fat mass compared to healthy controls.[69]

2.2.2 Cardiovascular and Metabolic Disease

There has recently been increased attention given to the effects of ADT on the CV and metabolic systems of hypogonadal men.[68,70-72] Saigal et al. found that men undergoing ADT have a 20% increased risk of having a CV event such as a myocardial infarction (MI).[68] There are likely several factors affecting the development of these CV co-morbidities, but it could be partially explained by the reported increase in fat mass in men on ADT[65,66,69,73] or their increased risk of developing metabolic syndrome (MetS), insulin resistance, and DM.[70,72]

MetS is a term used to describe a group of cardio-vascular disease (CVD) risk factors including increased fasting glucose, elevated triglycerides, reduced high-density lipoprotein (HDL), increased waist circumference, and elevated blood pressure.[72] According to reviews by Traish et al., MetS has received substantial attention in recent years likely in part due to its close association with CVD, type 2 diabetes mellitus (DM) and ED.[74,75] In 2007, Taskinen stated that the main public health threat in the 21st century is MetS.[76] This serious health issue is especially concerning to androgen-deficient men as it has been shown in longitudinal studies that the development of MetS is independently predicted by low testosterone levels.[77,78] Braga-Basaria et al. reported the prevalence of MetS in men undergoing ADT was 55% compared to 22% in the non-ADT PCa group and 20% in the healthy control group.[72]

In a cohort study with 22,816 subjects the prevalence of cardiac risk factors, specifically DM and hypertension, was 2 – 3% greater ($p = 0.002$) for men receiving ADT compared to men with PCa not receiving ADT.[68] In this same study, Saigal et al. concluded that for men undergoing ADT the greatest risk of developing CV morbidity occurred within the first 12 months of treatment.[68] This risk remains elevated since men undergoing ADT are more likely to have a CV event in the 1 – 5 year time period after diagnosis compared to men not undergoing ADT (24% vs. 18% respectively, $p = 0.001$).[68]

A second population-based study investigated the 10-year incidence of DM, coronary heart disease (CHD), MI and sudden cardiac death in men with a first time diagnosis of PCa ($n = 73,196$).[70] LHRH agonist treatment was associated with significantly higher risk of DM (44%), CHD (16%), sudden cardiac death (16%), and MI (11%).[70] In contrast, men who underwent bilateral orchiectomy showed an increased risk for only DM (34%).[70] The authors expected similar results among ADT treatments and felt that their study may have been underpowered for men undergoing orchiectomy to accurately measure the association between CVD and orchiectomy.[70]

2.2.3 Strength and Functional Performance

The long term use of ADT has also been associated with reduced muscle strength,[66,69] which could be partially if not fully explained by the previous reports of decreased lean tissue.[25,65,66,73] Basaria et al. reported differences in upper body strength in men on ADT compared to men with PCa and healthy age-matched controls.[69] To measure strength, a 1 repetition maximum (1-RM) test was used. The 1-RM is the maximal weight an individual can lift through full range of motion one time. The ADT group had a mean 1-RM of 47.6 ± 15.6 pounds (lbs) on the bench press compared to the control group with a mean 1-RM of 61.1± 21.4 lbs.[69] The PCa group not receiving ADT, however, had a significantly higher mean 1-RM of 79.6 ± 35.2 lbs, which demonstrates that men living with PCa can maintain good muscular strength.[69] It also supports the thought that decreased strength is likely due to the ADT treatment as opposed to the disease process itself.[69] This study found no significant differences in lower body strength measured using a 1-RM leg press test.[69]

Muscle strength and endurance were measured by Galvão et al. in a cross-sectional study design comparing men on ADT (n = 48) to healthy controls (n = 70).[66] In the 1-RM chest press test the ADT group had a mean of 32.4 ± 10.5 kilograms (kg), which was significantly less than the control group with a mean 37.5 ± 9.1 kg ($p = 0.006$). The 1-RM seated row test showed similar results with a mean of 38.7 ± 6.6 kg for the ADT group and 42.4 ± 8.4 kg for the control group ($p = 0.014$).[66] In assessing lower extremity strength, only the quadriceps muscle strength (1-RM leg extension test) was reduced in men undergoing ADT compared to healthy controls at 36.3 ± 13.0 kg and 44.9 ± 12.4 ($p < 0.001$), respectively.[66] Congruent with the previous study, there was no significant difference in the 1-RM leg press test. Galvão et al. also evaluated muscle endurance by measuring the maximal number of repetitions performed at 70% of 1-RM for chest press and leg press, but they did not find any significant differences.[66]

Given the numerous potential physical changes caused by low testosterone levels, it is not surprising that men on ADT experience a decline in functional

performance.[24,27,66,79] A 2008 study by Galvão et al. used several outcome measures to quantify the differences in various aspects of functional performance in men receiving ADT versus healthy age-matched controls.[66] The most significant difference between groups was seen in the chair rise to standing test with a mean increase of 1.5 seconds ($p = 0.004$) in the ADT group.[66] In the 400-m walk test, a measure of cardio-respiratory fitness, men on ADT reported slower times (273.3s $\pm$ 32.7s) compared to healthy controls (256.1s $\pm$ 34.0s; $p = 0.005$).[27] The 6-m usual walk, 6-m fast walk, and 6-m backward walk tests were also slower in the ADT group ($p < 0.05$) further supporting the evidence that hormone therapy causes functional decline in men with PCa.[66]

The Short Physical Performance Battery (SPPB) is used to evaluate aspects of physical function including standing balance, gait speed, and the ability to rise from a chair. Scores can range from 0 to 12 where lower scores indicate worse performance.[24,25] The SPPB was used in a cross-sectional study by Clay et al. that compared 100 men in four groups: men with PCa ($n = 25$), men with PCa on short-term ADT (< 6 months) ($n = 13$), men with PCa on long-term ADT ($\geq$ 6 months) ($n = 42$), and older men without PCa ($n = 20$).[25] The men on long-term ADT group showed significant decreases in SPPB scores compared to men with PCa (95% C.I. 0.1 – 1.6), men on short-term ADT (C.I. 0.2 – 1.9), and healthy controls (95% C.I. 0.4 – 1.2).[25] The only significant finding in gait speed was that men on long-term ADT had a mean gait speed of 0.99m/s, which was on average 0.18m/s slower than the control group.[25] A prospective cohort study examined the prevalence of falls and physical performance deficits in men undergoing ADT for at least three months.[24] Abnormal scores (≤ 9) were reported on the SPPB in 56% of the cases at baseline testing.[24] Furthermore, at the 3 month follow-up, 40% of the participant's performances deteriorated.[24] A large proportion (22%) of men undergoing ADT reported falls in the 3 months prior to baseline testing. In fact, 10% of men reported two or more falls.[24]

2.2.4 Bone Density and Fractures

The increased probability of falls is especially concerning given that several studies have confirmed that ADT negatively impacts bone strength[66,69,73] and subsequently men are at increased risk for fractures.[73,80] It is well known that estrogens play a role in the maintenance of bone formation and bone turnover in the female skeleton.[56,81] In post-menopausal women estrogen-deficiency has been linked with bone loss and osteoporosis.[81] In men, testosterone is converted to the primary estrogen 17-β estradiol, which helps maintain bone integrity.[56,81] Because ADT decreases the amount of available testosterone it also lowers 17-β estradiol levels. As expected, men on ADT experience decreases in bone mineral density [BMD (g/cm^2)].[66,69,73]

In 2005, Greenspan et al. concluded that men who undergo ADT have significant loss of BMD, which is most evident in the first year of treatment.[73] This 12 month prospective study compared the bone health of four groups of men: men with PCa without ADT (n = 72), men with PCa on short-term ADT (< 12 months)(n = 30), men with PCa on sustained ADT (> 12 months)(n = 50), and healthy age-matched controls (n = 43).[73] The long term consequence of hormone therapy on bone health was demonstrated at baseline testing for osteoporosis. This study used the World Health Organization criteria for diagnosis of osteoporosis (BMD that is 2.5 standard deviations or more below the average value).[73] A two to three fold increase in the proportion of men classified with osteoporosis was observed in the sustained ADT group (24%) compared to the other three groups (7 – 14%).[73] Only short-term ADT caused significant reductions in BMD: total hip (-2.5 $\pm$ 0.6%), trochanter (-2.4 $\pm$ 1.0%), total radius (-2.6 $\pm$ 0.5%), posteroanterior spine (-4.0 $\pm$ 1.5%), and total body (-3.3 $\pm$ 0.5%).[73] Galvão et al. showed similar trends in reductions in BMD in men after receiving 36 weeks of ADT with the highest loss in the spine (-3.9%) followed by whole body (-2.4%), total hip (-1.5%), and upper limbs (-1.3%) with insignificant changes in the lower limbs (-0.6%).[66] Basaria et al. found that total body BMD is inversely related to the length of time on ADT.[69] When compared to men with PCa who were not receiving ADT and healthy men, men with castrated levels of testosterone had lower total body and lumbar spine BMD.[69] In the

lumbar spine, there were significant differences in BMD observed between all three groups: ADT (0.87 ± 0.12 g/cm²), non-ADT (1.04 ± 0.16 g/cm²), and controls (1.13 ± 0.24 g/cm²).[69] Differences in bone mass at other sites are described in a cross-sectional study comparing 48 men on ADT to 70 controls.[66] The treatment group had diminished upper limb BMD ($p = 0.002$), lower limb BMD ($p = 0.013$), total body BMD ($p = 0.013$), and total hip BMD ($p = 0.034$).[66]

The reduced bone density in men on ADT explains the findings from a retrospective cohort study that described the prevalence and relative risk of fractures in a sample of 12,120 men with PCa (3779 men on ADT).[80] The researchers concluded that LHRH agonist treatment was associated with fracture risk with relative risks of 1.76 for hip fractures (95% C.I. 1.33 – 2.33), 1.21 for any fracture (95% C.I. 1.09 – 1.34), and 1.18 for vertebra fracture (95% C.I. 0.94 – 1.48).[80]

2.2.5 "Androgen Deprivation Syndrome"

The term "androgen deprivation syndrome" was coined to describe a group of adverse events including depression, anxiety, malaise, fatigue and cognitive difficulties.[19] The effects of ADT on mood and cognition are, however, conflicting. Two studies of men on ADT showed no difference on the mental composite scores of the SF-36[21,69] and recently Pirl et al. reported no difference in the prevalence of depression using the Beck Depression Inventory.[82] Conversely, a small pilot study involving 45 men undergoing ADT reported a 12.8% prevalence rate of depression, which is two to three times that of the general male population in North America.[83] In that study, depression was positively correlated with fatigue and inversely related with level of functioning.[83] Pirl et al. also reported significant changes on the Fatigue Severity Scale (FSS) from baseline to six months of treatment which remained steady at 12 months.[83] In a retrospective study, DiBlasio et al. reported the prevalence of depression, anxiety, and dementia to be 8.6% pre-ADT treatment, which then increased to 27.9% at mean follow-up of 87.4 months after starting ADT.[84] Recently Cherrier et al. released the results of a prospective study

which tracked the effects of intermittent ADT on cognitive function and mood at baseline and following three and nine months of CAB and then three months after treatment ceased.[85] They conclude that ADT negatively affects cognitive skills such as executive functioning and spatial reasoning plus it causes changes in mood including depression, irritability, tension, and fatigue.[85]

2.2.6 Quality of Life

According to the World Health Organization, "QOL is defined as individual's perceptions of their position in life in the context of the culture and value system where they live, and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept, incorporating in a complex way a person's physical health, psychological state, level of independence, social relationships, personal beliefs and relationship to salient features of the environment."[86]

Clinicians have increasingly recognized the impact of the various potential side effects of ADT on QOL outcomes. Dacal, Sereika and Greenspan used a self-reported health-related QOL measure called the Short-Form 36 health survey (SF-36) to examine the difference in scores between men with PCa on short-term ADT, long-term ADT, or no ADT and healthy controls (n = 96).[21] In the physical health component, men receiving ADT, regardless of duration of treatment, scored significantly lower (46.52 + 9.48) compared to men not receiving ADT (52.30 + 7.11; P = 0.001).[21] Love et al. found that men with PCa scored significantly lower in all four psychosocial dimensions of the SF-36 including vitality, social functioning, role-emotional, and mental subscales.[29] One study reported that men on ADT scored significantly lower than controls in the areas of physical function, physical role limits, and health perception.[69] Soyupek et al. reported significant differences in the 15-Dimensional QOL questionnaire when comparing men on LHRH agonists (0.53 + 0.07) and healthy age-matched controls (0.81 + 0.08; P < 0.001).[23]

The changes in QOL scores seen with the use of intermittent MAB demonstrate how closely testosterone levels are associated with various aspects of physical and emotional well-being.[22] Once MAB was initiated, QOL scores declined steadily until the testosterone recovery phase ("off" period) where QOL scores peaked after 9 – 12 months and then declined thereafter.[22] During this intermittent treatment, Spry et al. also reported that the rate of deterioration was faster than the rate of improvement.[22]

2.2.7 Psychosocial Issues

Topics surrounding social support and quality of marital relationships appear to play a key role in QOL for patients with Ca.[87,88] Impotence, urinary incontinence, and body feminization (e.g. gynecomastia) are worries that are common to men with PCa who are receiving ADT.[28] Although only a cosmetic concern, gynecomastia can be so debilitating for men that intervention is warranted.[89] Patients report sexual dysfunction as a very troublesome problem.[88] Sexual dysfunction can affect masculinity, sexual intimacy with partners, and fantasy lives of patients.[88] These changes may be accompanied by shame, fear of social stigmas and altered body image.[28, 89]

Navon & Morag used qualitative methods in their study to describe how men on ADT cope with psychosocial problems such as body feminization, sexual dysfunction, and disruptions of spousal ties.[90] Some participants described feelings of self-hatred because of weight gain, breast development, decrease in penis size and hot flashes.[90] They reported wearing loose clothes to hide breast enlargement and long-sleeve shirts or pants to cover their hairless bodies.[90] They simply avoided locations like swimming pools and facilities where change rooms do not provide total privacy and some refrain from looking at themselves in mirror.[90]

Couples dealing with PCa and the side effects of ADT may experience deterioration in their relationship for many reasons including sexual dysfunction and loss of intimacy.[91,92] In one study, the problems most reported by patients included erectile

dysfunction (78%), decreased sexual enjoyment (74%), and decreased sexual interest (58%).[93] Spouses in this study reported their chief problems to be tiredness (56%), worrying (56%), and decreased sexual enjoyment (49%).[93] They also found that spouses reported much greater psychological distress compared to the patients themselves,[93] which could be explained by a later study that found that spouses had significantly less self-efficacy and social support than the patients.[94] Couples at highest risk for distress in the areas of physical, emotional, functional and total QOL are those dealing with the advanced phase of this disease.[94]

2.3 Exercise and Physical Activity

2.3.1 Overview of Cardiovascular Risk Factor Reduction

Sedentary individuals are, on average, twice as likely to develop CVD compared to people living active lifestyles.[32] Exercise clearly reduces one's risk of CVD, but it remains unclear how much is attributed to direct changes in coronary vasculature or to indirect changes in reduction of known risk factors.[34] Jennings suggested that exercise decreases CVD by influencing several factors such as: enhancing aerobic capacity, increasing tolerance of myocardial ischemia, reduction of arrhythmias, lessening atherosclerosis formation, lowering blood pressure, increasing arterial compliance, decreasing insulin sensitivity, reducing sympathetic activity, and improving lipid profiles.[32]

There is conflicting evidence regarding exercise and its ability to improve lipoprotein and lipid levels in older adults.[95] A meta-analysis of 22 studies (n = 1427) concluded that aerobic exercise increases high-density lipoprotein (HDL) cholesterol and decreases the ratio of total cholesterol to HDL cholesterol, but this beneficial effect was not seen with triglyceride levels.[95] Another review, by Sasaki and Santos, concluded that aerobic exercise reduces CVD by preventing and reversing atherosclerosis through regulation of endothelium-dependent vasodilation and intima-media thickness.[35] They

also reported that exercise attenuates CVD risk factors such as obesity, DM, and hypertension (HTN).[35] Mora et al. found that 59% or less of the CVD risk reduction observed with exercise is accounted for by risk factor modification, most notably decreased blood pressure and improvements in inflammatory and hemostatic markers.[33]

Aerobic fitness is a strong predictor of CV events and death in men and women.[96,97] Roger et al. recently published results of a large retrospective, population-based study (n = 2193) aimed at determining the prognostic value of exercise testing on a treadmill.[97] The risk of CVD decreased by 17% in men and 23% in women with a workload increase of one metabolic equivalent (MET).[97] The same change in aerobic capacity was associated with a mortality risk reduction of 20% in men and 25% in women.[97] Another large population-based study (n = 6213) reported lower survival rates of 12% with each 1 MET increase in maximal oxygen consumption (VO_{2max}). These authors also concluded that peak exercise capacity is superior to other risk factors in predicting CVD.[96]

Duscha et al. found that 6 months of walking 19km/week at a low intensity of 40 – 55% of VO_{2max} is adequate to increase aerobic capacity significantly ($p \leq 0.001$).[98] They found that higher intensity exercise, however, had increased benefits.[98] Similarly, Cornelissen et al. reported that weight reduction, body composition changes and better lipid profiles were observed with high intensity exercise (~ 66% of heart rate reserve), but not low intensity training (~ 33% of heart rate reserve).[99] Systolic sitting and exercise blood pressures improved significantly regardless of exercise intensity by approximately 3.3 – 6.3mmHg.[99]

Evidently, exercise can directly or indirectly improve a person's cardiopulmonary health in many ways. Although the above studies did not include men undergoing ADT (they are discussed in a later section), it is not unreasonable to expect that the reduction of CVD risk and improvement of survival observed in other patient populations will be seen in these men as well.

2.3.2 The Connection to QOL, Fatigue, Mood, and Relationships

Improved peak aerobic capacity is not only associated with less risk for CVD, it has also been associated with improved overall QOL ($r = 0.45$; $P < 0.01$).[36] A randomized controlled trial (RCT) involving breast Ca survivors had participants in the intervention group ($n = 25$) perform 15 weeks of aerobic exercise while the participants in the control group ($n = 28$) performed no exercise.[36] The researchers used the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire to measure overall QOL.[36] From baseline to post-intervention, participants in the exercise group scored 9.1 points higher whereas the participants in the control group reported a much smaller increase of 0.3 points ($p = 0.001$).[36] This is a clinically meaningful change for the FACT-B given that it is a difference of at least five points.[100] Significant differences between groups was also noted for happiness ($p = 0.019$) assessed by the Happiness Measure, self-esteem ($p = 0.010$) assessed by the Rosenberg Self-Esteem Scale, and fatigue ($p = 0.006$) measured by the Functional Assessment of Cancer Therapy-Fatigue (FACT-F).[36]

Milne et al. chose to implement a 12 week combined aerobic and resistance exercise program in another RCT involving women with breast Ca.[37] The program included 20 minutes of CV exercise and 12 resistance exercises.[37] Clinically meaningful improvement in QOL and reduction of fatigue for the exercise group was also observed in this study on the FACT-B questionnaire ($p < 0.001$) and the Schwartz Cancer Fatigue Scale ($p < 0.001$).[37] These changes were evident after only six weeks of training and continued to improve after 12 weeks.[37] This study found that aerobic fitness was significantly associated with overall QOL ($r = 0.26$; $P = 0.034$) and fatigue levels ($r = -0.28$; $P = 0.038$).[37] Interestingly this group also reported that decreased scores on the Social Physique Anxiety Scale was associated with improvements in upper body strength ($r = -0.27$; $P = 0.040$).[37]

Breast, colorectal, and prostate Ca survivors ($n = 316$) were included in a study investigating the association of lifestyle behaviours and health-related QOL.[38]

Significant improvements in QOL, measured by the SF-36, were reported for participants who met PA recommendations (150 minutes/week) compared to those who did not ($p < 0.001$).[38] They did not find any association between QOL and Ca site, fruit and vegetable intake, or time since diagnosis.[38] Another study looked at the association between exercise and QOL specifically in bladder Ca survivors.[39] They described a dose-response relationship in which sedentary individuals reported the lowest QOL and the highest QOL being reported by those individuals who were meeting PA recommendations.[39] Karvinen et al. suggested that the mechanisms responsible for these change in QOL may be improved aerobic fitness, muscular strength, range of motion, balance, body composition, and co-morbidity profile.[39] Erectile function (EF) was positively associated with PA, which is particularly important given that this is a main QOL issue for men with bladder Ca.[39] Body image was also found to be positively associated with PA.[39] Sexual and urinary problems experienced by bladder Ca survivors may lead to body dissatisfaction and altered body image.[39] If exercise can enhance sexual function, it may also serve to improve body image concerns in Ca survivors.[39]

Fatigue is a common complaint of Ca survivors.[40,41] The reasons for fatigue are likely multi-factorial, but it has been suggested that it may be caused by inefficient muscle function, increased resting heart rate and respiratory work, and metabolic acidosis caused by Ca or its treatment.[41] Fatigue can be described in different ways. Mental fatigue refers to a lack of concentration and loss of memory, volitional fatigue describes an inability to begin tasks or to avoid social situations, and physical fatigue is tiredness from activities requiring physical effort.[41] Fatigue levels may have a significant impact on a patient's QOL because of the related functional impairment, reduced ability to participate in ADL, or inability to return to work.[40,41] Mock et al. found that fatigue and emotional distress were highly correlated ($r = 0.83$) and both variables were reduced with a moderate intensity home-based walking program.[40] Furthermore, a review by Dimeo concluded that endurance exercise is a promising strategy for managing cancer-related fatigue.[41]

People with depression and anxiety who exercise regularly report less psychological distress compared to those who do not.[42,43,45,47] One study involving healthy, formerly sedentary adults found a significant reduction in depression after only 10 weeks of moderate CV exercise three times per week for 20 – 30 minutes.[42] For patients with major depressive disorder, a single bout of 30 minutes of moderate intensity exercise was sufficient to improve mood, well-being, and feelings of vigor.[46] A systematic review on the effects of exercise on depression stated that more rigorous studies are needed to draw accurate conclusions, but it appears that exercise has a moderate effect on depression.[44] It is not well understood how exercise improves mood, but it has been proposed that both physiological and psychological reasons are responsible.[45] Endorphin and monoamine levels can be altered by physical exertion and these changes can lead to improved mental health.[45] People who exercise may also experience improved well-being because of behavioural and social perceptions associated with exercise.[45] These include improved self-efficacy, more social interactions and distraction from daily stressors.[45]

No studies to date have measured the effects of exercise on dyadic or spousal relationships for men on ADT. However, there are reasons to believe that the benefits of exercise will translate in to enhanced quality of spousal or partner relationships. If exercise can improve physical function and reduce fatigue, men will need less help with daily tasks, which is primarily a role transferred to their spouse.[101] Feeling that they are better able to manage the disease may relieve stress for a couple.[94] Improvement in a patient's QOL and mood states caused by exercise may also be associated with higher quality relationships. If exercise causes a patient to report improved physical, emotional, functional, and social well-being, it may seem reasonable to expect that their spouse will be positively affected by these changes.

Exercise may also improve relationship status due to enhancement of sexual activities. A meta-analysis provided evidence demonstrating that exercise decreases a man's risk of ED in a dose-response manner.[102] Higher physical activity may be able to

reverse existing ED or play a protective role where ED doesn't yet exist.[102] There are several ways in which exercise can improve EF. Vasculature changes such as improved endothelial function or body composition changes such as reduced visceral fat or weight loss have been proposed as possible mechanisms.[103] Risk factors for ED including hypertension and insulin resistance can also be reduced with PA.[103] Maio et al. summarized additional ways in which PA can benefit ED.[104] These include: "increase in endothelium-derived nitric oxide, penile cyclic guanosine monosphosphate levels, and number of endothelial progenitor cells, changes in lipid profile, fibrinogen, carbohydrate metabolism, neurohormonal release, and vascular inflammatory markers decrease".[104]

A two-year intervention study looked at the effect of BMI and PA on erectile and endothelial function.[105] Physical activity increased and BMI decreased significantly ($p < 0.001$) in the intervention group compared to the control group. The exercise intervention group showed a decrease in non-specific markers of inflammation, interleukin 6 ($p = 0.03$) and C-reactive protein ($p = 0.02$).[105] Scores on the International Index of Erection Function (IIEF) also improved significantly more in the intervention group ($p < 0.001$).[105] They concluded that approximately one third of obese men with ED experience improved sexual performance due to lifestyle changes such as exercise.[105] Another study involving 674 men aged 45-60 years looked at the association between PA, using the Paffenbarger score, and EF, using the IIEF.[106] They found a positive correlation ($r = 0.164$, $p < 0.001$) between EF and PA when participants were exercising between 1000 kcal/week up and 4000 kcal/week on the Paffenbarger score.[106] The equivalency of 1000 kcal/week is walking briskly for approximately 3 km, five times per week. This is promising given that ED can be affected by as little as 1000 kcal/week of PA. Interestingly, after 4000 kcal/week, the benefits of PA on ED were no longer evident.[106] Another note of importance is that men who reported PA of at least 3000 kcal/week had a decreased risk of having severe ED by as much as 82.9% ($p = 0.018$).[106]

A recent study investigated the effect of phosphodiesterase type 5 inhibitors (PDE5i) alone versus PDE5i and aerobic PA on ED.[104] After three months, the PA group

showed significantly higher scores on most items of the IIEF including: EF (0.003), mild disease severity ($p = 0.004$), normal erection ($p = 0.004$), confidence ($p = 0.006$), sexual desire ($p = 0.028$), intercourse satisfaction ($p = 0.001$), overall satisfaction ($p = 0.009$), and IIEF total score ($p = 0.007$).[104] They concluded that three hours of PA per week for three months led to substantial improvement in ED in the PDE5i and PA group of 77.8% versus PDE5i alone group of 39.3%.[104]

2.3.3 For Men with PCa Receiving ADT

The therapeutic role of exercise for Ca survivors is well-supported in the literature.[2,107,108] Exercise is effective in increasing cardio-respiratory fitness, altering physiologic outcomes, reducing disease-related symptoms, and decreasing treatment related side effects in people with various types of Ca.[107] Exercise interventions may also lead to reduced fatigue, but more studies are needed to determine if these reported changes in fatigue would be considered clinically significant.[107] To date, the majority of exercise intervention studies have focused on aerobic training for women with breast Ca, which is the most common malignancy in women.[2, 107, 108] Since PCa is a leading cause of malignancy for men, it is surprising that PCa survivors have not been included in more clinical trials. Men with PCa receiving hormone therapy are affected by disease-related issues as well as physical and emotional challenges that are unique to ADT. Only in the last decade has the role of exercise in managing the adverse effects of ADT been examined. However in the past eight years, seven studies have looked at the effects of exercise or PA interventions in men undergoing ADT.

The first study was a large, two-site, RCT ($n = 155$) conducted by Segal et al. in 2003.[48] All the men included in this trial were scheduled to receive ADT for at least three months after recruitment. Participants, with a mean age of 67.9 years, were randomly assigned to one of two groups: resistance exercise intervention ($n = 82$) and wait-list controls ($n = 73$).[48] Segal et al. chose to look at the effects of resistance exercise

instead of aerobic exercise because the existing literature involving Ca survivors was heavily weighted on aerobic exercise modalities.[48]

Participants attended exercise sessions three times per week for 12 weeks in a supervised setting.[48] They completed two sets of 8 – 12 repetitions of nine resistance exercises including: leg extension, calf raises, leg curl, chest press, latissimus dorsi pull-down, overhead press, triceps extension, biceps curls, and modified curl-ups.[48] Weight was initially determined using 60% of 1-RM and then progressed by 5 lbs once the participant could complete more than 12 repetitions.[48] It is known that resistance exercise at > 80% of 1-RM can increase testosterone levels in healthy individuals, therefore men in this study trained to a maximum of 70% of 1-RM.[48] The wait-list control group did not receive any intervention during the 12 week study period, but were given the opportunity to participate in an exercise program after that time.[48]

Men in the training program reported significantly less fatigue on the FACT-F scale compared to the control group ($p = 0.002$).[48] A positive change indicates reduced fatigue and a negative change indicates greater fatigue. The exercise intervention group increased by 0.8 ± 5.8 points, whereas the control group decreased by 2.2 ± 5.8 points.[48] This was the first study to show that exercise can improve QOL in men with PCa. The Functional Assessment of Cancer Therapy – Prostate (FACT-P) is a PCa-specific health-related QOL outcome measure where a positive change indicates improved QOL and a negative change indicates decreased QOL.[48] QOL scores on the FACT-P improved by 2.0 ± 9.1 points in the exercise intervention group in contrast to the control group scores, which decreased by 3.3 ± 10.2 points ($p = 0.001$).[48]

Muscular fitness was determined using the standard load test, which measures the maximum number of repetitions completed at a cadence of 22 repetitions per minute using resistances of 20 kg for chest press and 40 kg for leg press.[48] In the intervention group, upper body and lower body muscular fitness improved significantly by 42% and 32%, respectively.[48] The number of repetitions for the chest press increased by 13.1 in

the intervention group, but decreased by 2.6 in the control group leading to a significant difference in change between the groups ($p = 0.009$).[48] Lower body muscular fitness also differed significantly between groups ($p < 0.001$).[48] The intervention group showed an increase of 11.8 repetitions in the leg press whereas the control group showed a decrease of 1.6 repetitions.[48] The improvements in muscular fitness reported in this study are important because they showed that despite castrate levels of testosterone, men on ADT can benefit from strength training. Also it is this gain in muscular strength and endurance that could be responsible for reducing fatigue and improving QOL.[48] The authors felt that length of time on ADT and intention of treatment could impact how these participants responded to exercise.[48] Through exploratory analyses they found that significant differences still existed between the groups for fatigue and QOL changes regardless of whether the ADT treatment was for short- or long-term use or for curative or palliative intent.[48]

Body composition measurements including weight, BMI, waist circumference or sum of skin folds did not change significantly over the study period in either group.[48] Importantly, there were no significant differences between groups for testosterone levels ($p = 0.24$) or PSA levels ($p = 0.31$) implying that exercise does not hinder the therapeutic goal of androgen suppression.[48]

The major strength of this study is the large sample size of men undergoing ADT. It is also impressive that adherence rates were reported to be > 75% of all the prescribed sessions.[48] This is noteworthy as it demonstrates that men undergoing ADT are able to attend most of the supervised sessions and can safely complete the training program. A study limitation is that 12 weeks may not allow sufficient time to fully understand the impact of resistance exercise for men undergoing ADT. Also, to account for cross-contamination, the usual care group should have tracked their activity because it is possible that some participants engaged in exercise in other settings.

Windsor et al. conducted the next exercise study involving men on ADT. They examined the effects of aerobic conditioning for men with PCa undergoing four weeks of radiotherapy with ADT (n = 19) or without ADT (n = 47).[52] Men in the intervention group walked at least three times per week at a target heart rate of 60 – 70% maximum heart rate.[52] These men demonstrated improvement in aerobic capacity and no increase in fatigue following a 4 week home-based walking program compared to men in the usual care group.[52] Aerobic capacity was reported as the distance completed in the modified shuttle walk test, which involves keeping pace with stages of incremental speeds.[52] The authors observed improvements of 13.2% in the exercise group from baseline (511.6 ± 31.2m) to end of radiotherapy (579.1 ± 27.0m; $P < 0.001$), but no significant differences in the control group ($p = 0.49$).[52] At the follow-up visit, four weeks post-intervention, the control group reported increased levels of fatigue on the Brief Fatigue Inventory ($p = 0.053$) whereas the exercise group reported no significant differences ($p = 0.132$).[52] This suggests that exercise is able to prevent increased feelings of fatigue that are common among men undergoing radiotherapy and ADT, even with a short intervention period of four weeks.

Galvão and colleagues conducted a small, non-randomized clinical trial with 10 men (mean age = 70.3 years) undergoing ADT completing a high intensity progressive resistance exercise program.[50] Half of the men were on short-term ADT and half were on long-term ADT.[50] Participants exercised two times per week for 20 weeks in a supervised setting. The first 10 weeks consisted of concentric muscle strength training with the addition of eccentric movement in the remaining 10 weeks.[50] Intensity in both training phases was progressed in the following way: two sets of 12-RM during weeks 1 – 2, three sets of 10-RM during weeks 3 – 4, three sets of 8-RM during weeks 5 – 7, and four sets of 6-RM for weeks 8 – 10.[50] Exercises included chest press, seated row, shoulder press, latissimus dorsi pull-down, triceps extension, bicep curl, leg press, squat, leg extension, leg curl, abdominal crunch, and back extension exercises.[50]

Muscle strength and endurance increased dramatically over the training period. Significant improvements were observed from baseline to the 10 week point in all measures of muscle function, which further increased at the end of the 20 week training program.[50] From baseline to 20 weeks, the chest press 1-RM increased by 40.5 ± 18.5% ($p < 0.001$), the seated row 1-RM test increased by 41.9 ± 21.4% ($p < 0.001$) and the leg press 1-RM increased by 96.3 ± 25.7% ($p < 0.001$).[50] The chest press endurance test increased by 114.9 ± 42.6% ($p < 0.001$) and leg press endurance test increased by 167.1 ± 143.6% ($p < 0.001$).[50] According to the authors, these reported changes in muscle function are likely mediated by non-hypertrophy related factors such as neural adaptation and motor learning.[50] It is note-worthy, however, that despite castrate levels of testosterone, muscle thickness (measured with ultrasound) increased significantly in the quadriceps muscle by 15.7 ± 12.1% ($p = 0.050$).[50] No explanation was given as to why muscle thickness did not change in the biceps (3.5 ± 6.9%; $P = 0.621$), triceps (5.5 ± 17.0%; $P = 0.875$) or hamstrings (0.2 ± 10.0%; $P = 0.483$).[50] The authors proposed that the above changes in muscle function will lead to more efficient use of energy thus allowing men undergoing ADT to carry out their ADL with less fatigue.[50]

Several functional performance measures were significantly improved from baseline to week 20 including: chair sit to rise (-26.8 ± 7.1%; $P < 0.001$), 6-m usual walk test (-14.1 ± 10.2%; $P = 0.002$), 6-m backwards walk test (-22.3 ± 21.9%; $P = 0.017$), 400-m walk (-7.4 ± 5.9%; $P = 0.003$) and stair climbing (-10.4 ± 9.8%; $P = 0.014$).[50] The 6-m fast walk test scores did not improve significantly (3.5 ± 0.7%; $P = 0.227$).[50] The sensory organization test was used to measure balance under six trial conditions. The scores improved significantly post-intervention (7.8 ± 6.9%; $P = 0.042$), but the mid-term score changes were insignificant.[50] Given that men on ADT are at increased risk of skeletal fractures, it is encouraging that an exercise intervention can improve balance in this population, which could potentially reduce the risk of falling. Bone mineral content (total) and BMD (femoral neck, trochanter, Wards triangle) was preserved during the intervention period.[50] There were no significant differences in body composition, but this

finding is still positive in that exercise preserved whole-body lean mass and prevented increases in fat mass and percent body fat.[50]

Although this study offered a comprehensive look at the effects of exercise for men on ADT by using a wide range of outcome measures, it was a small study of only 10 men without a control group.[50] Also, the authors stated that this cohort of men may not have been representative of for all men with PCa undergoing ADT because these men were quite high functioning and motivated to exercise.[50]

In 2007, Culos-Reed et al. introduced a PA program for men undergoing ADT.[51] Men with PCa at any stage of disease who were scheduled to receive ADT for at least 6 months were included in this study.[51] This was a non-randomized trial with 31 men being prescribed an individualized, home-based, 12-week PA program.[51] Participants were encouraged to engage in PA three to five times per week.[51] The program consisted of walking, stretching, and light resistance exercises with elastic bands and Fitter exercise balls.[51] Every two weeks participants also attended a group-based "booster" session for an education/discussion portion (0.5 hours) and an activity portion (1.0 hour).[51] The education portion focused on topics that are often concerns for new exercisers such as goal setting and overcoming barriers to exercise.[51]

The Leisure Score Index (LSI) of the Godin Leisure Time Exercise Questionnaire was used to assess the frequency of past exercise.[51] At baseline and at post-intervention, participants were asked to report their activity levels for the past 12 weeks. At post-test, PA increased significantly for moderate exercise ($p = 0.04$), strenuous exercise ($p < 0.01$), and total PA ($p = 0.02$).[51] Cardio-respiratory fitness was determined using the 6 minute walk test.[51] At baseline, participants walked 1874.39 ± 345.03 ft, which increased significantly to 2081.17 ± 413.48 ft ($p < 0.01$) at post-test.[51] The exercise intervention also caused a decrease in resting heart rate ($p = 0.03$), which indicates improved aerobic fitness.[51] The increase observed in both heart rate after walking ($p < 0.01$) and rate of perceived exertion after walking ($p < 0.01$) is most likely due to the participant's

increased ability to exercise at higher intensities over the course of the intervention.[51] Weight remained constant ($p = 0.08$).[51]

Measure of QOL and fatigue were assessed at baseline, 12 weeks, and 4 months post-intervention.[51] Quality of life, which was measured using the European Organization for the Research and Treatment of Cancer QOL Questionnaire, improved in the global QOL subscale during the intervention, although this change was not statistically significant ($p = 0.13$).[51] It should still be considered clinically relevant that exercise prevented a decrease in QOL in men undergoing ADT especially considering that global QOL decreased significantly ($p = 0.04$) once the exercise program was stopped.[51] These researchers used the FSS to measure fatigue levels.[51] Fatigue was significantly decreased during the PA intervention ($p = 0.05$).[51] At the 4 month follow-up fatigue scores increased, but not significantly ($p = 0.07$).[51] This supports previous reports by Segal et al. that exercise can reduce fatigue in men undergoing ADT and facilitating one's ability to perform ADL.[51]

Although this study had a small sample size and did not have a control group, it still provides encouraging data regarding the effects of exercise in improving QOL, fatigue, and physical fitness in men who are undergoing ADT. Furthermore given the financial and scheduling demands on patients with Ca, the fact that a home-based PA program was effective in targeting the side effects of ADT is important.

The potential benefits of resistance exercise for men on ADT were further exemplified in a second study by Segal et al.[49] This supervised, 24-week RCT compared the effects of resistance training ($n = 40$), aerobic exercise ($n = 40$), and usual care ($n = 41$) in men with PCa receiving radiation therapy with or without ADT (mean age = 66.3 years).[49] There were 74 men receiving ADT treatment and all participants were stratified based on the duration of ADT (none/< 16 weeks vs. > 16 weeks).[49]

The resistance exercise training protocol used in this trial was identical to the protocol used in 2003 with the exception of one additional exercise: low back extension.[48, 49] The participants in the aerobic exercise group also attended three times per week, but their training protocol included the use of cycle ergometers, treadmills, and elliptical machines.[49] The intensity of exercise started at 50 – 60% of VO_{2max} for weeks 1 to 4 progressing to 70 – 75% VO_{2max} for weeks 5 to 24.[49] Participants initially performed 15 minutes of exercise increasing by five minutes every three weeks to a maximum of 45 minutes.[49] The usual care participants were asked not to initiate exercise and were offered an exercise program after the 24 week intervention period.[49]

Baseline assessments for all outcome measures were performed prior to the start of radiation treatment. Mid-intervention (12 weeks) and post-intervention (24 weeks) scores were obtained for the FACT-F, FACT-P, and Functional Assessment of Cancer Therapy – General (FACT-G).[49] Fatigue scores for the aerobic exercise group were superior to usual care at 12 weeks (95% C.I. 1.47 – 7.80; P = 0.004), however, this difference was no longer significant at 24 weeks (95% C.I. -0.29 – 5.58; P = 0.080).[49] The resistance exercise group, on the other hand, reported significant reductions in fatigue compared to the usual care group at mid-intervention (95% C.I. 0.87 – 7.35; P = 0.010) and post-intervention (95% C.I. 1.77 – 7.78; P =0.002).[49] Fatigue scores were associated with upper-body strength (r = 0.21; P = 0.03), but not with hemoglobin levels (r = 0.14; P = 0.13), suggesting that exercise reduces fatigue through improvements in neuromuscular efficiency.[49] Other possible mechanisms for reduction in fatigue as suggested by the authors include reduced depression, improved sleep, and increased socialization.[49] Although these results are encouraging and support the findings from their previous study, the stratified results for men receiving ADT showed no significant difference in fatigue for the resistance exercise group (p = 0.148) or the aerobic exercise group (p = 0.082) when compared to usual care.[49]

Scores on the FACT-P, a disease-specific QOL scale, did not change significantly between groups regardless of whether the men were receiving ADT.[49] FACT-G scores

did differ significantly between the resistance group and usual care at 12 weeks (95% C.I. 0.86 – 8.65; P = 0.017) and 24 weeks (95% C.I. 0.88 – 7.80; P = 0.015), but aerobic exercise did not significantly alter cancer-specific QOL.[49] In 2003 Segal et al. reported increased QOL with resistance exercise training for men on ADT using a combined FACT-P and FACT-G score.[48] Their second study shows that exercise is more likely to impact general Ca symptoms rather than symptoms that are related specifically to PCa.[49] Contrary to their initial study however, men receiving ADT did not report significant differences in the FACT-P for the resistance exercise group (p = 0.914) or the aerobic exercise group (p = 0.247) nor did they score differently on the FACT-G for the resistance exercise group (p = 0.489) or the aerobic exercise group (0.906).[49]

Objective measures were assessed at baseline and at 24 weeks. Covariates included age, Ca stage, ADT (yes/no), and Gleason score.[49] Cardio-respiratory fitness measured by VO_{2max} was significantly higher in the resistance exercise group compared to usual care (95% C.I. 1.0 – 3.1; P = 0.037) while the aerobic training group, where improvements would be expected, showed no significant difference (95% C.I. 0.08, 2.8; P = 0.063).[49] Upper and lower body strength was improved in the resistance exercise group: leg press (95% C.I. 18.7, 32.6; P < 0.001) and chest press (95% C.I. 8.8, 13.0; P < 0.001). [49] Aerobic exercise was superior to usual care in the chest press at post-intervention testing (95% C.I. 1.2 – 6.9; P = 0.006) which was mostly due to a decline in upper body strength in the usual care group.[49] For men on ADT, resistance exercise remained superior to usual care for upper-body strength (p < 0.001) and lower-body strength (p < 0.001) while aerobic exercise was superior to usual care for upper-body strength (p = 0.020), but not for lower-body strength (p = 0.777).[49] Between-group differences for weight or percent body fat were insignificant across all groups, except resistance exercise helped to prevent the weight gain common to ADT.[49]

This large clinical trial was the first to compare resistance exercise to aerobic exercise in men with PCa using a series of comprehensive outcomes measure. The above results suggest that resistance exercise is more effective than aerobic exercise for men

with PCa in improving fatigue, QOL, strength, VO_{2max}, and triglycerides. It is difficult to draw conclusions, however, because there was a large amount of cross-contamination among groups. It was stated that six usual care participants "dropped in" to aerobic training sessions and eight resistance training participants reported vigorous aerobic exercise. Also, it is discouraging, but expected, that men on ADT showed fewer positive outcomes after participating in an exercise intervention compared to men not on ADT, but it is again difficult to conclude whether this could be caused by the variation in exercise regimens within the groups.

Culos-Reed et al. conducted a second trial in 2010 that investigated the effects of a home-based PA program, similar to their previous protocol.[51,53] This was a 16-week, RCT with men on ADT being assigned to the intervention group (n = 53) or the wait-list control group (n = 47).[53] Significant differences in the Leisure Index Score ($p = 0.004$), waist girth ($p = 0.044$) and neck girth ($p = 0.019$) were observed.[53] Non-significant changes in heart rate, blood pressure, 6-minute walk test, sit and reach test, hip girth, QOL, fatigue, depression, and PSA levels were reported.[53] The authors suggested that this intervention may not have affected QOL due to lack of sensitivity of the measures used or because the baseline QOL scores were quite high.[53] The high drop-out rate of 34% and an adherence rate of only 77.8% may have contributed to the lack of effectiveness of this intervention.[53] Additionally, the authors did not account for confounding variables such as disease stage or anemia.[53] This is the only RCT investigating PA for men on ADT. The exact reason for the lack of significant differences between groups in various outcomes is not known, but it is perhaps due to an inadequate training regimen. Because this was a home-based program it is impossible to know what activities were completed and at what intensity they were being done at. Also, elastic bands may not provide enough resistance to cause muscle strength and lean mass changes as seen in other studies using weight lifting equipment.[48-50,54] It is thought that fatigue may be reduced by an increase in muscle strength and endurance,[50] which would explain why participants in this study did not experience a reduction in fatigue.

Finally the authors felt that a 16-week intervention period may not be sufficient time to observe changes in all of the outcome measures.[53]

The first study to evaluate a combined resistance and aerobic exercise program for men receiving ADT was Galvão et al. in 2010.[54] Men in the study were randomly assigned to the exercise group (n = 29) or the usual care group (n = 28) for 12 weeks.[54] The supervised exercise intervention included training twice per week.[54] Resistance exercises included the chest press, seated row, shoulder press, triceps extension, leg press, leg extension, leg curl, and abdominal crunches.[54] This program was progressed from 12- to 6- repetition maximum with participants completing two to four sets per exercise.[54] Cardiovascular exercises included cycling, walking or jogging.[54] Participants completed 15 to 20 minutes of aerobic exercise at an intensity of 65% to 80% maximum heart rate.[55] Exercises sessions were supervised and performed in small groups.[54]

All measurements were performed at baseline and at 12 weeks (the end of the exercise intervention). Dual x-ray absorptiometry was used to measure body composition including: whole body and regional lean mass, fat mass, and percent fat.[54] Total lean body mass was 0.8 kg higher in the exercise group compared to the usual care group post-intervention ($p = 0.047$). Significant differences in lean body mass between the exercise group and usual care group were also seen for the upper limb ($p < 0.001$), lower limb (0.019), and appendicular skeleton ($p = 0.003$). Fat mass, percent fat, and body weight did not differ significantly between groups

Four muscle strength tests were performed including the 1-RM chest press, seated row, leg extension, and leg press.[54] All tests differed significantly among groups post-intervention.[54] The 1-RM chest press differed by 2.8 kg ($p = 0.018$) while the 1-RM seated row differed by 5.1 kg ($p < 0.001$).[54] The difference observed between the groups in the leg press was 30.8 kg ($p < 0.001$) and leg extension was 11.5 kg ($p < 0.001$).[54] Upper and lower body muscle endurance was measured as the maximal number of repetitions completed at 70% of 1-RM for baseline and final values for chest press and

leg press.[54] Men in the exercise group completed a mean of 5.2 repetitions more than the usual care group for the chest press ($p < 0.001$) and 10.8 repetitions more for the leg press ($p < 0.001$).[54]

The cardio-respiratory outcome measure used in this study was the 400-m walk test, which showed a borderline improvement of seven seconds in the exercise group after 12 weeks ($p = 0.080$).[54] It is possible that the lack of improvement in aerobic fitness is due to an inadequate training schedule. These men were exercising two days per week as opposed to following the American College of Sports Medicine (ACSM) guidelines which recommend exercising five days per week and over 250 minutes per week.[54] After the12 week period, differences in physical performance and balance were evident.[54] Men in the exercise group had better scores for the 6-meter usual walk ($p = 0.024$) and backwards walk test (0.039).[54] They also measured C-reactive protein, a non-specific marker of inflammation, which decreased in the exercise group and increased in the control group ($p = 0.008$).[54] No other blood biomarkers showed significant differences between groups.[54] These included PSA, testosterone, glucose, insulin, lipids, and homocysteine.[54]

The SF-36 was used to assess QOL. The researchers found that the exercise group improved in three areas including general health ($p = 0.022$), vitality ($p = 0.019$), and the physical health composite ($p = 0.020$).[54] There was a significant association between change in general health and whole body lean mass ($r = 0.385$; $p = 0.039$).[54] Also, a change in general health was closely associated with change in average muscle strength ($r = 0.249$; $p = 0.064$).[54] QOL was also assessed using the Quality of Life Questionnaire-C30.[55] Change scores improved for the exercise group in role ($p < 0.001$), cognitive ($p = 0.007$), fatigue ($p = 0.021$), nausea ($p = 0.025$) and dyspnea ($p = 0.017$).[54]

No other studies have investigated the effects of a structured aerobic and resistance exercise program in men receiving ADT.[54] This short-term training program led to several benefits including increased muscle mass and strength, improved physical

function, and enhanced QOL.[54] Furthermore, this program was well-tolerated among the participants confirming its feasibility.[54]

The number of studies focusing on the effects of exercise for men on ADT continues to grow, but there remains some gaps in the literature. To date, three studies have looked at the effects of resistance exercise and all studies reported benefits.[48-50] One of these was a large randomized trial[48], while the other had a small sample size and was an observational study.[50] The third study was a large randomized trial that examined the differences between resistance exercise, aerobic exercise, and usual care.[49] In this study, resistance exercise was seen as the most successful training method.[49] However, another fair sized randomized study found that aerobic exercise mitigates fatigue.[52] One combined resistance and aerobic exercise program that was also a randomized trial showed some benefits, but interestingly not in the cardio-respiratory fitness measures.[54] The question remains as to which type of exercise program is best. Is the addition of aerobic exercise beneficial over resistance exercise alone? This is particularly important in regards to cardiovascular risk and cardio-respiratory fitness.

The training protocol in the current study is based on the strengths and weaknesses of the above studies for men receiving ADT. A supervised program was used because the most successful trials have been completed under the supervision of an exercise specialist. At the initiation of my study there were no trials for men on ADT that used a combined resistance and aerobic exercise program. At present, only one other study has used this type of program therefore further research is warranted.[54] I also chose a combined exercise program as it is what is currently recommended by the ACSM for optimal health.[3] The intervention time frame that I used for my study is based on several factors. Muscle hypertrophy in healthy individuals who start resistance training takes approximately eight weeks.[109] The participants in my study are older men on ADT and may require more time to observe the same results as healthy individuals.[110] Additionally, 16 weeks is approximately the mean intervention time (range = 4 – 24 weeks) for all the studies involving men on ADT.

In summary, men on ADT who exercise or participate in PA experience both physical and psychological benefits. Resistance exercise results in increased lean mass, large gains in muscle strength and endurance, improvements in functional performance, enhanced QOL, and reduced fatigue. Aerobic exercise training for men on ADT can lead to improved cardio-respiratory fitness and less fatigue. PA programs have led to improved cardio-respiratory fitness and enhanced QOL. Although there are a limited number of studies in this area, exercise or PA is now viewed as the most promising method in ameliorating the adverse effects associated with ADT. Given that the risk of PCa and the use of ADT are greater in older men, exercise is also essential to prevent age-related decline and loss of independence. Prostate Ca and ADT can have a widespread and substantial impact on a patient's physical function and psychological well-being. Research in this area is needed to fully understand if and how exercise should be used as a complement to traditional management strategies.

CHAPTER 3
Methodology

3.1 Participants and Setting

This study took place at the Dalhousie University School of Physiotherapy in Halifax, Nova Scotia, Canada. The study protocol was approved by the Capital District Health Authority Research Ethics Board and all participants provided written informed consent. Men were eligible for this study if they were between the ages of 50 and 80 years old and were receiving medical or surgical ADT for any stage of PCa. Participants must have been on ADT for at least three months prior to starting the study and must having been planning to be on ADT for the duration of the study (24 weeks). Men were excluded from the study for the following reasons: living outside the Halifax Regional Municipality, undergoing chemotherapy, brain metastases, bone metastases at high risk for fractures, severe cardiac disease (New York Heart Association class > III), uncontrolled HTN (blood pressure > 160/95 mmHg), uncontrolled pain, and any other CV, neurological, or musculoskeletal impairment that would limit the person's ability to participate in this study protocol. All eligible participants also obtained approval from their treating oncologist.

Participants were primarily recruited with the assistance of radiation oncologists at the Capital Health Queen Elizabeth II Health Sciences Centre. Letters were sent to their patients who were receiving ADT to briefly explain the study. Those interested in participating were instructed to contact me. Details of the study were communicated to physicians in the genito-urology and oncology groups in the Halifax area who could refer patients directly to me. Posters were placed in the examination rooms of the Nova Scotia Cancer Centre in the Dickson Building and in various QEII Health Sciences Centre outpatient clinics. The director of the local PCa support group and myself communicated the information about the study through announcements at monthly meetings and email newsletters. Also, postings were displayed on the Notice Digest News at dalnews.dal.ca.

3.2 Study Design and Procedures

This was a prospective randomized controlled trial that used pre-test – post-test group design. All eligible participants were randomly assigned to the exercise intervention group (EIG) or the usual care group (UCG) prior to their initial assessment. Outcome measures were assessed at three time periods: baseline (0 weeks), the end of the exercise intervention (16 weeks), and follow-up (24 weeks). Cardio-respiratory fitness and muscle strength were also tested at the midpoint of the exercise intervention (8 weeks) for the purpose of re-evaluation and adjustment of appropriate exercise parameters for those in the EIG.

Staff at the Radiation Oncology Clinic of the QEII contacted potential participants by mail. Interested participants gave the clinic permission for me to contact them with further information and to screen for eligibility. Other forms of recruitment had the interested participants contact the Principle Investigator directly. Eligible participants were scheduled for their assessment at the Lab [Exercise Lab (room 315) on the 3rd floor of the Forrest Building]. Each participant in the UCG attended three assessment sessions (0 weeks, 16 weeks, and 24 weeks) and those in the EIG attended four assessment sessions (0 weeks, 8 weeks, 16 weeks, 24 weeks). Each session lasted no longer than 3 hours. Informed consent was obtained at the initial assessment prior to any testing procedures.

Men in the intervention group attended supervised exercise sessions in the same lab three times per week to complete the training program outlined below. Lab hours were flexible, but all participants needed to book exercise times so that the Principle Investigator was available to supervise. The Principle Investigator was a physiotherapist with training in exercise testing and prescription. Each exercise sessions lasted approximately one hour to one and a half hours.

3.3 INTERVENTIONS

3.3.1 Exercise Intervention Group

Subjects in the EIG attended supervised exercise sessions three times per week for 16 weeks. Each of these sessions lasted approximately one hour to one and a half hours. During this time subjects performed both aerobic exercise and resistance training. Warm-up, cool-down, and light stretching were also performed.

Aerobic exercise included mostly treadmill walking with the option of using a stationary bicycle once weekly. Subjects started with 15 minutes and progressed to 40 minutes of training. Training intensity began at 60 – 70% of the subject's VO_{2max} and progressed to 70 – 80% of the subject's VO_{2max} as shown in Table 3.1. Exercise intensity was monitored using a pulse oximeter to measure heart rate.

Table 3.1: Aerobic exercise training schedule

Week	Intensity	Time
	Determine VO_{2max}	
1 – 2	60 – 70% VO_{2max}	15 minutes
3 – 5	60 – 70% VO_{2max}	20 minutes
6 – 8	70 – 80% VO_{2max}	25 minutes
	Determine new VO_{2max}	
9 – 11	60 – 70% *new* VO_{2max}	30 minutes
12 – 14	60 – 70% *new* VO_{2max}	35 minutes
15 – 16	70 – 80% *new* VO_{2max}	40 minutes

Participants completed resistance exercises on the Hoist H4400 multi-station gym. The starting weight was 60% of the predicted 1-RM which progressed to a maximum of 70% of the predicted 1-RM. The maximum amount was chosen because it is known that testosterone increases when performing exercises at 80% of 1-RM.[48] Once the subject was able to perform more than 12 repetitions, the weight was be increased by 5 lbs increments. Participants performed 11 exercises as shown in Table 3.2.

Table 3.2: Resistance exercises classified into body region

Upper Body	Lower Body	Torso
Biceps curl	Leg extension	Seated mid-row
Triceps push-down	Leg press	Latissimus dorsi pull-down
Chest press	Hip abduction	Abdominal crunch
Pectoral fly	Toe raises	

3.3.2 Usual Care Group

Participants in the UCG continued with their current medical care as usual. They were asked to continue with their normal daily activities during the intervention period (24 weeks). They were given counseling about exercise after the study period if they were interested.

3.4 Objective Outcome Measures

A summary of the objective outcome measures is available in Appendix A.

3.4.1 Body Composition

Bioelectrical impedance analysis was performed using the Tanita BC-1000® (Tokyo, Japan). This allowed for measurements of weight (kg), total body fat percentage (%) and total body water percentage (%). Weight and height in metres (m) was used for calculation of an individual's BMI in kg/m^2, generally classified as follows: underweight (< 18.5), normal (18.5 – 24.9), overweight (25 - 29.9), or obese (> 30).[3] This analysis also included an estimation of muscle mass which is pre-determined by the software and calculated as: total body weight - body fat weight - estimated bone mass (derived from variables such as height, gender, and activity level). This system is reported to be accurate within +/- 5% of dual energy x-ray absorptiometry (DEXA), the institutional standard of body composition analysis.[111] Chest, waist, and hip circumferences (cm) were also measured using a fabric tape measure. Classification of disease risk based on BMI and waist circumference can be found in Appendix B.

3.4.2 Cardio-respiratory Fitness

A widely accepted and valid measure for cardio-respiratory fitness is VO_{2max}.[3] To determine VO_{2max} participants completed a maximal graded exercise test on a treadmill while wearing the Jaeger Oxycon Mobile® (Höchberg, Germany) wireless, portable, ergospirometry system. The system consists of two compact modules which are mounted to the subject's back or chest: the sensor box and the data exchange box. The sensor box analyzes the levels of oxygen and carbon dioxide in the air-tight mask that is positioned on the subject's face. Data collection is done on a breath by breath basis. This information is sent to the data exchange box along with vital signs from the pulse oximeter. All data collected by the data exchange box gets sent telemetrically to the base station which is connected to a computer with Lab Manager V5.3.0 software. The base station is also equipped with a fully automated calibration system for gas analyzers, volume and flow control. Prior to data collection the Oxycon Mobile® was calibrated

under three conditions: ambient conditions, automated volume calibration, and gas analyzer. A mixture of 4% CO_2 and 16% O_2 is used for the gas analyzer calibration.

The Modified Bruce Protocol, a symptom limited graded exercise test, was used for testing VO_{2max} according to the American College of Sport Medicine's Guidelines for Exercise Testing Prescription.[3] The VO_{2max} was calculated as the mean of the breath by breath values within 15 seconds on each side of the peak point of the VO_2 for a total sample of 30 seconds. Resting and peak heart rate (HR_{peak}) was determined using an automated oxygen saturation monitor that was part of the Oxycon Mobile® system. Resting blood pressure was measured using a manual sphygmomanometer and stethoscope.

3.4.3 Muscular Fitness

Upper and lower body strength and endurance were measured using the chest press and leg press exercises. All muscular fitness testing was performed on the Hoist H4400™ multi-station gym. The gold standard for measurement of muscle strength is the 1-RM test, which is the maximum amount of weight that can be lifted one time.[3] Determining a 1-RM can be difficult in a clinical setting because it leads to fatigue and can be time consuming when allowing for proper rest periods. There is also a greater risk for injury to both the subject and the spotter. For these reasons, this study determined muscle strength using a method described by Brzycki for estimating 1-RM (Table 3).[112] Muscle endurance was measured using a method described by Galvão et al. where the participants lift 70% of their estimated 1-RM and complete as many repetitions times as possible while keeping proper form.[50] Procedures for these tests can be found in Appendix C.

3.5 SUBJECTIVE OUTCOME MEASURES

A summary of the subjective outcomes measures can be found in Appendix D.

3.5.1 Short Form 36 Health Survey

The SF-36 is a 36 item self-reporting questionnaire that is a commonly used valid tool for measuring functional health status and well-being in the clinical setting and for research purposes.[113] The SF-36 has been used with various patient populations making it easy to compare results from other exercise intervention studies for people with chronic illnesses. The SF-36 is comprised of physical and mental health components. The physical health scales include physical functioning, role-physical, bodily pain, and general health.[113] The mental health component scales are vitality, social functioning, role-emotional, and mental health.[113] The reliability of the SF-36 has been looked at in over 25 studies.[114] The minimal alpha reliability coefficient was reported as 0.70 with most studies reporting reliability coefficients over 0.80.[115] There are also a large number of studies reporting strong evidence for content, concurrent, criterion, construct, and predictive validity for the SF-36.[114]

3.5.2 Functional Assessment of Cancer Therapy – General and Functional Assessment of Cancer Therapy – Prostate

The FACT-G measures global QOL experienced by Ca survivors.[116] It contains 27 items with four subgroups: physical well-being, social/family well-being, emotional well-being, functional well-being.[116] The FACT-P is a 12 item multidimensional subscale that measures disease-specific concerns.[117] Internal consistency is high for the FACT-G and PCa subscale with reliability coefficients of 0.85 to 0.87 and 0.87 to 0.89, respectively.[117] The alpha coefficient ranged from 0.61 to 0.84, which is an acceptable to good range.[117] This scale is able to distinguish between diseases stages, performance status, and baseline PSA levels indicating that the concurrent validity is good.[117] Both

questionnaires use a Likert-type scale (0 = 'not at all' to 4 = 'very much'). The total and subscale results are calculated according to the FACT scoring guide. Higher scores represent better QOL where a change of 5-10 points in the total FACT score has been associated with meaningful change in QOL.[118] This tool and the FACIT-F, a subscale of the FACT-G (see below), were chosen because they have been used by two past studies on exercise interventions for men undergoing ADT facilitating comparison to previous results.[48,49]

3.5.3 Functional Assessment of Chronic Illness Therapy

Another subscale of the FACT-G, this 13 item questionnaire is used to measure fatigue levels in various populations with chronic illnesses such as Ca.[119] The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) also uses a Likert scale of 0 to 4. Higher scores represent less fatigue where a change of 3.0 points is considered the minimal clinically important difference.[100] It has a good internal test-rest reliability of 0.87 and a high internal consistency of alpha = 0.95.[119] When tested against other known measures of fatigue, the FACIT-F showed good convergent and discriminant validity.[119]

3.5.4 Hospital Anxiety and Depression Scale

Psychological well-being was measured using this widely-used 14 item scale with 2 subscales: depression and anxiety.[120] The Hospital Anxiety and Depression Scale (HADS) is a Likert scale scored from 0 to 3 with higher scores indicating more distress. The maximum overall score is 42 or subscale scores of 21. Rodgers et al. reported acceptable reliability coefficients among breast Ca survivors for the HADS (0.85), HADS-depression (0.87), and HADS-anxiety (0.79).[121] Walker et al. reported that the HADS has been used extensively in studies involving Ca patients and is considered a

useful screening tool for major depressive disorder.[122] "Significant emotional distress" is suggested to be a total score of 15 or more.[122]

3.5.5 Dyadic Adjustment Scale

Only subjects who have partners were asked to fill out the Dyadic Adjustment Scale (DAS), which is a questionnaire that assesses the quality of adjustment in spousal relationships.[123] The DAS is best used when filled out by both partners[124] therefore the partners of these subjects were asked to complete the DAS-partner (DAS-P) questionnaire. This measure contains 32 items with four subscales: consensus, satisfaction, cohesion, affectional expression.[124] The validity of the DAS has been well-established in many ways because of its frequent use by clinicians and its use in over 1000 research studies.[124] Several studies have measured the internal consistency of the DAS reporting a range of 0.71 – 0.96 for individual subscales and total scores.[124,125]

3.5.6 Godin Leisure-Time Exercise Questionnaire

Activity levels among participants were evaluated using the Godin Leisure-Time Exercise Questionnaire.[126] This brief four-item questionnaire provides an overview of exercise habits for a typical seven day period.[126] Scores can be described individually by exercise intensity (strenuous, moderate, mild) or as a total score called the LSI.[126] The LSI is calculated as 9(# of strenuous sessions) + 5(# of moderate sessions) + 3(# of mild sessions). The last item is used to calculate how often the subjects pursue physical activities that are "long enough to work up a sweat".[126] This questionnaire was chosen to account for potential cross-contamination between the exercise and usual care group participants, which is a common issue reported during exercise trials. Variation from the prescribed levels of PA can significantly alter results leading to inaccurate conclusions. The test – re-test reliability of this questionnaire was reported as 0.48 to 0.94 for the

individual questions and 0.74 for the total score.[126,127] Godin and Shephard found that this questionnaire can be used to correctly classify individuals by body fat and VO_{2max} with activity data 66 – 69% of the time.[126]

3.6 Statistical Analyses and Sample Size Calculation

For a power of 0.80 with an α=0.05, this study required 16 participants in each group (exercise and control) for n = 32. The sample size was calculated using previously reported results for a significant increase in VO_{2max} of 2.7 ± 2.6 mL/kg/min during an exercise intervention for Ca survivors.[36] To account for a potential drop-out rate of 25%, the goal was to recruit 20 participants in each group for n = 40.

Baseline characteristics were compared using univariate analysis of variance for continuous variables (age, height, weight, BMI, length of time on ADT) and χ^2 analyses for categoric variables (marital status, employment status, Ca stage). Descriptive statistics (mean and standard deviation) were calculated. The means for each group were plotted for all outcome measures (section 4.4 and Appendix E). Outcome measures were tested for normality (skewness and kurtosis) and equal variance (Levene's test). Data that were not normally distributed were log transformed. All data were analyzed using a repeated measures analysis of variance to compare the main effect of the intervention (EIG and UCG) over time (baseline, 16 weeks, 24 weeks) on the response variables (VO_{2max}, chest press 1-RM and endurance, leg press 1-RM and endurance, BMI, chest, waist and hip circumferences, SF-36, FACT-G, FACT-P, FACIT-F, HADS, DAS, LSI). When sphericity could not be assumed, the Greenhouse-Geisser correction was used. All tests were two tailed with an α level of 0.05 required for significance. A mixed methods 2 x 3 ANOVA design was chosen to test the effectiveness of the exercise program. This model was chosen because of its ability to test the main effects of group and time and the interaction effects of group by time. In this model, the intervention group is considered an independent factor (EIG or UCG) and time is considered a repeated measure (baseline, 16 weeks, 24 weeks). This type of analysis is useful when examining whether the effects

of treatment exist immediately following the intervention and whether these effects are more long lasting.[128]

Post-hoc, Bonferroni pair-wise comparisons were used to test all significant effects where a p value of less than or equal to $\alpha = 0.05$ was considered significantly different. Cohen's d effect size was calculated for each variable at each time period. Pearson Correlations were also performed. Data analysis was done using SPSS™ V.17 and Minitab™ V.15 statistical packages and Microsoft Excel.

CHAPTER 4
Results

4.1 Participant Flow and Follow-Up

The recruitment period ran from December 2009 to April 2010 (Figure 4.1). We recruited 15 (17%) of 88 eligible participants. Reasons for exclusion were: no longer met the inclusion criteria (n = 12), illness or surgery (n = 9), unable to meet time commitment (n = 5), not wanting to travel to the study site (n = 4), refusal (n = 3), unwilling to pay travel expenses (n = 2), already exercising (n = 1), and unable to complete the study protocol due to physical limitations (n = 1). Complete follow-up data were obtained for 13 (87%) of 15 participants. Two participants in the EIG did not finish the study. One participant sustained an injury at home preventing him from completing the study protocol. The other participant was not assessed at the 16 week period making it impossible to use his data for comparison purposes.

4.2 Participant's Characteristics

Participants' characteristics are presented in Table 4.1. There were no significant differences between groups at baseline. Participant adherence with the exercise program was 89%. Three participants in the UCG reported participating in a regular aerobic exercise program during the study period. Generally they exercised three to five times per week at low to moderate intensity. None reported resistance training.

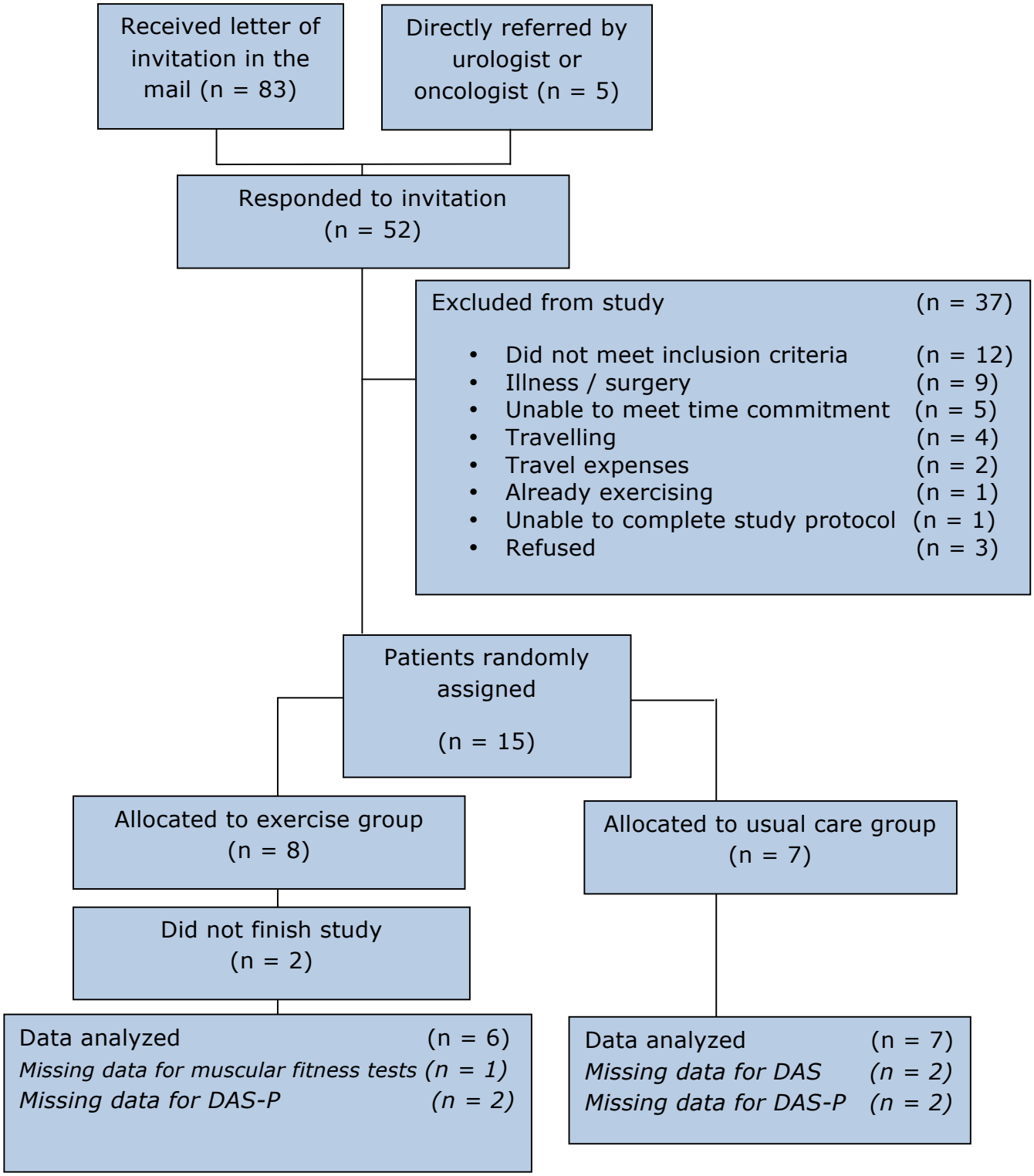

Figure 4.1 CONSORT diagram

Table 4.1: Participant characteristics at baseline

	Exercise n = 6	Usual Care n = 7	Between Group p value
Age (years)	67.3 ± 10.8	73.0 ± 6.5	0.267
Marital status			
Married	6 (100%)	6 (85.7%)	1.000
Divorced	0 (0%)	1 (14.3%)	
Employment status			
Full-time	2 (33.3%)	2 (28.6%)	0.967
Part-time	1 (16.7%)	1 (14.3%)	
Retired	3 (50.0%)	4 (57.1%)	
Height (m)	1.72 ± 0.04	1.74 ± 0.09	0.621
Weight (kg)	90.6 ± 7.76	84.8 ± 13.6	0.384
BMI (kg/m^2)	30.3 ± 2.02	27.3 ± 4.6	0.167
Stage of cancer			
I	1 (16.7%)	0 (0%)	
II	1 (16.7%)	2 (28.6%)	0.331
III	0 (0%)	2 (28.6%)	
IV	4 (66.7%)	3 (42.9%)	
Length of time on ADT (days)	423 ± 429	811 ± 430	0.133
Type of ADT			
Leuprolide	0	3	
Leuprolide + Casodex	2	1	
Goserelin	0	2	Not
Gosereline + Casodex	1	1	assessed
Buserelin	1	0	
Buserelin + Casodex	1	0	
Triptorelin	1	0	

4.3 DESCRIPTIVE STATISTICS AND NORMALITY

Table 4.2 and Table 4.3 show the means, standard deviation, skewness and kurtosis for each of the outcome measures at baseline, 16 weeks, and 24 weeks. Table 4.2 shows results for objective outcome measures while Table 4.3 shows results for subjective outcome measures.

The data for BMI, body fat, muscle mass and SF-36 were normally distributed. The remaining variables were not normally distributed (skewness or kurtosis > ±1.96) and were log transformed for further analysis. The log transformation is most often used to normalize a skewed distribution and equalize variances.[128] This transformation allowed for the use of parametric tests rather than needing to use non-parametric tests.

Table 4.2: Descriptive statistics and normality tests for objective outcome measures

Variable	Group	Baseline				16 Weeks				24 Weeks			
		Mean	*SD*	*Skewness*	*Kurtosis*	*Mean*	*SD*	*Skewness*	*Kurtosis*	*Mean*	*SD*	*Skewness*	*Kurtosis*
Weight (kg)	EIG	90.60	7.76	0.581	-0.423	92.12	6.73	1.139	1.464	90.68	6.46	0.943	0.694
	UCG	84.89	13.59	1.437	3.476	84.70	14.44	1.409	3.383	85.46	15.54	1.658	3.895
BMI (kg/m^2)	EIG	30.32	2.02	0.916	-1.379	30.78	1.56	0.787	-1.858	30.30	1.50	0.817	-1.809
	UCG	27.33	4.55	0.842	0.288	27.89	4.71	0.949	0.763	27.56	5.13	1.056	1.020
Body Fat (%)	EIG	28.83	5.46	-0.083	-1.016	28.68	5.48	-0.720	-0.355	29.38	5.52	-0.617	-0.105
	UCG	28.03	7.25	0.007	-1.333	27.66	6.72	0.093	-1.687	28.20	8.65	0.478	-0.484
Muscle Mass (kg)	EIG	61.3	6.07	-0.368	-1.025	62.50	6.87	-0.196	-1.623	60.93	6.67	-0.265	-1.518
	UCG	57.51	6.96	0.941	-0.873	57.76	7.91	0.702	-1.261	57.54	6.98	0.969	-0.146
Chest Circumference (cm)	EIG	111.58	3.64	0.098	-2.812	111.67	3.63	0.647	0.499	110.17	3.56	1.143	2.184
	UCG	103.64	7.38	0.670	1.665	103.14	6.16	2.171	5.200	102.86	7.66	1.812	4.657
Waist Circumference (cm)	EIG	104.08	4.02	1.677	2.256	106.92	6.01	1.524	2.498	104.08	3.58	0.850	-1.096
	UCG	104.07	10.95	0.933	1.784	103.00	10.74	2.243	5.599	102.57	11.08	1.846	4.696
Hip Circumference (cm)	EIG	106.83	6.15	0.074	0.360	105.92	1.96	-0.381	-0.839	106.33	1.91	-0.131	-2.448
	UCG	105.36	6.59	-1.645	2.979	104.50	4.58	-1.260	2.672	103.86	5.79	-1.097	3.325
VO_2peak (mL/kg/min)	EIG	24.08	4.98	1.865	4.015	28.15	5.00	1.319	0.706	28.42	8.86	1.699	3.100
	UCG	21.00	4.78	0.498	0.120	22.70	4.42	0.482	-1.774	21.87	4.34	0.707	-1.220
Treadmill Time (minutes)	EIG	20.82	2.08	0.530	-0.431	23.76	0.97	-0.343	-1.710	24.14	2.66	-1.432	3.528
	UCG	18.31	3.77	0.085	1.950	20.22	2.55	0.892	1.132	21.06	2.48	0.472	-1.210
HR_{max} (bpm)	EIG	150.83	21.93	-0.251	-0.926	148.17	26.26	-0.713	-0.568	141.17	26.30	-0.726	-1.420
	UCG	130.57	17.62	-1.734	2.717	134.14	15.10	-0.785	0.152	141.29	28.58	-0.698	0.968
Chest Press 1-RM (kg)	EIG	38.50	5.43	0.983	-0.029	44.48	8.10	2.373	5.703	40.74	10.91	1.525	2.541
	UCG	28.09	5.41	0.954	0.901	27.07	4.76	0.992	0.774	24.74	2.87	1.645	2.625
Leg Press 1-RM (kg)	EIG	197.98	41.09	1.294	0.464	262.93	110.27	1.889	3.488	215.06	87.26	1.904	3.703
	UCG	134.61	38.77	-0.721	0.102	141.70	40.82	-0.419	-0.386	132.30	41.48	0.343	-0.228
Chest Press 70% of 1-RM (reps)	EIG	14.17	2.99	0.431	1.166	19.67	6.65	1.574	2.619	16.40	7.16	0.832	-0.306
	UCG	11.14	3.24	-0.385	-1.610	11.29	2.14	-0.517	-0.771	11.43	4.98	1.292	1.901
Leg Press 70% of 1-RM (reps)	EIG	18.00	3.52	-0.495	-1.925	28.50	10.50	0.963	-1.782	20.40	13.24	1.744	3.382
	UCG	18.43	3.55	0.224	-0.889	22.57	12.41	2.363	5.957	17.71	8.30	0.266	-1.539

Table 4.3: Descriptive statistics and normality tests for subjective outcome measures

Variable	Group	Baseline				16 Weeks				24 Weeks			
		Mean	*SD*	*Skewness*	*Kurtosis*	*Mean*	*SD*	*Skewness*	*Kurtosis*	*Mean*	*SD*	*Skewness*	*Kurtosis*
SF-36 Total	EIG	73.67	21.91	-0.970	-0.762	72.00	25.62	-0.642	-1.929	69.00	20.02	-0.355	0.591
	UCG	79.71	7.67	0.409	-1.697	69.71	14.16	-0.158	-0.411	69.71	13.47	0.822	-0.938
FACT-G	EIG	86.28	20.36	-0.816	-1.920	84.68	23.40	-0.863	-1.837	85.12	22.87	-1.139	-0.553
	UCG	94.49	3.69	0.963	-0.894	88.03	10.15	-1.435	1.054	92.26	2.86	-1.826	3.885
FACT-P	EIG	18.82	4.86	-0.551	-1.575	18.45	6.20	-1.180	0.278	18.95	4.71	-1.047	0.608
	UCG	21.57	2.07	0.489	-0.361	19.00	4.00	-1.12	0.091	18.57	4.32	-1.315	3.088
FACIT-F	EIG	21.67	1.51	-1.270	1.531	19.83	4.45	-1.432	1.050	19.67	4.80	-2.292	5.452
	UCG	22.00	2.00	-1.575	2.650	21.14	2.41	-0.832	0.065	21.00	2.16	0.000	-1.200
HADS	EIG	5.67	5.96	1.204	1.010	7.67	8.85	1.258	0.835	6.50	8.38	1.638	2.393
	UCG	3.86	2.79	0.397	-0.607	7.00	5.03	0.296	-0.848	6.43	4.24	-0.012	0.052
DAS	EIG	118.00	15.07	-0.395	-1.455	117.00	21.58	-1.185	1.539	121.50	25.00	-0.724	-0.028
	UCG	111.80	21.09	-1.224	1.639	106.00	22.36	-0.465	-2.995	116.40	17.62	-0.606	-2.717
DAS – Partner	EIG	127.25	9.91	0.437	1.166	122.50	5.69	-1.958	3.871	132.75	13.18	0.212	-2.994
	UCG	119.80	13.77	-0.614	1.556	118.80	18.42	-1.062	-0.450	117.40	14.33	-0.638	-2.679
Godin	EIG	35.92	27.20	1.993	4.276	36.33	21.33	1.036	0.933	41.833	25.63	0.001	-1.595
	UCG	26.86	20.87	0.685	-0.625	31.43	22.76	0.220	-2.183	39.86	20.29	-0.940	-0.829

4.4 MAIN RESULTS

The results of the ANOVA are displayed in Table 4.4. In theory, due to the randomized design of the study, baseline measurements for the two groups should not differ. A main effect of group may suggest that the two groups do not start at the same level. Ideally, to accept the alternative hypotheses of this study, the two groups would start at the same level for a given variable and then the EIG would change more over time showing an interaction.

The effect size is the standardized difference in means.[129] It was measured to observe the magnitude of the observed differences. Cohen defined effect size as the "the degree to which the phenomenon is present in the population" or "the degree to which the null hypothesis is false".[130] Cohen's d effect size was calculated as the mean value of a particular variable for the UCG subtracted from mean for the EIG divided by the pooled standard deviation (Table 4.5). When interpreting the Cohen's d effect size here, $d \geq 0.20$ is a small effect, $d \geq 0.50$ is a moderate effect, and $d \geq 0.80$ is a large effect.[128] Ideally, to accept the alternative hypothesis of this study, the effect size would be small at baseline and large at 16 weeks.

Table 4.4: Mixed model ANOVA results

Variable	GROUP		TIME		GROUP x TIME	
	F	p value	F	p value	F	p value
Weight (kg)	1.211	0.295	0.644	0.483	2.168	0.158
BMI (kg/m^2)	2.218	0.164	0.689	0.513	2.275	0.126
Body Fat (%)	0.074	0.791	0.940	0.406	0.087	0.917
Muscle Mass (kg)	1.063	0.325	3.400	0.052	1.838	0.183
Chest Circumference (cm)	7.060	0.022**	0.898	0.391	0.184	0.750
Waist Circumference (cm)	0.247	0.629	0.892	0.424	1.258	0.304
Hip Circumference (cm)	0.579	0.463	0.327	0.627	0.140	0.772
VO_2peak (mL/kg/min)	3.410	0.092	6.520	0.006**	1.069	0.361
Treadmill Time (minutes)	5.174	0.044**	15.456	0.001**	0.153	0.859
HR_{peak} (bpm)	0.766	0.400	0.022	0.979	2.982	0.071
Resting HR	0.248	0.628	0.042	0.959	5.827	0.009**
Chest Press 1-RM (kg)	22.729	0.001**	4.718	0.021**	3.759	0.041**
Leg Press 1-RM (kg)	7.439	0.021**	9.406	0.001**	3.303	0.058
Chest Press 70% of 1-RM (reps)	6.506	0.029**	2.300	0.126	1.398	0.270
Leg Press 70% of 1-RM (reps)	0.251	0.627	3.185	0.063	0.351	0.708
SF-36	0.025	0.876	4.194	0.029**	1.244	0.308
FACT-G	0.845	0.378	1.676	0.210	0.436	0.652
FACT-P	0.261	0.619	1.863	0.179	1.362	0.277
FACIT-F	0.545	0.476	2.555	0.101	0.547	0.586
HADS	0.064	0.806	1.701	0.206	1.058	0.364
DAS	0.340	0.574	3.201	0.065	0.801	0.464
DAS – Partner	1.090	0.331	1.234	0.321	1.841	0.195
Godin	0.373	0.554	2.396	0.114	1.006	0.382

** significant term ($p < 0.050$); chosen for post-hoc pairwise comparisons

Table 4.5: Cohen's d effect sizes at baseline, 16 weeks, and 24 weeks

Variable	Baseline	16 Weeks	24 Weeks
Weight (kg)	0.505	0.640	0.426
BMI (kg/m^2)	0.824	0.962	0.699
Body Fat (%)	0.124	0.166	0.160
Muscle Mass (kg)	0.576	0.636	0.495
Chest Circumference (cm)	1.328	1.650	1.190
Waist Circumference (cm)	0.001	0.440	0.177
Hip Circumference (cm)	0.231	0.390	0.554
VO_2peak (mL/kg/min)	0.633	1.162	0.965
Treadmill Time (minutes)	0.804	1.770	1.198
HR_{peak} (bpm)	1.029	0.670	-0.004
Resting HR	0.193	-0.898	-0.199
Chest Press 1-RM (kg)	1.921	2.680	2.209
Leg Press 1-RM (kg)	1.591	1.511	1.296
Chest Press 70% of 1-RM (reps)	0.966	1.762	0.837
Leg Press 70% of 1-RM (reps)	-0.121	0.512	0.254
SF-36	-0.382	0.113	-0.043
FACT-G	-0.586	-0.192	-0.459
FACT-P	-0.762	-0.107	0.084
FACIT-F	-0.186	-0.376	-0.369
HADS	0.401	0.095	0.011
DAS	0.345	0.502	0.232
DAS – Partner	0.607	0.257	1.109
Godin	0.383	0.222	0.086

4.4.1 Body Composition

There were no significant differences in the main or interaction effects in most of the body composition variables (weight, BMI, body fat, muscle mass, waist circumference, hip circumference). There was a group difference for chest circumference ($p = 0.022$). This difference existed at baseline ($p = 0.035$), 16 weeks ($p = 0.011$), and 24 weeks ($p = 0.048$). In the EIG, chest circumference increased slightly from 111.6 ± 3.64 at baseline to 111.7 ± 3.63 at 16 weeks and then decreased at 24 weeks to 110.2 ± 3.56. The UCG had chest circumferences of 103.6 ± 7.38, 103.1 ± 6.16 and 102.9 ± 7.66 cm at baseline, 16 weeks, and 24 weeks, respectively. The effects sizes for body fat and hip and waist circumferences were small or negligible. There was a large effect size for chest circumference at every time period. There was a large effect size for BMI at baseline which was even larger at the 16 week mark. This decreased to a moderate effect size at follow-up.

There was no significant difference in muscle mass at baseline. Muscle mass had borderline significance for time effects ($p = 0.052$) (Figure 4.2). This figure clearly demonstrates that there is a distinct difference in the pattern of change between the two groups. For the UCG there is no change in muscle mass, but participants in the EIG increased their muscle mass from baseline to 16 weeks by 1.2 kg. Muscle mass showed a moderate effect size at baseline and 16 weeks. It decreased in the EIG after the completion of the exercise program when the effect size diminished to small.

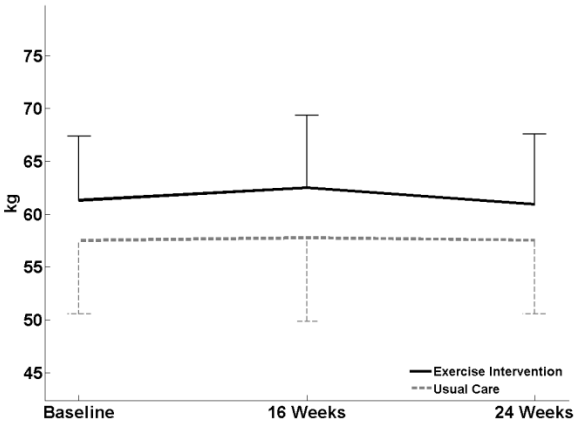

Figure 4.2: Plot of mean muscle mass of both exercise and usual care groups

4.4.2 Cardio-respiratory Fitness

At baseline VO_2peak was comparable between groups. The EIG increased from 24.1 ± 4.98 at baseline to 28.2 ± 5.00 mL/kg/min at 16 weeks while the UCG increased from 21.0 ± 4.78 at baseline to 22.7 ± 4.42 mL/kg/min at 16 weeks. VO_2peak demonstrated significant time effects (p = 0.006)(Figure 4.3). Post hoc analysis showed that this difference occurred between baseline and 16 weeks (p = 0.019). At baseline the difference between the groups achieved a moderate effect size. This increased to a large effect size at 16 and 24 weeks.

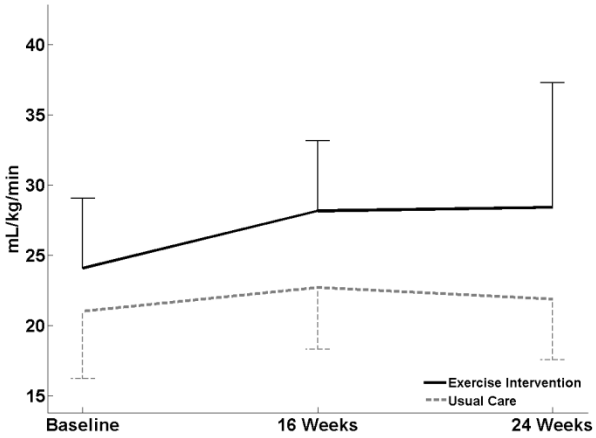

Figure 4.3: Plot of mean VO_2peak of both exercise and usual care groups

Over the study period the EIG had treadmill test times ranging from 20.8 ± 2.08 to 24.1 ± 2.66 minutes while the UCG had times ranging from 18.3 ± 3.77 to 21.1 ± 2.48 minutes. Figure 4.4 illustrates that the main effects of treadmill time were significant. There was a between group difference (p = 0.044) and difference over time (p < 0.001). At baseline there were no significant differences in treadmill time. The group differences existed at the 16 week mark (p = 0.009). Significant time changes occurred between baseline and 16 weeks (p = 0.004) and baseline and 24 weeks (p = 0.002). The treadmill test duration has a large effect size at baseline which was even greater and 16 and 24 weeks. There were no interaction effects for VO_2peak or treadmill test time.

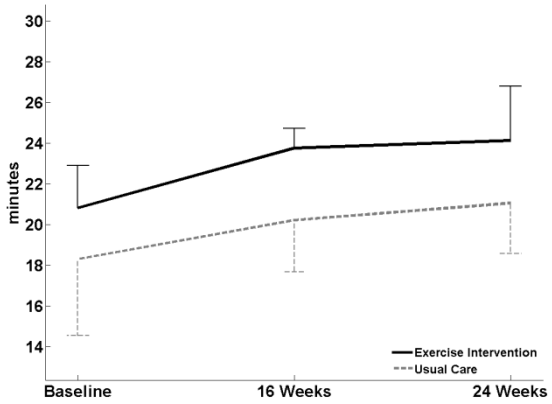

Figure 4.4: Plot of mean treadmill time of both exercise and usual care groups

Resting HR was significant for interaction effects ($p = 0.009$) (Figure 4.5). In the EIG the resting HR decreased from baseline to 16 weeks, but in the UCG the opposite occurred. This indicates that there was a training effect among the EIG. Also, for resting HR the effect size was small at baseline, large at 16 weeks and returned to small at 24 weeks. Peak HR had a large effect size at baseline which steadily declined over the 24 weeks.

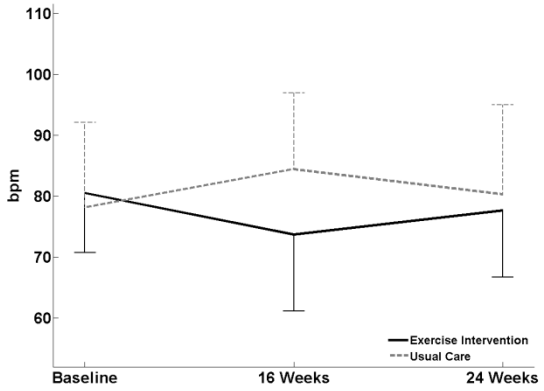

Figure 4.5: Plot of mean resting HR for both exercise and usual care groups

4.4.3 Muscular Fitness

The 1-RM for chest press in the EIG was 38.5 ± 5.43 kg at baseline and increased to 44.5 ± 8.10 kg at the end of the exercise intervention. There was a nonsignificant decrease from 28.1 ± 5.41 kg at baseline to 27.1 ± 4.76 kg at 16 weeks in the UCG. Figure 4.5 clearly demonstrates how the EIG chest press strength peaked post-intervention while the UCG saw a small, but steady decline in chest press strength over the whole study period. The chest press 1-RM, a measure of strength, showed a significant difference in the main effects of group ($p = 0.001$) and time ($p = 0.021$) (Figure 4.6). Groups differences were apparent at baseline ($p = 0.005$), 16 weeks ($p < 0.001$), and 24 weeks ($p = 0.001$). The difference in time existed between 16 weeks and 24 weeks ($p = 0.017$), where both groups experienced a significant decrease in the chest press 1-RM. The chest press 1-RM also showed significant interaction effects ($p = 0.041$). The interaction was a difference between groups from baseline to 16 weeks ($p = 0.016$) indicating that there was a treatment effect. For the chest press strength, the 16 week effect size was much larger than baseline and declined at follow-up.

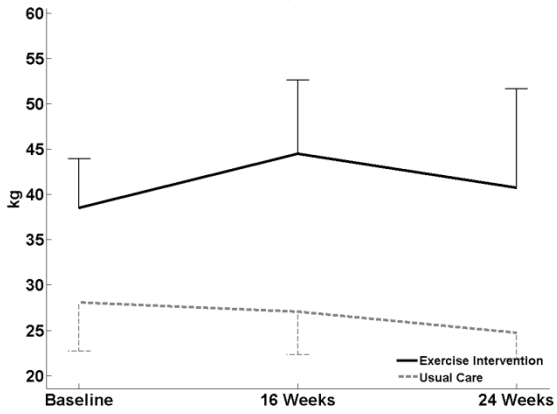

Figure 4.6: Plot of mean chest press strength for both exercise and usual care groups

Men in the EIG recorded 1-RM leg press values of between 198.0 ± 41.1 kg at baseline to 262.9 ± 110.3 kg at 16 weeks while the UCG recorded values of 134.6 ± 38.8 kg at baseline to 141.7 ± 40.8 kg at 16 weeks. There were also significant main effects of group ($p = 0.021$) and time (0.001) for the leg press 1-RM. At baseline, the group

difference was significant (p = 0.023) and this continued at the 16 week (p = 0.008) and 24 week marks (p = 0.036). Post hoc analysis showed that significant differences in time existed between baseline and 16 weeks (p = 0.016) and 16 weeks and 24 weeks (p = 0.005). The interaction effect was approaching significance for the leg press 1-RM (p = 0.058) (Figure 4.7). There was a large effect for leg press strength across all time periods.

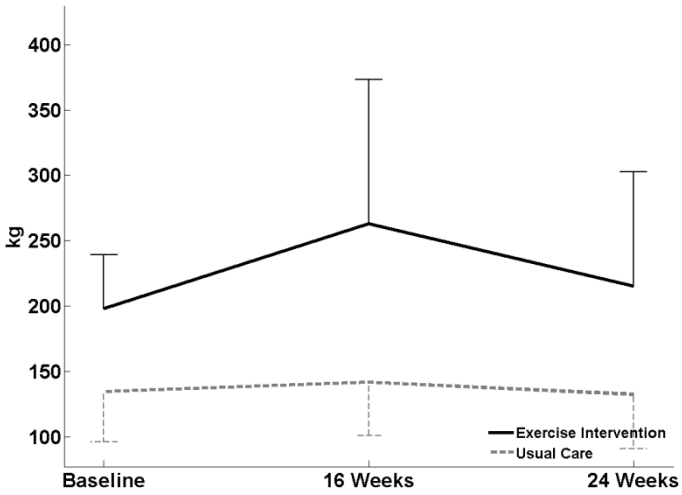

Figure 4.7: Plot of mean leg press strength for both exercise and usual care groups

Muscular endurance was measured as the number of repetitions completed at 70% of their baseline 1-RM value (Appendix E). The EIG recorded 14.2 ± 2.99 repetitions at baseline in the chest press endurance test. This increased to 19.7 ± 6.65 repetitions at 16 weeks, and then decreased at 24 weeks to 16.4 ± 7.16 repetitions. The UCG recorded values of 11.1 ± 3.24 repetitions at baseline, 11.3 ± 2.14 repetitions at 16 weeks, and 11.4 ± 4.98 repetitions at 24 weeks. There was a significant group effect for chest press endurance (p = 0.029). This difference was not significant at baseline or at 24 weeks, but was significant at 16 weeks (p = 0.003). The effect size was large at baseline, even larger at 16 weeks and then decreased at 24 weeks.

In the leg press endurance test men the EIG recorded 18.0 ± 3.52 repetitions at baseline, 28.5 ± 10.5 repetitions at 16 weeks, and 20.4 ± 13.24 repetitions at 24 weeks. The UCG groups recorded values of 18.4 ± 3.55 repetitions at baseline, 22.6 ± 12.41 repetitions at 16 weeks, and 17.7 ± 8.30 repetitions at 24 weeks. There were no main or interaction effects for leg press endurance. The effect size at baseline was negligible and this increased to a moderate effect size at 16 weeks which then decreased to a small effect size at 24 weeks.

4.4.4 Quality of Life

At baseline the EIG recorded a score of 73.7 ± 21.91 on the SF-36 which declined to 72.0 ± 25.62 at 16 weeks. This group saw a further decline to 69.0 ± 20.0 at 24 weeks. The UCG started at a higher QOL score of 79.7 ± 7.67 which decreased to 69.7 ± 14.16 at 16 weeks and remained at this level at 24 weeks. There was a significant effect of time for the SF-36 ($p = 0.029$) (Figure 4.8). This difference existed from baseline to 16 weeks ($p = 0.044$) but had disappeared by 24 weeks. Both groups reported a decline in QOL from baseline to 16 weeks with the UCG reporting a larger drop. The effect size for these changes was small to nonexistent for the SF-36 over the study period.

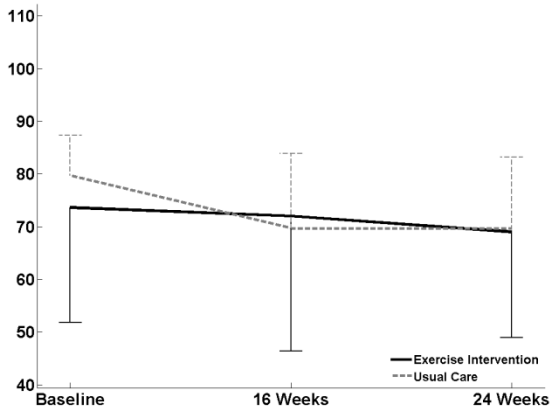

Figure 4.8: Plot of mean SF-36 scores for both exercise and usual care groups

This study also looked at cancer-specific QOL and PCa-specific QOL using the FACT-G and the FACT-P, respectively. Men in the EIG reported lower scores on the FACT-G at baseline of 86.3 ± 20.36, which declined at 16 weeks slightly to 84.7 ± 23.40 and remained similar at 24 weeks at 85.1 ± 22.87. Conversely, the UCG reported a large decline in QOL from baseline (94.4 ± 3.69) to 16 weeks (88.0 ± 10.15) followed by an increase at the 24 week mark (92.3 ± 2.86). For the FACT-P, men in the EIG reported similar scores across the study period while the men in the UCG reported a steady decline from 21.6 ± 2.07 to 18.6 ± 4.32 in PCa-specific QOL from baseline to 24 weeks. There were no significant differences in the main or interaction effects when responses on these questionnaires were considered (Appendix E). None of these changes are considered clinically meaningful as a change of less than five points in not considered significant in the FACT.[100] All measures of QOL including the SF-36, FACT-G, and FACT-P showed a decline in effect size at the 16 week period compared to baseline.

4.4.5 Fatigue

Fatigue was measured using the FACIT-F. A lower score on this questionnaire indicates increased fatigue. Although fatigue increased in both groups from baseline to 24 weeks, the EIG experienced a larger increase from baseline to 16 weeks. The EIG reported scores of 21.7 ± 1.51, 19.8 ± 4.45, and 19.7 ± 4.80 at baseline, 16 weeks, and 24 weeks, respectively. The UCG reported scores at the same time points of 22.0 ± 2.00, 21.1 ± 2.41, and 21.0 ± 2.16. There were no significant differences in the main or interaction effects for this parameter (Appendix E). These changes are not considered clinically meaningful since they are less than three points on the FACIT-F.[100] Based on the effect size, there was no difference in fatigue between the two groups at baseline. At 16 and 24 weeks the effect size increased to small.

4.4.6 Mood

There were no significant differences in the main or interaction effects for the HADS, a measure of mood (Appendix E). However both groups reported higher levels of anxiety and depression at the 16 weeks period compared to baseline. The EIG increased from 5.7 ± 5.96 to 7.7 ± 8.85 while the UCG increased from 3.9 ± 2.79 to 7.0 ± 5.03. These increases were slightly reduced at 24 weeks. The effect size of the HADS was small at baseline and steadily declined to no effect over the 16 and 24 weeks.

4.4.7 Partner Relationships

There were no significant differences in main or interaction effects for the DAS, a measure of partner relationships (Appendix E). Men in the EIG recorded scores of 118.0 ± 15.07 at baseline which decreased slightly to 117.0 ± 21.58 at 16 weeks. The DAS score then increased to 121.5 ± 25.00 at 24 weeks. Men in the UCG recorded scores of 111.8 ± 21.09, 106.0 ± 22.36, and 116.4 ± 17.62 at baseline, 16 weeks, and 24 weeks respectively. The DAS-partner scores for the UCG steadily declined from baseline to 24 weeks. Scores for the EIG decreased from baseline to 16 weeks and then increased to values larger than baseline by 24 weeks.

The effect size for the DAS increased from a small effect at baseline to a moderate effect at 16 weeks. The effect size of the DAS-partner was moderate at baseline, decreased to a small effect size at 16 weeks and increased again to a large effect size at 24 weeks.

4.4.8 Exercise Behaviour

There were no significant differences in the main or interaction effects for the Godin Leisure-Time Exercise Questionnaire, which measures leisure time exercise behaviour. Both groups reported a progressive increase in exercise over the 24 week period. The EIG reported scores of 35.9 ± 27.20 at baseline, 36.3 ± 21.33 at 16 weeks,

and 41.8 ± 25.6 at 24 weeks while the UCG reported scores of 26.9 ± 20.87 at baseline, 31.4 ± 22.8 at 16 weeks, and 39.9 ± 20.29 at 24 weeks. The Godin had a small effect size at baseline and 16 weeks and decreased to no effect size at 24 weeks.

4.5 PEARSON CORRELATIONS

The Pearson product-moment coefficient of correlation is the most commonly reported measure of correlation.[128] The objective of using correlation analysis is to understand the strength and nature of the relationship between two variables.[129] The relationship is positive if one variable increases as the other increases.[129] The relationship is negative or inverse if one variable increases as the other decreases.[129]

All Pearson Correlations are displayed in Appendix F. In this section, only statically significant results that are also clinically meaningful will be presented. Age was correlated with most of the objective outcome measures including BMI ($r = -0.505$; $p = 0.001$), chest circumference ($r = -0.375$; $p = 0.019$), waist circumference ($r = -0.442$; $p = 0.005$), treadmill time ($r = -0.383$, $p = 0.016$), HR_{peak} ($r = -0.360$, $p = 0.024$), VO_2peak ($r = -0.590$; $p = 0.000$), chest press strength ($r = -0.554$; $p = 0.000$), leg press strength ($r = -0.535$; $p = 0.001$), chest press endurance ($r = -0.372$; $p = 0.021$), and leg press endurance ($r = -0.419$; $p = 0.009$). Days on ADT was correlated with muscle mass ($r = -0.491$; $p = 0.002$) and chest press strength ($r = -0.394$; $p = 0.014$). The measures of muscular fitness (strength and endurance) were correlated with several measures of CV fitness. Chest press strength was correlated with treadmill time ($r = 0.475$; $p = 0.003$), HR_{peak} ($r = 0.407$; 0.011) and VO_2peak ($r = 0.602$; $p = 0.000$). Leg press strength was correlated with treadmill time ($r = 0.500$; $p = 0.001$), HR_{peak} ($r = 0.497$; $p = 0.001$) and VO_2peak ($r = 0.627$; $p = 0.000$). Chest press endurance was correlated with treadmill time ($r = 0.543$; $p = 0.000$), HR_{peak} ($r = 0.392$; $p = 0.015$) and VO_2peak ($r = 0.675$; $p = 0.000$). Leg press endurance was correlated with treadmill time ($r = 0.389$; $p = 0.016$) and VO_2peak ($r = 0.534$; $p = 0.001$). As expected several subjective measures correlated with global and cancer-specific QOL. The SF-36 was correlated with fatigue ($r = 0.760$;

$p < 0.001$), mood ($r = -0.902$; $p < 0.001$), marital adjustment ($r = 0.571$; $p = 0.001$), marital adjustment – partner's perspective ($r = 0.386$; $p = 0.047$), and exercise behaviour ($r = -0.390$; $p = 0.014$). The FACT-G was correlated with fatigue ($r = 0.722$; $p < 0.001$), mood ($r = -0.844$; $p < 0.001$), marital adjustment ($r = 0.409$; $p = 0.018$), and exercise behaviour ($r = -0.485$; $p = 0.002$). Mood was correlated with fatigue ($r = -0.839$; $p < 0.001$). Marital adjustment was correlated with fatigue ($r = 0.513$; $p = 0.002$) and mood ($r = -0.691$; $p < 0.001$). Interestingly marital adjustment from the partner's perspective was not significantly correlated with fatigue, but was correlated with mood ($r = -0.571$; $p = 0.002$).

4.6 Power Calculation

Power was calculated using the reported results for the VO_2peak variable. This study had a power of 0.22 to detect a change of 2.7 mL/kg/min.

CHAPTER 5
Discussion

Androgen deprivation can be detrimental to a man's physical and mental health and QOL. Some of the adverse effects of ADT have been ameliorated with resistance exercise,[48-50] aerobic exercise,[49,52] a combination of both,[54] or physical activity programs.[51,53] The purpose of this study was to examine whether a 16 week combined resistance and aerobic exercise program would improve body composition, CV fitness, muscular fitness, and reports of QOL, mood, marital adjustment, and exercise behaviour. This study is unique because it is the first to examine the effectiveness of an exercise program on mood and marital adjustment for men receiving ADT. Also, at the start of this study, there were no studies that had examined the effectiveness of a combined resistance and aerobic exercise program for men receiving ADT. During the course of this study Galvão et al. published work that described a combined intervention for men receiving ADT.[54] Their results were similar to this study in some ways, but differed in others, which will be discussed in this chapter. The results of my study show that exercise has beneficial effects for men receiving ADT including improvements in strength, muscle mass, and possibly cardio-respiratory fitness. Surprisingly this exercise program did not improve body fat, QOL, fatigue, mood, or marital adjustment. This study is important as it will add to the small body of existing literature on exercise and PCa.

5.1 Body Composition

Moderate to high intensity aerobic and resistance exercise are expected to decrease BMI due to weight loss. Conversely a resistance training induced increase in muscle mass could lead to a healthy increase in BMI. For a number of years exercise-based cardiac rehabilitation has demonstrated that exercise at an appropriate intensity leads to weight loss and lower body mass index.[131] Similar effects have been demonstrated in women with breast Ca.[132] However, in the present study no significant

differences were found in the measures of weight, BMI, or body fat. This finding was similar to that reported in all other exercise intervention studies for men on ADT that reported body composition findings.[48-51,53,54]

The relationship between body fat, weight and testosterone is complicated. After beginning ADT men have been reported to gain as much as 9.4 – 13.8% in body fat in as little as 36 weeks.[65, 66] These studies assumed no increase in caloric intake occurred. Testosterone, which is suppressed in men on ADT, is a fat-reducing hormone.[5] A primary role of testosterone is to normalize the lipolytic response, which refers to the breakdown of triglycerides (TG) into free fatty acids (FFA) and glycerol. This lypolytic response, which is normally activated by catecholamines, is decreased when hypogonadism is present. Testosterone encourages lypolysis by increasing the number of lipolytic β3-adrenergic receptors, adenylate cyclase, and protein-kinase A (PKA).[5] It also inhibits the expression of β2-adrenergic receptors and hormone-sensitive lipase (HSL) activity, which is the final rate limiting step in the hydrolysis of triglycerides into fatty free acids (Figure 5.1).[4] Interestingly, the lypolytic activity of testosterone is only observed in subcutaneous fat, not visceral fat.[4] This is perhaps why many men on ADT complain of increased subcutaneous fat around the abdomen, commonly known as the "positive Lupron sign". Another avenue by which testosterone may affect body fat is through inhibition of leptin production in both types of fat.[4] Leptin is a marker of adipose tissue accumulation.[133] Since it has been shown that leptin and free testosterone levels have a strong negative association, it can be assumed that testosterone plays a role in changes in body fat.[134]

Testosterone is also responsible for inhibiting the uptake of lipids and the enzyme action of lipoprotein-lipase in adipocytes.[5] In healthy individuals, lipoprotein-lipase is responsible for the hydrolysis of triglyceride-rich lipoproteins in the circulation. This results in free fatty acids being delivered to the adipocytes. This was demonstrated when men who were given supplemental testosterone experienced an inhibition of lipid uptake.[135] Finally, testosterone is able to inhibit mesenchymal cells from differentiating

into adipocyte precursor cells.[5] In conclusion, testosterone is an important determinant of regional fat distribution and metabolism in men (Figure 5.2).[5,135] Given this, hypogonadal men experience changes in metabolism that reduce triglyceride turnover and accumulate body fat.[5] The changes in fat metabolism resulting from testosterone suppression may make it very difficult to affect fat deposition, weight gain, and the increased BMI commonly associated with ADT.

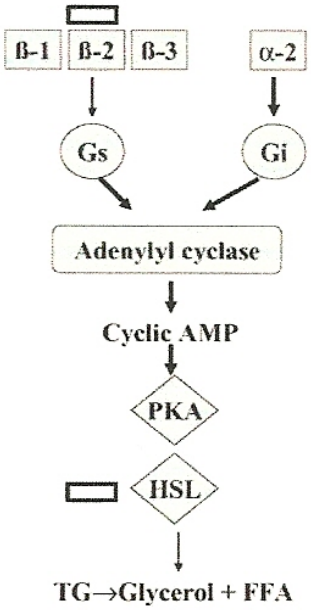

Figure 5.1: Effects of testosterone on catecholamine signal transduction and lyposis in human subcutaneous fat cells. The minus sign (▭) indicates inhibition.[4] PKA, protein kinase A; HSL, hormone-sensitive lipase; TG, triglycerides; FFA, fatty free acids

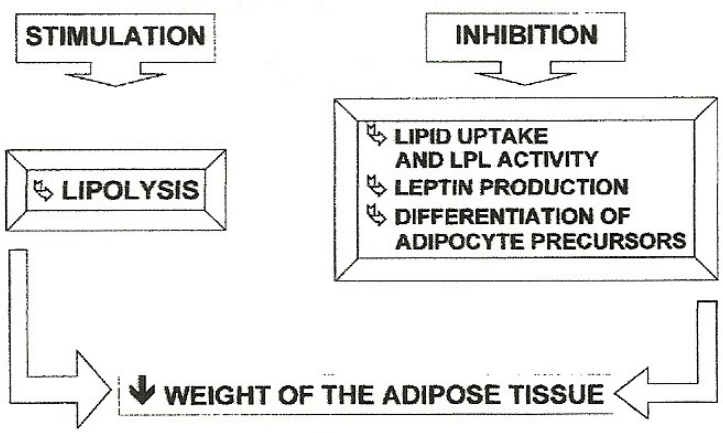

Figure 5.2: Effects of testosterone on male adipose tissue metabolism. [5]

It is important to note that this study did not account for or track caloric intake, which could greatly affect weight loss and body fat results. However, one participant did start a strict low fat, low calorie diet during the intervention period and still only lost 1.8 kg during the 16 weeks exercise program. Hassen et al. were the first to identify the need to evaluate the efficacy of a dietary and PA intervention for PCa patients receiving ADT.[136] Given that exercise alone has been unsuccessful in reducing the weight gain associated with ADT, this research group is now exploring the role caloric intake plays in this problem.[136] The authors have released their study protocol which lists body composition as a primary outcome along with fatigue and QOL. Weight loss is an important issue among men receiving ADT, because of the association of being overweight or obese to an increased risk of CVD, DM, some forms of Ca, and recurrence of Ca.[136]

There was a small increase of 1.2 kg in muscle mass in the EIG from baseline to 16 weeks. The effect size was moderate at baseline at increased slightly at 16 weeks. Although this change was not significant it suggests that men on ADT are able to build muscle despite the catabolic effects of ADT. A study that is appropriately powered might demonstrate a significant difference. Interestingly in my study there was an even greater, but still insignificant, decline (1.57 kg) in muscle mass from 16 weeks to 24 weeks.

These results suggest that the muscle hypertrophy was directly related to the exercise. In healthy subjects, testosterone is anabolic, leading to greater protein synthesis and increased muscle mass.[137] Hypertrophy can be expected after two months of resistance training in healthy individuals,[109] but hypogonadal men may have to train for a longer time to see this same effect.[110] This was first explored in men receiving ADT by Galvão et al. in 2006 who reported an increase of 15.7% in quadriceps thickness with 20 weeks of resistance exercise.[50] Another study by Galvão et al. in 2010 reported a significant increase in lean mass of 0.8 kg ($p = 0.047$) following a 12 week training program that used a similar training regimen as this study.[54] A larger sample size in my study may have yielded statistically positive results similar to those reported by Galvão et al. in 2010.[54]

5.2 Cardio-respiratory Fitness

Both groups demonstrated improvements over time in the measures of cardio-respiratory fitness. The EIG saw a decline in the resting HR which indicates a training effect while the men in the UCG saw an increase in resting HR during the intervention period. The large effect size in the resting HR at the 16 week period also demonstrates that a training effect took place. The EIG started at a higher HR_{peak} which declined over the study period suggesting that they were able to do higher workloads at a lower HR. This implies that they had improved CV fitness. Participants in the UCG showed increasingly elevated HR_{peak} values as the study went on. Furthermore the effect sizes of treadmill time and VO_{2peak} increased significantly from baseline to 16 weeks indicating that the exercise group showed improvements in cardio-respiratory fitness. The ANOVA results, however, suggest that the exercise intervention did not cause a significant difference in treadmill time or VO_{2peak} between the two groups, which was unexpected based on the findings of some exercise intervention studies for men receiving ADT,[50-52] but consistent with others.[49,53,54]

There are a number of factors that could account for the lack of difference. Improvements in both groups could have occurred due to cross-contamination (UCG members reported exercising). Exercise participation in both groups (cross-contamination), as noted by Segal et al.[49], was a contributing factor to their unexpected results and was clearly present in my study as well. The increase in VO_{2peak} for the UCG could be partially explained by the fact that three members of the UCG reported regular aerobic exercise in the form of walking. Generally, people who volunteer for this type of study are positive about exercise and hope they will be assigned to the treatment arm. Current research highlights the importance of exercise in this population so an increase in PA in the motivated UCG is difficult to suppress.

This increase in VO_{2peak} from baseline to 16 weeks to 24 weeks may be due to the learning effect of the graded exercise test itself. The majority of the participants had never completed a graded exercise test prior to this study and they were possibly better prepared for the second and third tests. It may have been helpful to provide a training session to all participants to reduce this effect. There may also have been a competitive aspect to this test. Many of the men in the study wanted to improve their previous time in the graded exercise test.

Furthermore, some participants were not able to achieve the prescribed exercise intensity for a number of reasons including: physical difficulty reaching the desired exercise intensity and the possibility of inaccurate exercise prescription related to the choice of exercise test. It is possible that the men in my study were not exercising at an adequate intensity to experience CV effects. The ability of the participants to complete the exercise program was affected by co-morbidities such as orthopedic or cardiac conditions. Three of the six men in the EIG were on beta-blockers for cardiac conditions making it difficult to properly prescribe and monitor exercise intensity. Beta-blockers work by blocking the effects of adrenaline. When taking this class of drugs, the heart beats more slowly and with less force making it challenging to reach the prescribed training heart rate. All men in the EIG were instructed to use the rate of perceived

exertion scale to judge exercise intensity. While this has been shown to be an accurate estimate of exercise intensity, individuals vary in their ability to use it accurately. Several of the men reported hip, knee, ankle or back pain as reasons for not progressing their intensity or time on the treadmill or stationary bicycle. For example, four of the six participants in the EIG did not progress their intensity to a jogging pace. Two of the six participants did not progress to the protocol maximum of 40 minutes, reaching a maximum of approximately 30 minutes. While the lack of change is disappointing, the difficulties my participants experienced are typical of men in an age group likely to receive ADT.

The lack of difference in CV fitness reported may also be due to the choice of outcome measure. The Modified Bruce protocol with direct measurement of oxygen consumption was chosen as the graded exercise test for this study. Ideally a maximal graded exercise test would be stopped due to fatigue or shortness of breath. Sizeable increases in grade during the test caused pain due to osteoarthritis of the hip or knee and this limited some of the participant's ability to reach their VO_2max. Since exercise prescription was based on these results, intensity may have been underestimated. In addition the Oxycon Mobile system did not function normally for five of the initial exercise tests. In these cases, VO_{2max} was estimated using the test stage.[138] During the test with the Oxycon Mobile some of the men who wore either a mask or a mouthpiece (for those with facial hair) reported discomfort or claustrophobia and stopped the test for this reason. Also, it may have been useful to include a constant workload test to measure CV endurance since it is known that increases in endurance can occur in the absence of increases in VO_{2peak}.

5.3 Muscular Fitness

Chest press strength was the only variable showing a significant treatment effect. This change in strength was expected as men were training at high intensities of between 60-70% of their 1-RM. Several studies have reported improvements in strength at

training intensities comparable to this.[139] Men in the EIG showed a 15.5% increase in the weight they lifted from baseline to 16 weeks. These significant changes were observed even though two participants in the EIG reported shoulder pain during the activity and did not complete the exercise at every session. The effect sizes of the chest press 1-RM supported a training effect. The 16 week effect size was significantly larger than the baseline effect size.

There was no statistically significant change seen in the leg press strength which was surprising given the large increase in the weight lifted in the EIG. The finding was perhaps due to the variability and small sample size. The fact that one person in the EIG could not do this training also affected the results. There was certainly a trend toward a treatment effect with an increase of 64.95 kg or 32.8% from baseline to 16 weeks for the EIG. For this variable, the effect size stayed relatively constant over the study period.

Two previous studies with larger sample sizes have reported substantial increases in both upper and lower extremity strength from an exercise intervention.[49,54] In one study that lasted 24 weeks, men in the resistance exercise group gained a mean of 10.9 kg (22%) in the chest press and 25.6 kg (24.5%) in the leg press.[49] Another study involving 12 weeks of a combined aerobic and resistance exercise program reported a change in chest press strength of 3.8 kg (11%) and in leg press strength of 36.2 kg (36.8%).[54] The resistance exercise program and the results from my study are comparable to these studies suggesting that this exercise program is effective in strengthening men receiving ADT.

Chest and leg press endurance were not significantly different between groups in my study. For the chest press, this lack of difference between groups was likely due to the small sample size. The EIG showed a marked increase of 38.8% from baseline to 16 weeks, followed by a decline from 16 to 24 weeks. On the other hand, the UCG recorded similar scores for all three time periods. This led to a very large effect size at 16 weeks compared to baseline. The lack of difference in the leg press endurance between groups may be attributed to the fact that lower extremity muscle endurance may be more easily

maintained or gained during activities of daily living such as stair climbing. Also, at the 16 week point there was an outlier in the UCG who completed 50 repetitions on the endurance test compared to 20 repetitions at the baseline assessment. A pre-baseline training session may have helped to improve the reliability of the leg press endurance test. It could be argued that had this study been appropriately powered the results may have been more similar to those reported by Galvão et al. who conducted a larger, combined 12 week exercise study.[54] In that study, chest press endurance improved by 46.8% in the exercise group while leg press endurance improved by 68.5%.[54] That being said, a small study involving only 10 participants reported impressive improvements in chest press endurance of 114.9% and leg press endurance of 167.1% after 20 weeks of resistance training.[50] In my study, the lack of difference between groups in muscular endurance may be attributed to the fact that the muscular fitness training was targeted solely on strength training and not endurance.

There were some issues with the weight training equipment which may have affected the accuracy of the results. There was a lack of adaptability for the leg press, particularly for those men with abdominal obesity or hip problems. Also, two of the participants in the EIG surpassed the maximum weight of the leg press during their strength tests. External weights were placed on the multi-gym, but one of the men could have lifted more than could be safely placed on the machine. This too, may have contributed to why my study did not show the same gains in strength as other studies.

5.4 Quality of Life

Although QOL is defined differently across the health-care literature, it is clear that QOL includes all aspects of a person's life and is a multi-dimensional concept.[140] Changes in QOL can be caused by a variety of factors. For Ca survivors, QOL is mainly predicted by fatigue and depression.[141] So et al. found that patients reported a "cluster" of symptoms including mainly fatigue and pain, but also depression and anxiety and this was correlated with negatives changes in QOL.[142] Exercise has been shown to improve

QOL for patients with many types of Ca. Karvinen et al. found that bladder Ca survivors who met public health guidelines for activity (i.e. > 60 minutes of strenuous activity or 150 minutes of moderate activity per week) were more likely to report a higher QOL.[39] The more active participants in this study reported significantly higher overall QOL as well as disease-specific QOL, and improvements in the subdomains of functional well-being, physical well-being, sexual interest, and body image.[39] Results from an exercise intervention study involving colorectal Ca survivors were similar.[143] The authors found that participants who increased their physical fitness over the course of the intervention reported improvements in disease-specific QOL and anxiety.[143]

Quality of life, assessed using the SF-36, steadily declined in both groups over the study period. This finding was surprising given that other studies involving men on ADT have demonstrated that QOL can be enhanced with exercise interventions.[48,49,51,54] Galvão et al. had a similar training program to my study abd found that exercise had significant effects on the general health and vitality components of the SF-36.[54] My study shows that despite a regular exercise program, global QOL declined in men on ADT, but this decline was much smaller than that observed in the UCG. On a positive note, this suggests that exercise may slow the decline in QOL. It has been shown that general health is significantly positively associated with whole lean body mass and closely associated with strength,[54] so the findings of this study are puzzling given that lean body mass and strength increased in the EIG.

Cancer-specific QOL, as measured with the FACT-G questionnaire, did not change over the course of the study period for the men in the EIG. This was an unexpected finding given that Segal et al. found that 24 weeks of resistance exercise improved scores on the FACT-G.[49] In contrast to the EIG, the UCG showed a marked decline from baseline to 16 weeks and then an increase from 16 to 24 weeks. This decline in QOL in the UCG is difficult to explain. It could be that some men were having particularly "bad days" when they filled out their forms at the 16 week period. This again supports the fact that the study was underpowered and a larger sample size might help to

resolve these unexpected findings. Similarly, PCa-specific QOL did not improve with exercise in this study. Segal et al. also found that exercise did not cause significant differences in the FACT-P between the intervention groups.[49] The FACT-P may not have been a sensitive tool to assess exercise-related changes in QOL because it assesses symptoms such as difficulty urinating or trouble moving bowels, which would not be expected to change with exercise.

It can't be ignored that QOL, according to three questionnaires, worsened during the intervention period. One possible reason for a decrease in QOL is disease progression, however given the short intervention period, it is likely not the only factor. In my study, QOL was correlated with mood and fatigue (Appendix F). Perhaps the psychological stress of living with PCa played a role in this observed decline in QOL. This might have been accentuated by the fact they were taking part in a study that focused attention on their cancer.

5.5 Fatigue

Fatigue is one of the most common complaints of Ca survivors.[41] It can be debilitating enough to influence physical performance while inducing feelings of anxiety and depression, which can all negatively affect QOL.[41] Several studies have shown that cancer-related fatigue can be mitigated with exercise or physical activity.[36,37,39,41] Segal et al. used the FACIT-F to show that resistance exercise can improve fatigue in a clinically meaningful way.[48,49] Fatigue did not significantly change in my study. Men in both groups reported slightly more fatigue at 16 and 24 weeks compared to baseline and this increase in fatigue was more pronounced in EIG. This suggests that moderate exercise cannot counteract the effects of ADT in regards to fatigue and may in fact lead to an increase in fatigue. This was somewhat surprising because it has been proposed that exercise causes a reduction in fatigue because of gains in muscle strength and endurance.[50] Perhaps the increases in strength observed in my study was not sufficient to produce improvements in fatigue caused by neuromuscular efficiency.

5.6 Mood

Scores on the HADS show that both groups had increases in depression and/or anxiety from baseline to 16 weeks. This is an important finding as this is the first study to report on the effects of exercise on mood for men on ADT. However, this negative finding must be put in perspective, given that the study was underpowered. The lack of difference between groups demonstrates that this exercise program was not successful in ameliorating mood as it has been shown to do in healthy individuals. This was surprising and brings about the question of whether mood changes in men on ADT are different from healthy individuals who experience improvements in their moods with exercise programs. Perhaps this is a normal response in trying to come to terms with their illness. If this is the case, exercise is not likely to change anything. Time since diagnosis may have played a role in these findings as well. It is also difficult to assess mood at a given time period. Some people may be feeling particularly depressed, anxious, or happy on the day they are filling out the questionnaire, which may not be representative of their overall mood.

5.7 Marital Adjustment

It was hypothesized that exercise-related improved physical function, reduced fatigue, decreased stress, increased independence with tasks, enhanced QOL, better moods, and enhanced sexual activity could improve partner relationships. In this study marital adjustment in the EIG, measured with the DAS, decreased from baseline to 16 weeks and improved to before baseline values at the 24 week mark. One explanation for this finding is that men in the EIG were away from home three days a week and this was interfering with couple activities or home duties. The effect of exercise on partner relationships has never been studied in men receiving ADT. To my knowledge there is only one study that has looked at the effect of an exercise program on marital adjustment.[144] This study involved an eight week pulmonary rehabilitation program with 52 participants.[144] The author found that marital adjustment improved over time and it was associated with psychological well-being, QOL, and functional capacity.[144]

Pulmonary rehabilitation usually results in improved participant independence, which decreases caregiver stress and that could improve marital adjustment. All the men in this study were functionally independent so the same effect may not have come into play. Recently, Zhou et al. concluded that for men with PCa undergoing ADT both mental and physical health are associated with dyadic adjustment for both patients and partners.[145] In the current study, the DAS was correlated with QOL ($p = 0.050$), fatigue ($p = 0.002$), and mood ($p < 0.001$).[145] This is consistent with Galbraith et al. who reported a link between health-related QOL and marital satisfaction in couples living with PCa.[146] Therefore, the lack of improvement in QOL, mood, and fatigue in this study may explain the lack of positive changes in marital adjustment.

Response rate on the DAS also affected the interpretation of this data. Frequently questions about sexual activity were unanswered. Even if the exercise program had improved erectile function, it may not have been captured because the men were too embarrassed or unwilling to answer these questions. This was a small study being run by one person and participants may have felt that they could be identified personally. I would recommend having a second person who does not know the participants to mark and input the questionnaire results and be sure to tell participants this.

5.8 Exercise Behaviour

Both groups reported increases in the Godin Leisure-Time Exercise Questionnaire from baseline to 24 weeks. Because of this exercise intervention the EIG should have reported an increase from baseline to 16 weeks. In this study, the leisure time activity increased from baseline to 16 weeks and further increased at 24 weeks in both groups. These findings may be reflective of the fact that this study was started in the winter months with follow-up occurring in the spring and summer months when people are more active. Participants told me that they found this questionnaire hard to complete. They found it difficult to allot time to certain activities for a given week. An activity journal

describing daily activity or exercise may have been a better way to discern the difference between the two groups, however this can be time consuming for participants.

5.9 Study Limitations

Several limitations existed in this study. The most important was the small sample size which led to this study being underpowered. Recruitment was difficult given that there were a small number of men living in Halifax who fit the inclusion criteria. Two participants in the EIG did not finish the study. This was unfortunate, but comparable to other studies involving men on ADT. Cross-contamination, which is commonly reported in exercise studies involving Ca survivors, also affected this study's results. Some men in the UCG reported walking regularly during the invention period. One of these men reported walking 5 km a day. The timing of the study intervention may have contributed to these findings as well. Most baseline assessments were done in the winter months and follow-up visits happened in the spring or summer when people tend to be more active. At least three men in the UCG reported vigorous work around their houses and/or yard in the weeks leading up to their 16-week visits.

The proposal for this study included laboratory results for cholesterol, triglycerides, PSA, and testosterone. Unfortunately, I was unable to obtain results for all the participants. Some men did not have the requested blood draws and some results were not recorded by lab services. Cardiovascular disease risk is closely related to cholesterol and triglycerides and aerobic and resistance has been shown to affect them. Not having this information limited my ability to assess the effectiveness of this exercise program, particularly the aerobic exercise component. It would also have been helpful to have PSA and testosterone levels to assess whether disease progression was affecting my results, especially for QOL, mood, fatigue, and marital adjustment.

5.10 Clinical Implications

Currently in Canada, men starting on ADT do not receive information about or referral to an exercise program. This study and others have found positive benefits of exercise for men on ADT. Here, it was demonstrated that a combined resistance and aerobic exercise program improves chest press strength and there was a trend toward an increase in leg press strength. This is clinically important as an improvement in strength can lead to functional improvements such as chair sit to rise, stair climbing, or lifting heavy objects. Enhancement of function is crucial in this group of men as many are over age 65 and are already at risk for functional decline. Since ADT is aimed at extending the lives of men with PCa it is especially important for them to remain functional.

Anecdotally, body fat and weight was the primary concern of many of the men in the study. No study to date has reported that exercise reduces body fat or weight in men receiving ADT.[48-51, 53, 54] It is crucial that clinicians are honest with patients about these findings so that patients do not have unrealistic goals for weight loss. For men receiving ADT, the hormone imbalance may outweigh the added caloric expenditure of an exercise program in regards to weight loss. For example, in my study, 77% of all men who participated were classified as overweight (BMI = 25 – 29.9) or obese (BMI > 30) at baseline. Perhaps the more important thing is the association of BMI and waist circumference with CVD, DM, and HTN (Appendix B). According to this table, most of the men in this study were at risk. Eight percent of men were at increased risk for co-morbidities while, 39% and 31% were at high and very high risk, respectively. Finding ways to reduce weight should be seen as an important clinical matter.

Prospective longitudinal studies are needed to examine whether a combination of resistance and aerobic exercise decreases the risk of CVD, HTN, and DM in men receiving ADT. Galvão et al. proposed that exercise can act as a countermeasure to ADT-induced CVD and metabolic problems (Figure 5.3).[6] A ten step approach to promoting general health during ADT was developed by Moyad.[147] He included resistance exercise as an essential factor to improvements or maintenance of health status

for these men.[147] Since aerobic exercise has been shown to improve cardio-respiratory fitness, ideally, men who are starting ADT or already receiving ADT should be prescribed a combined aerobic and resistance exercise program.[1,6]

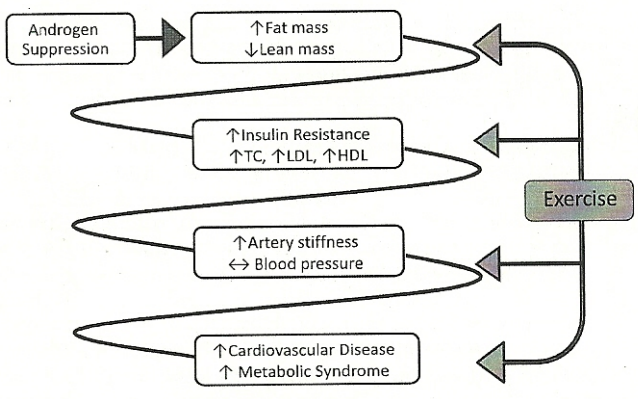

Figure 5.3: Theoretical model of exercise of a countermeasure to ADT-induced cardiovascular- and metabolic-related toxicities. ↑, increase; ↓, decrease; ↔, no change; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein.[6]

The parameters of an ideal exercise program have yet to be determined, but some researchers recommend the program outlined in Table 5.1 for Ca survivors. Many men in the current study could not achieve these recommended intensities. In such cases it could be appropriate for them to see an exercise specialist or physiotherapist prior to starting an exercise program. Assessment and management of conditions such as back, knee, and foot pain will allow for more successful participation in an exercise program. Adjustment of the prescribed exercise program may also be necessary. For example, if orthopedic conditions limit the participant's ability to reach the desired intensity in their aerobic exercise, they may have to exercise for a longer period of time at a lower intensity.

Table 5.1: Recommended exercise guidelines for men receiving ADT.[1, 2]

	Resistance Exercise	Aerobic Exercise
Frequency	2 – 3 times/week	3 – 5 times/week
Intensity	50 – 70% 1-RM	55 – 90% HR_{max}
Type	i.e. weights machine, free weights, elastic bands	i.e. walking, bicycle, swimming, elliptical
Time/Volume	8 – 12 repetitions 1 – 4 sets	15 minutes progress to > 30 minutes

5.11 Conclusions

There is an enormous amount of research supporting exercise as a means of addressing both the effects of Ca and the adverse effects of Ca treatments.[2,148,149] My study showed that a combined resistance and aerobic exercise intervention can lead to improvements in strength, small increases in muscle mass, and possibly increases in cardio-respiratory fitness. Although the majority of the results in this study were not statistically significant, these findings should not be viewed as discouraging. It is also noteworthy to mention that this study reported medium and large effect sizes in some of the outcome measures supporting the effectiveness of this exercise program. As previously mentioned, this study was under powered and a larger sample size would probably have provided a more realistic description of the value of exercise in this patient population. Aerobic exercise is less studied in men with PCa, but I believe it is a valuable addition to resistance training. This was not clearly demonstrated in this study because of the cross-contamination among groups. Cardio-respiratory fitness improved in both groups likely because some men in the UCG reported doing regular aerobic exercise. In conclusion, I recommend that all men on ADT be prescribed a combined resistance and aerobic exercise program to counteract some of the adverse effects of their treatment. At the same time they need to be realistic about the fact that this may not improve their mood, fatigue levels, or lead to weight loss.

5.12 Recommendations for Future Research

Maintaining function in this aging population is important because it will allow these individuals to live independently for longer. Exercise is known to play a crucial role in maintaining function. My study did not look at function, but future studies should.

Cross-contamination made it difficult to assess the study results. To avoid the issue of cross-contamination between groups, which often occurs in exercise studies, it is recommended that future studies examine the effects of different exercise programs rather than having a UCG. For example, combined exercise programs versus resistance exercise alone. If a UCG is used, a detailed activity journal should be kept to enable researchers to clearly see if and what activity differences existed between the groups.

Another topic needing attention is whether a home-based or supervised program is best. In this study, compliance was quite high, but this may not be the case in all populations. Having said that, the most successful trials to date for men on ADT have been supervised programs. One study involving men on ADT that relied on participant's doing their PA at home and involved very little education about PA showed no positive results in the measures of QOL, body composition, endurance, or PA.[150] The possible lesson here is that men receiving ADT require additional assistance or external motivation to increase their PA enough to observe changes in health domains. Research in this area is warranted because no previous study had examined the effectiveness of home-based versus supervised exercise programs for men receiving ADT.

Further research is needed to investigate the effects of exercise in ameliorating the adverse effects of ADT. This is especially true in the areas of mood and relationship adjustment. Another interesting topic of research that was emphasized in this study was the inability of men on ADT to lose weight or body fat. Future studies should explore the mechanisms of testosterone-related lipolysis and how this is affected by ADT so that the role of exercise in facilitating weight loss would be clearer.

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APPENDIX A

Summary of Objective Outcome Measures

Table A.1: Summary of objective outcome measures

OUTCOME OF INTEREST	DEPENDENT VARIABLES		EQUIPMENT
Body Composition	% Body fat Muscle mass	% kg	Bioelectrical impedance analysis
Anthropometric Measurements	Weight Height Body Mass Index Chest/ hip/waist circumference	kg m kg/m^2 cm	Lab scale and tape measures
C/R Fitness	$VO_{2\ max}$	mL/kg/min	Oxycon Mobile ergospirometry & Treadmill
Muscle Strength	Chest press & Leg press Estimated 1-RM test	Kg	Hoist H4400 multi-station gym
Muscle Endurance	Chest press & Leg press # reps at 70% of 1-RM	# of reps	Hoist H4400 multi-station gym
Vital Signs	Resting & Peak Exercise HR Resting & Peak Exercise BP	bpm mmHg	O_2 saturation monitor Manual cuff & stethoscope

APPENDIX B

Classification of disease risk based on BMI and waist circumference

Table B.1: Classification of disease risk based on BM and waist circumference

		DM, HTN, CVD risk relative to normal weight and waist circumference	
Weight Class	**BMI, kg/m^2**	*Men ≤ 102cm* *Women ≤ 88cm*	*Men > 102cm* *Women > 88cm*
Underweight	< 18.5	…	…
Normal	18.5 – 24.9	…	…
Overweight	25.0 – 29.9	Increased	High
Obesity			
Class I	30.0 – 34.9	High	Very high
Class II	35.0 – 39.9	Very high	Very high
Class III	≥ 40	Extremely high	Extremely high

* Adapted from ACSM's Guidelines for Exercise Testing and Prescription, 6th ed. (pg. 64)[3]

APPENDIX C

Steps to muscular fitness testing

Muscle strength (estimating 1RM)

1. Familiarize the subject with the weight equipment and make necessary seat adjustments for the bench and leg press exercises
2. Have the subject perform a light warm-up of 12 repetitions minimal weight and check for proper form during each exercise.
3. Estimate the weight that the subject can lift 5 - 6 times
4. Have the subject perform the chest or leg press exercises until muscle fatigue and momentary failure. Count the number of repetitions completed.
5. If the numbers of repetitions fall within 1 and 10, the following equation can be used to predict 1RM:

   $$1RM = (\text{weight lifted})/[1.0278 - (\text{repetitions} \times 0.0278)]$$ [112]

6. If the number of repetitions exceeds 10, take a 3-5 minute rest and repeat steps #1 – 5. A higher number of repetitions will lead to greater error in estimating 1RM.

Muscle endurance

7. Determine 70% of the 1RM values for the chest and leg press
8. Have the subject perform the exercises until muscle fatigue and momentary failure. Count the number of repetitions completed.

Figure C.1: Steps to muscle strength and endurance testing

APPENDIX D

Summary of Subjective Outcome Measures

Table D.1: Summary of subjective outcome measures

OUTCOME OF INTEREST	QUESTIONNAIRE	SCALE	# QUESTIONS / SUBSCALES
Global QOL	SF-36[113] Short Form Health Survey	Likert	36 Physical Health Composite Mental Health Composite
Cancer-specific QOL	FACT – G[116] Functional Assessment of Cancer Therapy – General	Likert 0 – 4 0 – 108 pts	27 Physical Well-Being (7) Social/Family Well-Being (7) Emotional Well-Being (6) Functional Well-Being (7)
PCa-specific QOL	FACT – Prostate[117] Functional Assessment of Cancer Therapy – Prostate	Likert 0 – 4 0 – 48 pts	13
Fatigue	FACIT – Fatigue[119] Functional Assessment of Chronic Illness Therapy – Fatigue	Likert 0 – 4 0 – 52 pts	13
Mood	HADS[120] Hospital Anxiety and Depression Scale	Likert 0 – 3 0 – 42 pts	14 Depression (7) Anxiety (7)
Marital Adjustment	DAS[123] Dyadic Adjustment Scale	QuikScore Forms 20 – 80 pts	32 Consensus (13) Satisfaction (10) Cohesion (5) Affectional Expression (4)
Physical Activity Level	Godin Leisure-Time Exercise Questionnaire[126]		4

APPENDIX E

Mean Plots

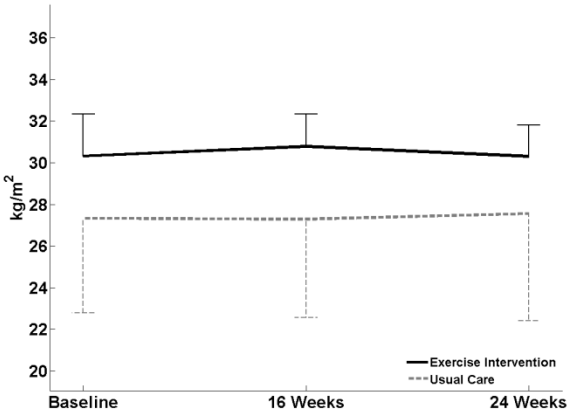

Figure L.1: Plot for mean BMI for both the exercise and usual care groups

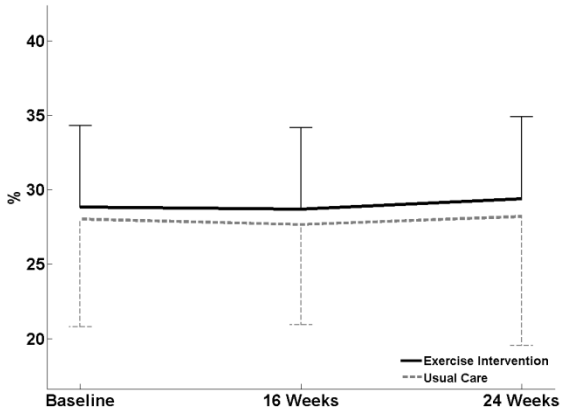

Figure L.2: Plot for mean body fat for both the exercise and usual care groups

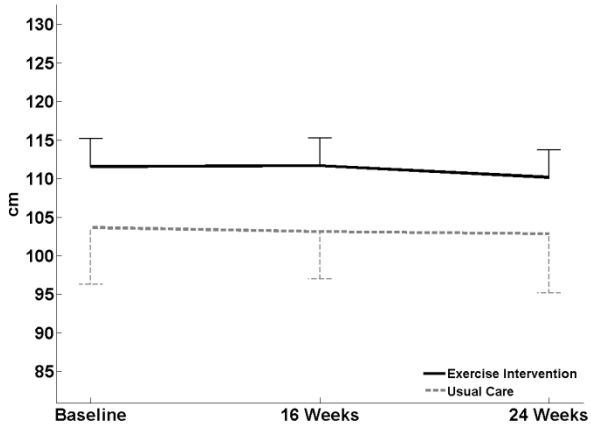

Figure L.3: Plots for mean chest circumference for both exercise and usual care groups

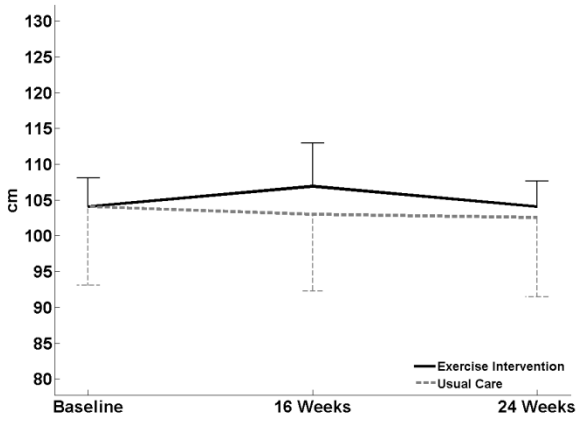

Figure L.4: Plots for mean waist circumference for both exercise and usual care groups

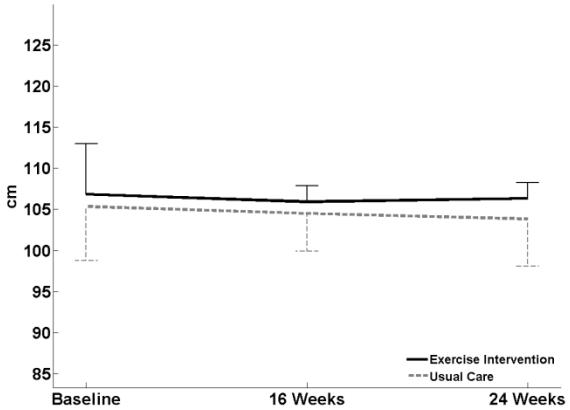

Figure L.5: Plots for mean hip circumference for both exercise and usual care groups

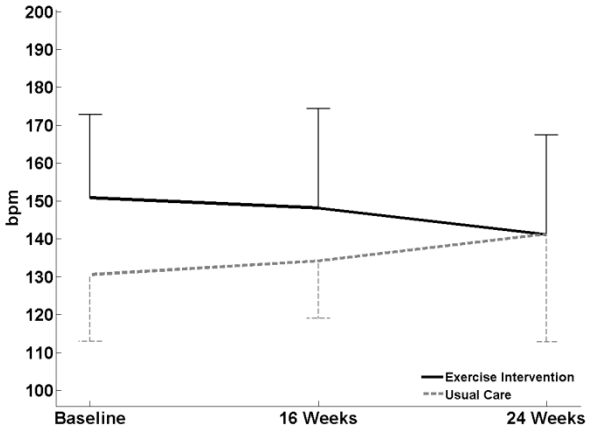

Figure L.6: Plots for mean HR_{peak} for both exercise and usual care groups

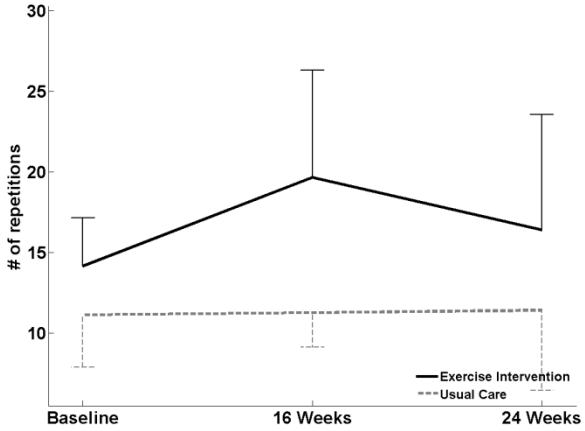

Figure L.7: Plots for mean chest press endurance for both exercise and usual care groups

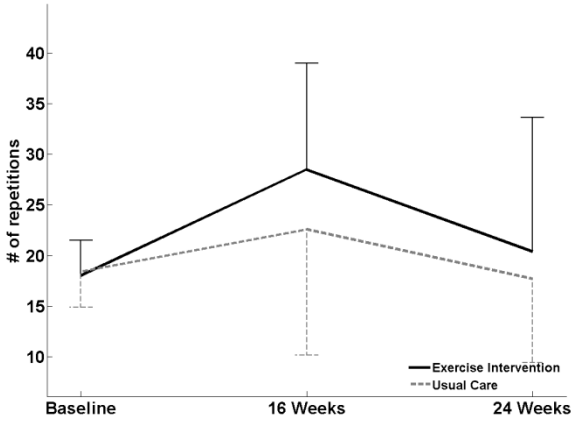

Figure L.8: Plot for mean leg press endurance for both exercise and usual care groups

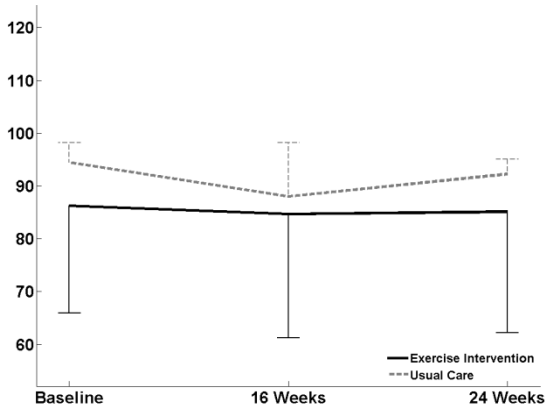

Figure L.9: Plot for the mean FACT-G for both the exercise and usual care groups

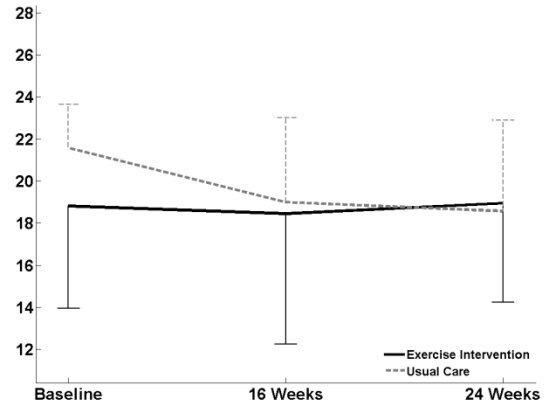

Figure L.10: Plots for the mean FACT-P for both the exercise and usual care groups

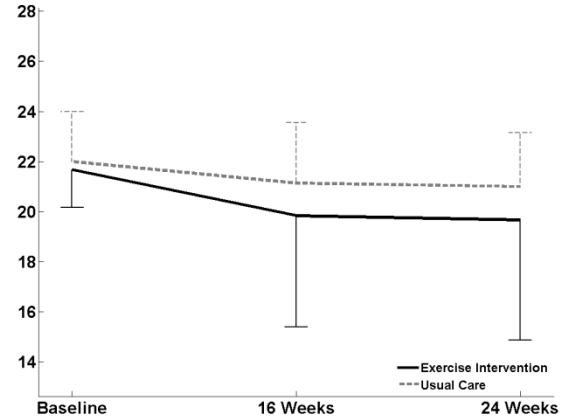

Figure L.11: Plots for the mean FACIT-F for both the exercise and usual care groups

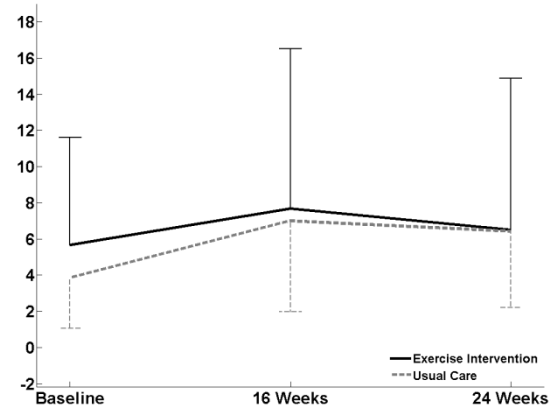

Figure L.12: Plot for the mean HADS for both the exercise and usual care groups

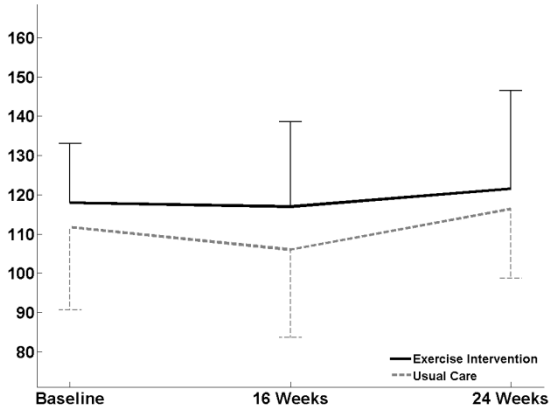

Figure L.13: Plots for the mean DAS for both the exercise and usual care groups

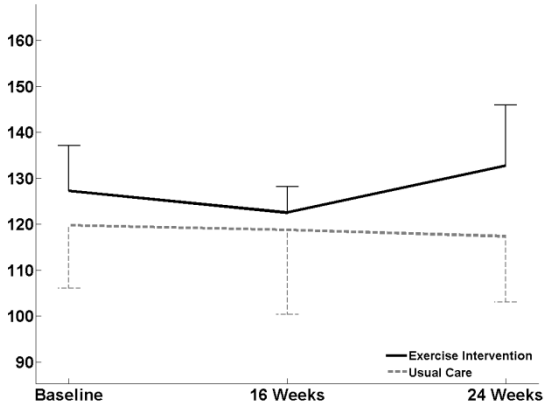

Figure L.14: Plot for the mean DAS-Partner for both the exercise and usual care groups

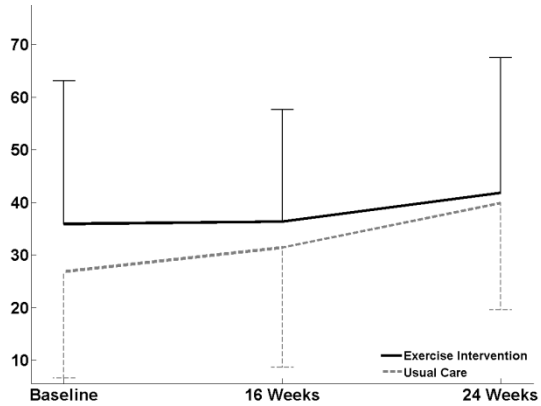

Figure L.15: Plot for the mean Godin Leisure-Time Exercise Questionnaire for both the exercise and usual care groups

APPENDIX F

Pearson Correlations

	AGE	CASTAGE	DAYSADT	HEIGHT	WEIGHT	BMI	BODYFAT	MUSCLEM
CASTAGE	-0.077							
	0.640							
DAYSADT	0.197	0.026						
	0.230	0.874						
HEIGHT	0.100	0.362	-0.248					
	0.546	0.024	0.128					
WEIGHT	-0.422	-0.009	-0.269	0.323				
	0.007	0.957	0.098	0.045				
BMI	-0.505	-0.253	-0.118	-0.313	0.794			
	0.001	0.120	0.474	0.052	0.000			
BODYFAT	-0.232	-0.112	0.263	-0.460	0.488	0.765		
	0.156	0.498	0.106	0.003	0.002	0.000		
MUSCLEM	-0.269	0.079	-0.491	0.715	0.720	0.283	-0.243	
	0.098	0.634	0.002	0.000	0.000	0.081	0.136	
CHESTC	-0.375	0.054	-0.274	0.007	0.842	0.845	0.561	0.512
	0.019	0.746	0.092	0.966	0.000	0.000	0.000	0.001
WAISTC	-0.442	-0.052	-0.197	0.091	0.893	0.824	0.634	0.477
	0.005	0.753	0.230	0.580	0.000	0.000	0.000	0.002
HIPC	0.052	-0.239	-0.019	0.090	0.581	0.526	0.494	0.303
	0.754	0.142	0.907	0.586	0.000	0.001	0.001	0.060
TMTIME	-0.383	-0.074	-0.146	-0.141	0.046	0.177	-0.118	0.153
	0.016	0.656	0.376	0.393	0.781	0.281	0.475	0.353
MaxHR	-0.360	-0.204	-0.474	-0.127	0.182	0.297	0.006	0.181
	0.024	0.212	0.002	0.443	0.269	0.066	0.970	0.269
VO2peak	-0.590	-0.047	-0.199	-0.150	-0.048	0.083	-0.096	0.033
	0.000	0.775	0.223	0.362	0.772	0.617	0.559	0.840
1RMCHST	-0.554	-0.251	-0.394	-0.246	0.464	0.642	0.378	0.246
	0.000	0.129	0.014	0.137	0.003	0.000	0.019	0.136
1RMLEG	-0.535	-0.256	-0.231	-0.331	0.382	0.609	0.364	0.144
	0.001	0.121	0.164	0.042	0.018	0.000	0.025	0.388
ENDCHST	-0.372	0.088	-0.159	-0.122	0.139	0.231	0.061	0.123
	0.021	0.601	0.341	0.467	0.404	0.163	0.716	0.462
ENDLEG	-0.419	0.071	-0.171	0.332	0.309	0.109	-0.064	0.383
	0.009	0.671	0.304	0.042	0.059	0.516	0.700	0.018
SF36PHY	-0.114	-0.182	-0.302	0.142	-0.001	-0.086	0.047	-0.044
	0.488	0.267	0.062	0.387	0.997	0.605	0.778	0.789
SF36MEN	0.054	-0.177	-0.131	0.153	-0.161	-0.262	-0.007	-0.195

	0.744	0.281	0.428	0.351	0.327	0.107	0.968	0.234
SF36TOT	-0.056	-0.163	-0.229	0.120	-0.047	-0.125	0.086	-0.137
	0.737	0.321	0.161	0.467	0.775	0.449	0.601	0.407
FACTG	0.038	-0.375	-0.032	-0.137	-0.263	-0.185	0.044	-0.346
	0.818	0.019	0.849	0.405	0.106	0.260	0.792	0.031
FACTPWB	-0.011	-0.328	-0.065	-0.152	-0.216	-0.132	0.097	-0.347
	0.948	0.041	0.693	0.356	0.187	0.423	0.555	0.030
FACTSWB	-0.003	-0.463	0.226	-0.606	-0.288	0.086	0.301	-0.558
	0.988	0.003	0.167	0.000	0.075	0.602	0.062	0.000
FACTEWB	0.224	-0.340	-0.062	0.038	-0.104	-0.138	0.161	-0.256
	0.170	0.034	0.708	0.816	0.530	0.401	0.329	0.116
FACTFWB	-0.043	-0.187	-0.131	0.128	-0.256	-0.336	-0.269	-0.088
	0.794	0.255	0.426	0.436	0.116	0.037	0.097	0.596
FACTPC	-0.024	-0.178	0.028	-0.049	-0.292	-0.255	-0.086	-0.261
	0.883	0.279	0.866	0.767	0.071	0.117	0.605	0.109
FACITF	0.000	-0.106	-0.209	0.106	-0.099	-0.164	-0.060	-0.096
	0.999	0.521	0.202	0.520	0.547	0.319	0.718	0.562
HADSTO	-0.101	0.322	0.275	-0.107	0.100	0.167	0.019	0.117
	0.543	0.045	0.091	0.516	0.547	0.309	0.907	0.479
HADSA	-0.080	0.373	0.261	-0.124	0.048	0.121	0.006	0.068
	0.630	0.019	0.109	0.451	0.772	0.464	0.971	0.682
HADSD	-0.120	0.233	0.272	-0.078	0.158	0.213	0.035	0.171
	0.468	0.153	0.094	0.639	0.337	0.192	0.832	0.299
GODIN	-0.178	0.252	0.232	0.272	0.009	-0.124	-0.269	0.241
	0.277	0.121	0.155	0.094	0.955	0.453	0.098	0.139
DAS	0.205	-0.089	-0.302	0.023	-0.059	-0.094	0.117	-0.200
	0.254	0.621	0.087	0.898	0.743	0.603	0.515	0.264
DAS-P	0.146	-0.029	-0.254	0.294	0.069	-0.052	0.087	-0.014
	0.468	0.886	0.201	0.137	0.732	0.796	0.665	0.945

	CHESTC	WAISTC	HIPC	TMTIME	MaxHR	VO2peak	1RMCHST	1RMLEG
WAISTC	0.781							
	0.000							
HIPC	0.579	0.573						
	0.000	0.000						
TMTIME	0.133	-0.025	-0.070					
	0.419	0.881	0.674					
MaxHR	0.141	0.163	0.034	0.488				
	0.393	0.321	0.838	0.002				
VO2peak	0.008	-0.111	-0.097	0.763	0.492			
	0.960	0.502	0.556	0.000	0.001			
1RMCHST	0.615	0.390	0.333	0.475	0.407	0.602		

	0.000	0.015	0.041	0.003	0.011	0.000		
1RMLEG	0.477	0.295	0.159	0.500	0.497	0.627	0.874	
	0.002	0.073	0.341	0.001	0.001	0.000	0.000	
ENDCHST	0.222	-0.008	-0.004	0.543	0.392	0.675	0.694	0.804
	0.180	0.960	0.981	0.000	0.015	0.000	0.000	0.000
ENDLEG	0.139	0.179	-0.054	0.389	0.231	0.534	0.398	0.477
	0.406	0.281	0.749	0.016	0.164	0.001	0.013	0.002
SF36PHY	-0.100	0.023	0.211	0.145	0.260	0.334	0.332	0.163
	0.544	0.890	0.198	0.379	0.110	0.037	0.042	0.327
SF36MEN	-0.273	-0.110	0.104	0.022	0.070	0.206	0.107	-0.041
	0.093	0.506	0.529	0.892	0.672	0.208	0.521	0.809
SF36TOT	-0.143	0.010	0.180	0.062	0.172	0.248	0.248	0.071
	0.386	0.954	0.274	0.708	0.295	0.128	0.134	0.673
FACTG	-0.347	-0.118	0.074	0.102	0.048	0.167	0.075	-0.057
	0.030	0.476	0.655	0.538	0.770	0.310	0.656	0.733
FACTPWB	-0.312	-0.066	0.054	0.084	0.087	0.154	0.083	-0.051
	0.053	0.692	0.746	0.611	0.598	0.350	0.620	0.762
FACTSWB	-0.146	-0.058	0.076	0.061	-0.169	0.021	0.113	0.067
	0.376	0.728	0.645	0.710	0.304	0.901	0.501	0.690
FACTEWB	-0.279	0.002	0.217	-0.118	0.056	-0.036	0.013	-0.136
	0.085	0.989	0.185	0.474	0.733	0.828	0.940	0.417
FACTFWB	-0.368	-0.219	-0.046	0.242	0.128	0.323	0.041	-0.063
	0.021	0.180	0.783	0.138	0.439	0.045	0.809	0.707
FACTPC	-0.306	-0.187	0.009	0.155	0.145	0.235	0.092	-0.063
	0.058	0.256	0.955	0.345	0.378	0.150	0.584	0.708
FACITF	-0.237	-0.073	0.037	0.200	0.385	0.210	0.070	0.008
	0.145	0.660	0.821	0.223	0.016	0.200	0.675	0.964
HADSTO	0.222	0.078	-0.116	-0.091	-0.223	-0.141	-0.165	-0.017
	0.174	0.636	0.483	0.580	0.172	0.391	0.321	0.920
HADSA	0.167	0.044	-0.153	-0.106	-0.212	-0.135	-0.186	-0.038
	0.311	0.791	0.352	0.521	0.195	0.414	0.263	0.820
HADSD	0.276	0.116	-0.059	-0.066	-0.221	-0.139	-0.122	0.014
	0.089	0.481	0.720	0.690	0.176	0.398	0.465	0.931
GODIN	-0.030	-0.206	-0.238	0.217	0.044	0.259	-0.071	0.030
	0.857	0.208	0.145	0.184	0.792	0.112	0.670	0.857
DAS	0.003	-0.131	0.010	0.073	0.109	0.127	0.283	0.247
	0.986	0.468	0.955	0.685	0.547	0.481	0.116	0.173
DAS-P	0.171	-0.049	-0.031	-0.078	-0.273	-0.010	0.222	0.128
	0.395	0.809	0.877	0.700	0.168	0.959	0.267	0.524

	ENDCHST	ENDLEG	SF36PHY	SF36MEN	SF36TOT	FACTG	FACTPWB	FACTSWB
ENDLEG	0.482							
	0.002							
SF36PHY	0.158	0.305						
	0.344	0.063						
SF36MEN	0.027	0.211	0.908					
	0.872	0.204	0.000					
SF36TOT	0.086	0.240	0.976	0.966				
	0.606	0.146	0.000	0.000				
FACTG	-0.065	-0.042	0.798	0.836	0.835			
	0.699	0.801	0.000	0.000	0.000			
FACTPWB	-0.049	-0.046	0.792	0.827	0.832	0.953		
	0.772	0.782	0.000	0.000	0.000	0.000		
FACTSWB	-0.117	-0.290	0.250	0.330	0.309	0.605	0.526	
	0.486	0.078	0.124	0.040	0.056	0.000	0.001	
FACTEWB	-0.159	-0.009	0.791	0.824	0.835	0.865	0.822	0.377
	0.340	0.956	0.000	0.000	0.000	0.000	0.000	0.018
FACTFWB	0.058	0.140	0.741	0.737	0.736	0.860	0.774	0.255
	0.729	0.403	0.000	0.000	0.000	0.000	0.000	0.117
FACTPC	0.047	-0.032	0.657	0.717	0.702	0.752	0.730	0.401
	0.777	0.847	0.000	0.000	0.000	0.000	0.000	0.011
FACITF	0.124	0.124	0.749	0.732	0.760	0.722	0.779	0.118
	0.460	0.460	0.000	0.000	0.000	0.000	0.000	0.473
HADSTO	0.020	-0.095	-0.875	-0.895	-0.902	-0.844	-0.843	-0.308
	0.904	0.569	0.000	0.000	0.000	0.000	0.000	0.056
HADSA	0.014	-0.103	-0.850	-0.881	-0.879	-0.818	-0.814	-0.347
	0.931	0.540	0.000	0.000	0.000	0.000	0.000	0.031
HADSD	0.027	-0.077	-0.841	-0.845	-0.863	-0.813	-0.815	-0.236
	0.874	0.645	0.000	0.000	0.000	0.000	0.000	0.148
GODIN	0.164	0.324	-0.356	-0.315	-0.390	-0.485	-0.500	-0.505
	0.324	0.047	0.026	0.051	0.014	0.002	0.001	0.001
DAS	0.280	0.127	0.520	0.615	0.571	0.409	0.426	0.141
	0.121	0.488	0.002	0.000	0.001	0.018	0.013	0.434
DAS-P	0.114	0.174	0.281	0.502	0.386	0.163	0.168	0.086
	0.571	0.385	0.156	0.008	0.047	0.417	0.402	0.669

	FACTEWB	FACTFWB	FACTPC	FACITF	HADSTO	HADSA	HADSD	GODIN
FACTFWB	0.668							
	0.000							
FACTPC	0.586	0.713						
	0.000	0.000						
FACITF	0.699	0.699	0.639					
	0.000	0.000	0.000					
HADSTO	-0.825	-0.759	-0.697	-0.839				
	0.000	0.000	0.000	0.000				
HADSA	-0.803	-0.704	-0.660	-0.784	0.974			
	0.000	0.000	0.000	0.000	0.000			
HADSD	-0.791	-0.771	-0.690	-0.847	0.958	0.867		
	0.000	0.000	0.000	0.000	0.000	0.000		
GODIN	-0.445	-0.228	-0.366	-0.249	0.411	0.366	0.439	
	0.004	0.162	0.022	0.126	0.009	0.022	0.005	
DAS	0.448	0.360	0.344	0.513	-0.691	-0.679	-0.650	-0.235
	0.009	0.039	0.050	0.002	0.000	0.000	0.000	0.189
DAS-P	0.211	0.090	0.089	0.080	-0.571	-0.607	-0.428	-0.139
	0.292	0.655	0.659	0.692	0.002	0.001	0.026	0.489

	DAS
DAS-P	0.885
	0.000

Cell Contents: Pearson correlation
P-Value