A Feasibility Study of a Home-Based Exercise Intervention for Prostate Cancer Patients on Androgen Deprivation Therapy

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A DISSERTATION SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN
PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

Graduate Programme in the
School of Kinesiology and Health Sciences

York University

December 2012

Abstract

Purpose: Androgen deprivation therapy (ADT) is an effective treatment for advanced-stage prostate cancer. Unfortunately, ADT has several adverse effects that significantly impair health-related quality of life (HRQOL). In patients receiving ADT, resistance training has been shown to improve important physical and psychosocial outcomes. However, little is known about the effects of aerobic exercise in this population. This feasibility study compares the effects of aerobic and resistance exercise interventions on a panel of psychological, physical fitness, and biological outcomes related to prostate cancer and ADT.

Methods: 66 men receiving ADT for prostate cancer were recruited for this prospective, randomized trial. Participants are assigned to either a resistance or aerobic, moderate-intensity exercise 3-5 times per week for 30-60 minutes/session. Participants were provided with equipment so that they could exercise at home. The primary outcomes were related to feasibility for future, large-scale trials. Secondary outcomes included: fatigue, HRQOL, physical fitness, adipokines, insulin-like growth factor axis proteins, and exercise adherence. Outcomes were assessed at baseline and at 3, 6, and 12 months.

Results: Preliminary findings are presented. 205 patients were approached for participation, 66 of which agreed to participate (n=34 in the resistance training group and 32 in the aerobic training group). Over the intervention period we experienced an attrition rate of 33%. There were no adverse events and biweekly booster sessions were poorly attended (n=27 aerobic training participants and n=22 resistance training participants did

not attend any booster sessions). Intention-to-treat analyses showed that fatigue and HRQOL were not significantly different between groups; however, in a per-protocol analysis the resistance-training group demonstrated clinically significant improvements in HRQOL. Differential within-groups effects on physical fitness and biomarkers were also observed at various time-points. At all time-points, the aerobic training group engaged in significantly more physical activity than the resistance training group.

Conclusion: Our findings suggest that both resistance and aerobic training can have positive effects on body composition with differential effects on psychosocial and biological outcomes. It appears that the aerobic exercise intervention was more effective at producing long-term, clinically significant increases in physical activity volume than resistance training. Our study has set the framework to conduct future clinical trials investigating the effects of exercise in men treated for prostate cancer.

Dedication

I dedicate this work and my career in exercise and cancer to the men and women who insist on moving when the disease and treatment suggest otherwise. I also dedicate this work to my inspiration for working in this field, our dear friend Mr. Bobby Hundal – we miss you everyday.

Acknowledgments

The extent to which this work was supported cannot be appropriately summarized in any volume of words. I have been mentored through each step of this endeavor by a group of caring, patient, generous, motivating, creative and brilliant clinician-scientists who have positively impacted so many careers. I am deeply appreciative that you chosen to help me with my career by accepting me as your student. Thank you Dr. Paul Ritvo, Dr. Andrew Matthew, Dr. Shabbir Alibhai, Dr. John Trachtenberg, Dr. Joel Katz, and Dr. Jane Irvine for all that all of you have done to help me realize my goal. I must also thank the Ritvo Lab and the unsung heroes of the Prostate Centre at PMH. I would especially like to thank Dr. Crissa Guglietti, Noah Wayne, Daniel Perez, Kristen Currie, and Michael Nesbitt whom were there from the beginning.

Equally important has been the support of the participants in my study and patients within our clinical practice, the Survivorship Exercise Program at the Princess Margaret Hospital. You have made this work enjoyable and entertaining. Despite being participants and patients of our programs, it has been your intervention of constant encouragement that has propelled me through this work. Your kind words and support have meant a lot to me and I have done my best to honour your interests in pursuing better treatment for cancer survivors.

There is another cast of individuals that have helped me survive the rigours of this process through patience, support, and appropriate distraction. To my brothers-from-

other-mothers, you know who you are, thanks for the help you didn't know you were providing.

To my family, those past and present, that have guided me and loved me unconditionally: this achievement is shared with you all. To my Mom and Dad: I couldn't have asked for a better set of teammates who were willing to do whatever it took. You have shown me the meaning of strength, patience, and love and these qualities are the foundation of my work. I hope I have made you proud.

And finally, but most importantly, I must acknowledge my wife with the most heartfelt 'thank you', 'I'm sorry', and 'I love you'. The *only* thing that you still do not understand is how much you mean to me and how thankful I am to have you as my partner through it all. Thank you for doing this with me, every step of the way. No one other than you will know exactly what this collection of pages cost and I will always be indebted to you for the patience you have shown me. I'm excited for the next phase of our life together.

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1.0 Introduction

Among Canadian men, prostate cancer (PCa) is the most common cancer diagnosis (excluding skin cancer) and the second leading cause of cancer-related death (1). While more than 80% of PCa diagnoses are in men aged 60 years or older (1), improved detection methods (e.g. prostate specific antigen testing) have progressively lowered the mean age of diagnosis and treatment (2, 3). Advances in PCa treatment and an increased survival rate (1) challenge clinicians to develop comprehensive treatment programs to maximize health-related quality of life (HRQOL) during lengthier survivorship periods.

Many patients with locally advanced or metastatic PCa receive androgen deprivation therapy (ADT) because it increases survival when used alone (4), or adjuvantly with radiotherapy (5) or radical prostatectomy (6). Unfortunately, detrimental physical, functional and psychological effects are associated with ADT: including deleterious changes in haemoglobin (Hb) levels, thyroid functioning, cognitive functioning, body composition (decreased lean mass and bone mineral density and increased fat mass) (7-16) and, in some patients, cardiovascular function (17). These adverse effects collectively reduce HRQOL over the years of ADT, which are often the remaining years of life (13, 18, 19).

Fortunately, exercise interventions are associated with significant improvements in fatigue, physical fitness, and HRQOL in ADT-treated PCa patients (20-30). However, questions remain regarding the efficacy of different exercise modalities and program delivery strategies aimed at long-term exercise participation, such as: i) how to instil a

chronic change in exercise behaviour that overcomes the problem of discontinued exercise and consequential rapid loss of benefits (24, 31); ii) can home-based exercise programs be effective at improving essential elements of HRQOL given their inherent logistic strengths (low cost of participation, potential for long-term program adherence, reduced barriers to routine exercise); and iii) does aerobic exercise training (AET) confer equivalent effects to the more established modality of resistance exercise training (RET) when implemented in the home-based setting. Accordingly, the objectives of this study were to examine the feasibility of conducting a large-scale, adequately powered trial that would test the effects of six months of home-based AET versus RET in a randomized trial of ADT-treated PCa patients with a six-month post-intervention follow-up.

2.0 Background

2.1 Overview of Prostate Cancer and Androgen Deprivation Therapy

PCa is an androgen-dependent cancer, which means that malignant cell growth and proliferation relies on androgens, primarily testosterone and dihydrotestosterone (DHT) (32-34). Thus, the acute or chronic suppression of androgens is central to the management of locally advanced or metastatic PCa (35). ADT is commonly used as an adjuvant (and/or neo-adjuvant) therapy, in combination with radiation therapy or radical prostatectomy, to mitigate or respond to biochemical relapse (i.e. post-treatment increase in prostate-specific antigen) (5, 36, 37). ADT is increasingly used as a primary PCa management strategy (37, 38). Initially, orchiectomy (removal of the testes) was used as the primary type of ADT (39) but contemporary androgen suppression is primarily achieved pharmacologically through three pharmacological approaches: luteinizing hormone-releasing hormone (LHRH) analogues; androgen receptor blockers; and 5α-reductase inhibitors (37, 40-42). Due to the numerous physiological roles of androgens, ADT has metabolic, musculoskeletal, and cardiovascular consequences (19, 43) that lead to an increased risk of developing diabetes, osteoporosis and cardiovascular disease (44-47).

ADT rapidly produces significant deterioration in healthy body composition by reducing bone and muscle, and increasing fat mass (36, 48, 49). As PCa is typically diagnosed in older men (often 65 years of age or older (1, 50)), ADT effects can accelerate and amplify age-related sarcopenia, osteoporosis, and general frailty (51). Such changes in body composition are overtly manifested as declining of physical fitness

and functional capacity (52, 53) to levels more comparable with men 10-20 years older (54). Moreover, poor cardiorespiratory and musculoskeletal fitness increases the risk of falls likely to produce fractures in these often-osteoporotic men (47, 55). This is of particular concern given the increased mortality risk of men with PCa who sustain a fracture (56).

One of the more evident and distressing psychological/physical manifestations of ADT-related changes in physiology is fatigue (57-61). Stone et al (61) found that fatigue severity increased in almost 70% of patients 3 months after starting ADT, 14% of whom had severe fatigue. ADT-related fatigue is not well understood but may have several underlying physiological mechanisms, including anemia, reduced psychological vigor/vitality, and impaired functional capacity (36, 48, 61). Fatigue in ADT patients interferes with daily tasks and recreational activity that ultimately adds to the HRQOL reductions associated with PCa and its medical management. To optimize HRQOL in PCa patients receiving ADT, new strategies to maintain physical and mental capacity and to combat fatigue are needed. Exercise is an intervention with many demonstrated physical and psychosocial benefits in cancer survivors during and after therapy, including improvement in fatigue (62, 63). Recent evidence indicates that exercise is acutely (i.e. during the intervention period) effective in improving many facets of the ADT sequelae and enhancing overall HRQOL (20-25, 64-67). Research is specifically needed to assess which modalities are most effective and how exercise behaviour can be sustained to ensure that the acute benefits can be extended throughout the course of ADT and into post-treatment survivorship.

2.2 Exercise and Prostate Cancer

2.2.1 Exercise, Physical Activity and Prostate Cancer Prevention

The etiology of PCa is multifaceted and largely unexplained, but both modifiable and non-modifiable risk factors have been identified that alter disease progression. The most common non-modifiable risk factors are age, ethnicity, and family history (68, 69), while modifiable lifestyle risk factors include diet and obesity (70, 71), smoking (72), alcohol consumption (73), and sexual activity (74). A growing body of recent research has examined the influence of physical activity in PCa incidence that has demonstrated mixed results. To date, 22 cohort studies (75-95) and 10 case-control studies (96-105) have examined the relationship between PCa incidence and physical activity. Fifteen of these studies found a protective effect based on aerobic fitness (86), occupational physical activity (80, 85, 97, 98, 102, 106), recreational physical activity (76, 77, 82, 88, 94, 105, 107), and both occupational and recreational physical activity (78). However, 15 other studies have found no association between physical activity and PCa incidence (75, 79, 81, 83, 84, 87, 90-93, 95, 96, 99, 102, 104) and four studies have found either an increase or possible increase in PCa risk with physical activity (89, 100, 101, 103). This inconsistency led the World Cancer Research Fund and American Institute for Cancer Research to conclude that a formal judgment on the relationship between physical activity and PCa cannot be made based on the current available research (108). Nevertheless, there appears to be a role for research that examines the effect of an exercise-based primary prevention strategy in this population.

Several criticisms of the epidemiological (pre-diagnosis/primary prevention) literature have been articulated; namely, that i) selection bias might be influential in much of this research since physically active men are more likely to be screened for, and thus diagnosed with, PCa (106, 109); and ii) given the latency and insidious nature of PCa, many men will die *with*, rather than *from,* PCa undermining some estimates of association between physical activity volume and PCa incidence as the subclinical diagnoses made at autopsy (if conducted) have not been included in these estimates (109).

In terms of secondary prevention, only one study has assessed the relationship between physical activity and PCa survival. Kenfield et al (110) recently examined the effect of post-diagnosis physical activity on PCa-specific, and overall, survival in 2,705 men with non-metastatic PCa from 1990-2008 in the Health Professionals Follow-Up Study. In that study, the researchers collected self-reported physical activity information every two years and then reviewed diagnosis and cause of death information in patients who had survived for at least four years after recruitment into the study. The results demonstrated: i) a 51% reduction in all-cause mortality with more than 10 hours of vigorous exercise per week versus less than one hour per week of non-vigorous activity; ii) a 36% reduction in all-cause mortality for those who walked more than seven hours per week versus less than 20 minutes per week, with additional risk reduction with brisk walking; and iii) a 49% reduction in all-cause mortality and 61% reduction in PCa-specific mortality for those vigorously active for more than three hours per week when compared with less than one hour per week. It is also worth noting that the authors of

this study indicate that for those men with ≥ 9 MET-hrs/wk compared to < 9 MET-hrs/wk had a hazard ratio of 0.65 (95% CI = 0.43 - 1.0). Thus a change of 9 MET-hrs/wk appears to be a reasonable estimate of clinical significance in this population. Furthermore, these effects were independent of pre-diagnosis physical activity volume suggesting that physical activity interventions following diagnosis may have a significant influence on life-expectancy for men with PCa.

Proposed biological mechanisms for the decreased risk and/or attenuated progression of PCa with physical activity include a reduced exposure to circulating androgens, lower body fat and associated adipokines, improved immune system function, and improved antioxidant availability and function (111, 112). A series of studies investigating the effects of a low-fat diet and/or regular physical activity have suggested these healthy lifestyle modifications can elicit serum changes *in vivo* that can reduce *in vitro* cancer cell proliferation and increase the apoptosis of androgen-dependent cell lines (i.e. PCa cells that are responsive to ADT) (113-117). The protective effects of these studies are likely due to reductions in insulin and insulin-like growth factors (e.g. IGF-1) and anti-apoptotic proteins (Bcl-2), amidst concomitant increases in sex-hormone binding globulin, insulin-like growth factor binding protein-1 (IGFBP-1), and apoptotic proteins (p53 and p21) (116, 118, 119). Theoretical concerns of accelerating tumour growth due to transient increases in serum testosterone levels have not been borne out in exercise studies with PCa patients (21, 23, 120, 121).

2.2.2 Exercise during Treatment for Prostate Cancer

Several studies have investigated the effect of exercise during PCa treatment (21, 23, 24, 26-28, 30, 65, 66, 120-123) with additional publications pertaining to study protocols describing ongoing research (123-128). Table 1 shows a summary of exercise and physical activity trials in men after a PCa diagnosis. The first examination of exercise as a HRQOL and health optimizing strategy for PCa patients was conducted in 2003 in response to observations of the numerous physical and psychosocial detriments associated with treatment (120). To date, several reviews of exercise interventions for PCa patients have been conducted (54, 129, 130). Thus far, exercise interventions have been essentially limited to PCa patients undergoing external beam radiation and/or androgen suppression (as detailed in subsequent sections). There is a noticeable dearth in the literature regarding the effects of exercise during other treatments for PCa, namely radical prostatectomy and chemotherapy. Only one trial has examined the role of exercise in 10 post-prostatectomy patients that were between 8-169 months post-surgery (27). In fact, postoperative exercise may be less appropriate to mitigate the effects of surgery than is preoperative exercise training, known as prehabilitation which has been shown to be effective in lung cancer (131, 132) and colon cancer patients (133). The investigation of exercise during chemotherapy is also particularly important because of the severe deconditioning effect on patients and long-lasting adverse effects of chemotherapy (134). Whether these elder patients on intensive chemotherapy regimens can endure routine exercise is still in question, but a growing body of literature suggests

that exercise is tolerable and beneficial during chemotherapy in several other cancers (135-142). The next two sections will focus on the literature that describes the effects of exercise on external beam radiation therapy and ADT.

2.2.2.1 Exercise during Radiation for Prostate Cancer

There have been three published trials investigating the effect of exercise on PCa patients undergoing external beam radiation. Windsor and colleagues (66) conducted a randomized controlled trial (RCT) that focused on the effects of a home-based, moderate-intensity, walking program on PCa patients (n = 66) over four weeks of their radiation therapy. The intervention group exercised three times weekly for 30 minutes at 60-70% of the maximum heart rate. At the end of the intervention period, control participants reported increases in fatigue compared to baseline ($p = 0.013$), whereas fatigue scores remained unchanged for the exercise group ($p = 0.203$). Exercise improved physical functioning as measured by a modified 10-meter walking shuttle test ($p = 0.0025$). A 100% self-reported adherence rate was noted; all patients in the exercise group reported at least 90 minutes per week of aerobic exercise. This excellent adherence rate is promising, but further studies with objective measures of physical activity participation (e.g. accelerometry) and longer-term follow-ups are required to demonstrate reproducibility and sustainability.

Monga et al (65) conducted a RCT to examine the effects of an eight-week aerobic exercise program for PCa patients undergoing external beam radiation. Intervention participants (n = 11) were required to participate in supervised aerobic

exercise three times weekly, prior to treatment while control participants (n = 10) did not undergo any exercise. The exercise protocol consisted of 30 minutes of moderate-intensity treadmill walking. Pre- to post-intervention improvements were observed in cardiovascular fitness ($p < 0.001$), lower extremity strength ($p < 0.001$), flexibility ($p = 0.006$), depression ($p = 0.02$), fatigue ($p = 0.02$), physical wellbeing ($p = 0.002$), social wellbeing ($p = 0.02$), and overall HRQOL ($p = 0.04$). Compared to controls, exercising participants showed improvements in cardiovascular fitness ($p = 0.006$), lower extremity strength ($p < 0.001$), flexibility ($p < 0.01$), and reported less fatigue ($p = 0.001$), and better physical wellbeing ($p = 0.001$), social wellbeing ($p = 0.002$), functional wellbeing ($p = 0.04$), and overall HRQOL ($p = 0.006$). This was the first study to demonstrate improvements in fatigue and HRQOL with a supervised, aerobic exercise program for PCa patients undergoing radiation. Caution is required in interpreting results because of small sample size, potential for selection bias, and retention difficulties (approximately 20% attrition). Intervention adherence was not reported.

Segal et al (21) conducted a three-arm RCT of 121 radiation-treated PCa patients (74 of whom were receiving adjuvant ADT) that examined supervised 24-week RET or AET interventions versus wait-list controls. The AET group engaged in 15 to 45 minutes of moderate-intensity stationary cycling, treadmill, or elliptical machine exercise three times weekly. RET consisted of nine weight-training exercises using machines and free-weights for one to two sets of 8-12 repetitions at 60% of the subject's one-repetition maximum (1RM or the maximal weight or load that can be lifted once) three times weekly. Participants were instructed to increase their exercise load by five pounds when

they were able to complete more than 12 repetitions. An improvement in fatigue from baseline to 12 weeks was observed for both exercise groups compared to controls, but only the RET group showed less fatigue compared to the control group at 24 weeks (RET: $p = 0.002$; AET: $p = 0.08$). From baseline to post-test, the RET group showed improved aerobic fitness ($p = 0.037$) and upper/lower body strength ($p < 0.001$), while participants in the AET group demonstrated improved upper body strength ($p = 0.006$). A recruitment rate of 37% was noted for all eligible participants and the median adherence to the exercise program was 85.5% (as calculated by number of sessions attended/prescribed). In this trial three adverse events related to exercise were reported, one of which was serious (myocardial infarction) in the AET group following a training session on the third day of the program. The participant made a full recovery but did not complete the intervention.

This group of authors continued their study of this cohort of participants by conducting two supplemental analyses. In the first (published as online additional content to the original paper), the authors examined the effect of the exercise interventions at 24 weeks, stratified by treatment (radiation $\pm$ ADT). Compared to control participants, the RET group on radiation only ($n = 23$) demonstrated improvements in fatigue ($p = 0.004$); cancer-related and disease-specific HRQOL ($p = 0.002$ and $p = 0.02$, respectively), VO_2 peak ($p = 0.037$), and upper and lower body strength ($p < 0.001$). The AET group receiving radiation only ($n = 25$) only showed improvements in disease-specific HRQOL ($p = 0.023$). In participants receiving adjuvant ADT, RET ($n = 17$) showed improved upper and lower body strength ($p < 0.001$), and

reductions in body fat percentage ($p = 0.005$), whereas AET ($n = 15$) only improved in upper body strength ($p = 0.02$) when compared to controls. Although this analysis was exploratory and lacked adequate statistical power, the findings suggest that RET may be more beneficial than AET for men treated with radiation with and without ADT. These findings were confirmed in the authors' second ancillary analysis (separately published by Alberga et al (143)), in which they further stratified patients receiving ADT into age groups of ≤ 65 years ('younger') versus > 65 years ('older'). In this analysis, the authors found that younger men had significantly greater improvements in muscular fitness compared to control or AET participants, but no difference in body composition. Similarly, older men benefitted more from RET since they were the only group to improve body composition and muscular fitness over the course of the intervention. Most importantly, for men receiving radiation *and* ADT, only RET showed improved body composition and muscular fitness compared to controls. In men undergoing radiation *only*, only RET showed improved aerobic and muscular fitness.

These findings from the Segal et al analyses (21, 143) underscore the importance of incorporating RET into a lifestyle/wellness program. However, there were acknowledged limitations to the analyses and interpretations. First, the authors noted the subgroup analyses were underpowered and that there was considerable variance within the sample in the duration of hormone suppression in ADT patients. This is important since previous research has shown that ADT duration for more than six months is associated with lower physical function and higher body fat percentage than PCa patients not receiving ADT or short term ADT (less than 6 months) (53). Second, although the

baseline differences were not statistically significantly different, there was a large difference in terms of lower baseline muscular strength for the RET group, particularly in lower extremity strength, compared to AET and controls (upper extremity strength (kg): RET = 49.5 $\pm$ 13.3, AET = 55.2 $\pm$ 13.3, Control = 53.4 $\pm$ 12.1; lower extremity strength (kg): RET = 104.7 $\pm$ 37.7, AET = 125.6 $\pm$ 55.8, Control = 117.4 $\pm$ 53.5). These differences were not observed for aerobic fitness (VO_2 peak (mlO_2/kg/min): RET = 28.19 $\pm$ 6.94, AET = 29.42 $\pm$ 6.5, Control = 28.78 $\pm$ 5.08) and may have been a factor that contributed to the lack of a significant between group effects in aerobic fitness observed. These findings are noteworthy for two potential reasons. First, RET participants who started with a lower level of muscular strength had a greater capacity for improvement (i.e. floor effect). Second, the novel nature of RET may make it a modality in which participants invest more time, focus, and energy during training. Together, these may explain why greater improvements observed in muscular fitness and body composition and the comparative absence of difference in aerobic fitness in the RET group. Unfortunately, only between-group comparisons of change from baseline, and not absolute values for post-test outcomes, were reported.

2.2.2.2 Exercise during ADT for Prostate Cancer

Despite the growth of exercise research in the primary/curative treatment setting for PCa, the majority of exercise intervention research has been predominantly conducted in patients with locally advanced, hormone-sensitive metastatic disease treated with ADT (20-25, 67). Given the detrimental effects of ADT on physical function and fatigue from

prolonged hypogonadism (described earlier), it is fortunate that exercise appears to mitigate ADT-related adverse effects. The typical chronic duration of hormone ablation necessitates the incorporation of acute and, ideally, long-term exercise interventions that provide relief and often reversal of the various physical, functional, and ADT adverse effects.

Segal et al (20) conducted the first investigation into the effects of exercise on ADT-treated PCa patients in a study that met high-quality methodological criteria (144, 145). In that study, 155 men were randomly assigned to a 12-week supervised RET group (n = 82) or to a wait list control group (n = 73). The RET program consisted of nine exercises targeting upper and lower body muscle groups, performed three times weekly, at 60-70% of 1RM, for two sets of 10-12 repetitions. Participants increased the resistance of an exercise by five pounds when able to complete more than 12 repetitions. Results indicated that at the end of the intervention, compared with controls, intervention participants reported less fatigue ($p = 0.002$), higher levels of HRQOL ($p = 0.001$), and better scores on measures of upper ($p = 0.009$) and lower ($p < 0.001$) body muscular fitness. In fact, at the end of the study, control participants reported increases in fatigue and declines in HRQOL as well as upper and lower body muscular fitness. This study had a 30.6% participation rate, with a program-adherence rate of 79%, which demonstrated initial evidence of the willingness and motivation to register and comply with exercise intervention parameters in a meaningfully sized proportion of PCa patients. This landmark study provided two salient findings for patients on ADT: 1) clinically important improvements in physical function, fatigue, and HRQOL, are attainable within

a relatively short duration of exercise programming; and, 2) treatment as usual was associated with physical function declines that likely increased fatigue and reduced HRQOL. The authors recommended that future studies follow patients for a longer duration (beyond 12 weeks) to determine whether additional benefits are achieved by a more sophisticated body composition analysis, as well as assess different modes of exercise, such as AET.

Galvao et al (121) examined the effects of a 20-week supervised, progressive RET program in 10 men undergoing ADT for localized PCa. Patients were required to be on ADT for a minimum of two months with at least five months of subsequent treatment planned. In small groups (n = 1 - 4) and under direct supervision, participants were required to complete 12 upper and lower body exercises. All exercise sessions were one hour in duration, including flexibility training and warm-up. The intervention improved upper body strength and endurance ($p < 0.001$), functional performance ($p < 0.05$), and quadriceps muscle thickness ($p < 0.05$). No differences were found in lean mass, fat mass, body fat percentage, whole body bone mineral content, or BMD, Hb, or cortisol. PSA level, testosterone, and growth hormone levels were unchanged suggesting no exacerbation of the disease. Weaknesses of the study were that it was non-randomized, not controlled (i.e., no control group), and recruited a small sample size. However, the authors used several additional objective measures of functional performance and, as advocated by Segal and colleagues (120), sophisticated measures of body composition and serological outcomes (e.g. hormones and Hb). Furthermore, the study employed an intense/strenuous RET protocol (6-12 RM using hydraulic and isotonic strength training

machines for two to four sets over 20 weeks) and reported no adverse events, which demonstrated the safety of high-intensity training in this relatively fragile population.

Carmack-Taylor et al (30) conducted a three-arm RCT named the Active for Life After Cancer Trial that evaluated the impact of a group-based lifestyle physical activity program (Lifestyle Program) or educational support program versus standard care in PCa patients undergoing ADT (for a minimum of one year). Participants in the lifestyle and educational support programs were required to attend small, 90-minute group meetings for six months (16 weekly meetings plus four 'biweekly' meeting). Specifically, participants in the Lifestyle Program (n = 46) were taught cognitive-behavioural strategies derived from the Transtheoretical Model (146, 147) and Social Cognitive Theory (148, 149) to increase physical activity adherence to 30 minutes at a moderate intensity on most days of the week (which meets Health Canada and American College of Sports Medicine recommendations). Although physical activity instruction was not provided, patients were occasionally engaged in five-minute periods of walking, an information session regarding injury prevention and stretching, and a facilitated discussion on a variety of PCa-related topics. Participants in the educational support program (n = 51) discussed PCa-specific issues, including diet, treatment side effects and sexuality. Seventy percent and 82% of the participants attended at least half of the lifestyle and educational sessions, respectively. Significant differences were not found for HRQOL, body composition, endurance, seven-day physical activity volume, caloric expenditure, or social support in any intervention arm.

In discussing the negative results, the authors suggested that the lack of efficacy may be a result of the relatively healthy status (e.g. low levels of anxiety, depression, and pain) of patients at baseline (i.e. a ceiling effect). Furthermore, the authors noted that the sample size was insufficiently powered, due to the onerous and costly nature of conducting a three-arm RCT with strict eligibility criteria (more than 1,100 patients were approached). Although the intervention was relatively well received with similar adherence rates as previous trials, the authors recommended formal physical activity skills training in conjunction with cognitive-behavioural training to improve the benefits of, and adherence to, a physical activity program. The results also raise the possibility that professional supervision may be an important component of physical activity interventions in this group of patients, but this has not been directly tested in a RCT.

Culos-Reed et al (24) examined the effects of 12-week home-based physical activity intervention on 31 PCa patients treated with ADT in a single arm, prospective trial. A group-based, introductory session familiarized participants with various exercises, consisting primarily of walking, stretching, and light RET. Resistance bands and exercise balls were provided to participants to support adherence to the exercise prescription of three to five times per week. Group-based "booster sessions" that incorporated exercise and discussion, were held every two weeks to encourage social support, adherence to the program, and measurement of compliance with the program parameters. Results showed that 81% of participants attended at least five of the six booster sessions, with post-test differences in volumes of strenuous and total physical activity ($p < 0.01$), functional capacity ($p < 0.01$), resting heart rate ($p = 0.03$), BMI ($p <$

0.01) and fatigue ($p = 0.05$). A subgroup ($n = 18$), which was followed for four months post-intervention, revealed decreases in strenuous physical activity participation ($p = 0.01$) and global HRQOL ($p = 0.04$) compared to post-treatment results. The authors noted that reductions in global HRQOL at the 4-month follow-up may be a result of a failure to maintain intervention levels of physical activity, which echoed previous findings suggesting that the benefits of exercise are sustained for only as long as the routine exercise is maintained (31).

More recently, Culos-Reed et al (25) tested their intervention using a RCT design over 16 weeks in 100 patients scheduled to receive ADT for at least six months. Exercising participants demonstrated increased physical activity volume ($p = 0.004$), and smaller waist circumference ($p = 0.044$) and neck girth ($p = 0.019$) compared to controls. A significant difference between controls and exercisers was not observed for HRQOL, depression, or fatigue. Participants attended 78% of the weekly booster sessions; however, the drop-out rate over the 16 weeks was 34%. The authors reported that no adverse events occurred in either of these trials. The results of the two studies by Culos-Reed et al suggest that home-based physical activity interventions are safe, but require strategies to minimize attrition. Moreover, the lack of effect on HRQOL outcomes and some measures of physical fitness indicated that the intervention may have lacked sufficient intensity and/or exercise prescription compliance required for physical adaptation. The investigators are currently monitoring long-term adherence and benefits in a study subgroup.

A pilot study by Hansen et al (27) of supervised, progressive eccentric RET in men with PCa was conducted to determine whether patients receiving ADT had a blunted response to RET versus PCa patients that are not receiving ADT. Sixteen men were enrolled in this study; however, six participants withdrew (four from the ADT group) leaving five in each of the two groups. All patients underwent radical prostatectomy for primary treatment, except for one that elected active surveillance. Two participants also underwent adjuvant radiation therapy after surgery, both in the ADT group. All participants engaged in 12 weeks of high-force eccentric ergometer training on three days per week[1]. Eccentric training was incorporated into this protocol likely because it allows for a greater amount of force to be applied to the muscle group and produces the greatest structural and functional muscle adaptation while incurring a low metabolic (caloric/cardiovascular) cost when compared to conventional concentric training (150-154). All participants completed the 36 sessions of training and there were no adverse events associated with training. After the intervention, ADT patients showed improved performance on the six-minute walk test ($p = 0.01$) and isometric knee strength ($p<0.05$). And, although not statistically significant, these participants also demonstrated a clinically important improvement in HRQOL (as measured by the Functional Assessment of Cancer Therapy – Prostate; mean change of 8.2 points, p-value and 95% confidence interval not reported). The non-ADT group improved in the physical subscale of the HRQOL ($p = 0.03$) and left quadriceps muscle volume ($p = 0.04$). Significant within-

[1] Eccentric loading occurs when resistance is applied to a muscle while it is lengthening, and in this particular case the resistance is applied to the quadriceps using a cycle-like device that loads or 'pushes' the knee back causing the quadriceps to lengthen and the knee to flex.

group improvements were not found for the timed-up and go test or fatigue (via the Functional Assessment of Cancer Therapy – Fatigue); nor were there any between-group differences. Limited by a small sample, non-controlled design, large attrition rate (especially in the ADT group), and unmatched baseline characteristics between groups, these findings must be interpreted cautiously. Yet it is important to underscore the importance of RET, and particularly eccentric RET, as a training modality that appears to be efficacious at maintaining functional capacity despite ADT. It is also worth noting that the authors reported significant difficulty with recruitment, stating that attendance at a university-based program was a contributing factor to non-participation. However, the program adherence of those that did attend was 100%. The authors recommend using a more convenient location for the program such as the individual's home, to improve program participation.

Galvao and colleagues (23) examined the effects of a 12-week combined AET + RET intervention in a RCT of 57 patients receiving ADT. Treatment group participants completed eight RET exercises at 6-12 RM (moderate to strenuous RET) for 2-4 sets per exercise. The AET component consisted of 15-20 minutes of cycling, walking, or jogging at 65-80% of maximum heart rate or 11-13 out of 20 on the Rating of Perceived Exertion (Borg) Scale (155). Participants completed exercises in a facility-based, supervised setting in small groups of one to five participants. Primary outcomes were whole body and regional lean mass measured by dual energy x-ray absorptiometry (DEXA). At the end of 12 weeks, the exercising participants demonstrated significantly greater lean mass, muscle strength, and functional capacity than controls. Over the

course of the trial, exercising participants also showed improved HRQOL scores and, reduced fatigue, and reduced C-reactive protein, an inflammatory marker that is associated with poor function, diabetes and obesity, mortality, and some cancers including PCa (156-163). This was the first trial to demonstrate a reversal in muscle loss in androgen suppressed PCa patients and demonstrated significant HRQOL, fatigue, and muscle strength outcomes with a mixed-modality exercise intervention.

The most recent published exercise trial in ADT has been conducted by our research team. We investigated differences in performance outcomes and HRQOL associated with training in a one-on-one versus group setting with an exercise instructor (26). In this pilot study, 10 men undergoing ADT for PCa were randomized to eight weeks of group-based exercise or personal training for three one-hour sessions per week. To examine the role of facility location on participation and adherence, sessions were held on alternate weeks at either the University Health Network (downtown Toronto) or the University of Guelph-Humber (suburban Toronto). Each session was mixed-modality (i.e. AET + RET) at a moderate to vigorous intensity. The mean attendance rate for the personal training and group exercise sessions was comparable (91% and 88%, respectively; $p = 0.645$). Participants attended sessions at each site with a similar frequency (94% to the hospital-based setting versus 83% to the university-based setting, $p = 0.582$). From baseline to post-test, there were no statistically significant within- or between-group differences in HRQOL (FACT-P) or fatigue (FACT-F); however, the personal training group had a clinically important improvement in fatigue that trended towards significance ($p = 0.09$). In terms of physical outcomes, the personal training

group demonstrated improvements from baseline in resting systolic blood pressure ($p = 0.033$), body fat percentage ($p = 0.001$), and maximal lower body strength ($p = 0.002$). Group comparisons indicated that the personal training group had greater lower body strength improvements ($p = 0.038$), whereas the group-based exercise participants had better upper body strength improvements ($p = 0.013$). There were no within or between group differences for aerobic fitness, balance, BMD (as measured by quantitative ultrasound), grip strength, or body composition. All participants declared that the program was a positive experience that was beneficial to their HRQOL, whereas 60% of the sample preferred to do personal training rather than group exercise. Although this was the first study to compare delivery models of exercise for PCa survivors, it was limited by sample size and lack of a long-term follow-up. Despite these limitations, the pilot nature of this work was important to provide estimates of effect size that have been used for subsequent research proposals to examine delivery modalities and cost-effectiveness.

2.3 HRQOL and Prostate Cancer Survivors Undergoing ADT

Patients and healthcare practitioners must consider therapeutic options for life-threatening medical conditions by weighing survival in terms both the number of years of survival and the overall quality of life of those years. Consequently, HRQOL has evolved to broadly encompass the general aspects of global wellbeing, including psychological/emotional, social, functional and physical health (164). In the cancer-specific model proposed by Courneya et al (165), HRQOL outcomes represent the state

of happiness and satisfaction with life, that is affected by symptom occurrence, interference, and distress. Courneya and colleagues further suggest that fatigue is the root psychophysical contributor to overall HRQOL that pervades each aspect of symptom status (i.e. occurrence, interference and distress). This perspective is corroborated by research that indicates that fatigue is the most common and distressing adverse effect of cancer treatment, affecting 70-90% of all cancer survivors (140). Cancer-related fatigue can persist for several years after cancer treatment terminates, negatively impacting HRQOL and interfering with activities of daily living (166). Therefore, strategies that specifically address this fundamental aspect of HRQOL are sorely needed.

For men with PCa HRQOL is compromised from many angles despite knowledge that current curative approaches to disease management confer a 90% 15-year survival rate (2, 167). Common radical therapies, such as radiation and prostatectomy, are nearly always associated with adverse effects, such as urinary and/or bowel incontinence (UI) and sexual dysfunction (SD), that profoundly impair HRQOL (168-170). Irrespective of primary treatment, ADT is indicated for approximately half of all men with PCa for biochemical relapse or as a palliative approach when the cancer is diagnosed in the extracapsular or metastatic stages (37, 38, 171). This is problematic for HRQOL because ADT further compounds deleterious changes physical and psychosocial wellbeing by diminishing physical fitness (including detrimental changes to body composition), energy/vigor, sexual interest, and cognitive function (36, 48, 170). Moreover, ADT has been correlated with increased incidence of diabetes and cardiovascular morbidity that additionally exacerbate physical and psychosocial wellbeing (44-46). Accordingly,

urologists and scientists have advocated broadening the metrics of therapeutic success beyond simply disease-free survival to include overall HRQOL (2, 172-175).

Given that the PCa and treatment sequelae are unique and profound, measurement of HRQOL in PCa is complex. These specific psychological and physical adverse effects have yielded the development of PCa-specific HRQOL measurements, such as the Functional Assessment of Cancer Therapy – Prostate (FACT-P) (176), the Patient-Oriented Prostate Utility Scale (PORPUS) (177), and the Expanded Prostate Cancer Index Composite (EPIC) (178), aimed at capturing the true essence of living with the disease. The advantage of using a disease-specific measure is that, in addition to providing insight on overall HRQOL, there is an assessment of distinct PCa outcomes; such as, genitourinary symptoms, sexual interest/satisfaction, fatigue, and emotional health. These measures are often able to distinguish between a distinct set of deficits in the localized versus locally advanced/metastatic disease setting.

Across all cancer diagnoses, exercise has been an effective ameliorative therapy positively influencing several psychosocial and physical adverse effects of cancer and associated therapies. The roots of cancer-exercise literature are founded firmly in psychosocial oncology with a vast majority of studies reporting on some component of HRQOL. This emphasis stems from a coping model within cancer survivorship, as exercise has traditionally been regarded as an adjuvant therapy to mitigate the effects of the disease and/or its treatment (165). Ultimately, it appears that exercise can positively influence global wellbeing and HRQOL via multiple pathways, providing benefits at the molecular/biologic levels that improve disease management and treatment tolerance,

while improving the negative impact of the disease on patients' psychological wellbeing (165). More recently, exercise intervention literature has approached cancer survivorship with a quasi-curative, rather than simply palliative approach, as findings continue to emerge that suggest exercise has anti-tumourigenic effects (114-117). Evidence of disease control can further improve HRQOL by enhancing optimism and personal control with respect to cancer (179). In aggregate, the body of literature in cancer and exercise now represents a more comprehensive, or biopsychosocial approach, with benefits described across all domains HRQOL. In response to the multilevel benefits of exercise, it is prudent, and arguably essential, that exercise be examined in a biopsychosocial context, using outcomes measures that reflect all physical wellbeing, psychosocial wellbeing, and disease control markers.

2.3.1 The Effect of Exercise on HRQOL for Prostate Cancer Survivors Undergoing ADT

The prevalence of ADT-related declines in HRQOL and the general benefits ascribed to exercise make them virtually inseparable in the research. This is evidenced by the fact that all but two (121) exercise studies have incorporated some measure of general or PCa-specific HRQOL measurements. Unfortunately, the effects of exercise do not appear universal across trials that appear to be related to intervention delivery strategies despite heterogeneity in HRQOL measurement usage.

The most commonly used measure of HRQOL among ADT-treated PCa patients is the FACT-P which has been employed in five of the 10 existing studies (21, 27, 28,

120, 180). The first research in this population conducted by Segal et al (120) used the FACT-P and found that scores were improved with RET compared to controls in all sample stratifications (e.g. all participants, men treated with curative or palliative intent, and men receiving ADT for greater than or less than one year; $p = 0.001$ to $p = 0.02$). In Segal et al's second RCT in PCa patients receiving radiation $\pm$ ADT (21), significant worsening was found in the PCa-specific symptoms subscale of the FACT-P from baseline to 12 weeks in both the AET (mean $\Delta = -3.17$, 95% CI: -4.98 to 1.37, $p < 0.001$) and RET (mean $\Delta = -1.91$, 95% CI: -3.79 to 0.02, $p = 0.047$) groups, as well as in the usual care group (mean $\Delta = -4.17$, 95% CI: -5.97 to 2.38, $p < 0.001$) although the usual care controls experienced the greatest reduction in HRQOL (mean $\Delta = -4.17$, 95% CI: -5.97 to -2.38, $p < 0.001$). Significant differences between groups were not found, nor did any group sustain these changes to 24 weeks. With respect to generalized cancer-related HRQOL (FACT-General component of FACT-P), RET was associated with a clinically significant improvement in HRQOL from baseline to 24 weeks (mean $\Delta = 4.17$, 95% CI: -4.98 to 1.37, $p < 0.001$), as was AET, although this finding was only borderline significant (mean $\Delta = 2.35$, 95% CI: -0.06 to 4.77, $p = 0.055$). Between-groups comparisons found that RET improved cancer-specific HRQOL compared to usual care at 12 and 24 weeks ($p = 0.017$ and $p = 0.015$, respectively).

Likely inspired by Segal's initial work in the field, several other research groups have employed the FACT-P to assess HRQOL changes associated with exercise. Bourke et al (28) found within-group improvements, and exercise versus control group differences in total FACT-P scores that approached clinical significance but were

underpowered to produce statistical significance ($p = 0.21$). Hansen et al (27) reported a within-group improvement in the physical subscale of FACT-P for exercising PCa patients not receiving ADT, but not in exercising patients who *were* receiving ADT. Additional pre-post or between-group differences were not observed. In their single-arm trial, Serda et al (180) found a clinically and statistically significant improvements in total FACT-P scores after 24-weeks of RET (mean $\Delta = 9.4$, $p = 0.003$). In the most recent trial, our group found the largest improvement in FACT-P scores over the course of an 8-week personal training intervention but the small (underpowered) sample undermined statistical significance (mean $\Delta = 12.3$, SEM = 7.0, $p = 0.136$). In summary, the FACT-P has demonstrated sensitivity to changes in cancer-specific, PCa-specific, and other HRQOL elements in each study that has employed the measure. Interestingly, the FACT-P has not been the primary outcome of a study and it has been used exclusively in facility-based exercise trials and not home-based exercise studies. The FACT-P should be considered among the most appropriate choices for exercise interventions given the prevalence of usage in this field of study, and should be integrated in home-based exercise trials in order to effectively compare the HRQOL benefits across intervention delivery settings.

Beyond the FACT-P, PCa-specific HRQOL responses to exercise have also been assessed using the PORPUS (26) and the EPIC (Expanded Prostate Cancer Index Composite) (122). In our recent study (26), we observed an approximate clinically-significant change in total PORPUS scores from baseline to 8 weeks for participants engaging in group-based exercise, but this was not statistically significant (mean $\Delta = 7.9$,

SEM = 5.3, p = 0.374) (26). Culos-Reed et al (24) observed a marginally significant improvement in hormone symptoms compared to controls after 16 weeks of home-based exercise (122) as assessed by the EPIC.

Other studies have elected more general cancer-based HRQOL scales. Three studies used the European Organization for the Research and Treatment of Cancer – Quality of Life Questionnaire (EORTC-QLQ) to assess cancer specific HRQOL (23, 24, 122). Using the EORTC-QLQ, Galvao et al (23) found improvements in role function ($p < 0.001$), cognition ($p = 0.007$), nausea ($p = 0.025$) and dyspnea ($p = 0.017$), but not global HRQOL (95% CI: -4.3 to 12.2, p-value not reported) when mixed-modality exercisers were compared to controls over 20 weeks of training. In Culos-Reed et al's (24) first study of PCa patients receiving ADT, the physical function role dimension of the EORTC-QLQ improved ($p = 0.03$) but not global HRQOL ($p = 0.13$) with 12-weeks of home-based exercise. However, global HRQOL declined four months post-intervention ($p = 0.04$) which was concomitant with declines in strenuous physical activity volume ($p = 0.01$). This is noteworthy because there was also a trend towards significance for a relationship between general physical activity volume and global HRQOL in the post-program period ($r = 0.34$, $p < 0.1$). In their second home-based exercise study, an RCT, Culos-Reed et al (122) observed that exercisers and controls were similar in EORTC-QLQ scores after the 16-week intervention period. They addressed this unique finding through suggestions that the EORTC-QLQ lacked sensitivity to detect changes in global HRQOL for PCa patients participating in an

exercise program or that there was a potential ceiling effect of their sample due to the relatively high baseline values of HRQOL.

Two studies used generic HRQOL measures to assess exercise-related changes in men undergoing ADT for PCa. The Short Form – 36 Health Survey (SF-36) is designed to capture changes in HRQOL across eight dimensions, including: physical functioning; role limitations resulting from physical health problems; bodily pain; general health; vitality (energy/fatigue); social functioning; role limitations resulting from emotional problems; and mental health (psychological distress and psychological wellbeing) (181, 182). The SF-36 is frequently used in physical activity research across clinical populations (e.g. (183-188)). Carmack-Taylor et al (30) found that the SF-36 or its subscales remained unchanged from baseline following their lifestyle intervention that incorporated 30-minutes of home-based physical activity on most days per week over 6 months. However, in a facility-based, mixed-modality exercise trial over 12 weeks, Galvao et al (23) observed improvements in the SF-36 subscales of general health ($p = 0.022$); vitality ($p = 0.019$); and physical health composite scores ($p = 0.02$).

To summarize the effect of exercise on HRQOL in PCa patients undergoing ADT, among the six facility-based trials that measured HRQOL, three studies (21, 23, 120) demonstrated statistically significant improvements in HRQOL while two others (26, 28) reported clinically significant improvements but lacked sample size to achieve statistical significance. Only one facility-based trial found that exercise had no effect on HRQOL for ADT patients (27). In contrast, the effects of exercise programming for ADT-patients in the home-based setting has been less impressive; none of the three studies with

HRQOL outcomes observed improvements in global HRQOL or in a majority of subscales. In each of Culos-Reed et al's trials only one subscale of HRQOL was improved (24, 122). The stronger HRQOL benefits observed in facility-based trials, compared to home-based trials, may be due to one or more of the following factors: social interaction with peers and training staff, greater programmatic adherence through motivation and external motivation (responsibility to training staff/partners/group), enhanced physical fitness benefits via more intensive, more supervised training. Non-intervention-related reasons for this discrepancy may be the different measures used in the home-based and facility-based trials as the FACT-P and the EORTC-QLQ have almost exclusively been used in the former and latter, respectively. Bourke et al (28) utilized the FACT-P to assess the effect of a hybrid delivery model (i.e. combined facility and home-based) of a lifestyle intervention on disease-specific HRQOL. Utilizing the FACT-P in a strictly home-based intervention, as well as providing routine support from training staff and peers, will provide the most appropriate comparison for HRQOL benefits across delivery settings.

2.4 Fatigue and Prostate Cancer Survivors Undergoing ADT

As previously described, cancer-related fatigue appears to be an essential component of the negative effects of PCa and ADT on HRQOL. Cancer-related fatigue is a unique type of fatigue characterized as a 'subjective feeling of tiredness, weakness or lack of energy' (189) that interferes with normal functioning and is **not relieved** by rest or sleep (190). Fatigue's profound effect on HRQOL forcing cancer patients to abandon

their usual activities and social roles (191). A 59 year old stage IV PCa patient described cancer fatigue as "a crushing, all-encompassing, incapacitating fatigue that is indescribable other than to say that its completely draining" (192). Unfortunately, cancer-related fatigue is the most prevalent adverse effect impacting nearly every cancer patient (140). With an increase in the frequency of multi-modal, high-intensity cancer treatment protocols, the burden of cancer-related fatigue continues to rise (193).

The experience of cancer-related fatigue spans the disease continuum, with approximately 40% of people reporting abnormal fatigue at cancer diagnosis (193, 194) and a continual burden for years after systemic treatment (195, 196). Specifically for PCa patients, ADT worsens fatigue and is reported as being the most highly problematic adverse effect associated with this treatment (48, 61). Stone et al (61) found that 66% of ADT-treated patients reported an increase in fatigue severity after initiating therapy, with 14% reporting significant/severe fatigue. Joly et al (197) found that fatigue severity was significantly worse in non-metastatic PCa patients compared to healthy, age-matched controls. Herr et al (198) found that PCa patients that were receiving ADT had more fatigue than patients not receiving therapy or that underwent localized treatment. Thus, while it is clear that cancer and primary therapies are inherently associated with increased fatigue, ADT patients are particularly vulnerable to experience significantly worse fatigue. Management of fatigue in ADT is, therefore, of great importance given the chronic nature of this treatment and HRQOL-compromising nature of this adverse effect.

Despite its prevalence and highly distressing nature, researchers have yet to comprehensively describe the etiology of cancer-related fatigue, although it is generally

accepted that cancer-related fatigue is a multi-factorial concept with biological and psychosocial determinants (190, 199-201). This has ultimately hampered approaches to an effective resolution. Potential causes of general cancer-related fatigue include: altered metabolic function, hormonal dysregulation/changes, chronic stress response (sympathetic activation), general anxiety and/or depression, anemia, and disrupted sleep patterns (190, 202). In addition to these, ADT patients may have worsened fatigue directly related to the absence of testosterone as this hormone protects against fatigue in healthy men (203) and, conversely, hormonal replacement therapy has been shown to improve fatigue in females (204).

To date, pharmacological management strategies to address cancer and ADT-related fatigue have provided limited benefit to patients. To address anemia-related fatigue, exogenous erythropoiesis-stimulating drugs, such as erythropoietin and darbopoietin, have demonstrated some efficacy at reducing fatigue, but the benefits are only modest (205, 206). Exogenous erythropoiesis-stimulating drugs do not adequately address the severity of overall and idiopathic cancer fatigue (207). Moreover, there are concerns regarding increased risk of venous thromboembolism and mortality with these drugs (208). Ritalin (methylphenidate), a mild central nervous system stimulant commonly used in children with attention-deficit hyperactivity disorder, has shown some promise in improving fatigue in melanoma patients undergoing interferon therapy. A randomized, double-blind, placebo controlled trial at the Princess Margaret Hospital in Toronto is currently investigating the effect of Ritalin in the management of fatigue in

PCa patients undergoing ADT and should provide intriguing information regarding this potential treatment (ClinicalTrials.gov identifier: NCT00593853).

Psychosocial interventions for cancer-related fatigue were reviewed in two meta-analyses (209, 210). Jacobsen et al (209) included 18 trials that used psychological interventions, such as cognitive, behavioural, or coping skills, and found a modest, but statistically significant effect on cancer-related fatigue. The effect of relaxation-based fatigue management strategies were assessed across 15 RCTs by Luebbert et al (210), finding that relaxation was associated with significant benefits in numerous psychosocial and physical symptoms, such as blood pressures, heart rate, nausea, pain, depression, tension, anxiety, mood and hostility. Unfortunately, fatigue was not among the symptoms that improved with relaxation. A limitation to the literature has been that few studies have actually screened for severe fatigue, suggesting that the samples may not be representative of those patients who are most affected (209).

The positive effects on mental and physical wellbeing that exercise produces have made exercise a popular intervention for fatigue management among cancer researchers and clinicians. A recent Cochrane review by Cramp and Daniel identified 22 studies that assessed exercise interventions for the management of cancer-related fatigue in over 2000 cancer survivors during and after treatment (211). The results of the meta-analysis demonstrated that exercise improved fatigue compared to usual care during and after cancer treatment (211). It should be noted, however, that (1) the effect sizes were rather modest (standardized mean difference *during* therapy = -0.18; 95% CI = -0.32 to -0.05; standardized mean difference *after* therapy = -0.37; 95% CI = -0.55 to -0.18), (2) a

majority of the trials were among breast cancer patients (n = 16), and (3) few studies assessed fatigue as a primary endpoint. Despite these limitations, major cancer organizations have eagerly and enthusiastically endorsed exercise as an important fatigue-combating lifestyle approach (193).

2.4.1 Exercise and Fatigue in Prostate Cancer Survivors Undergoing ADT

For PCa patients undergoing ADT, the effect of exercise on fatigue has been mixed. This may, in part, be due to variability in the methodological quality of the studies and differences in the measurement instruments used to assess fatigue. Although most studies have been randomized trials (k = 7 out of 10), methodological quality has been undermined by the use of small sample sizes; only 2 of the 10 studies assessing fatigue powered their studies for this outcome measure (21, 120). In terms of fatigue measurement, five studies used the FACT-F (21, 26-28, 120); two used the Fatigue Severity Scale (24, 122), and one study used the Brief Fatigue Inventory (66). Two other studies used a subscale of a general HRQOL measure to assess fatigue symptoms (23, 30). Similar to the effects of exercise on HRQOL in ADT-treated PCa patients, the impact of exercise on fatigue in participants undergoing facility-based versus home-based exercise programs has been equivocal.

In the four home-based, unsupervised exercise trials that assessed fatigue (24, 30, 66, 122), only one found that fatigue was significantly improved (24). In contrast, four of the six facility-based trials noted statistically significant improvements in fatigue in exercising participants (21, 23, 28, 120) and one study noted a clinically significant

improvement with personal training (and not group-based exercise), but was underpowered to detect statistical significance (26). This pattern of fatigue improvement in facility-based trials compared to home-based trials is consistent in PCa patients who were not undergoing ADT as Windsor et al (66) observed no change in fatigue symptoms during their 4-week home-based exercise program while Monga et al (65) found a reduction in fatigue after 8 weeks of supervised, facility-based AET.

The multi-factorial nature of fatigue challenges the exercise researcher to determine the most effective pathway(s) towards ameliorating fatigue. On one hand, the diverse facets of cancer-related fatigue provide multiple paths for exercise to exert a beneficial influence. On the other hand, disentangling the effects of exercise on those avenues is extremely difficult, and researchers generally resort to measuring the aggregate effects of exercise on fatigue. Further, to this latter point, while the overall experience of disabling fatigue is of utmost importance and should be the primary objective, tailoring an exercise intervention to obtain the greatest effect is impossible without determining which aspects of fatigue are best addressed by certain types of exercise. The current state of literature on exercise for fatigue in ADT patients provides preliminary clues as to which types of interventions improve fatigue, which appear to be facility-based. The lack of success in reducing fatigue across home-based exercise programs is currently unexplained and there is limited evidence to support the idea that any specific modality of exercise (i.e. AET versus RET) has any distinct benefit on fatigue. Only Segal et al (21) investigated modality-specific effects and found, in a secondary analysis of men undergoing both radiation and ADT, fatigue was improved in

the AET group compared to controls but this subanalysis was underpowered to detect a statistically significant difference (fatigue measured by the FACT-F in n = 74, mean between groups $\Delta = 3.3$, 95% CI: -0.4 to 7.0, $p = 0.082$). This is in contrast to Segal et al's (120)earlier work showing that fatigue was less intense after RET than after standard care (mean between groups $\Delta = 3.0$, $p = 0.002$). In light of these discrepant findings and inconsistency across delivery settings, examining AET compared to RET in the home-based setting will add important insight to the question of exercise efficacy for fatigue.

2.5 Physical Fitness and Body Composition in Prostate Cancer Survivors Undergoing ADT

Men undergoing ADT have immediate and profound changes to their body composition and physical fitness related to suppression of testosterone which is reduces muscle mass and bone mass while increasing fat mass (212). In healthy men with age-related hypogonadism (i.e. lowered testosterone), androgen replacement therapy increases muscle mass (213) but its effect on adiposity is unclear (213-215). ADT, on the other hand, unequivocally worsens body composition and these effects occur shortly after the onset of treatment and steadily progress over the course of ADT (216). Luteinizing hormone-releasing hormone analogues (LHRHa) have been associated with significant increases in total weight and fat mass and concomitant decreases in muscle mass and bone mineral density in men with locally advanced or metastatic PCa (11, 49, 217-219).

In a single arm, prospective trial, Smith et al (11) examined the effect of a standard regimen of a LHRHa (leuprolide 3-month depot 22.5 mg intramuscular every 12

weeks for 48 weeks) on body composition outcomes using dual energy x-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) in 32 men with locally advanced (lymph node-positive or biochemical relapse), non-metastatic PCa. In that study, clinical effectiveness of androgen ablation via LHRHa was demonstrated as serum testosterone was reduced by 96.3% ($p < 0.001$), prostate-specific antigen (PSA) decreased by 88.4% ($p < 0.001$), and sex-hormone binding globulin remained unchanged over the 48-week period. Over this period, mean body mass index (BMI) and weight each increased by 2.4% ($p = 0.005$) and body fat percentage increased by 9.4% ($p < 0.001$). The increased fat mass was primarily due to increases in subcutaneous fat (increase of 11.1%, $p = 0.003$) rather than intra-abdominal (visceral) fat (no change from baseline to post-test). These changes in body composition were accompanied by increases in serum total cholesterol (9.0%, $p < 0.001$), low-density lipoprotein (LDL) cholesterol (7.3%, $p < 0.001$), and triglycerides (26.5%, $p = 0.01$) (interestingly, high-density lipoprotein (HDL), the 'good cholesterol' also improved by 11.3%, $p < 0.001$). In addition to these serum markers, fasting glucose and Hb_{A1c} levels have been examined which have shown to be increased in association with ADT (218, 220).

With respect to muscular fitness, ADT alters the androgen receptor complex which compromises muscular development and consequently force production capacity (221). Total body lean mass has been shown to be reduced by 2.0% to 2.7% over 36 to 52 weeks of ADT (10, 11, 49). ADT-related changes in muscle maintenance and adaptation to training stimulus have been attributed to a decrease in the number of androgen receptors on skeletal muscle, the neuromuscular junction via acetylcholine

receptor desensitization as well as reductions in insulin like growth factor-1 (IGF-1) (221). These physiological changes are directly related to the proportion of muscular volume and capacity that routine tasks require and the subsequent recovery from muscular exertion. ADT-related reductions in muscle mass are clinically significant because they accelerate the rate at which elder men approach minimum functional thresholds for independent living and HRQOL (221, 222).

Essentially, the clinical relevance of decreased muscle is reduced physical strength. Basaria et al (223) found that upper body strength (but not lower body strength) was reduced in men on ADT (average duration of ADT = 45 months) compared to age-matched controls. Soyupek et al (224) compared 20 patients with locally advanced PCa on ADT to healthy aged-matched controls and found that grip strength and hand dexterity was worse in ADT users. Clay et al (53) found that compared to controls, men on chronic ADT had significantly slower walking speed and lower extremity function, which was worse in men on long term treatment (> 6 months of ADT). In a RCT of RET compared to standard care controls, Segal et al (120) found significant reductions in upper and lower body muscular endurance over the 12 week intervention period in the control participants. These fitness declines may be more overtly manifested in reductions in overall activity as Galvao et al (49) found a significant reduction in physical activity volume over 36 weeks of ADT. However, not all studies have shown significant declines in functional fitness. Stone et al (225) found that grip strength, a predictor of upper extremity strength and mortality in older adults (61, 226), was unaffected after three months of ADT. Potosky et al (227) observed no difference in limitations to daily

activities in 661 PCa patients receiving ADT versus no PCa-treatment. Collectively, these findings suggest that maximal physical capacity is likely reduced (as demonstrated by consistent findings regarding decrements in fitness tests) whereas functional fitness may be less impaired (as demonstrated by mixed findings regarding ability to adequately complete daily tasks and grip strength measurements).

The effects on fitness are not limited to musculoskeletal parameters, but extended to cardiorespiratory aspects of physical capacity. Reduced haemoglobin (Hb) resulting from ADT is widely established, and although the exact mechanisms lack definitive description, anaemia likely results from inhibition of erythropoeisis through androgen suppression (13). Strum and colleagues (8) reported that rapid declines in Hb in 133 patients as early as one month after the initiation of combined hormone blockade and reaches nadir at six months with an average decline of 25.5 g/L in 133 patients. Chandler et al (14) also reported average reductions in Hb of 10.1g/L over 16 months in a population of 69 ADT patients, with nadir reached at 4 months. The negative effect of ADT on erythropoiesis is a plausible explanation given the recovery of Hb concentrations among ADT patients when treatment is discontinued (along with recovery of testosterone levels) or concurrent recombinant human erythropoietin administration (8, 13, 14). Moreover, the anaemic state of cancer patients may also be attributed to reduced erythrocyte production from bones at metastatic sites (vertebral bodies, pelvis, and long bones) or iron deficiency from poor dietary intake (10, 11).

In men, circulating androgens and estrogens play fundamental roles in the maintenance of BMD (228, 229). The effects of ADT on bone health have been widely

examined with osteoporosis noted as a common adverse effect of treatment that often motivates pharmacological intervention (9, 13, 15, 16, 42, 223, 230-239). In the most definitive epidemiological study conducted to date, Shahinian et al (42) examined the records of 50,613 PCa patients from the Surveillance, Epidemiology, and End Results (SEER) database and found that men who survived for five years or more post-diagnosis had a fracture risk of 19.4% if they received ADT versus 12.6% for men that did not receive ADT. Moreover, fracture risk was associated with reduced survival in a prospective cohort study of 195 men receiving ADT (235). Contributing to the fracture risk is an increased risk of falls due to poor musculoskeletal and aerobic fitness (47, 240)

Another distressing adverse effect of ADT is gynecomastia, i.e. an enlargement of the glandular tissue of the breast in men (241). For ADT patients, gynecomastia is caused by an imbalance in the bioavailable androgens and estrogens, stimulating the development of subareolar fat (241, 242). The early stages of gynecomastia are characterized by proliferation of breast glandular ducts, epithelial hyperplasia, expansion of the stroma, increased vascular tissue, and periductal edema (243). Over approximately one year, proliferation subsides and hyalinisation and fibrosis of the stroma occur which are typically irreversible (243, 244). The incidence of ADT-related gynecomastia depends on the therapeutic approach with patients undergoing non-steroidal anti-androgens alone (such as bicalutamide, flutamide, or nilutamide) suffering the most with incidence rates that range from 30 -79% (243). PCa patients treated with LHRHa produce gynecomastia in approximately 1 to 13%, while surgical castration is related to gynecomastia in 1 to 14% of patients (243). Complete androgen blockade, that is

castration plus anti-androgen, is associated with a gynecomastia incidence of 13 to 22% (243). Unfortunately, the assessment of ADT-related gynecomastia is complicated by the occurrence of idiopathic gynecomastia that is prevalent in many older males (245). Current treatment options for PCa treatment-related gynecomastia include radiation, surgery, anti-oestrogens, and aromatase inhibitors (242, 243). To our knowledge, exercise has never been examined for its effect on gynecomastia and the biological plausibility of a reversal of chronic gynecomastia is unlikely. However, diet and exercise have been recommended for the treatment of pseudogynecomastia (enlargement of breast due to excessive adipose tissue and not glandular tissue (241)) for their combined general effect on muscle and adipose tissue (246). Aesthetically, this may be sufficient to appease men with PCa that are concerned with the appearance of overall excessive fat mass in the breast area. A chest skinfold, taken midway between the axilla and nipple, is utilized to measure subcutaneous fat in the breast region representing a relatively easy approach to assess the effect of exercise on fat tissue in this problematic region.

These changes in body composition, metabolism, and muscular strength may negatively affect HRQOL in several ways. First, body image dissatisfaction is commonly reported, which can negatively affect self-esteem, self-confidence, and potentially cause patients to refrain from social engagement (247, 248). Second, deterioration in physical capacity can reduce recreational physical activity participation and leisure activity that may have physical, mental, and social implications. Third, reductions in general physical activity that have been reported (49) and are particularly important given the positive relationship between obesity and sedentary behaviour and a number of chronic diseases,

including cardiovascular disease, diabetes, hypertension, cerebral vascular accident, osteoarthritis (249, 250). These are notwithstanding the direct association between ADT and metabolic and cardiovascular disease as well as osteoporosis (44-46). The aggregate effect of multi-morbidity further diminishes HRQOL (251). Collectively, the physical adverse effects of ADT have profound, undesirable effects on a several aspects of overall wellbeing (13, 198, 200, 223, 252). Exercise, because of its unparalleled benefit for physical health, has been an obvious lifestyle intervention strategy to ameliorate and reverse many of the physical changes associated with ADT.

2.5.1 The Effect of Exercise on Body Composition for Prostate Cancer Survivors Undergoing ADT

All exercise studies with PCa patients undergoing ADT (including concurrent radiation therapy) have reported on body composition outcomes. This is expected in light of the anthropometric adverse effects of the treatment and the anticipated clinical benefit of exercise for body composition. Researchers have assessed muscle and adipose tissue using numerous techniques, including: dual energy x-ray absorptiometry (DEXA) for localized and total body lean and fat mass (21, 23, 121), DEXA for BMD and bone mineral content (121), quantitative ultrasound for BMD (26), magnetic resonance imaging for quadriceps thickness (27), body fat percentage via skinfold measurements (triceps, biceps, subscapular, and iliac crest sites) (120), and waist circumference (24, 30, 120, 122). Despite the universal hypothesis that exercise would improve some facet of body composition, the effects on body composition have been relatively modest

irrespective of the modality of exercise prescription parameters. However, it is apparent that exercise in the facility-based context provided more benefits for body composition outcome. Among the four home-based exercise programs, no study demonstrated an improvement in a body composition outcome. Culos-Reed et al (24) observed a slight increase in weight ($p = 0.08$) and body mass index (BMI) ($p = 0.02$). In the second trial in ADT patients by Culos-Reed et al (122) using the same home-based intervention in an RCT, exercising participants did not show an improvement in any measurement of body composition; however, neck girth (mean $\Delta = 0.71$cm; $p = 0.046$) and waist circumference (mean $\Delta = 2.06$cm; $p = 0.059$) increased from baseline to 16-weeks in control participants. These differences contributed to a Group x Time interaction effect for both variables ($p < 0.05$). One study examined the effect of a 12-week intervention that incorporated six weeks of primarily facility-based exercise followed by six weeks of primarily home-based exercise, in conjunction with dietary guidance that also did not provide body composition benefits (28).

Four out of seven facility-based exercise intervention studies that examined body composition outcomes among ADT patients found an improvement in at least one measure (21, 23, 26, 121). Of the four studies that demonstrated an improvement in body composition, one was a pure RET program (121) while the rest were combined-modality programs (21, 23, 26). In the one pure RET intervention, Galvao et al (121) found that quadriceps muscle thickness increased by nearly 16% (SD = 12.1; $p = 0.05$). Unfortunately none of the other 10 measures of body composition were altered, including total body fat mass, BMD, lean mass or upper arm thickness. In contrast to their original

trial, Galvao et al's second study of combined AET and RET intervention versus usual care controls found between-group differences for all of their measures of lean mass (total body, upper limb, lower limb, and appendicular skeletal muscle; all $p < 0.05$) but no difference in fat measures. In the subgroup of PCa patients undergoing radiation and ADT, Segal et al found that RET, and not AET, reduced total body fat percentage compared to controls (RET: - 2.79%, 95% CI= -4.71 to -0.87, $p = 0.005$; AET: -0.4%, 95% CI=-2.6 to 1.8, $p = 0.726$). Finally, we recently reported that personal training improved waist circumference by approximately 2 cm ($p < 0.1$) and body fat percentage by almost 8% ($p < 0.05$) after 8 weeks of mixed-modality training (26). We did not observe, however, any improvements in weight, BMI, or BMD in either group-based exercise or personal training participants.

The absence of meaningful benefit to body composition in home-based or partial home-based exercise trials for PCa patients may be attributed to a lack of programmatic intensity that failed to stimulate adaptation. In only two of these trials were exercise prescription details reported, and interestingly, both of these trials also included dietary recommendations or education but neither produced a change in body composition (28, 30). In both trials by Culos-Reed et al (24, 122), although home-based exercise equipment was provided (resistance bands and an exercise ball), no specific intensity or duration of the three to five recommended exercise sessions was described. Another possible reason for poor fat and muscle response to the exercise intervention may be low adherence to one or all dimensions of the exercise prescriptions (intensity, frequency, or duration). To facilitate adherence, three studies investigated theory-based group exercise

classes designed to enhance motivation and social support while addressing barriers to exercise (24, 30, 122). However, only one home-based program provided actual objective monitoring of physical activity volume, providing their participants with pedometers (30). Unfortunately, pedometers do not address the critical element of intensity in an exercise program. A heart rate monitor would likely provide better information regarding intensity because they often allow for the input of upper and lower limits of exercise intensity with audible cues that can alert participants to stay within their prescribed intensity range.

Further distinctions in the evidence regarding the effect of exercise on body composition in this population are drawn between AET and RET. All three of the facility-based programs that did not improve body composition were pure RET programs (27, 120, 180). In the two other pure RET programs, one found significant improvements in body fat percentage by almost 3% compared to controls (21) and the other found an increase in quadriceps muscle thickness by ~16% (121). Across both of these trials, these were the only two body composition outcomes that improved of the 13 that were measured. Conversely, it appears that mixed-modality exercise has been most effective at improving body composition, although the relative contribution of AET to anthropometric changes has not been studied thoroughly. Only Segal et al (21) used a pure AET intervention in ADT therapy patients undergoing concurrent radiotherapy and found no difference between exercisers and controls. In theory, the metabolic cost of AET should exceed that of RET given the prolonged continuous activity required. Alternatively, RET should stimulate the muscular development to a greater extent than

AET because of the adaptation to microtears of the muscle fibers that occurs. It appears that a combination of AET and RET is most appropriate; however, the relative contributions of each modality, particularly in the home-based setting are unclear. Thus, further examination of modality specific training among ADT-only patients is warranted to clarify the roles of these training approaches. This is especially important in the home-based setting as chronic physical activity is required to maintain healthy body composition.

2.5.2 The Effect of Exercise on Physical Performance for Prostate Cancer Survivors Undergoing ADT

Compared to the effects of exercise on body composition, physical capacity has been considerably more responsive to training in men with PCa treated with ADT. As would be expected, all exercise studies in this population have assessed exercise or functional capacity in some way as a measure of intervention efficacy. The most common measure used to assess fitness has been the six-minute walk test, which was used in four trials (24, 27, 30, 122) and is generally considered a reliable measure functional capacity in older adults that correlates well with direct measures of maximal oxygen consumption (225, 253, 254). In addition to the six-minute walk test, functional capacity has been measured by the sit to stand test (23, 28, 121), six-meter walking test (forward and backward) (23, 121), hand grip dynamometry (24, 122) and the timed-up and go test (27). In addition to functional tests, more conventional performance-based fitness tests have been employed, such as directly measured VO_2 peak (21, 26), isokinetic

muscular strength (23, 26-28, 121), and upper and lower body muscular endurance by a standard load test (21, 23, 120, 121).

Again, discordant effects have been observed in the home-based and facility-based setting. Two of the four home-based studies assessing physical fitness have produced statistically significant improvements in findings, but have been relatively minor and the clinical utility of such changes may be questioned. In a sample of ADT-only patients, Culos-Reed et al (24) found an approximate seven meter increase in six-minute walk test performance from baseline to 12 weeks, but this is far below even conservative estimates of clinically important improvements (54 to 80 meters) (255). Windsor et al (66), however, found that walking distance using the Modified Shuttle Test improved by approximately 70 meters over four weeks of home-based AET. It should be noted that more than 70% of participants in this trial were not undergoing ADT, but rather, were receiving radiation therapy only and no stratified analysis was provided for patients receiving concurrent therapy.

Facility-based exercise, on the other hand, has produced fitness benefits in all studies with ADT patients, with many of the improvements having clinical relevance. Segal et al (120) observed an approximate 20-40% improvement in upper and lower extremity muscular endurance after 12 and 24 weeks of RET compared to controls in men receiving ADT with and without external beam radiation (21, 120). In a small sample of ADT patients (n = 10) undergoing 20 weeks of high-intensity RET, Galvao et al (121) demonstrated between 40 and 96% improvements in muscle strength (chest press, seated row, and leg press; $p < 0.001$) and between 115% and 167% in muscular

endurance (chest press and leg press; $p < 0.001$). In their second trial that combined AET and RET versus usual care controls over 12 weeks in a sample of n = 57, Galvao and colleagues (23) reported comparable effect sizes for the exercising group which were significantly greater than controls. Hansen et al (27) found an almost 20% improvement in right leg isokinetic strength after 12 weeks of eccentric resistance training in ADT patient . Finally, in terms of musculoskeletal fitness, we recently observed a 90% and 40% improvement in maximal leg strength in personal training and group-based exercise, respectively.

The findings regarding the effect of exercise on aerobic fitness have been less impressive across facility-based trials. In the two studies assessing cardiorespiratory fitness using directly measured VO_2 peak, the measure remained unchanged following mixed modality, AET, or RET interventions (21, 26). Functional measures of cardiorespiratory function appeared to be only slightly more responsive to exercise training. Galvao et al (121) observed modest improvements in timed walking performance or chair-rise tests compared to controls after 12 weeks of mixed modality training (400-meter walking time, mean between groups Δ = -7.0 seconds, 95% CI: -15.0 to 0.88, $p = 0.08$; chair rise test: mean between groups Δ = -1.0 seconds, 95% CI: -0.1 to 2.1, $p = 0.074$). Although, in Galvao's 20-week pure RET single arm trial, more substantial improvements in 400-meter walk test and chair rises were observed (400-meter walking time, mean within groups Δ = -26.8%, SD: 7.1, $p < 0.001$; chair rise test: mean with groups Δ = -7.4%, SD: 5.9, $p = 0.003$) (121).

Across trials that have investigated the effect of exercise on physical fitness outcomes, the findings have been generally positive with more substantial benefits related to facility-based, RET programs. However, pure AET programs have received minimal investigation with one study in each of the facility-based and home-based settings using this type of training approach. Moreover, in both of these trials, AET was investigated among patients that were undergoing ADT *and* radiation therapy. Pure AET programs have yet to be examined in an ADT-only population. This is significant because radiation therapy is associated with significant fatigue and physical deconditioning independent of ADT, and ADT tends to be a chronic treatment with long-lasting adverse effects that would benefit from sustained exercise. Common AET prescriptions, such as walking, are likely more amenable to sustained participation because they are familiar and easily adaptable to training settings. In this respect, facility-based trials are not generalizable to many sectors of the population that cannot afford to continue supervised training in a fee-for-service institution and tertiary care hospitals are, at present, not able to sustain clinical exercise programs. As such, a comparison of AET and RET, as well as an independent evaluation of their pre-post intervention effects, is necessary in the home-based context will provide important information about the clinical efficacy and long-term sustainability of the two primary modalities of exercise training.

2.6 Fitness-related Biomarkers and their Role in Tumourigenesis in Prostate Cancer

The overt, physical manifestations of androgen suppression, physical fitness, increased fat mass, and reduced muscle mass and bone density, result from a fundamental

alteration of endocrine balance (42, 48, 49, 52). While distressing, more insidious are the changes that contribute to a tumourigenic environment that may facilitate tumour progression. The paradox of ADT, and other cancer therapies is that their anti-proliferative effects are often eventually counterbalanced by increased risks of cellular mutation of the original tumour, rendering it subsequently unresponsive to many therapies and possibly resulting in the growth of secondary cancers (256-258). It is well recognized that PCa in the presence of ADT eventually develops into a castrate-resistant state (also termed androgen independent or hormone refractory), meaning tumour proliferation resumes despite the low androgen environment (259). This advanced stage of PCa is associated with significantly higher mortality despite intensive chemotherapy (260). A hypothesis for hormone-refractory PCa is that the PCa phenotype is inherently aggressive and maintains stem-cell properties that do not require androgens for survival and growth (259). Therefore, alternative growth factors, or local adipokines, may figure in the development or progression of PCa. Creating an anti-tumourigenic environment through the limitation of alternative growth factors may have an important contribution to disease control. Lifestyle interventions, such as diet and exercise, have shown to favourably influence human biology and potentially reduce the risk of PCa progression/recurrence, although the mechanisms remain elusive and not well understood (261).

2.6.1 Effect of Leptin and Adiponectin on Prostate Cancer

The effect of androgens on PCa development and progression is well documented. It is less clear, however, how obesity and excess weight affect androgen levels and subsequent PCa risk. Age-related declines in testosterone in addition to obesity-related hypoandrogenemia (262) are potential reasons why a higher proportion of advanced PCa is diagnosed in obese men. This is especially true when abdominal adiposity exceeds healthy recommendations (263, 264). In this scenario, obesity-related hypoandrogenemia provides an environment where aggressive and androgen-insensitive disease may flourish while coincidentally reducing the incidence of low-grade, non-aggressive disease (264). Beyond the effects of obesity on testosterone, there are direct mechanisms of cell-cycle control via adipokines (cell signalling proteins originating in fat/ adipose tissue) notably adiponectin and leptin. Adipokines have cell-cycle accelerating and arresting qualities through autocrine and paracrine effects[2]. With respect to PCa, adipokines may exert a paracrine effect on localized disease due to excess adipokine excretion from the retropubic, periprostatic fat pad (265). The adipokines adiponectin and leptin, in particular, work in mutually antagonistic ways, with leptin being pro-proliferative and adiponectin being anti-proliferative. Therefore, the ideal anti-proliferative effect would involve relative reductions in leptin and increases in adiponectin.

Leptin, first identified in 1994, is an adipokine predominantly secreted by white adipose tissue (266). Leptin's role is to regulate satiety and energy expenditure by

[2] autocrine: a form of cell signalling where the cell secretes a chemical messenger, or hormone, that influences its own subsequent activity; paracrine: a form of cell signalling where the cell secretes a chemical messenger that influences other proximal cells.

informing the brain of energy stores (i.e. fat) (267). The coding gene for leptin, known as the 'obesity gene' or *Ob* gene, has been termed such because of its association with human obesity (268). Given its relationship with obesity and its tumourigenic properties, several studies have assessed the association between leptin and several cancers, including PCa (269). In a review of thirteen epidemiological studies, Hsing et al (270) reported inconclusive evidence linking leptin with PCa incidence. Nonetheless, leptin's effects on PCa cells *in vitro* have been shown to stimulate growth of androgen-dependent and independent PCa cells (LNCaP versus DU145 and PC-3, respectively) (271-277). Recent findings suggest that leptin-mediated cell cycle regulation is also linked to alterations in p53 and BCl-2 expression (277), which may also have influences on cancer recurrence following treatment.

Adiponectin has the highest serum concentration of all adipokines, accounting for up to 0.05% of all plasma protein (278) and is inversely correlated with obesity and several morbidities, including cardiovascular disease and diabetes (265, 278). Adiponectin deficiencies have been associated with leukemia, and cancer of the breast, liver, and prostate (279-286). Low adiponectin levels have also been correlated with histological grade and stage of PCa (286). Adiponectin has been termed the "anti-cancer adipokine" because of its demonstrated anti-proliferative effects on various cancer cells (287). These protective benefits occur through many potential pathways that impact carcinogenesis, proliferation, and angiogenesis (287, 288).

Dysregulation of leptin and/or adiponectin is related to obesity in humans and has been implicated as a risk factor for PCa incidence and progression. ADT has consistently

shown to increase body fat percentage and waist circumference, as well as increase risks of diabetes mellitus (46). This is relevant because the core elements of metabolic syndrome (associated with Type 2 diabetes) have also been shown to increase cancer risks (289). Changes in total and regional adiposity may contribute to adverse leptin/adiponectin ratios. Conversely, maintenance of a healthy weight and/or weight loss may contribute to healthier levels of these hormones and subsequently improved PCa prognosis. Healthy body composition may be achieved through lifestyle interventions like exercise which has been shown to improve PCa survival (110), although with few direct investigations of the potential biological, tumour control mechanisms (115-118).

2.6.1.1 Effect of Exercise on Adiponectin and Leptin with Reference to Cancer Control

In the oncologic literature, there is a paucity of research on both the acute and long-term effects of exercise intervention on adiponectin and leptin levels, despite the aforementioned tumourigenic properties of various adipokines In a pre-post test study of 16 older, obese adults (without cancer) participating in a 12-week AET and stretching program, O'Leary et al (69) demonstrated significant reductions in body weight and fat mass, as well as leptin, but no change in adiponectin. Fatouros et al (70) examined the impact of a 48-week RET program for elder men (N=50) that compared various intensities (low, moderate, and high-intensity) of training. At post-test, the researchers found that leptin was reduced in each intervention group ($p<0.05$) and adiponectin was increased in the high intensity intervention group only ($p<0.05$). They additionally

reported that changes in leptin were positively associated with changes in BMI and sum of skinfolds. They also found that leptin was negatively associated with changes in VO2 max; a relationship first reported by Pasman et al (71) in a study of 15 obese males that described exercise-related changes in leptin that were independent of changes in body fat. Despite these promising results, the effects of exercise on an elder population of PCa patients that is susceptible to deleterious changes in body composition that can affect adiponectin/leptin ratios, have not yet been examined.

2.6.2 Effect of Insulin-Like Growth Factors on Prostate Cancer

Insulin-like growth factors (IGF) were discovered in 1957 and share similar structural characteristics to insulin (290). Whereas insulin primarily acts on the liver, muscle and fat, IGFs are produced by the liver under regulatory control of the hypothalamus (via growth hormone-releasing hormone) and the pituitary gland (via growth hormone) (290, 291). IGFs can be produced by most tissues in the body and cell-cycle regulation (and hence proliferation, differentiation, and apoptosis) through autocrine and paracrine mechanisms (292). IGFs are regulated by high-affinity binding proteins (IGFBPs) that are regulated by dietary factors, whereas IGFBP concentrations are lowest in the nutritionally satiated state versus highest in the fasting state (293, 294). Of the 6 IGFBPs, IGFBP-3 is the most abundant pairing with nearly all of the circulating IGFs (292, 295).

IGF increases cellular proliferation by increasing DNA synthesis and by stimulating cyclin D1 (a key cell-cycle regulator that promotes transition from the G1 to

S phase) (295). IGF also has anti-apoptotic qualities as it increases the expression of Bcl and suppresses Bax (296) to mediate the activity of p53 (an apoptotic protein) (117). IGF has also been shown to stimulate vascular endothelial growth factor (VEGF) in the promotion of angiogenesis (297, 298). These 'pro-growth' qualities have implicated IGF in a number of cancers, including PCa (97, 299-305). The risk of PCa relative to IGF may be more than 4 times greater in those in the highest quartile compared to those in the lowest quartile (305). Increased risk is also associated with decreased IGFBP-3 concentrations (306-309). Mechanistically, the IGF-axis may be linked to PCa through lifestyle risk factors. Abdominal adiposity and hyperinsulinemia reduce sex-hormone binding globulin (SHBG) which increases bioavailable testosterone and reduces IGFBPs (71, 114, 119, 303, 310, 311). Furthermore, a diet high in fat is known to increase PCa risk (104) and IGF-1 is positively associated with red meat and fat intake and negatively associated with carbohydrate and protein intake (312-314).

As previously stated, ADT can negatively influence body composition in ways that increase adiposity and is related to insulin insensitivity. These deleterious changes in body composition and metabolism create an environment for the IGF-axis to favour malignant growth. Impeding the typical transition into a state of, or approaching, metabolic syndrome through lifestyle approaches such as exercise would be advantageous in terms of reducing the bioavailability of these tumour promoting growth factors.

2.6.2.1 Effect of Exercise on the IGF Axis

Chronic physical activity has been associated with reduced levels of circulating IGF-1 (300, 303, 315, 316). The effect of exercise on the IGF-axis is not well described but generally considered to be intimately related to insulin and metabolism. Exercise may reduce liver and muscle insulin-resistance and increase glucose uptake through postreceptor insulin signalling (including the Glut-4 pathway), increasing glycogen synthesis, increased metabolism of free fatty acids, elevated muscle glucose delivery through greater capillary density, and changes in muscle composition that favour increased glucose metabolism (317). As previously stated, insulin suppresses IGFBP concentration (318, 319), therefore means to reduce insulin are protective against the proliferative qualities of IGF-1. It is worth noting, however, that increases in IGF-1 following acute bouts of exercise have been observed and may be due to an acute increase in pituitary activity and growth hormone secretion (320).

At present there is no interventional research that has examined the effect of exercise on the IGF axis in men with PCa. A recent series of studies in older men demonstrated that chronic (>14 years) and relatively acute (11 days) participation in an exercise program combined with maintenance of a low-fat diet resulted in serum changes *in vivo* that reduced the proliferation and increased the apoptosis of androgen dependent PCa cell lines (LNCaP and LAPC-4) *in vitro* (113-116). In a follow-up study to this series, Barnard et al (118) sought to determine the relative role of chronic exercise (without dietary intervention), by culturing LNCaP cells in serum from elderly men participating in a long-term fitness program only. They found that, *in vitro,* tumour cell

proliferation was reduced with concomitant increases in apoptosis when serum from the exercising men was compared to serum from obese, sedentary men. To determine the relative role of IGF in this experiment, they strategically blocked IGF using tryphostin in the serum from sedentary men and observed that the anti-proliferation and enhanced apoptosis effects were comparable to those seen in the exercise serum (indicating that IGF was likely driving the proliferative and anti-apoptotic characteristics of serum from less healthy men). This suggested that the chronic exercise effects on the IGF-axis might be similar to the administration of known IGF-1 inhibitors and likely due to changes in apoptotic and anti-apoptotic proteins (p53, p21, and Bcl-2). It is worth re-emphasizing that these studies have only been conducted with serum **healthy men** and measurement of IGF-1 concentrations *in vivo* have not been conducted in a PCa population undergoing exercise.

Only one RCT within a cancer population has investigated the effects of an acute exercise intervention on the IGF axis. Fairey et al (321) demonstrated reduced IGF-1 ($p = 0.045$), increased IGFBP-3 ($p = 0.021$), and decreased molar ratio of IGF-1:IGFBP-3 ($p = 0.017$), all anti-proliferative changes, in a population of post-menopausal breast cancer patients undergoing 15 weeks of AET compared to controls. Other intervention-based studies in healthy, older adults have yielded inconsistent results regarding the impact of exercise on the IGF-axis (322-329). When juxtaposed to the rather convincing literature regarding chronic exercise and IGF, whether or not IGF axis is responsive to short duration interventions remains unknown. Furthermore, what exactly constitutes a 'short-duration' is also difficult to discern from existing literature. Intervention-based research

that serially collects IGF-axis proteins over an extended period (>15 weeks) is needed to assess when the IGF-axis is responsive to changes in physiology associated with exercise and whether or not exercise modalities that have distinct metabolic benefits have differing influence on these biomarker concentrations. Ultimately, the essential objective in this strategy is to reduce IGF-1 and increase IGFBP-3 as quickly as possible and to maintain these changes as long as possible.

2.7 Determinants of Exercise Adherence

Research concerning the psychosocial determinants of physical activity in cancer survivors is essential because exercise benefits are rapidly lost when exercise is discontinued (24, 330). Thus, adherence is essential during the intervention to achieve benefit and after the intervention to maintain benefit. To effectively promote and support adherence throughout the continuum of exercise behaviour, a deeper understanding of the psychosocial factors that determine exercise adherence is needed. In healthy populations this is challenging as individual variability in motivation and attention must be considered. The task is even more daunting in clinical populations where individual variability in motivation and intention are compounded by additional disease-related psychosocial and physical barriers to health behaviours. This is apparent in the existing literature that generally describes a reduction in physical activity during cancer treatment, which often does not return to baseline, even several years after treatment completion (331-335).

Early research on the determinants of physical activity after a cancer diagnosis has lacked a consistent theoretical orientation. However, researchers have generally gravitated towards established cognitive-behavioural theories to understand health behaviours in the oncological context (340). Health-behaviour models commonly used to describe and predict physical activity in cancer survivors include Ajzen's Theory of Planned Behaviour (TPB) (341), Bandura's Social Cognitive Theory (SCT) (148, 149), and Prochaska and DiClemente's Transtheoretical Model (TTM; also known as the Stages of Change Model) (146, 147). More recently, measures of social support and exercise-induced feelings have been integrated as independent correlates or potential mediators of other theoretical frameworks (30, 342-346). As scientists continue to explore various determinants of exercise behaviour, multiple theoretical constructs can be tested across different cancers.

2.7.1 Theoretical Models of Exercise Behaviour in Cancer Survivors

2.7.1.1 Theory of Planned Behaviour

The TPB is the most frequently used theoretical model to describe exercise behaviour in cancer survivors during and after treatment. The TPB proposes that the intention to perform a behaviour is highly predictive of the actual performance of that behaviour because intention reflects motivation and the willingness to invest effort in actualizing behaviours (341). This model contends that attitude, subjective norm, and perceived behavioural control all influence intention and subsequently behaviour change (see Figure 2 for TPB model). The element of 'attitude' refers to one's positive or

negative evaluation of performing the behaviour (e.g. "I feel that exercising is..."). Subjective norm reflects the perceived social pressure that one may feel to perform or not perform the behaviour (e.g. "I believe that exercise will be perceived favourably by important others"). Finally, perceived behavioural control can be defined in a similar fashion to self-efficacy, that is, the perceived ease or difficulty with which the behaviour may be performed, reflecting one's control over a behaviour (e.g. "I believe that I can routinely complete my exercise prescription"). Using the example of exercise, the TPB proposes that individuals will exercise if they *intend* to exercise because they 1) maintain a positive evaluation of exercise, 2) believe that important others think they should exercise, and 3) perceive that the successful performance of exercise is within their control.

In describing physical activity behaviours, the TPB has been studied in breast cancer (340, 347-356), colorectal cancer (332, 357), bladder cancer (358), lymphoma (359-361), multiple myeloma (362), ovarian cancer (363), brain cancer (364), head and neck cancer (365), mixed-cancers (including child and adolescent cancer survivors) (366-373), and specifically in PCa (339, 347, 374). Across studies, the TPB has explained between approximately 30% - 70% of the variance in intention to exercise, with specific TPB dimensions (i.e. social norm, perceived behavioural control, and attitude) independently contributing to the overall explained variance depending on cancer type (375).

2.7.1.2 Social Cognitive Theory (SCT)

Self-efficacy is the central determinant of behaviour change according to Bandura's Social Cognitive Theory (SCT) and is arguably the strongest and most consistent predictor of exercise behaviour in current literature (148, 149, 376). Self-efficacy refers to people's beliefs about their capacities to successfully perform specified behaviours (148). Relative to exercise behaviours, self-efficacy is often referred to as the confidence to overcome various barriers to physical activity participation (i.e. *barrier efficacy*) and the confidence to perform the constituent components of healthy exercise behaviour appropriately (i.e. *task efficacy*) (342). The inclusion of *barrier efficacy*, specifically, allows for the consideration of environmental factors that may influence exercise behaviours, like the availability of exercise facilities or equipment and transportation to exercise facilities. Also fundamental to the SCT are outcome expectancies, oriented towards positive or negative self-evaluations (e.g. an emotional response), physical outcomes (e.g. pain or pleasure), and/or social outcomes (e.g. approval or disapproval from peers).

The SCT has been used to explain physical activity behaviours in breast cancer (342, 354, 377-385, 388, 389), colorectal cancer (384, 386), lung cancer (387), and PCa (30, 384). Some researchers have used the SCT as a guiding theoretical model in developing exercise interventions, by focusing on exercise instruction and strategies to overcome barriers to exercise (e.g. setting time aside for daily exercise, providing participants with home-based exercise equipment or training manuals, routine discussion with an exercise professional to address unique barriers, etc.). While these approaches

have been relatively effective at increasing physical activity volume in those that are not exercising, their effect compared to exercise programming that does not included an efficacy-boost strategy is unknown. Furthermore, their effects on measures on exercise-specific self-efficacy have not been described.

2.7.1.3 Transtheoretical Model

The TTM is another well-established psychological framework that has been used to describe physical activity behaviours in cancer survivors, albeit to a lesser extent than the SCT and the TPB. According to the TTM, people move through six stages of readiness with respect to health behaviours (146): 1) pre-contemplation (unaware of or not acknowledging an unhealthy behaviour that requires change), 2) contemplation (aware/acknowledgment of an unhealthy behaviour, debating the pros and cons of behaviour change), 3) preparation (taking necessary steps towards a healthy behaviour change), 4) action (actual participation in the desired health behaviour), 5) maintenance (continuing to participate or act in a desired way, relative to the health behaviour), and 6) relapse (returning to the previous unhealthy behaviour) (146). While transitioning between stages of the TTM, individuals engage in various cognitive and behavioural processes of change (e.g. self and/or circumstantial evaluation, purchase of exercise equipment, contingency management) that play significant roles in the initiation and maintenance of health behaviours. This model of health behaviour change is useful for characterizing the motivational state that can be targeted with specific approaches to intervention delivery. For example, for the cancer patient in a pre-contemplation state,

education-based interventions may be most effective in raising awareness of the benefits of exercise. The TTM has been applied to explain exercise behaviours among breast (354, 379, 382, 385, 388-392), lung (387, 393), and mixed cancer patients(384). Two trials have also incorporated the TTM into exercise interventions for PCa patients (30, 391).

2.7.1.4 Self-Determination Theory

An emerging theoretical approach to assessing and enhancing the psychosocial determinants of exercise in cancer is the Self-Determination Theory (SDT) which postulates that healthy behaviours are regulated by motives that are internally and externally oriented (394). These motives range across a continuum from completely extrinsic motivation (external influence on motives) to completely intrinsic motivation (internal desire to complete a behaviour) (see Figure 4). People may perform extrinsically motivated behaviours in response to a threat (including the threat of chronic disease) or, conversely, in response to an external reward system. Conversely, their intrinsically motivated behaviours may satisfy an inner pleasure or challenge orientation. A state of amotivation may also exist with respect to a particular behaviour when a person feels no intrinsic or extrinsic motivation to perform a behaviour. Deci and Ryan (394) suggest that intrinsically motivating factors are most predictive of health behaviour change owing to greater personal interest, confidence, and persistence for that behaviour. Only a few studies have used the SDT to predict physical activity in cancer patients (395-

399), but some investigators believe its application has provided additional insights beyond the more established theoretical frameworks in this field (399).

2.7.2 Theoretical Models of Exercise Adherence in Prostate Cancer

Only 30% of men with PCa maintain an exercise program sufficient for health benefit (336-339). However, when PCa patients are offered an exercise intervention, they appear relatively receptive as participation rates in research-based exercise programs range from 64% to 100%. Participation in the exercise program once enrolled, on the other hand, is more difficult to ascertain because of the considerable variance in interventions employed and exercise adherence assessment methods used. Nonetheless, it is important to gain whatever insights are possible into the 'quality' of adherence and the determinants of exercise behaviour to effectively design interventions that result in better adherence and benefits that extend beyond programmatic periods. The ultimate goal in this respect is to achieve a lifestyle change or enhancement that includes more routine exercise.

Determinants of programmatic exercise adherence in PCa is not well understood as few studies have applied psychosocial theoretical framework investigations during the intervention periods (64, 337, 339, 347). In a RCT by Courneya and colleagues (64), the researchers examined TPB and TTM-based predictors of adherence to RET in ADT-treated PCa survivors (as measured by number of supervised sessions attended) and found that intention, age (higher age predicted lower adherence) and exercise stage-of-change were the strongest predictors of exercise adherence, accounting for 20.4% of the

variance. Blanchard and colleagues (339) found that intention (TPB) explained 36% of the variance in exercise behaviour among 46 PCa survivors participating in a mail-in survey of physical activity volume and behavioural determinants. The TPB constructs of subjective norm and perceived behavioural control have also been shown to be independent predictors of physical activity in PCa survivors (337, 347).

In an attempt to improve physical activity in breast and prostate cancer survivors via print-based materials, researchers have combined SCT and the TTM to improve the fidelity of their interventions (384, 400-402). In the largest of these trials, Demark-Wahnefried and colleagues examined the role of print-based health lifestyle materials in the FRESH START trial for breast and prostate cancer patients in a randomized, single blind trial (400-402). The intervention was designed to promote healthy changes in eating and exercise with the following specific goals: 150 minutes or more of moderate to vigorous exercise per week, consumption of more fruits and vegetables per day, and restriction of total and saturated fat to less than 30% and 10% of daily caloric intake, respectively (400). To achieve this substantial change in healthy behaviours, the researchers developed a comprehensive theory-driven, home-based program using the SCT and TTM. The SCT was implemented by focusing on improving self-efficacy, self-monitoring, and goal setting to improve health behaviour intention, and subsequently, performance (400). The TTM was incorporated through tailored print messages mailed to participants which were constructed based on their current stage of change, providing stage-related motivation and/or education to facilitate behaviour change (400). To support the home-based program, patients were provided with a workbook, resistance

bands, a pedometer, and a series of personalized mailed-out newsletters meant to encourage participants throughout the program (400). N = 543 breast (n = 306) and prostate cancer survivors (n = 237) were randomly assigned to the FRESH START intervention or to an attention-control group. Participants in both groups completed fitness assessments and questionnaires over the 12-month intervention period and at one-year post-intervention (401, 402). At 12 months, both study groups improved their lifestyle behaviours ($p < 0.05$); however, FRESH START participants reported more frequent: practice of two or more goal behaviours ($p < 0.0001$), exercise minutes per week ($p = 0.02$), fruit and vegetable consumption per day ($p = 0.01$), and less dietary fat intake (total: $p<0.0001$; saturated fat: $p=0.004$) (401). Over 12-months, both groups decreased BMI although more participants in the intervention arm shifted from overweight (BMI = 25.0 to 29.9 kg/m^2) to normal weight (BMI = 18.5 to 24.9 kg/m^2). At one-year post-intervention, participants in both groups were engaging in similar physical activity volume, which was achieved by a reduction from post-intervention physical activity volume levels in the intervention group and a slight increase in physical activity volume from baseline in the control group. This suggests that, over time, home-based print materials can help improve chronic physical activity, but adherence eventually decays to levels comparable to non-intervention participants. This study once again emphasizes the importance of long-term adherence and current deficits in our understanding and influencing adequate chronic behaviour change in this population.

2.7.3 New Theoretical Approaches to Facilitating and Understanding Post-Intervention Exercise Adherence in Men with Prostate Cancer Receiving ADT

Exercise interventions for PCa survivors receiving ADT have been effective at improving a number of clinically relevant outcomes over the course of study. Given this demonstrated efficacy, greater attention must be shifted towards understanding the maintenance of post-intervention exercise adherence, especially because the determinants of exercise initiation and adherence are not always similar (403). Furthermore, preliminary investigations into the determinants of exercise in PCa have incorporated established behavioural theories, while the roles of exercise-specific social support and the experiential effects of exercise (e.g. exercise-induced feelings or sensations) as they relate to exercise motivation behaviours remain under-studied. Exercise-specific social support and exercise-induced feelings require more investigation to understand their roles as potential determinants of health behaviours as they appear logically connected with exercise motivations, adherence and the subsequent effects on overall HRQOL (344, 345, 404).

As demonstrated in the FRESH START trial, physical activity participation in those that are intervened with by correspondence can achieve equivalence with participants that are not intervened with one year following the physical activity program. In that study, the intervention was personalized but not *personal* (i.e. face-to-face), per se, as all intervention-related communication was done through mail. Conversely, Culos-Reed and colleagues (24) did intervene for 12 weeks in a more face-to-face fashion with PCa survivors receiving ADT, yet also observed that four months following the

intervention, vigorous physical activity participation declined with corresponding declines in HRQOL. These findings indicate that intervention-related motivations, exercise behaviours, and resulting benefits subside over a relatively short period following the formal programmatic period and can remain there for the indefinite future. An approach that combines the theoretical strengths of the FRESH START study and that of Culos-Reed and colleagues may be to provide a personalized, home-based exercise program that is initially delivered face-to-face (i.e. exercise prescription that is based on a fitness assessment to personalize the parameters of exercise and demonstrated by an instructor to ensure basic competence with the program), followed up with routinely in-person and via the telephone encounters to address barriers and support physical activity, that also incorporates theory-based print materials for immediate reference and exercise monitoring. Within this intervention design, an expanded face-to-face intervention period of 24 weeks (rather than 12 weeks) may be warranted to ensure that exercise comfort and familiarity are satisfactorily achieved and that a post-intervention follow-up occur somewhere between the 4 and 12 month follow-ups incorporated thus far. Specifically, 6 months appears to be an ideal time-point to measure adherence given the likelihood of people to continue exercising if they reach this milestone (350). Finally, objective measures of fitness such, as exercise sustained capacity following an intervention, would provide more reliable information regarding the adherence post-intervention that is not obtainable through self-report. This type of intervention and adherence measurement approach would add considerable insight into the determinants

of exercise behaviour using the strengths (and acknowledging the weaknesses) of previous research groups.

Given that a diverse range of factors likely influence physical activity in PCa survivors and that most survival expectancies of PCa survivors extend beyond six months, interventions for participants must incorporate a long term plan for activity. Fundamental to this element of exercise interventions will be to establish which factors are related to long-term adherence and then develop ways to exploit them for optimal long-term behaviour change.

3.0 Summary of Identified Empirical Gaps in the Literature of Exercise for Men with Prostate Cancer Receiving ADT

1) A growing body of literature demonstrates the efficacy of AET and RET to improve a variety of physical and psychosocial outcomes for PCa patients; however, their respective effects, especially in the home-based setting, are not well understood among those treated with ADT-only. Furthermore, important aspects of body composition, such as body fat percentage or chest skinfolds, have not yet been examined in home-based exercise.
2) Given that a) the duration of ADT treatment is often 2 years or more, and b) the benefits of an exercise intervention diminish when exercise is discontinued, strategies to enhance long-term adherence are essential. However, the extent to which PCa patients adhere to a personalized exercise prescription after the intervention ends is poorly understood. Furthermore, we know little about the psychosocial determinants of exercise in this population, especially with respect to social support and the experiential effects of exercise.
3) Little is known about the effects of exercise during ADT for PCa in terms of the biomarker outcomes related to the tumourigenic environment, in particular the IGF axis and adipokines. ADT patients represent an important group to examine given the effects of ADT on body composition that may contribute to tumourigenesis when malignant cells become hormone-refractory. To our knowledge, no studies have examined these biomarkers in relation to cancer progression, nor have any assessed modality-specific effects.

4.0 Rationale for Feasibility Assessment

Important questions remain regarding what type of exercise is best for PCa patients receiving ADT and if home-based exercise interventions can elicit comparable results to facility-based interventions, while producing better long-term adherence. To appropriately address these questions through conventional hypothesis testing research approaches, large sample sizes with appropriate institutional infrastructure, support, and expertise are needed. Given the scale and cost of such a study, it is prudent to ensure that conducting such a trial is feasible by the investigative group. According to Arain et al (405), a feasibility study is "research done before the main study...used to estimate important parameters that are needed to design the main study". Arain et al continue to describe the role of the feasibility study as a study that does not necessarily intend to definitively evaluate the outcome of interest (which should be left to the main study), but to determine estimates of outcome variance for sample size calculations and evaluate characteristics and suitability of the proposed outcomes measures for a given population. Additional essential elements of a feasibility study are to assess the willingness of participants to be randomized, recruitment participation from affiliate staff, the available pool of potential participants, adherence to protocols and compliance with follow-up schedules. While hypothesis testing is not the primary aim of a feasibility study, analyses are required to formally establish effect size estimates for future sample size calculations. Because they are statistically underpowered to detect clinically important changes in outcomes, feasibility studies must be interpreted as inconclusive, but the results of

hypothesis testing within this context are worth discussion in the hypothetical narrative to guide intervention or protocol re-evaluation and/or re-design (406).

The Princess Margaret Hospital is internationally recognized as leader in cancer care and research, but it has not attempted a research study to investigate the role of exercise in disease management of this magnitude. Fortunately, a group of clinician-scientists with expertise in psychosocial oncology, exercise, and urology have demonstrated significant interest and willingness to collaborate on exercise-based research; but evidence of support and capacity to overcome logistic challenges was needed. Thus, before embarking on such substantial research endeavour, it was deemed prudent to conduct a formal feasibility assessment of the research design and protocols before proceeding with a large-scale study. The intent of the feasibility study was to be as comprehensive as possible in order to assess methodological approaches for participant recruitment, data collection and management, site-based exercise program delivery, home-based exercise program delivery, routine follow-ups, adverse event occurrence and management, serum sample collection, and estimates of overall success of the intervention. The significant breadth of this undertaking was considered to provide an appropriate understanding of delivery capacity for multi-purpose exercise studies in the future.

5.0 Objectives

Primary Objective: Feasibility Assessment

Logistic and conceptual feasibility for a large-scale, adequately powered trial was assessed in this feasibility study using the following indices:

1) Recruitment rate (recruitment-success percentage)
2) Reasons for non-participation
3) Study retention rate (throughout the intervention period and follow-up)
4) Attendance rates to the group-based booster sessions
5) Prevalence and management of adverse events
6) Effect size of efficacy outcomes

Secondary Objectives: Hypothesis Testing for Main Trial Sample Size Calculation and Conceptual Framework

Aligned with the identified gaps in knowledge regarding exercise for men with PCa treated with ADT, our secondary objectives were:

1) To compare the effect of 6 months of home-based RET with 6 months of home-based AET on psychosocial and physical fitness outcomes that are clinically relevant to men with PCa treated with ADT. The specific efficacy outcomes of interest were:

Psychosocial Outcomes:

- Fatigue
- Disease-specific HRQOL

Physical Fitness Outcomes:

- Body mass index (BMI)
- Waist circumference
- Body weight
- Chest skinfold
- Cardiorespiratory fitness (peak oxygen consumption or VO_2 peak)
- Musculoskeletal fitness (grip strength)

2) To a) compare the effect of home-based AET and RET on physical activity participation and efficacy outcomes at 6-months post-intervention as a measure of long-term adherence and benefit, respectively; and b) assess program adherence using self-report measures of physical activity volume (questionnaire) and program compliance (exercise logbook) as well as an objective measure of physical fitness (aerobic fitness via VO_2 peak).

3) To compare the effect of home-based AET and RET on biological outcomes known to influence PCa cell proliferation. Specifically, these biomarkers are:

- Insulin-like growth factor-1 (IGF-1)
- IGF-binding protein-3 (IGFBP-3)
- Leptin
- Adiponectin

4) To elucidate potential psychosocial determinants of physical activity participation (quantified by self-report and objective measures). Specifically, we assessed:

- Self-efficacy
- Social support
- Exercise-induced feelings

6.0 Hypotheses

1) Recruitment and attrition rates will resemble previous observations in this population (20-40% and 10-20%, respectively) with few, if any, adverse events.

2) RET will be superior to AET at improving grip strength; while AET will be superior to RET at improving aerobic fitness, body composition, and psychosocial wellbeing (HRQOL and fatigue) at the end of 6 months of exercise training.

3) AET will be superior to RET at maintaining the benefits observed at post-intervention to 6 months post-intervention and will be superior in post-intervention physical activity volume.

4) AET will be superior to RET with respect to effects on biomarker outcomes (IGF-1, IGFBP-3, leptin and adiponectin) over 6 months of exercise training.

5) Self-efficacy, exercise-induced feelings, and social support will contribute significantly to the explained variance in program adherence measured by physical activity participation and VO_2 peak (as an objective proxy of sustained exercise).

7.0 Methodology

7.1 Design

This was a randomized feasibility study that compared the effects of AET to RET in a 6-month, home-based intervention for PCa patients undergoing ADT. The site of the research study was the Prostate Centre at Princess Margaret Hospital (PMH) in Toronto, Ontario, Canada. The study was approved by the institutional ethics boards at the University Health Network and York University.

7.2 Sample Size Determination

Approximately 15 patients per month receive ADT depot injections from participating urologists. With a conservative participation rate of approximately 30% (comparable to similar trials (20, 21, 67)), and a timeline for patient recruitment and data collection of two years (including 6-month, post-intervention follow-up), it was deemed appropriate to set a sample size of n = 60 (n = 30 randomized to AET and n = 30 to RET). The 60 patients provided an adequate sample size to test procedural aspects of the study, to refine the exercise intervention program and assessment protocols, and to estimate effect sizes and drop-out rates, for a future main RCT.

7.3 Participant Eligibility Criteria

Eligibility criteria were assessed using chart review, patient discussion, and screening questionnaires (Physical Activity Readiness Questionnaire; PAR-Q, and

Charlson Comorbidity Index, Appendix A and B, respectively) by an exercise physiologist with cancer specific training (DSM) and a physician (SA).

Participant Inclusion Criteria: i) histologically confirmed PCa with an indication for ADT (high-risk/locally advanced disease, rising PSA after definitive therapy, or metastatic disease); ii) initiating or currently receiving ADT for a planned duration equalling study duration (12 months); iii) willing and able to provide informed consent; iv) if metastatic, asymptomatic disease; v) no contraindications to exercise; vi) between the ages of 45 to 95 years.

Participant Exclusion Criteria: i) severe coronary artery disease (Canadian Cardiovascular Society class III or greater); ii) uncontrolled hypertension (BP>200/100) or significant congestive heart failure (New York Heart Association class III or greater); iii) uncontrolled pain; iv) neurological or musculoskeletal co-morbidity inhibiting participation in AET or RET; v) diagnosed psychotic, addictive, or cognitive disorders (using the Charlson Index and chart review).

7.4 Recruitment of Participants

Attending PCa specialists (urologists, medical oncologists, and radiation oncologists) identified eligible participants and notified the research assistant (someone other than DSM). The research assistant approached eligible patients and provided an information package, including study specifics. Patients that expressed interest were

contacted by the study coordinator/exercise physiologist (DSM) for further description of the study, to confirm eligibility (including review of medical records to determine cardiac morbidity via Canadian Cardiovascular Society and New York Heart Association rating scales), and to obtain informed consent (Appendix C). The refusal rate and reasons were documented using a standardized questionnaire (Appendix D). At the orientation meeting participants were also offered an opportunity to ask questions about the study and to set an appointment for baseline evaluation, randomization, and exercise prescription.

7.5 Participant Allocation to Treatment Conditions

Participants were randomly allocated to either six months of home-based RET or six months of home-based AET. Prior to study initiation, opaque envelopes were stuffed with a folded piece of paper that indicated "AET" or "RET", the envelopes were sealed and shuffled. After shuffling, the contents of any given envelope could not be determined. These envelopes were then sequentially numbered and assigned to each participant as they entered the study. The envelope was opened following the participant's baseline assessment which then made apparent the group allocation. The research team could not know group allocation until after the baseline assessment in accordance with a blinded randomization process. Subsequent outcome assessments were not conducted by blinded outcome assessors.

7.6 Intervention Provision

Patients allocated to the RET and AET groups were introduced to their designated exercise program after the baseline evaluation. Although there are inherent differences in the exercise modalities (AET versus RET) that cannot be completely reconciled, the RET and AET prescriptions were designed to approximate equivalent intensity and duration. Participants in each intervention arm received a detailed manual produced by the research coordinator (DSM) using principles of exercise adherence based on previous home-based interventions with PCa patients receiving ADT (24, 25). The manuals described the exercise prescription using narrative and visual descriptions, information about intensity monitoring, safety precautions, appropriate progression, and adaptation of the program, and an exercise log to record exercise participation. In addition to the manual, the research coordinator/certified exercise physiologist (DSM) demonstrated all of the required exercises to the point where patients could verbalize competence and confidence with their exercise program. Participants were also instructed on how to complete the exercise logs. To facilitate ongoing participation and exercise prescription compliance, the exercise physiologist contacted each participant every other week to ensure adherence to the program, completion of the exercise log, and to address any limitations/barriers to participation.

7.6.1 Resistance Exercise Training Prescription

Participants in the RET program were asked to perform their assigned exercises 3 to 5 times per week, for approximately 30-60 minutes each session at a moderate to

vigorous intensity, for 6 months. RET guidelines indicate that a minimum of 48 hours between resistance exercises of the same muscle group be provided to ensure adequate recovery of muscle tissue. The present exercise prescription encouraged participants to complete the entire set of 10 exercises two to three times weekly. For participants that were new to exercise, it was recommended that they complete half of the exercises on alternate days to ensure that enough recovery time was available. No participant was asked to complete all exercises five times weekly. To complete the exercises at home, each RET subject was provided with a set of 3 resistance bands (light, moderate, and heavy resistance), an exercise mat, and a 55 cm or 65 cm exercise ball (dependent upon the participant's height). Each resistance exercise was performed for 1 to 3 sets of 8 to 12 repetitions at an intensity of 12-15 out of 20 on the Rating of Perceived Exertion (RPE) scale (approximately 60-80% of 1RM) (155). Initial intensity was based on the performance of the exercises during the exercise prescription session. The ten RET exercises that were prescribed were: ball squats, hamstring curl, push-ups, upright row, triceps extension, bicep curl, seated row, lateral raise, abdominal crunches, and hip extension. All exercises were designed to have three levels of intensity (beginner, intermediate, and advanced) to accommodate varying degrees physical fitness and exercise experience. Additionally, movement-specific accommodations or adaptations for patients with functional limitations were made.

7.6.2 Aerobic Exercise Training Prescription

Participants in the AET program were asked to participate in aerobic exercise of their preference 3 to 5 times per week, for 15-60 minutes at a moderate to vigorous intensity (RPE of 12-15 out of 20 or 60-80% of heart rate reserve), for 6 months. Although participants were able to choose their preferred modality, walking was the primary/default modality for the exercise prescription. To ensure appropriate intensity was maintained during the course of the exercise sessions, patients were provided with heart rate monitors (Polar® Heart Rate Monitor FS2, Kempele, Finland) that provided audible cues when they were outside of their prescribed training zone (pre-set by the research coordinator based on findings from the cardiorespiratory fitness test).

7.6.3 Booster Sessions

To promote adherence to the exercise interventions and address barriers to exercise, participants were invited to attend booster sessions every two weeks in a group-based format for the 6-month intervention. Each 1.5-hour session included a one hour exercising training session and a 30-minute education/discussion component. The training sessions consisted of equivalent AET and RET durations (20 minutes each) with a 10-minute warm-up and cool-down. The education component was developed by Dr. Culos-Reed and addressed various topics related to exercise participation and long-term adherence, such as goal setting, barriers to exercise, and social support (see Appendix E for a description and the sequence of booster session topics). Booster sessions have been

useful and well attended in previous studies with PCa patients receiving ADT (24, 25). Attendance was taken at each booster session.

7.7 Outcome Assessment

Participants were required to attend the study site (Princess Margaret Hospital) on four occasions to complete outcome assessments. Outcomes were measured at baseline (after randomization), mid-intervention (3 months), intervention completion (6 months), and a post-intervention follow-up (6 months after the completion of the intervention. Each assessment took approximately 60 minutes. All assessments were conducted by the research coordinator and CEP (DSM), who were not blinded to the treatment assignments.

7.8 Outcome Measures

7.8.1 Psychosocial Outcome Measures

7.8.1.1 Functional Assessment of Cancer Therapy-Fatigue (FACT-F)

The FACT-F is a 13-item measure that assesses cancer-specific fatigue (194, 201, 407-413). The FACT-F uses a 5-point Likert scale ranging from 0 (not at all) to 4 (very much so) to describe how true various fatigue-related statements are for participants over the last seven days (Appendix F). The total sum score ranges from 0 (worst fatigue) to 52 (no fatigue). The FACT-F has high test-retest reliability (r = 0.87), excellent internal consistency (Cronbach's α=0.93-0.95), and good convergent/discriminant validity (412,

413). The FACT-F has been used extensively in PCa research (61, 197, 199), including trials assessing the effect of exercise in PCa patient receiving ADT (20, 21).

7.8.1.2 Functional Assessment of Cancer Treatment-Prostate (FACT-P)

The FACT-P is a widely used instrument that uses 35 items from the generic FACT (FACT-G; a cancer-specific HRQOL measure) scale plus 12 items that are specific to PCa to produce a 47-item questionnaire (Appendix G). The FACT-G is an extensively validated cancer-specific measure with high reliability and internal consistency estimates and has been translated into several languages (176, 414-418). The FACT-P has discriminated between PCa patients differentiated by disease stage, performance status and PSA score and is sensitive to performance status and meaningful clinical change over 2 month intervals (176). The FACT-P has been validated in older cancer patients (417) and has shown significant differences in PCa patients related to exercise intervention in 3 previous studies (20, 21, 65).

7.8.1.3 Patient-Oriented Prostate Utility Scale (PORPUS)

To further assess PCa specific HRQOL changes associated with exercise, we also employed the PORPUS (177). The PORPUS is a psychometric and utility HRQOL scale that has been found to be reliable in discriminating between groups of PCa patients with metastatic versus nonmetastatic disease, men being administered ADT versus no-ADT, and men whose Charlson Comorbidity score was ≤ 2 versus > 2, as well as change over time in these known groups (419). The PORPUS is a 10-item questionnaire that asks

patients to selecting 1 of 5 possible conditions in the following domains: pain and disturbing body sensations, energy, support from family and friends, communication with doctor, emotional wellbeing, urinary frequency, bladder control, sexual function, sexual drive, and bowel problems (Appendix H). The PORPUS has been used in several studies to assess treatment-related changes in HRQOL (420-424). A clinically important difference in the PORPUS (psychometric) is 5 points (425).

7.8.2 Physical Fitness Outcomes

7.8.2.1 Body Composition

Three measures of body composition associated with health-related fitness were employed: body mass index (BMI), waist circumference (WC), and body fat percentage using sum of three skinfolds (3SKF). BMI was calculated using the participant's weight and height (BMI = weight (kg)/height $(m)^2$). WC was measured using anthropometric tape according to protocols defined by the World Health Organization (tape placed horizontally mid-way between the bottom of the rib cage and the iliac crest) (426). Measurements were taken to the nearest 0.5 cm. To assess body fat percentage, 3 SKFs were measured using Harpenden Calipers (FitSystems Ing, Calgary, Alberta) at the chest, abdominal, and thigh sites (426). All measurements were taken on the right side of the body. Body density and body fat percentage were calculated using population-specific standardized equations for men (426, 427):

- Body Density (dB) in g/cm^3 $=1.109380-(0.0008267*(\Sigma 3SKF))+(0.0000016*(\Sigma 3SKF)^2)-(0.0002574*$ age)
- Body Fat % = (4.95)/dB-4.50

(At present, cancer-specific skinfold-based body fat percentage equations are not available and the equation for white adult males, aged 18-61 years was used as the most accurate approximation of the study sample). Body composition changes are highly prevalent in PCa patients receiving ADT (11, 49), are associated with poor prognosis and PCa mortality (264, 270), and have been shown to be beneficially augmented with exercise (22-25).

7.8.2.2 Cardiorespiratory Fitness

Cardiorespiratory fitness refers to the ability of one's heart and lungs to deliver oxygen to working tissues and is important for most functional tasks. Cardiorespiratory fitness is often expressed in maximum or peak volume of oxygen consumption (VO_2 max or VO_2 peak) and is typically described relative to one's body weight (millilitres of oxygen consumed per kilogram of body mass per minute; ml O_2/kg/min). To assess VO_2 peak in AET and RET participants, the modified Bruce treadmill protocol (426, 428) was selected because it uses a prolonged warm-up and walking (rather than running) combined with increases in grade (incline) to bring participants to maximum intensity (429, 430). The modified Bruce Treadmill protocol requires participants walk at 1.7 to 3.7 mph (5.95 km/h) at elevations from 0-18% grade, with speed/grade increased every 3 minutes to a point of subjectively described 'maximal' effort using the 10-point Borg Rating of Perceived Exertion Scale (155). VO_2 peak is estimated using standard American College of Sports Medicine (ACSM) metabolic equations (429).

A certified exercise physiologist (CEP) accredited to conduct testing in symptomatic/asymptomatic populations, and certified in Basic and Advanced Cardiac Life Support (ACLS), with ACLS equipment and supplies on-hand, conducted all tests. Standard termination criteria for clinical graded exercise testing was applied: chest discomfort, nervous system symptoms (ataxia, dizziness, near syncope), cyanosis/pallor, or participant's desire to stop (426). In a clinical population, the risk of complications associated with exercise testing is typically extremely small when the testing protocol and guidelines for exercising tolerance testing are carefully followed, as well as continuous monitoring the client's physiological response (426). The risk of a fatality during an exercise test is approximately 0.00005% (1/20,000), and for a myocardial infarction is approximately 0.0004% (1/2,500) (426). Maximal cardiorespiratory fitness testing has been safely assessed in previous exercise intervention studies with PCa patients (21, 65).

7.8.2.3 Musculoskeletal Fitness

To assess musculoskeletal function grip strength was measured using a Jamar Dynamometer (Sammons Preston, Bolingbrook Illinois, U.S.A.) according to the Canadian Society for Exercise Physiology protocol (431). Grip strength is an independent predictor of mortality in older adults and may identify patients, including those with a high level of function, who are at risk of deteriorating health (225, 432). Grip strength has been used frequently as a measure of physical function in PCa patients undergoing ADT (24, 25, 197, 433).

7.8.3 Biological Outcomes

To assess the effect of exercise on biomarkers associated with cancer progression, DSM collected serum samples at the hospital and transported to York University under the care of Dr. Michael Connor, who supervised the analysis by the research coordinator (DSM). Each participant provided a whole blood sample, but due to budgetary constraints, only 26 participants had their samples analyzed at baseline, mid-intervention, and intervention-completion time points. These participants were the first 26 to complete the first three time points. Given that assays were only available on a small proportion of participants, we consider these analyses only exploratory in nature.

7.8.3.1 Blood Collection

Twelve mL of whole-blood was drawn by the research coordinator (DSM) who is a certified research phlebotomist at the University Health Network. Whole-blood was labeled and centrifuged at a lab at Princess Margaret Hospital to separate red blood cells from serum. Red blood cells were discarded and serum (~5 ml) was stored in duplicate, labeled aliquots at -30 degrees Celsius before batch transfer to York University.

7.8.3.2 Serum Analysis

A 'sandwich' Enzyme-Linked Immunosorbent Assay (ELISA) was used to quantify the amount of the proteins of interest (insulin-like growth factor-1 (IGF-1), IGF-binding protein (IGF-BP3), leptin and adiponectin). Aliquots of co-culture serum were incubated in a 96-well plate with protein antibodies for each protein (IGF-1, IGF-BP,

leptin or adiponectin). The desired proteins adhere to their antibodies and remain on the plate after washing. Following the wash, protein biotinylated primary antibodies (biotin) were added to the wells and bind to the specific protein present during a 2-hour incubation period at room temperature. Following this incubation, excess primary antibody was washed away and streptavidin-linked horseradish peroxidase (HRP) is added to the wells. The streptavidin on the HRP binds to the biotin on the primary antibodies and after incubation (1 hour) any excess HRP is washed from the wells, the HRP substrate is added, and the luminescence in each well is measured/recorded using an ELISA analyzer. The amount of luminescence is indicative of the amount of protein present in the wells. These values are compared to a standard curve to determine the specific amount of each protein present in each well.

7.8.4 Program Adherence Outcomes

7.8.4.1 Godin-Shephard Leisure Time Exercise Questionnaire (GLTEQ)

As a proxy of adherence to the exercise prescription, past-week physical activity and exercise was assessed using the GLTEQ (434). The GLTEQ is a 3-item measure that assesses the frequency of mild, moderate and strenuous bouts of leisure physical activity or exercise performed for at least 15 minutes over the past week (Appendix I). To provide data in MET-hrs/wk that could yield insight into the activity volume relative to the ACSM (American College of Sports Medicine) guidelines for physical activity in cancer survivors (435), the questionnaire was modified by adding the specific duration for each intensity as per the previous work by previous groups (e.g. (350, 436)). An independent

evaluation confirmed its reliability and validity compared to nine other self-report measures of exercise participation (437). Specifically, The GLTEQ demonstrated reasonable 1-month test-retest reliability of 0.62 and concurrent validity coefficients of 0.32 with accelerometer-assessed physical activity, 0.56 directly measured VO_2 peak, and –0.43 with body fat percentage. A change of 15 MET-hrs/wk was considered clinically significant given its correspondence with health benefits (110, 435). The GLTEQ has been widely used with cancer patients and survivors participating in exercise interventions (331, 340, 357, 436, 438-444), including PCa patients receiving ADT (24, 25).

7.8.4.2 Physical Activity Logbook

Although the GLTEQ provides crude estimates of weekly physical activity volume, in order to gain a more detailed understanding of exercise behaviours, a physical activity log was included in the RET and AET manuals for analysis. These logbooks were created for patients to easily record the frequency and intensity of their respective programs. These logbooks also served as reminders to patients of what they have completed and what they needed to complete over the course of each week, and provided feedback regarding progress of physical fitness. Exercise logbooks were collected at the end of 6 months for examination and quantification of total physical activity volume in MET-hours per week (MET = metabolic equivalent, a measure of activity intensity relative to resting state).

7.8.4.3 Objective Proxy of Program Adherence: Cardiorespiratory Fitness

Home-based exercise research has been challenged to find an accurate, reliable, and feasible method of determining program compliance. At present time, the only method of objectively quantifying exercise behaviours is direct observation but it is often not feasible to implement, and the potential benefits are offset by the bias introduced by the routine presence of a researcher to examine active behaviours. With these limitations, indirect assessments of program adherence are commonly employed, such as the doubly-labeled water technique, accelerometry, self-report, and objective measures of physical fitness.

The doubly-labeled water technique measures changes in concentration levels of ingested 'heavy' isotopes of hydrogen and oxygen, which degrade and exit the body in a fashion that allows for the estimation of metabolic activity. The doubly-labeled water technique is the gold standard of measuring energy expenditure, but is expensive (~$250,000 USD for the analyzers), time-consuming, and the analysis does not provide specific information on adherence parameters, such as type, frequency, intensity, or duration of exercise sessions (445, 446). Accelerometry via pedometers and three-dimensional accelerometers are increasingly popular in exercise interventional research. Pedometers measure step count by monitoring vertical movement mechanically or electronically. Pedometers are small, easy to use, relatively inexpensive, and have demonstrated a moderate-strong correlation with activity heart rate (r = 0.54), doubly labeled water (r = 0.55), and direct observation (r = 0.69) (446). Unfortunately, they are not effective for assessing non-ambulatory exercises, such as cycling, swimming, or

resistance training (445). Modern accelerometers are now widely available and are able to measure activity in three dimensions, but they are more costly compared to pedometers and are still ineffective at measuring resistance training exercises.

Self-reporting of physical activity is the most commonly employed method of exercise adherence measurement and is quantified using data from logbooks and/or exercise questionnaires (both used in the present study) (445). These methods generally require participants to recall and/or describe their physical activity over a period of time which can be translated into a total physical activity volume given the frequency, intensity, time, and type of exercise performed. There are several advantages to self-report measures of physical activity, such as ease of completion/administration, convenience (they can be completed via telephone, mail, or in person), require few resources, and can provide relatively detailed information about exercise behaviours. Exercise logbooks provide a detailed account of exercise behaviour and can reinforce the actual prescription (by providing specific program parameters for each exercise session for the participant to complete and record). Unfortunately, they are often inconvenient for the participant and thus poorly maintained (446, 447). Recall surveys, such as the GLTEQ, may be quickly and easily administered and require respondents to recall aspects the activities in which they participated over the specified time period. Physical activity questionnaires used as a measure of adherence assume that an increase in physical activity volume from baseline is attributable to the adoption of the exercise prescription. Unfortunately, the specific details of the activities are often not available and specific exercise activities can be inferred only by changes in total physical activity

volume. Moreover, both exercise logs and activity volume questionnaires are subject to response bias and recall bias, which impair their validity and reliability (446-448).

A third method of indirectly assessing program compliance is through physiological/performance changes. Given the strong and direct correlation between physical activity and fitness performance measures, it is reasonable to assume that changes in performance over the duration of an intervention are likely due to some increase in physical activity, and hopefully, activity that corresponds with the provided exercise prescription. Physical fitness measures, such as musculoskeletal strength tests or cardiorespiratory fitness assessments, are modality-specific; however, a graded exercise treadmill test may be most generalizable to overall improvements in physical fitness given the muscular and cardiorespiratory demands of general physical activity. For example, Jones et al (131) found that for lung cancer patients who were 80% adherent to the facility-based/supervised exercise program (as indicated by direct observation), VO_2 peak increased by 3.3 mlO_2/kg/min; whereas no change in VO_2 peak was observed participants that were non-adherent (< 80% adherence). Furthermore, changes in cardiorespiratory fitness are indicative of extended periods of inactivity, which would correspond with program non-compliance (449, 450). Exercise and physical activity studies that employ fitness measures often show a stronger association between the behaviours and health outcomes because there is less error and they are not vulnerable to social desirability or recall bias (445).

In the present study, we used observed changes in cardiorespiratory fitness to provide an objective assessment of physical activity participation to supplement/validate

the exercise log and GLTEQ. The operational definition of adherence in this context, the threshold for determining an adherent participant, was an improvement in VO_2 peak of 3.3 mlO_2/kg/min. This cut-off closely resembles the generally accepted minimal clinically important difference of 3.5 mlO_2/kg/min (the equivalent of one metabolic equivalent or MET) and it has previously been correlated with exercise adherence in lung cancer patients (131). The protocol for VO_2 peak measurement is provided in Section 1.4.8.8.2.

7.8.5 Correlates of Exercise Adherence

The following measures were employed to examine various psychosocial correlates of exercise behaviour in our intervention.

7.8.5.1 Exercise-Induced Feeling Inventory-Chronic Training (EFI-C)

The Exercise-Induced Feeling Inventory for Chronic Training (EFI-C) contains two subscales that measure physical exhaustion and pleasant mood states associated with physical activity during the past week (451). The EFI-C was founded on the EFI-Acute, which measured acute changes in feelings to exercise using 4 subscales (452). The EFI-C is a 12-item measure that requires participants to rate how often they experience the stated feelings during physical activity, such as "refreshed", "worn-out", and "happy" (Appendix J). Both subscales (physical exhaustion and pleasant moods) of the EFI-C demonstrated strong internal consistency and reliability coefficients (~0.90) (451). The

EFI-A and the EFI-C have been used widely to describe predictors of physical activity participation and adherence in a diverse range of populations, including elders (453-456).

7.8.5.2 Self-Efficacy for Physical Activity Survey (SEPAS)

The SEPAS is a 12-item scale that assesses self-efficacy for exercise behaviours (457). The SEPAS uses two subscales to assess whether respondents are confident in allocating time and energy to exercise and resisting exercise relapse (return to sedentary) by 'sticking to' an exercise program under conditions of stress, added demands, depression, fatigue and peer disruption (457). In the SEPAS, respondents are asked to rate their confidence from "I know I cannot" to "I know I can" in various circumstances including "Get up early, even on weekends to exercise" and "Stick to your exercise program when you have household chores to do" (Appendix K). Self-efficacy is an important concept in improving adherence to novel behaviours, including exercise, and has been studied frequently in cancer populations (343, 380, 458-462). The SEPAS demonstrated acceptable test-retest reliability (r=0.68), internal consistency (Cronbach's alpha= 0.83-0.85), and construct validity (457). The SEPAS has previously been used to gauge self-efficacy in sedentary women who participate in novel strategies to improve physical activity (463) as well as in older patients with a cardiac diagnosis(464).

7.8.5.3 Social Support for Physical Activity Questionnaire (SSPAQ)

Social Support for Physical Activity (SSPAQ) Questionnaire (465) was used to measure the social support of family and friends in two separate subscales. Both

subscales (20 items in total) rate the frequency with which family members or friends have done or said something to support physical activity (Appendix L). For example, respondents are asked to rate how often their family or friends "exercised with me", "gave me encouragement to stick with my exercise program", or "changed their schedule so we could exercise together." The SSPAQ (complete questionnaire and selected items) has been used previously with a variety of populations, including cancer survivors (342, 346, 466).

7.8.5.4 Demographic, Disease, and Treatment Information

Demographics (e.g., age, education, marital status, etc.) and other information believed to have a possible influence on outcome (tumour stage and Gleason grade, previous treatments, etc.) were collected (Appendix M).

7.8.5.5 Comorbidity

Comorbidity was quantified by the research coordinator (DSM) using the Charlson Comorbidity Index (467) based on self-report information from the participant during each assessment. The Charlson Comorbidity Index rates 22 morbidities using scores of 1 (low morbidity), 2, 3, and 6 (high morbidity) to yield a total score that predicts one year mortality (467) (Appendix B). The Charlson Comorbidity Index has been used widely in exercise research for cancer patients (131, 468-471). Comorbidity index scores were used as a means of adjusting for individual medical conditions (472-474).

7.9 Data Management and Statistical Analysis

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 19.0 (IBM, Armonk, New York). All data were reviewed for completeness and accuracy by the research coordinator (DSM) and a research assistant. Obvious errors in data entry were compared against hard copies of the assessment documentation and corrected to ensure completeness and accuracy. For all hypotheses testing analyses, the alpha level was set to 0.05 to identify statistically significant differences and associations with minimal risk of making a Type 1 error.

7.9.1 Sample Characteristics, Baseline Equivalency, Normal Distribution, and Outliers

Descriptive statistics (e.g. mean, standard error, frequency) for all outcomes were assessed at baseline to describe the general sample. Prior to analyzing data relevant to the *a priori* objectives, independent samples t-test for continuous variables and chi square tests for categorical variables were conducted to assess group equivalency at baseline (AET versus RET and dropouts versus non-dropouts). Histograms of continuous variables were used to visually assess the distribution of data. Data distribution was also assessed using skewness and kurtosis statistics to screen for outcomes with potentially skewed or non-normal distributions. Screening for potentially skewed outcome measures was conducted by dividing the skewness and kurtosis factors by their standard errors, respectively (475). Values that exceeded the threshold of $\pm$ 1.96 were compared to

graphical (histogram) interpretation (475). Outcomes that were confirmed to be skewed were log-transformed for analysis. Outliers were maintained throughout all analyses. Data for HRQOL outcomes and adherence variables were re-coded when necessary such that increases in scores represent improvements in symptoms and higher levels of the adherence-supporting characteristic, respectively.

7.9.2 Efficacy Estimates

To assess and compare the efficacy of each intervention over time, a two-way (two factor) repeated-measures analysis of variance (RM-ANOVA) was used. This test produced main effects for Group and Time as well as the Group x Time interaction. When an interaction effect was significant, simple effects were calculated to determine the time points where the interaction occurred. In cases where violations of sphericity were observed (Mauchly's Test: $p > 0.01$), the Greenhouse-Geisser correction for F-statistic and statistical significance was used.

We also conducted paired-samples t-tests to derive effect size estimates from baseline to 3, 6 and 12 months and from 6 months (post-intervention) to 12 months (follow-up) within each intervention arm. This strategy was implemented to provide estimates of effect size for within group analyses in future trials that investigate the effect of varying durations of AET or RET.

7.9.2.1 Intention-to-Treat (ITT)

Given the large volume of data to be collected over two years in elderly PCa patients that likely have one or more co-morbidities, missing data and attrition were inevitable. To most stringently assess the effect of an exercise intervention (AET or RET) in this population, an intention-to-treat (ITT) approach was employed. While some debate exists regarding the most appropriate method of handling missing data (476, 477), imputation, using the last value carried forward (LVCF) is widely employed to provide conservative estimates of effects while maintaining sample sizes and statistical power which facilitate sample size calculation in future trials.

The exception to this approach was during the group and time analysis of the psychosocial correlates of physical activity behaviour (i.e. self-efficacy, exercise-induced feelings, and social support). In this case, only a per protocol approach was used to assess changes in outcomes as they reflect determinants of behaviour rather than efficacy (clinically relevant) outcomes. Because determinants of behaviour are sensitive to exposure and experience within an exercise program, use of the last value carried forward (LVCF) technique might 'wash out' potential changes in participants' experiences, without offering additional insight into behavioural mediators. In other words, if the 'participants' are not actually participating in the program (as per LVCF approach), their behaviour cannot be reliably determined. Thus, only participants that completed these questionnaires at each time point were used.

7.9.2.2 Per Protocol Analysis

A per-protocol analysis was conducted using only those participants that completed the assessments at the study time points. This was conducted to provide estimates of program efficacy for those participants who remained connected to the intervention, in contrast to the ITT analysis that provided conservative estimates of program delivery efficacy across the population.

7.9.2.3 Sub-Group Analysis of Biomarker Outcomes

As previously mentioned, only 26 participants (n = 13 from each of the groups) had their serum samples assayed for biomarker concentrations. These 26 participants were the first to complete all three intervention assessment time points in their respective intervention arms (i.e. baseline, 3 months, and 6 months). Their data were analyzed using RM-ANOVA with main effects and interaction effects described. Paired-samples t-tests were employed to assess within group changes for effect size, and subsequent sample size, calculations.

7.9.3 Correlational Analyses and Multivariate Models

7.9.3.1 Correlations and Explanation of Variance between Changes in Physical Outcomes and Biomarkers

Bivariate correlations were tested using Pearson's *r* to assess the relationship between physical outcomes and various biomarkers (e.g. body fat percentage and adipokines). These correlations were conducted on grouped data (AET + RET) to

determine the relationship between the outcomes irrespective of training modality. Pearson correlations were also conducted to examine whether *changes* in various physical outcomes were correlated with *changes* in biomarker concentration.

7.9.3.2 Bivariate Analysis of Adherence Measurements and Determinants of Exercise

To assess the relationship between self-report (GLTEQ and exercise logbook) and objective (VO_2 peak) measures of adherence, a Pearson's correlation coefficient, *r*, was conducted with combined group data. Pearson's *r* correlations were also conducted to assess the relationship between determinants of exercise variables (self-efficacy, exercise-induced feelings, social support), control variables (age and comorbidity status), and the self-report and objective measures of adherence (GLTEQ/exercise logbook and aerobic fitness, respectively) to confirm inclusion into subsequent multivariate regression models.

7.9.3.3 Multivariate Models of Psychosocial Correlates of Exercise Behaviour and Self-Report Physical Activity Volume and VO_2 peak

To determine the extent to which self-efficacy, social support, and exercise-induced feelings predicted adherence to the exercise interventions, we conducted a hierarchical multiple linear regression (similar variables are entered in blocks) to examine the relative contributions of each independent variable on the variance in physical activity volume (GLTEQ), logbook-determined physical activity volume, and VO_2 peak (as an

objective proxy of program adherence). *A priori*, we hypothesized that comorbidity status and age would contribute to the explained variance in adherence. As described previously, we conducted bivariate correlations of control variables with the outcome measures at each time-point to ascertain whether age and comorbidity were related inorder to decide whether one or both control variables should be included into the model. This was deemed necessary to ensure a comprehensive model while maximizing statistical power. Although most statistical textbooks indicate that a minimum of 10-20 participants per independent variable is required for adequate power in multiple linear regression (478), it was deemed appropriate to reduce the statistical power in light of the exploratory nature of this investigation and consequently interpret the findings cautiously.

Each regression model assessed the effect of self-efficacy, social support, and exercise-induced feelings (independent variables) on physical activity volume or VO_2 peak while controlling for exercise modality (AET versus RET) and comorbidity status (Charlson Index). These models were conducted for each time point (baseline, three months, six months, and six months post-intervention). To assess whether baseline psychosocial variables were predictive of changes in physical activity volume or VO_2 from baseline to post-intervention, a multiple linear regression was conducted using baseline values for social support and exercise-induced feelings, controlling for age and exercise group, on the change scores in physical activity volume and VO_2 over this period of time. Self-efficacy was excluded from this analysis given the smaller number

of participants completing the baseline self-efficacy measure with baseline and six-month data for all model covariates (n = 20).

7.9.4 Post-hoc Power Analysis and Sample Size Estimation of Efficacy Outcomes

For all analyses, observed effect sizes (partial $\eta 2$) and power were reported for between-factors analyses from the SPSS output (i.e. AET versus RET). Sample size calculations for the observed between-factor effect size were calculated using G*Power Statistical Analysis Software (261). For 'Sample Size Calculation for Observed Effect' the Observed Effect Size (*f*) was calculated in G*Power as $f=\sqrt{\text{partial } \eta 2 / (1 - \text{partial } \eta 2)}$. Sample size calculations were also conducted for hypothesized effect size using established minimal clinically important difference (MCID) and standard deviations (SD) from previous exercise-related research to calculate Cohen's d (d =MCID/SD) which was converted to Cohen's *f* (515). In circumstances where MCIDs were not established, a medium effect size ($f = 0.25$) was used as a conservative default. Correlation among repeated measures (required for sample size calculation) was conducted using the mean of the Pearson *r* values across all time points. For sample size calculations, alpha level and power were set to 0.05 and 0.80, respectively.

8.0 Results

8.1 Results of Feasibility Assessment

8.1.1 Recruitment

The CONSORT (Consolidated Standards of Reporting Trials) (479) diagram is presented in Figure 1. Sixty-six (n = 66) participants were recruited from among the 205 eligible participants we approached between June 2009 and July 2010 (recruitment rate = 32%). Reasons for refusal were: no time (n = 33), lack of transportation/too far to travel (n = 8), traveling during the intervention period (n = 12), not interested/no reason (n = 27), self-determined inability to participate (n = 35), or already exercising (n = 24).

8.1.1.1 Sample Characteristics

Participant demographics are presented Table 2. At baseline the AET and RET differed in IGFBP-3 concentrations (AET = 5582.7, SEM = 1514.3 versus RET = 4360.5, SEM = 1370.9, p = 0.05) and the emotional wellbeing subscale of the FACT-P (AET = 20.8, SEM = 0.52 versus RET = 18.5, SEM = 0.84, p = 0.02; data not shown).

8.1.2 Study Retention

From baseline to 6 months, attrition was 26% and 44% for the AET and RET groups, respectively. This difference between groups did not reach conventional levels of statistical significance (dropout versus non-dropout in AET versus RET; χ^2 = 1.941, p=0.164). In the AET group, reasons for dropout were: disease progression inhibiting continued participation (n = 1), loss of interest/motivation (n = 1), too far to travel for

assessments (n = 1), symptoms/comorbidities interfered with exercise participation (n = 2), no time (n = 4). In addition, four patients were lost to follow-up without explanation (i.e. they could not be reached after multiple attempts). For the RET group, reasons for dropping out were: advanced disease inhibiting continued participation (including deceased) (n = 3), loss of interest/motivation (n = 3), too far to travel for assessments (n = 3), symptoms or comorbidities interfered with exercise participation (n = 4), no time (n = 2). In addition, seven patients were considered lost to follow-up when they could not be reached after several attempts. From post-intervention to the 6 month follow-up, n = 5 and n = 8 participants were lost in the AET and RET groups, respectively. There were no statistically significant differences in the baseline characteristics between those who dropped out before the 6-month follow-up versus the non-dropouts ($p > 0.05$); however, there was a trend for the dropouts to be older ($p = 0.067$), heavier ($p = 0.077$), and to have lower aerobic fitness ($p = 0.052$) (Table 3).

8.1.3 Booster Session Attendance

The AET and RET groups attended a mean of 16.4% and 5.5% of the booster sessions, respectively ($p = 0.045$).

8.1.4 Adverse Events

There were no serious adverse events related to the exercise intervention in either group.

8.4.5 Exercise Logbook Completion

Only 43% and 30% or participants completed the exercise logbook at 3 and 6 months, respectively. Further, the quality of log completion was inadequate for an accurate quantification of adherence to the exercise prescription. Therefore, it was decided by the research team to exclude the exercise logbook from any analysis given the poor completion rate.

8.2 Distribution of Data

After statistical and graphical consideration, data were judged to be normally distributed across all outcomes and at all time points. Accordingly, data were analyzed using parametric tests. The only exception to this was physical activity volume at each time point, which was highly positively skewed because most participants at baseline and throughout the trial increased their physical activity volume from 0 MET-hrs/wk. In this scenario, central tendency was near 0 MET-hrs/wk with an apparent normal distribution above zero, but no values below zero (as zero is the absolute minimum), thus producing graphical skewness (as well as statistical skewness). The measure of physical activity volume, the GLTEQ, has been used in numerous exercise studies in cancer (including PCa) and despite similar issues with skewed distributions, most studies have not tried to normalize the distributions before conducting parametric statistical tests (e.g. (24, 122, 331, 374)). This has likely been done to maintain interpretability of findings. To circumvent this issue, numerous studies have elected to convert physical activity volume into categorical variables of sedentary (no physical activity), insufficiently active for

health benefit (1-149 minutes of physical activity) and meeting exercise guidelines (> 150 minutes of physical activity) (e.g. (370, 480, 481)). In the present trial, we decided to maintain the fidelity of the measure and keep physical activity volume in a continuous variable format. Moreover, adherence may be considered most appropriately in the context of degree or extent, rather than kind or type (374).

8.3 Results of Intention-To-Treat Analysis

8.3.1 Fatigue and HRQOL Outcomes

Fatigue and HRQOL outcomes, using an ITT analysis, are presented in Table 4. There was a significant main effect of Group for the FACT-P emotional wellbeing subscale ($F(1,58) = 7.3$, $p = 0.009$). Simple effects analysis indicated there were significant between-group differences at each time point ($p \leq 0.02$, See Figure 5). This was consistent with a discrepancy in baseline equivalency described earlier. There was a trend towards a significant main effect of Group for fatigue ($F(1,60) = 2.86$, $p = 0.096$) with simple effect analysis showing trends towards significance for between-groups differences favouring AET at 6 months (mean $\Delta = 4.5$, SEM = 2.63, $p = 0.092$) and 12 months (mean $\Delta = 4.7$, SEM = 2.69, $p = 0.084$; See Figure 6). The FACT-P social wellbeing subscale also demonstrated a trend towards group main effects ($F(1,58) = 3.65$, $p = 0.06$), with between-group differences favouring AET observed at 6 months (mean $\Delta = 2.9$, SEM = 1.26, $p = 0.027$). There were no additional significant main effects of Group or Time. There were no significant interaction effects. Within-group comparisons between time points by paired-samples t-tests did not reveal significant differences.

8.3.2 Physical Fitness Outcomes

Physical fitness and body composition outcomes, using an ITT analysis, are presented in Table 5. There was a significant main effect of Time for chest skinfolds ($F(1.99, 123.08) = 4.813$, $p = 0.01$), body fat percentage ($F(2.07, 126.36) = 5.554$, $p = 0.004$), and physical activity volume ($F(2.51, 152.89) = 5.491$, $p = 0.003$). There were trends towards significant main effects of Time for waist circumference ($F(3, 186) = 2.565$, $p = 0.056$) and VO_2 peak ($F(2.32, 127.65) = 2.655$, $p = 0.066$). There were no significant main effects of Group. There was a significant Group x Time interaction effects for physical activity volume ($F(2.51, 152.89) = 3.122$, $p = 0.003$; Figure 7). Simple effects analysis of this interaction indicated that only AET improved in GLTEQ scores from baseline to 3 months (mean $\Delta = 13.34$ MET-hrs/week, SEM = 4.35, $p = 0.003$), baseline to 6 months (mean $\Delta = 17.20$, SEM = 4.64, $p < 0.001$), and from baseline to 12 months (mean $\Delta = 14.18$ MET-hrs/week, SEM = 3.80, $p < 0.001$).

Paired-samples t-tests showed that, from baseline to 3 months, the AET group improved weight (mean $\Delta = -1.5$ kg, SEM = 0.6, $p = 0.013$), waist circumference (mean $\Delta = -1.4$ cm, SEM = 0.5, $p = 0.012$), BMI (mean $\Delta = -0.5$ kg/m^2, SEM = 0.2, $p=0.014$), chest skinfold thickness (mean $\Delta = -3.0$ mm, SEM = 1.2, $p = 0.020$), body fat percentage (mean $\Delta = -1.6\%$, SEM = 0.8, $p = 0.054$), and physical activity volume (mean $\Delta = 13.3$ MET-hrs/week, SEM = 5.2, $p = 0.016$). Significant improvements in physical activity volume for the AET group from baseline to 3 months were maintained at 6 months (mean $\Delta = 16.7$ MET-hrs/week, SEM = 5.5, $p=0.005$) and 12 months (mean $\Delta = 13.8$ MET-

hrs/week, SEM = 4.3, p = 0.003). At 12 months, the AET group showed significantly improved body fat percentage (mean Δ = -1.9%, SEM = 0.09, p = 0.029) and waist circumference (mean Δ = -1.4 cm, SEM = 0.6, p = 0.03) compared to baseline. From baseline to 6 months, the RET group displayed a significant increase in VO_2 peak (mean Δ = 2.2 mLO_2/kg/min, SEM = 0.8, p=0.011). The RET group also demonstrated reduced body fat percentage from 6 months to 12 months (mean Δ = - 1.4%, SEM = 0.5, p = 0.014).

8.4 Results of Per Protocol Analysis

8.4.1 Fatigue and HRQOL Outcomes

Fatigue and HRQOL outcomes, using a per protocol analysis, are presented in Table 6. There was a significant main effect of Time for HRQOL via the PORPUS (F(3,69) = 4.184, p = 0.009). There were no significant main effects of Group. There was a significant Group x Time interaction effect for HRQOL via the PORPUS (F(3, 69) = 3.431, p = 0.022; Figure 8). Simple effects analysis of this interaction indicated that only RET improved in PORPUS scores from baseline to 12 months (mean Δ = 8.90, SEM = 2.54, p = 0.002), from 3 months to 12 months (mean Δ = 6.92, SEM = 2.59, p = 0.014), and from 6 months to 12 months (Δ = 6.658, SEM = 2.50, p = 0.014).

In within-group comparisons via paired-samples t-tests, RET improved in PORPUS scores from baseline to 12 months (mean Δ = 8.09, SEM = 2.45, p = 0.008) with a trend towards a statistically significant difference from 6 months to 12 months (mean Δ = 4.92, SEM = 2.70, p = 0.093). From baseline to 12 months, the RET group

demonstrated a near clinically important difference from baseline for fatigue (MCID = 3.0 points, (120, 413)); however, this was not statistically significant (mean Δ = 2.83, SEM = 1.83, p = 0.145). There were no other significant within-group differences.

8.4.2 Physical Fitness Outcomes

Physical fitness outcomes, using a per protocol analysis, are presented in Table 7. There was a significant main effect of Time for waist circumference ($F(3,93) = 2.461$, p = 0.087), body fat percentage ($F(3, 90) = 5.483$, p = 0.001), and VO_2peak ($F(3, 78) = 2.876$, p = 0.041), with a trend towards a Time main effect for chest skinfold thickness ($F(3,93) = 2.461$, p = 0.087). There were no significant main effects of Group. There were no significant Group X Time interactions.

In within-group comparisons via paired-samples t-tests from baseline to 3 months, AET improved weight (mean Δ = -1.8 kg, SEM = 0.65, p = 0.012), waist circumference (mean Δ = -1.7 cm, SEM = 0.61, p = 0.011), BMI (mean Δ = -0.6 kg/m^2, SEM = 0.22, p = 0.014), chest skinfold thickness (mean Δ = -3.6 mm, SEM = 1.4, p = 0.02), body fat percentage (mean Δ = -1.9%, SEM = 0.9, p = 0.054), and physical activity volume (mean Δ = 16.0 MET-hrs/week, SEM = 6.1, p = 0.016). At 6 months, compared to baseline, AET participants had significantly greater VO_2peak (mean Δ = 3.0 mlO_2/kg/min, SEM = 1.3, p = 0.03) and physical activity volume (mean Δ =21.5 MET-hrs/week, SEM = 7.6, p = 0.01). At 12 months, compared to baseline, AET participants had lowered waist circumference (mean Δ = -1.8cm, SEM = 0.8, p = 0.037) and body fat percentage (mean Δ = -3.3%, SEM = 1.2, p = 0.013), while demonstrating increased physical activity

volume (mean Δ = 13.7 MET-hrs/week, SEM = 6.1, p = 0.038). RET participants improved chest skinfold thickness (mean Δ = -3.9 mm, SEM = 1.5, p = 0.018) and VO_2peak (mean Δ = 3.8 mlO_2/kg/min, SEM = 1.3, p = 0.011) from baseline to 6 months as well as body fat percentage from 6 months to 12 months (mean Δ = -3.0 MET-hrs/week, SEM = 1.0, p = 0.012). There were no other significant within-group differences.

8.5 Results of Exploratory Biomarker Assay Analysis

The subgroup analyses of those that underwent biomarker assays at baseline, 3 months, and 6 months are presented in Table 8. A main effect of Time was observed for IGFBP-3 ($F(2, 44) = 3.338$, $p = 0.045$). There were no main effects of Group. There were no interaction effects.

Within-group comparisons by paired-samples t-test demonstrated that the RET group demonstrated a significant reduction in IGF-1 (mean Δ = 20.9 ng, SEM = 7.7, p = 0.019). At 6 months compared to baseline, the AET group demonstrated a significant decrease in IGFBP-3 (mean Δ = -1332.9 ng, SEM = 591.2, p=0.049, a non-preferable trend), whereas the RET group showed a significant increase in IGFBP-3 (mean Δ = 527.4 ng, SEM = 234.0, p=0.044, a preferable change). These changes at 6 months corresponded with significant changes in IGF-1:IGFBP-3 ratios, with the AET group increasing the ratio by 0.01 (SEM = 0.01; $p < 0.05$) and the RET group decreasing the ratio by 0.01 (SEM = 0.003; $p < 0.05$).

8.6 Exploratory Analysis of Correlations between Outcomes

8.6.1 Correlations between Physical Fitness Outcomes and Biomarkers at Baseline

Correlations between physical outcomes and biomarkers at baseline are presented in Table 9. As would be predicted, weight, BMI, waist circumference, and body fat percentage were all significantly negatively correlated with adiponectin and positively correlated with leptin and leptin:adiponectin ratio ($p < 0.05$). Grip strength was inversely correlated with leptin (r = -0.415, p = 0.039) and trended towards a significant inverse relationship with IGFBP-3 (r = -0.394, p = 0.057) and leptin:adiponectin ratio (r = -0.381, p = 0.066).

8.6.2 Correlations between Changes in Physical Fitness Outcomes and Biomarkers at 3 months

Changes in physical outcomes and their association with changes in biomarker concentration at 3 months are presented in Table 10. At 3 months, changes in weight, BMI, and waist circumference were positively correlated with changes in leptin (r = 0.41 to 0.61, $p<0.05$), while an increase in VO_2 peak was associated with a decrease in leptin concentration levels (r = 0.41, $p < 0.05$). Changes in IGF-1:IGFBP-3 ratios were inversely associated with changes in weight, BMI, and waist circumference (r = -0.44 to -0.46, $p < 0.05$), with a trend towards a positive relationship with VO_2 peak (r = 0.38, p = 0.068).

8.6.3 Correlations between Changes in Physical Fitness Outcomes and Biomarkers at 6 Months

Changes in physical outcomes and their association with changes in biomarker concentration at 6 months are presented in Table 11. At 6 months, changes in leptin were positively correlated with changes in weight and BMI (r = 0.52 to 0.53, $p < 0.01$) and negatively correlated with increases in VO_2 peak (r = -0.471, p = 0.020). Leptin:adiponectin ratio changes were positively correlated with changes in weight and BMI (r = 0.52 to 0.53, $p < 0.01$) and negatively correlated with body fat percentage (r = -0.53, p = 0.008). A positive relationship between waist circumference and IGFI:IGFBP-3 was also observed (r = 0.432, p = 0.035) which is discordant with findings observed at 3 months (r = -0.456, p = 0.025).

8.6.4 Change in Determinants of Exercise Over Time

Self-Efficacy

Change in mean self-efficacy scores for both groups is presented in Figure 9. There was no significant main effect for Time or Group. There was no Group x Time interaction. Using paired-samples t-tests, a significant within-group difference was observed between baseline and 12 months for the AET group (mean Δ = -1.06, p = 0.014; 95% CI: 0.250 to 1.868). There were no other within-group differences for the AET or RET group.

Family Social Support for Exercise

Change in mean scores of social support from family for both groups is presented in Figure 10. There was no significant main effect for Time and no significant Group x Time interaction. There was a trend towards a main effect for exercise Group ($F(1, 58) = 3.443$, $p = 0.069$). Simple effects analysis of this interaction demonstrated that there was a between-groups difference at 12 months, with the AET group having significantly higher family social support than the RET group (mean $\Delta = 6.2$, $p = 0.037$, 95% CI: 0.398 to 12.002).

Friend Social Support for Exercise

Change in mean scores of social support from friends for both groups is presented in Figure 11. There was no significant main effect for Time or Group, and no significant Group x Time interaction. A significant within-group difference for aerobic exercisers was observed between baseline and 6 months (mean $\Delta = -0.443$, $p = 0.043$; 95% CI: -0.015 to -0.871). There were no other significant differences within-group differences for AET and RET participants.

Social Support (Total)

Change in mean scores of total social support for both groups is presented in Figure 12. There was no significant main effect for Time or Group, and no significant Group x Time interaction. Significant within-group differences for the AET group were

observed from 3 to 12 months (mean $\Delta = 0.258$, $p = 0.027$; 95% CI: 0.033 to 0.483) and from 6 to 12 months (mean $\Delta = 0.265$, $p = 0.030$; 95% CI: 0.028 to 0.502). There were no other within-group differences for AET and RET participants.

Exercise-Induced Feelings

Change in mean scores of exercise-induced feelings for both groups is presented in Figure 13. There was no significant main effect for Time or Group, and no significant Group x Time interaction. A significant within-group difference for the RET group was observed between 3 and 12 months (mean $\Delta = 0.439$, $p=0.018$; 95% CI: 0.082 to 0.797) There were no other within-group differences for AET and RET participants.

8.6.5 Relationship Between Determinants of Exercise, Self-Reported Physical Activity Volume and VO_2 peak

Bivariate correlations between determinants of exercise measures, control variables, and measures of program adherence (as assessed by the GLTEQ and VO_2 peak) at each time point are presented in Tables 12-15. Notably, age had a strong negative correlation with VO_2 peak at each time point (r = -0.61 to -0.70) and therefore was incorporated into the multivariate models. The Charlson comorbidity index was not significantly correlated with physical activity (GLTEQ) or VO_2 peak and therefore was excluded from the multivariate models. In terms of correlations between the candidate exercise-determinant variables, exercise-induced feelings had a moderate positive correlation with self-efficacy at every time point (r = 0.31 to 0.53). Social support for

exercise (total score) also had a low to moderate positive correlation with self-efficacy at every time point except at 6 months (r = 0.29 to 0.34). In terms of outcome measurements, physical activity volume and VO_2 peak had a low to moderate positive correlation at every time point (r = 0.29 to 0.53).

Model fit for multiple regression analyses of psychosocial determinants of exercise behaviour with physical activity volume and VO_2 peak at each time point are presented in Table 16 (individual predictor variable coefficients for physical activity volume and VO_2 peak are presented in Tables 17-20 and Tables 21-24, respectively). The models were not predictive of self-reported physical activity volume at any time point. While the models were significantly predictive of VO_2 peak, this relationship was driven largely by age. Model fit for multiple regression analyses of social support, exercise-induced feelings and control variables with change in physical activity volume and VO_2 peak from baseline to 6 months are presented in Table 25 (individual predictor variable coefficients are presented in Tables 26 and 27). Neither model explained a significant amount of the variance in the change-scores of the adherence outcomes (self-report or objective).

8.7 Post-hoc Power and Sample Size Calculations

8.7.1 Fatigue and HRQOL Outcomes

Post-hoc power and sample size calculations for fatigue and HRQOL outcomes are presented in Table 28. The effect size (converted from partial η^2 to Cohen's f) for a main effect of Group (between-factors analysis) in a RM-ANOVA for FACT-F, FACT-P,

and PORPUS was 0.22, 0.139, and 0.173, respectively (*f* of 0.1 is considered to be a 'small' effect size, *f* of 0.25 is considered to be a 'medium' effect size). For the observed effect sizes, sample sizes of between n = 172, n = 348, and n = 226 are required for the FACT-F, FACT-P, and PORPUS, respectively. However, *a priori* sample size calculations should be based on clinically important differences, which yield sample size requirements of n = 78 (FACT-F), n = 92 (FACT-P), and n = 134 (PORPUS) to provide 80% power at alpha = 0.05.

8.7.2 Physical Fitness Outcomes

Post-hoc power and sample size calculations for select, clinically important physical fitness outcomes are presented in Table 29. The effect size (converted from partial η^2 to Cohen's *f*) for a main effect of Group (between-factors analysis) in a RM-ANOVA was very low and thus sample sizes to reliably detect such small differences were quite substantive (n = 252 to n = 6668). N=110 (n = 55 per group) is required to provide 80% power at alpha = 0.05 using a medium effect size ($f = 0.25$) based on clinically important difference and previous research, for the other physical fitness outcomes.

8.7.3 Biomarker Outcomes

Post-hoc power and sample size calculations for the biomarker assay outcomes are presented in Table 30. The effect size (converted from partial η^2 to Cohen's *f*) for a main effect of Group (between-factors analysis) in a RM-ANOVA ranged from small to

medium (referent values for effect sizes using Cohen's *f*: 0.1 = small, 0.25 = medium, 0.4 = large). In the absence of any established MCID information regarding these outcomes, medium effect sizes (Cohen's $f = 0.25$) were used to calculate sample sizes yielding a sample of N=110 (n = 55 per group) per biomarker analysis with 80% power at alpha of 0.05.

8.7.4 Determinants of Exercise Outcomes

Typical recommendations for sample sizes in multiple linear regression models refer to Cohen's estimate of n = 10 per predictor variable with some texts recommending up to n = 20 per predictor variable (475, 478, 482). Some have criticized this approach for being over-simplistic and for not relying on the hypothesized effect size (475). The effect size in a multiple linear regression can be determined by the fit of the overall model (i.e. how much variance is explained by the model, denoted by R^2) or by the influence of the predictor variables (denoted by unstandardized (B) and standardized (beta) coefficients). Green (483) proposed an algorithm for effect size calculation based upon the type of information being pursued. Green suggests that $50+8k$ is necessary to test for model fit (where k = number of predictors). To test for individual predictor influence, Green suggests $104 + k$ (483). In circumstances where both the fit and strength of the predictors is desired, both sample sizes should be calculated with the larger of the two used in the design of the trial (483). Green's calculations generally fall within the 'rule of thumb' recommendations n = 10-20 per predictor variable with added consideration for the effect size of interest. In the present trial, sample sizes ranged from

n = 29 to n = 48 for models that examined the explained variance of determinants of exercise outcomes at specified time points (depending on the amount of participants with complete data for the model at the analyzed time point). In these models, there were 5 predictor variables. According to Green's recommendations, the necessary sample size to test for model fit would be n = 90 and for the individual predictors it we would need n = 109.

9.0 Discussion

The underlying premise of hormonal therapy for PCa is to minimize the exposure of PCa cells to testosterone, which is its primary growth factor. Unfortunately, this disruption of normal endocrinology has downstream effects that significantly undermine HRQOL by negatively interfering with normal physiological and psychosocial activity. Exercise has been shown to improve physical and mental wellbeing in healthy populations, with effects opposite to those of ADT. As ADT has demonstrated strong cancer-control efficacy, strategies that can reduce the negative burden of treatment and possibly enhance disease management are highly desirable. Accordingly, research over the last two decades has explored the actual benefit of exercise in PCa patients treated with ADT. Positive findings regarding the efficacy for exercise among ADT patients have led researchers to combine exercise with intervention design features aimed at enhancing long-term exercise (21, 24, 30, 121). Our study assessed the feasibility of conducting a randomized trial of distinct exercise programs (AET and RET) for PCa patients receiving ADT and provided exploratory hypothesis testing of several outcomes pertinent to participants' physical, physiological, and psychosocial wellbeing. Given the relatively immature state of exercise intervention literature for PCa patients, it is appropriate to begin the discussion of our results with both the position and relevance of this study in the context of the overall PCa-exercise body of research.

At the time of this study's conception, only five studies assessing exercise interventions for PCa patients were published, four of which were in men treated with ADT (24, 65, 66, 120, 121). These studies were highly heterogeneous in intervention

design, methodological quality, and results, even though exercise was generally associated with physical and/or psychosocial benefit. In the time since this study was initiated, seven additional exercise interventions for PCa patients have been published (21, 23, 26-28, 122, 180) and at least four additional studies are underway with published methodology (126-128, 484). Our study treated 66 PCa patients with an exercise intervention, which represents approximately 8% of all PCa patients (n = 868) participating in research-based exercise program among published trials. This is also comparable to the average sample size of PCa-exercise studies that have a mean of n = 62 participants. Given the growing interest and publication in this field, the effect of exercise on PCa management is arguably the most rapidly advancing area of exercise study in oncology with our study contributing a significant proportion to the overall data.

Our study adds numerous novel elements to the literature while re-examining important aspects that still require clarification and additional insight. The unique aspects of this study include: 1) a comparison of home-based AET to RET, 2) utilization of the PORPUS as a secondary disease-specific HRQOL measure, 3) independent analysis of chest skinfold thickness (apart from a sum of skinfolds calculation for body fat percentage), 4) use of an objective fitness measurement to validate self-report measures of program adherence, 5) assessment of the hormones adiponectin and leptin which may react to exercise and be altered in ways that prevent cancer progress, 6) inclusion of exercise-induced feelings as a potential determinant of exercise behaviour, and 7) a 6 month post-intervention follow-up (previous research followed participants for 4 months after the intervention). This was also the first exercise intervention for PCa

survivors at the Princess Margaret Hospital (PMH) that, prior to this study, did not contribute to the exercise oncology literature despite its international prominence as a centre for excellence in cancer care and research. This study also builds on the ground-breaking results of earlier research by supporting previous findings and raising questions about the generalizability of past results. The commonalities our research shares with earlier exercise intervention research in PCa are: 1) examining the efficacy of generalized home-based exercise programs, 2) group booster sessions that are theory-based to improve exercise adherence, 3) usage of validated measures of HRQOL, fatigue, and physical activity volume, 4) assessment of IGF-1 and IGFBP-3, 5) examination of social support and self-efficacy for exercise, and 6) reporting of recruitment, safety, and attrition findings. The present study's novelty juxtaposed to the commonality it shares with the greater body of exercise intervention research in PCa provides a strong foundation for generalizability of our findings as well as advancement in the research field.

Likely the key feature that this research contributes to the overall literature of exercise-related effects in ADT-treated PCa survivors is a better understanding of modality-specific effects in the home-based setting. It was important to assess the difference between AET and RET in this population for various reasons. For exercise professionals, there is significant utility in the ability to identify the modality-specific benefits in order to tailor exercise prescriptions based on patient symptoms and goals. It also provides information that assists patients and clinicians to make priority-based decisions on the relative investment of time that they focus on competing modalities.

Possibly most importantly, it is important to know which modality is most likely to yield chronic behaviour change in this population as ADT may be indicated for many years, and possibly for the remaining years of the patient's life. This importance is dramatically underscored by recent epidemiological evidence showing that men who exercise for ≥ 9 MET-hrs/wk *after* a diagnosis of PCa have a 33% and 35% reduction in all-cause and PCa-specific mortality, respectively (110). This includes men who were sedentary prior to a PCa diagnosis, highlighting the importance of exercise behaviour initiation during and/or after treatment. Men in the current trial assigned to AET increased their physical activity volume by 15-20 MET-hrs/wk which may provide survival benefit if the behaviour is maintained over time (110). Physical activity volumes of approximately 35-40 MET-hrs/wk as observed in the AET group of this trial are consistent with cancer-specific recommendations of moderate-vigorous activities on most days and have also been shown to reduce disease-specific mortality (110, 435).

Ultimately, a combination of AET and RET is most likely to produce the most comprehensive health benefits. A recent study completed by Galvao and colleagues (23) examined the effect of a 12-week combined AET+RET intervention in a RCT of 57 patients receiving ADT. Treatment group participants completed 8 RET exercises at 6-12 RM (moderate to strenuous RET) for 2-4 sets per exercise. The AET component consisted of 15-20 minutes of cycling, walking, or jogging at 65-80% of maximum heart rate or 11-13 out of 20 on the Rating of Perceived Exertion Scale. Participants completed exercises in a facility-based, supervised setting in small groups of 1 to 5 participants. Primary outcomes were whole body and regional lean mass measured by dual energy x-

ray absorptiometry (DEXA). At the end of 12 weeks, the exercising participants demonstrated greater lean mass, muscle strength, and functional capacity than controls ($p \leq 0.05$). Over the course of the trial, exercising participants also improved HRQOL, reduced fatigue, and reduced C-reactive protein ($p < 0.025$). Their study was the first to demonstrate a reversal in muscle loss in androgen-suppressed PCa patients and demonstrated significant HRQOL, fatigue, and muscle strength outcomes with a mixed-modality exercise intervention. These important findings highlight the importance of a comprehensive and relatively intense exercise intervention for men with PCa receiving ADT.

9.1 Discussion of Feasibility Findings

The primary objective of this study was to assess the safety and feasibility of conducting an adequately powered, single modality, home-based exercise intervention with PCa patients undergoing ADT. This was the first exercise intervention study to be conducted at the Prostate Centre, and the PMH in general, and there were a number of *a priori* concerns that we had regarding trial implementation which required resolution before attempting a large-scale research project that could appropriately assess efficacy outcomes. From inception to data analysis it has taken approximately 36-40 months to complete this feasibility-study which provided experiences and insights for future exercise trials and exercise program management at the Prostate Centre at PMH.

A total of 66 patients were recruited over 13 months ($n \sim 5$/month), which is comparable to other major cancer centres recruiting for exercise trials in PCa (21, 120).

As it was the first exercise intervention trial to be conducted at the Prostate Centre, it was questionable whether patients would be interested in participating in this type of study. Unfortunately, our recruitment rate of 32% of eligible participants was lower than anticipated and below the median recruitment rate of PCa-exercise intervention studies (median: 47.9%, range: 22- 86%). However, the most comparable trials (i.e. home-based exercise in ADT patients) have either not reported participation rates (24, 122) or rates have been comparable (22% participation rate in Carmack-Taylor et al's home-based lifestyle intervention; (30)). Thus, an appropriate comparison is lacking and reasons for refusal were similar to other exercise studies in ADT patients. One postulation regarding the relatively poor participation rate is that a majority of the other exercise interventions in PCa patients have been facility-based which may stimulate greater participation due to the appeal of a more intensive intervention, greater trainer-related motivation, or the feeling of safety/security of exercising in supervised setting. On the other hand, a recent *facility-based* trial among PCa patients undergoing ADT completed by our group (initiated following the completion of the present study) found similar recruitment rate to the home-based intervention utilized in the present trial (recruitment rate: 24%) (26) indicating that there may be regional reasons for lack of participation, such as traffic, cost of parking, or challenging public transit system. The challenge of recruiting participants to participate in an urban exercise program due to transportation barriers (distance, time, and cost) has been previously described in general exercise preference literature in populations with cancer (142, 400, 485-487).

An equally important concern was whether there would be institutional and physician support for an exercise intervention. It was apparent early in our trial initiation that our mandate and objectives were supported. We were able to proceed with capital equipment and consumable purchases through internal funding committed by the Prostate Centre. Furthermore, the physicians from the department of urology and radiation oncology with PCa patients undergoing ADT were amenable to trial participation and patient referral to our study. This was facilitated through departmental emails and research meeting presentations. Ultimately, the present study initiated the development of the Prostate Centre's Survivorship Exercise Program that is now an on-going clinical-research program founded on the home-based model described in this trial. A thorough description of the Survivorship Exercise Program has been recently published (26).

Attendance to the group-based exercise classes in PCa patients undergoing ADT was poor, in stark contrast with previous trials of home-based exercise programs (24, 26, 122). In two trials of home-based, mixed-modality exercise for PCa patients receiving ADT, Culos-Reed et al observed that approximately 80% participants in both trials attended at least 5 of the 6 offered booster sessions (24, 122). Our recently completed pilot study of mixed-modality group-based exercise versus personal training for ADT-patients found that group-based exercise participants attended 88% of their facility based sessions which were offered three days per week for eight weeks (26). However, the attendance differences may be due to the fact that these trials were fundamentally different in terms of the delivery strategy: the former being a home-based program and the latter being a facility-based program. Thus, participants may have identified the

expectation to attend group-based classes in the facility-based trial more than those in the home-based trial, explaining the difference in attendance rates (i.e. they were likely to be more committed to, and less bothered with, attending the frequent facility-based exercise sessions). In the present study, the most commonly cited reasons for non-attendance to the booster sessions were distance and travel time. Furthermore, due to resource constraints, it was not feasible to provide booster sessions specific to AET and RET which may have deterred participants from attending knowing that a portion of the session was not consistent with their home-based program.

We observed an overall attrition rate of 33% from baseline to 6 months. This was particularly problematic in the RET group that lost nearly half of the participants that started the intervention (although there was no statistically significant difference in attrition when compared to the AET group). Attrition in home-based exercise studies is not uncommon in the published literature in this population. From baseline to 6 months, Carmack-Taylor et al (30) lost 16% of their population; and from baseline to 4 months, Culos-Reed et al (24) lost 34% of their sample to dropout. Moreover, significant dropout is not limited to home-based research as facility-based exercise interventions in ADT patients have also reported significant attrition. Hansen et al (27) observed a 38% attrition rate over 3 months and our group recently found a 23% attrition rate over 2 months; but it should be noted that both of these studies employed very small sample sizes (26) ($n = 10$ and $n = 13$, respectively).

To facilitate sample size calculations for subsequent studies that examine comparable outcomes in this population, our efficacy results of all time points and change

scores between time points are presented with means and standard deviations. Using the established minimal clinically important difference (MCID) for fatigue via the FACT-F (3.5 points) to calculate sample size requirements for a three-arm RCT of AET versus RET versus usual care, Segal et al (21) reported requiring n = 37 per group (total: N = 111) for a 3-group ANOVA to compare change scores over-time. They recruited N = 121 to account for an anticipated 10% attrition. In the present two-armed randomized trial, appropriate estimates of effect size would similarly be based on the established MCID and the standard deviation (SD) from Segal et al's earlier work (120) describing change from baseline in a ADT-only group (SD = 5.8). The effect size, calculated in Cohen's d (d = MCID/SD) and converted to Cohen's *f* (using a reference table (515)) produced d = 0.6 (from 3.5/5.8) and *f* = 0.3. (Of note, these were the same parameters of effect size and variance that Segal used to calculate N=111 described above). The resultant sample size for the two-way RM-ANOVA (with 2 groups and 4 time points, as per the current analysis) at 80% power and alpha of 0.05 is N=78. Given this sample size requirement and accounting for the observed attrition in this trial of 33%, a total of 103 participants would need to be recruited. With an accrual rate of n~5 per month, the estimated duration of a full-scale trial incorporating the present study's design will be approximately 33 months (21 months of recruitment plus 12 months for intervention and follow-up). Furthermore, for n = 103, it would cost approximately $7,416 to provide each participant with home-based equipment (average cost per participant for the AET and RET equipment = $72).

The reasons for dropout do not appear to be related specifically to intervention design, as a majority of patients dropped out due to individual circumstances such as disease/symptom exacerbation, lack of time to exercise, or loss of interest/motivation to exercise. In light of these reasons, development and evaluation of participation-maintenance strategies is imperative to ensure continued participation in research and long-term exercise behaviour, in general. In the instances of 'lack of time' and/or 'loss of motivation', modifications to the exercise prescription and program design are warranted to maintain interest and address pragmatic barriers to participation. Given the lack of attendance to our booster sessions, one strategy might be to have participants switch to a facility-based program to enhance the connection between the training staff as attrition rates appear generally lower in facility-based, supervised trials. Another approach might be to arrange for home-based supervision of exercise to maintain motivation. Finally, for those that lose general interest, a completely different exercise approach might be necessary to appeal to the individual activity interests, by altering the activity prescription to be more aligned with their activity preferences (e.g. dance, dog-walking, hiking, etc). Unfortunately, these approaches will generally undermine the empirical process due to lack of standardization of programmatic approach within a specific study; however, they should be considered as options in the 'tool-box' for clinicians to enhance adherence and overall exercise participation.

Historically, exercise trials in PCa have been conducted safely with only one study reporting a severe adverse health event (21). Our study had no adverse events beyond typical post-exercise muscle soreness that normally occurs with the initiation or

re-initiation of exercise. These observations confirm the safety of exercise, and especially home-based exercise, for PCa patients. Noteworthy is that recent trials have examined considerably higher intensity training without incident and have yielded important improvements in physiological and functional outcomes (23, 27, 121, 222). A high-intensity home-based program would be an important study to consider given the convenience of home-based exercise and benefit of high-intensity training.

Finally, there was a significant amount of positive feedback from the participants to their attending physicians regarding satisfaction with the exercise program. Numerous participants anecdotally expressed appreciation, satisfaction, and enjoyment with the program; and they have maintained communication with the research group since trial completion. This has generated additional program interest from physicians in other departments and spawned the initiation of additional exercise trials at PMH.

9.2 Discussion of Fatigue and HRQOL Hypothesis Testing Findings

This is the first study to compare the effects of AET to RET delivered in a home-based setting in any cancer patient population. Furthermore, we are the first group to use common, disease-specific metrics of HRQOL and fatigue in a home-based exercise program that provides direct comparison to facility-based trials. In an ITT analysis, we did observe a significant between-group main effect for emotional wellbeing; however, after visual interpretation and in the absence of any main effect of time, it appears this reflects baseline group differences rather than true between group differences. Our ITT analysis also showed trends towards improved social wellbeing and fatigue in the AET

group compared to the RET group. These novel findings are in some contrast with Segal et al's previous work (21) that found RET to be better than AET when both were compared to controls for fatigue and HRQOL outcomes (however they did not do a direct intervention arm comparison). These findings were only very modest trends towards significance and be in part due to the inherent differences in facility-based training versus home-based training where RET is likely better supported in the presence of training staff compounded with AET (via walking or cycling, for example) likely being easier to do independent from a trainer and possibly with a friend or family member. In general, our ITT analysis found that HRQOL and fatigue were relatively unchanged over-time with AET and/or RET which is consistent with findings from previous home-based and hybrid physical activity/lifestyle interventions in this population (28, 30, 122).

In a per protocol analysis of participants that completed each assessment, we observed that RET was associated with a clinically and statistically significant increase in disease-specific HRQOL as measured by the PORPUS which was not apparent in the AET group. Our study is the first to use the PORPUS in an intervention-based exercise study in PCa patients and, interestingly, we did not observe similar differences in HRQOL measured by the FACT-P (including most subscales). These findings must be interpreted with caution given the limited sample size and because the sample is comprised of the most adherent and motivated participants. Further, the discordance between PORPUS and FACT-P results necessitates further investigation in larger samples for cross validation in exercising participants. Our finding that RET may be more effective than AET at improving HRQOL is novel and, in part, contrasts with Segal

et al's (21) findings in men undergoing radiation therapy and adjuvant ADT since neither AET nor RET improved HRQOL following 24 weeks of facility-based training in that trial. However, it is consistent with other studies in PCa populations that demonstrate an improvement in disease-specific HRQOL with RET (120, 180) but not with AET (66) or mixed-modality training (24, 28, 30, 122).

Reasons for the greater RET efficacy at improving general and disease-specific HRQOL may the novelty of the training modality for most participants. Although RET is the quintessential complement to AET, AET in the form that is utilized in most clinical exercise intervention trials (i.e. walking and/or cycling) is likely more familiar to most participants than various RET exercises. This novelty may have been amplified in the present trial (and comparable with others) that incorporated resistance bands, which require familiarization and confidence to be utilized correctly and effectively. The heightened level of concentration required for RET completion may serve as a distraction from distressing aspects of disease and/or treatment. Conversely, since AET can be rather monotonous, it may create a psychological environment susceptible to rumination about distressing aspects of PCa management compromising HRQOL (albeit, potentially benefiting ratings of fatigue, as indicated in our ITT analysis). The *acute* effects of exercise (RET and/or AET) on psychological wellbeing have not yet been assessed. One approach may be to examine measures of distress, HRQOL, or neurophysiological correlates of psychological wellbeing immediately before and after bouts of exercise. Our group is currently undertaking such a study, which we hope will add insight to the acute and enduring effects of exercise in this population.

Fatigue is arguably the most profound and distressing adverse effect of ADT and is specifically treated through lifestyle and cognitive-behavioural interventions (189, 193, 199, 201, 209, 410). Exercise is hypothesized to improve ADT-related fatigue via physical and psychological benefits by improving functional capacity and cognitive resilience, respectively. The physical and psychosocial effects of exercise have been lauded for their early benefits in PCa patients undergoing ADT (120). Unfortunately, the magnitude of benefit observed in the initial assessment of exercise for ADT by Segal et al (120) has not been replicated. In fact, of the 9 exercise trials in ADT patients that have employed a fatigue-specific outcome measure, only 3 have produced statistically significant improvements (21, 24, 120). Two of these trials used RET (21, 120), and only in one trial was the benefit observed to be clinically significant (120). Despite our observed trend towards between-groups differences in fatigue which maintained a small to medium effect size, our findings are generally consistent with most of the existing exercise literature with respect to null effects of exercise on fatigue over-time. Cancer-related fatigue is a multifaceted construct with a diverse and likely dynamic etiology with physical and psychological components. Within the context of an exercise intervention, improvements in physical capacity may be a more representative and appropriate measure of physical fatigue than self-report measures that ask respondents to reflect on the experience of fatigue. Compared to fatigue measures, physical fitness measures appear to be more sensitive exercise training for men on ADT. Although these physical/functional changes have not consistently translated into perceptual benefits regarding fatigue, they may be more reliable in describing physical fatigue components

but less accurate at describing the psychological components. Additional research into the etiology of ADT-related fatigue from a cognitive, emotional, and psychological perspective is necessary.

9.3 Discussion of Physical Fitness Hypothesis Testing Findings

This is the first study to compare training modalities in a home-based setting in a population of cancer survivors. Our findings contrast to those of Segal et al's facility based comparison of AET and RET to usual care controls (21). In that study, the authors found that RET was more consistently associated with benefit in physical fitness whereas we found that AET demonstrated greater benefit (versus RET) particularly at 3 months. In addition to being facility-based, the training provided to participants in the Segal et al trial was more closely supervised and participants could receive instruction and support during each of their training sessions. This likely reduces the learning curve for the RET program and accelerates musculoskeletal adaptation through earlier and more targeted intervention progression. Furthermore, the facility-based nature of RET allows for confidence and comfort with training intensity that is crucial for fitness improvement. AET, on the other hand, can be conducted at comparable intensities in the home-based, unsupervised setting via walking, jogging, and/or cycling programs. Moreover, the familiarity of AET as a functional and transportation-related training modality may allow for more confidence in meeting the upper limits of target intensity. Collectively, this may lead to better outcomes for AET participants in the home-based setting and RET in the facility-based setting.

Changes in physical activity volume were greater with AET at 3, 6, and 12 months compared to RET indicating a greater adoption and adherence of the prescribed intervention. This is likely why significant improvements in several body composition measures were observed in the AET group rather than the RET group. Greater physical activity volume for AET participants in both the ITT and per protocol analysis suggest that AET may be a more effective exercise prescription for stimulating and maintaining clinically relevant increases in physical activity. One reason for this may be that common modes of AET (e.g. walking) are more familiar to patients than RET and are more easily reproducible in the absence of the routine instruction or demonstration that may be required for RET. Furthermore, the home-based AET prescription provided in this study (primarily walking) is more amenable to partner or peer participation, thus facilitating a social element that may support ongoing behaviour change. Social support for exercise has been studied in only one trial among PCa patients (30) and several other studies in various clinical populations have noted the importance of a supportive social network in achieving and maintaining exercise behaviour (342-346). This may also be a reason for why walking is commonly described as a preferred modality for exercise among cancer survivors (468, 488).

Although consistent differences were seen between AET and RET in terms of physical activity volume, it should be noted that self-report measures of physical activity are vulnerable to social desirability and should be considered cautiously. Logbooks were also used to assess overall compliance with the exercise prescription but could not be reliably analyzed because too few participants completed them effectively. Objective

assessments of physical activity such as doubly-labeled water techniques and accelerometry would produce more definitive evidence regarding physical activity status. Unfortunately, they were cost-prohibitive within the context of this study. It is worth highlighting, however, that at 3 and 12 months the changes in physical activity volume were accompanied by beneficial changes in body composition that are suggestive of actual improvements in physical activity rather than simple response bias. As described previously, objective measures of fitness may represent the most important clinical outcome of an exercise intervention that may provide credence to self-report measures of activity.

Similar to the findings of previous researchers examining exercise in men with PCa, (21, 27, 121, 180) we observed an increase in aerobic fitness with RET. We did not observe an improvement in aerobic fitness with AET, which is also consistent with previous intervention studies in PCa patients (21, 65). The improved aerobic capacity in RET rather than AET may be due to a combination of factors. First, the aerobic benefits of AET can be achieved by simply increasing walking frequency and intensity as a matter of general physical activity or incorporation into commuting patterns. This is a possible source of contamination in our study, as participants assigned to RET may have engaged in this ancillary activity with subsequent benefits. In the absence of information regarding contamination in the RET group, we cannot conclusively determine whether this occurred in the present trial. However, in Segal et al's study, they reported that n = 8 RET participants engaged in AET $\geq$ 3 time per week versus n = 5 AET participants engaged in RET $\geq$ 2 times per week demonstrating that AET may be more frequently

integrated into an RET program, in contrast to the reverse integration. This could possibly account for the greater improvement observed in the RET group compared to the AET group.

An alternative hypothesis for greater aerobic benefit in RET participants is that, while AET is likely to improve overall oxygen consumption by facilitating cardiorespiratory adaptation, the observed change in aerobic capacity in the RET group is a function of improved lower extremity strength and subsequent increased capacity to complete the graded exercise test on a treadmill. Graded exercise testing for aerobic capacity using a treadmill relies on systematic increases in speed and incline. Participants engaged in home-based AET (without a treadmill) may not have routine access to walking routes that consist of significant elevations in grade and thus fail to stimulate neuromuscular adaptation for walking at incline. However, RET participants are trained to specifically improve lower extremity strength, thus facilitating neuromuscular adaptation that would support deeper walking strides (i.e. greater knee flexion) common to inclined walking at >10% incline during a graded exercise test on a treadmill. Future studies would optimally compare AET to RET on aerobic fitness using graded walking programs and measured via treadmill-based graded exercise testing protocols.

Finally, we are the first to report on exercise-related changes in chest skinfold thickness in men undergoing ADT for PCa. We observed a main effect of time on chest skinfold thickness in the ITT ($p = 0.01$) and per protocol ($p = 0.087$) analyses. Although ADT-induced gynecomastia is primarily due to changes in the glandular ducts, breast

epithelial tissue, and periductal edema (489), the size of the breast may be measured, in part, through a skinfold. Additionally, the subcutaneous fat accumulation that arises systemically with ADT may contribute to the undesirable changes in breast shape and size. Given the psychological distress associated with gynecomastia in ADT patients (243), therapies such as exercise, that may reduce the extent to which the breast is enlarged would be welcomed, as would investigations into the relationship between exercise and adaptions of body image. Conventionally, skinfolds are utilized in combination (i.e. a sum of skinfolds from multiple sites) to calculate body density (dB) and subsequently body fat percentage. Despite the absence of formal validation, we elected to examine chest skinfold thickness as an independent outcome because of its clinical relevance and potential meaningfulness to the participant. To our knowledge this is the first time chest skinfold thickness has been used and it will require further investigation to ensure its validity and reliability as an independent indicator of programmatic success.

9.4 Discussion of Exploratory Analysis of Biomarker Assays

A large body of literature suggests that IGFs play a role in the incidence of PCa (97, 299-303) but only one other study reported on the effects of exercise on these factors in men already diagnosed with PCa (28). To our knowledge, no studies have assessed the effect to which leptin and adiponectin concentrations can be modified with exercise programs for PCa patients receiving ADT and vulnerable to deleterious changes in body composition potentially negatively influencing these biomarkers. Hypothetically, IGFs

and adipokines can be beneficially altered, via healthy lifestyle changes, in ways contributing to improved cancer control and survival rate in PCa. The present trial is the first to report on the effect of an individually prescribed exercise program on leptin, adiponectin, and IGF-1 for men with PCa receiving ADT. This is particularly novel because it adds insight to the relationship between exercise, specific exercise modalities, and ADT-related changes in body composition that influence tumourigenic biomarker concentration. Although we did not observe a significant interaction effect, we did observe within group differences via paired samples t-tests that may guide further hypothesis testing. Specifically, we found that after 6 months of RET, IGFBP-3 was significantly increased compared to baseline (a preferable change) while AET demonstrated a decrease in IGFBP-3 (a non-preferable change). After 3 months of RET, we observed a significant reduction in IGF-1, this was not maintained at 6 months. As hypothesized, baseline indicators of adiposity were negatively associated with adiponectin and positively associated with leptin and leptin:adiponectin ratio. Our findings altogether suggest that a home-based exercise intervention, particularly involving RET, may have beneficial effects on adipokines and the IGF-axis possibly due to improved body composition.

Previous interventional studies with PCa patients have found that exercise does not exacerbate disease progression as indicated by levels of testosterone and prostate-specific antigen (PSA) levels not being increased (20-23, 28). PSA and testosterone levels in men with PCA were also observed to be unchanged after acute bouts of heavy resistance training (29). However, acute and high intensity RET was associated with

significant increases in serum growth hormone (GH), dehydroepiandrosterone (DHEA), interleukin-6, tumour necrosis factor-α (TNFα) and differential blood leukocyte levels. These positive changes in immune system markers and non-androgenic growth factors may have implications for chronic tumour control and physical wellbeing. Previous research has shown that acute increases in DHEA and GH may be related to observed improvements in functional capacity and muscle maintenance/development in the absence of testosterone (29).

To further support potential exercise-related effects on cancer control biomarkers, Galvao and colleagues (23) found that C-reactive protein (a systemic inflammatory marker) was decreased in exercisers and increased in controls after 12 weeks of mixed-modality exercise, although glucose, insulin, lipids, and homocysteine levels remained unchanged. These changes in C-reactive protein require further investigation as previous research has found no change in older adults, including those with breast or prostate cancer participating in exercise interventions (401, 490).

Beneficial changes in IGF-axis proteins have been observed in vivo with a low fat diet and/or routine exercise in older men at risk for PCa. These changes have been associated with *in vitro* reduction in PCa cell growth (114, 116, 117). To assess the effect of chronic exercise specifically, Leung et al (117) compiled serum from sedentary men and men with a minimum of 10 years of routine exercise, all of whom were not diagnosed with PCa. Compared to the serum from sedentary participants, LNCaP cell growth was reduced by 27% in the chronically active participants, with a concomitant 100% increase in p53 content and 371% increase in apoptotic activity (117). For men

undergoing ADT for PCa, Bourke et al recently found no difference between usual care participants and participants assigned to 3 months of mixed-modality exercise and dietary advice for insulin, IGFBP-3 IGFBP-1, or IGF-1. In the present trial, we report a significant reduction in IGFBP-3 and IGF-1:IGFBP-3 ratio with RET but an increase in these biomarkers with AET after 6 months of training. Our results differ from those of Fairey et al (321) that found beneficial changes in IGF-1, IGFBP-3, and IGF-1:IGFBP-3 in postmenopausal women with breast cancer after 15 weeks of AET compared to usual care. Our findings require further examination in larger trials given the study is underpowered for definitive statements regarding these effects. However, the current array of data appears to favour RET in terms of generating anti-tumourigenic changes

Research into the acute and short-term effects of exercise on adiponectin and leptin is lacking, particularly in interventional cancer research. This is likely due to the modest body of literature describing the tumourigenic properties of various adipokines. In a pre-post test study of 16 older, obese adults (without cancer) participating in a 12-week AET and stretching program, O'Leary et al (491) demonstrated significant reductions in body weight and fat mass, as well as leptin, but no change in adiponectin. No correlations between changes in adiposity and leptin or adiponectin levels were presented. In the current trial, changes in leptin were positively correlated with changes in weight, BMI, and waist circumference, although these anthropometric changes were not statistically significant over the course of the intervention. While these small changes may not necessarily be associated with exercise, these findings do reflect the sensitivity of leptin to changes in measures of adiposity. Furthermore, we found that VO_2 peak,

adjusted for body mass, was negatively correlated with leptin, corroborating earlier studies which demonstrate that aerobic exercise training can improve leptin levels independent of changes in body fat percentage (492).

9.5 Discussion of Correlational Analysis Findings of Determinants of Exercise

With research describing a relatively rapid withdrawal of benefits when cancer patients discontinue exercise (24, 332), there is a strong need to determine the predictors of chronic exercise adherence. Long-term exercise adherence for cancer patients has been defined as engaging in regular physical activity for at least six months post-intervention (403). For men with PCa undergoing ADT, the benefits of exercise with respect to multiple aspects of wellbeing are impressive, suggesting that exercise be included as part of a comprehensive disease management strategy over the long term. Chronic exercise for ADT patients is particularly essential, because ADT is typically administered over many years (often indefinitely) and the adverse effects persist long after ADT is discontinued.

Our study explored the relationship of established and novel determinants of health behaviour on physical activity participation, as well as an objective measure of fitness hypothesized to be an indicator of ongoing exercise participation. In bivariate and multivariate analyses, we found that age was the strongest predictor of VO_2 peak at any time point. This is consistent with the literature that describes a strong negative correlation between age and aerobic capacity, with sedentary adults typically losing 3.5 $mlO_2/kg/min$ (1 metabolic equivalent) every 7 years after the age of 25 (i.e. 0.5

mlO_2/kg/min per year) (493). It also underscores the necessity of continued aerobic activity in older men with PCa receiving ADT who are vulnerable to treatment-related exacerbations and/or functional decline.

Our bivariate analyses showed a low to moderate correlation between self-report physical activity volume and VO_2 peak, which provides some support for our hypothesis regarding using an objective measure (VO_2 peak) to validate a self-report assessment of program adherence. However, because the correlation is only moderate, additional measures of adherence are required for further validation. Given that logbook completion rates in our study were inadequate for analysis, future studies should consider emphasizing the importance of the logbook completion, possibly utilizing reminders and/or incentives. Ultimately, it would be ideal to utilize more than one objective measure of physical activity adherence to validate program participation and chronic physical activity. Pedometers and accelerometers have become less expensive and more commercially available, providing an objective source of physical activity volume that can be compared to self-report program compliance and objective measures of fitness. Dracup et al (494) conducted a RCT of home-based exercise in 173 heart failure patients over 12 months. The researchers in this study measured program compliance in three ways: sealed pedometers (sealed so that participants could not see how many steps were recorded in an effort to prevent tampering with data quality/integrity), self-report physical activity (walking) volume using a log sheet, and a weekly summary of total physical activity questionnaire. Nonetheless, Dracup et al also encountered difficulties in obtaining quality adherence data, with only 44% of the intervention group providing

complete pedometer and logbook data. However, they did observe that patients who demonstrated a $\geq$ 10% increase in pedometer scores had improved aerobic capacity scores at 6 months (measured by the six-minute walk test), with a strong, positive correlation between the two measures (r = 0.6, p=0.001). Collectively, our findings suggest that objective measures of physical fitness are reasonable proxies for program participation and are especially useful in light of poor data completion and quality from self-report measures.

We also sought to describe temporal patterns in behavioural determinants that could provide insight into why participants engage in routine exercise and possibly assist in the development of interventions to prevent, and recover from, relapse to sedentary behaviour. There was no main effect of time on any of the psychosocial determinants of exercise behaviour suggesting that participation in a general physical activity program may not significantly alter these variables. In exploratory analyses of within-group effects, however, we did observe the following novel findings. The AET group significantly decreased in self-efficacy from baseline to 12 months. This is inconsistent with previous findings from Demark-Wahnefried et al that showed an increase in self-efficacy for exercise 6 months after an exercise workbook and counselling intervention for older breast and prostate cancer patients (495). One reason for this discrepancy in findings is that our intervention was not principally predicated on education and information on exercise, but rather based on a provided individualized exercise prescription based on a fitness assessment. Demark-Wahnefried and colleagues, on the other hand, tailored their intervention delivery to reflect the constructs of SCT by

providing telephone counselling sessions that were "dedicated to increasing feelings of self-efficacy by setting achievable goals, monitoring progress and providing positive reinforcement" (it is worth noting, however, that their intervention did not produce statistically significant changes in physical activity volume in N = 182) (391). Our follow-up telephone calls and booster sessions attempted to support self-efficacy by facilitating similar patient-oriented positive attitudes towards exercise, but we did not explicitly strive for the incorporation of key aspects of SCT during each interaction. Our negative findings for the AET group may be explained with an inability to increase aerobic intensity sufficiently without the on-going support of the training staff (which ceased at 6 months), thus leading to a significant decrease in exercise self-efficacy between the intervention and follow-up phase. Conversely, the RET group had specific, fundamental instructions to increase resistance on the resistance bands and advance their training when 12-15 repetitions was no longer challenging. Therefore, their critical path to exercise efficacy may have included an initial phase of exercise technique acquisition followed by a reasonable understanding of exercise prescription progression. In our home-based exercise program, it was deemed unsafe for many of participants to engage in running or vigorous cycling, which may have undermined the AET group's ability to feel comfortable, competent, and confident with making appropriate exercise prescription progression. Additional research is required to assess longitudinal patterns in self-efficacy for exercise in people with cancer, specifically focusing on the post-programmatic period that appears vulnerable to a loss in exercise self-efficacy, particularly for those participating in AET.

Paired samples t-tests of social support for exercise from friends and family indicated social support was significantly greater at 12 months when compared to baseline and 6 months among AET participants. These findings may be indicative of AET being more suitable for partner exercise compared to RET. The primary mode of AET in this intervention was walking which can be a very social mode of activity given the ease with which one can converse with a 'training' partner. Walking has been repeatedly cited as a highly preferred form of exercise among cancer patients (e.g. (488, 496, 497)) and the American College of Sports Medicine suggests that exercise programs incorporate traditional exercise modalities, like walking, due to the numerous health benefits and ease with which it can be performed (429). This aligns with research among breast cancer patients that reveals that patients that preferred low intensity exercise also desire high social support, which is congruent with the idea that high intensity exercise presents difficulty for ongoing conversation (346). The added value of social engagement that accompanies aerobic activity and the fact that it can be incorporated into daily activities makes it an ideal form of general physical activity, although it cannot address many needs of upper extremity musculoskeletal fitness and will likely not be high intensity.

Only Carmack-Taylor et al (30) have assessed social support as a correlate of exercise behaviour in PCa survivors prior to this study. They found that social support did not change over 12 months in either the home-based healthy lifestyle or educational support programs. To facilitate family social support for exercise with the intent on improving exercise program adherence, Winters-Stone and colleagues (127) are currently

conducting a RCT called `The Exercising Together Project` designed to increase adherence to home-based RET by incorporating the PCa survivors` marital partners into the exercise program. This novel approach to exercise programming for cancer survivors reflects a scenario that favours partner-based approach to exercise: 1) many men with PCa are married, 2) PCa can put a significant strain on marital relationships given the detrimental effects to aspects of intimacy, and 3) PCa affects men that are commonly retired with partners who are also likely to be retired and therefore have free time to commit to partner-based activity. In light of these circumstances, exercise can be a uniting activity where couples can conjointly confront and overcome the physical and psychosocial challenges of PCa and associated treatment. The results of this study are eagerly awaited as outcomes address several unexamined areas in PCa-exercise literature, such as marital quality and partner physical activity/health status, as well as conventional ADT-relevant outcomes that pertain to physical fitness and psychological wellbeing. While our study and the studies by Carmack-Taylor et al and Winters-Stone et al remain the first to explore social support for PCa patients engaged in an exercise intervention, the balance of research in this field has been only among those with breast cancer. In these studies, social support has been shown to be related with several facets of exercise behaviour, such as intensity, desire to exercise with friends or family (and negatively correlated with preference to exercise alone), overall mood, vigour, and physical functioning, (342-346). Clearly, more research on social support and exercise for PCa patients is warranted as approaches that integrate training partners may be revealed to be an important strategy to enhance long-term exercise.

To our knowledge, this is the first study to examine the role of exercise-induced feelings in a population with cancer. Exercise-induced feelings, if positive, may play a role in enhancing exercise participation. Naturally, if participants do not enjoy exercise, they will likely discontinue exercise. Our findings suggest that (positive) exercise-induced feelings remain relatively stable for AET participants but may increase after 3 months for RET participants. This may be due a learning effect associated with familiarization with the exercises and subsequent integration into a routine that they are confident in and comfortable with. This hypothesis is supported by our findings in bivariate analyses showing that exercise-induced feelings are associated with self-efficacy, suggesting that participants that enjoy their exercises also feel confident in their exercises. Our findings are also consistent with previous literature that indicates modality differences in exercise-induced moods. Szabo, Mesko, Caputo and Gill (498) observed that persons participating in t'ai chi or yoga had higher tranquility scores (using an itemized analysis of exercise-induced feelings) and less physical exhaustion than persons engaging in martial arts, while RET participant demonstrated higher revitalization than the martial arts group. As a possible behavioural determinant, exercise-induced feelings represent a manifestation of some psychological, social, or physiological response to exercise. Our upcoming study in PCa patients (on and off ADT) that examines the role of an acute bout of exercise on exercise-induced feelings with concomitant transcranial electromagnetic stimulation aimed at assessing the duration of cortical silent period will shed new insight on the neurophysiology of acute exercise and its relationship to exercise-stimulated changes in mood. This is relevant to men with

PCa who are often depressed and anxious (499-501) as early findings suggest exercise can reduce anxiety and depression in this population (30, 65, 122). A greater understanding of the acute benefits of exercise on cancer patients may provide insight into the mechanisms of chronic positive shifts in mental wellbeing and factors that affect exercise program compliance (i.e. immediate experiences of psychological benefit may translate into routine physical activity). The usage of objective measures of psychological wellbeing circumvents the typical response biases (placebo effect, social desirability, recall bias) that confound self-report measures.

As the most extensively researched theoretical frameworks may provide the foundation on which many exercise interventions are based, current theoretical approaches to behavioural maintenance have been criticized for failing to make a distinction between determinants influencing the initiation of a health behaviour and those influencing its maintenance over time (502). To encourage long-term adherence, the literature supports use of cognitive-behavioural approaches predicated on the belief that an individual responds to his or her *perceptions* about the environment or situation rather than the *actual* environment (503). According to cognitive therapy, maladaptive behaviour is the product of faulty, or irrational thinking and cognitive approaches to behaviour change are designed to modify how an individual thinks about or perceives a situation (503). Behavioural therapies are based on the idea that new and constructive behaviours can be learned through various types of reinforcement and reward. Using such models, specific techniques can be used to educate patients on how to identify, monitor, and achieve valued long-term outcomes associated with exercise (504).

Moreover, attempts can be made at improving self-efficacy and social support for exercise as well as exercise-induced positive moods by focusing on process-oriented goals and outcomes. Culos-Reed and colleagues (122) used cognitive-behavioural therapy techniques (e.g., goal setting, monitoring behaviour, overcoming barriers, positive attitudes and social support) in their 16-week RCT in ADT-treated PCa survivors but provided no quantitative or qualitative evidence of effectiveness. An appropriate trial design may be to randomize participants to routine exercise with and without a theory-based adherence-boosting intervention. Given the established clinical efficacy of exercise in populations with cancer, this type of trial would fit with a movement towards improving sustained exercise adherence.

9.6 Study Limitations

The results of this study should be interpreted in light of various limitations. Our study's *a priori* mandate was to assess feasibility for a future randomized trial at the PMH for PCa patients and was not intended to be true hypothesis testing project. The study was underpowered to conclusively demonstrate between-group differences in RET and AET. Despite the underpowered nature of the efficacy analyses, this study provides an important initial assessment of distinctly different home-based exercise intervention arms.

Some may consider that a significant limitation to our study is the omission of a control group that prevents a full understanding of how these exercise modalities compare to standard care. However, the evidence for the beneficial effects of exercise for

cancer survivors, and PCa survivors particularly, suggests that both groups were likely to demonstrate significant improvements compared to non-exercising controls. At this juncture in the literature, it may be argued that exercise is unequivocally beneficial and that research should be targeted at identifying the most effective exercise prescriptions and adherence boosting strategies rather than re-examining common efficacy outcomes. The clinical benefit has been so widely described that several researchers, including our team, have published clinical calls-to-action and program descriptions to elicit a paradigm shift in disease management in oncology that integrates exercise with standard care (435, 505-508). Moreover, it could be perceived as unethical to knowingly withhold an effective therapy in the interest of research fidelity and thus all participants should, in some way, receive exercise support. One simple strategy to overcome this is to randomly assign patients to an intervention arm or a wait-list control where the control participants are asked to refrain from exercise until the intervention period is over. Unfortunately, this approach is susceptible to contamination in members of the control group who are aware of the benefits and likely motivated to start exercise in some fashion. Although contamination is under-reported in RCTs of exercise in patients with cancer, contamination rates of 15-50% have been cited (21, 140, 440). In Segal et al's comparison of AET and RET to controls, they found that 5 AET participants participated in RET, and AET was performed by 8 RET participants and 6 controls (21). Like others previously, we overlooked the necessity to collect data on possible sources of contamination. Nonetheless, we acknowledge the shortcomings of not having a control group but offer that, at this stage of empirical evidence, maintaining a usual care control

that is devoid of exercise advice/programming only does a disservice to patients and jeopardizes true exercise effect because of frequent contamination. In modality-comparative research, contamination across groups remains an essential component of trial design.

The significant attrition from baseline to 6 months, particularly in the RET group (although not statistically significant in comparison with the AET group) should be considered and represents a potential explanation for general lack of RET effect on many study outcomes. Across exercise intervention studies for PCa patients, attrition rates have ranged from 0 to 38% with a mean of approximately 16%. In PCa and exercise research, our attrition rate of 33% to 6 months with an additional loss of 30% (n = 13/44) from post-intervention to 6 month follow-up is higher than most; however, three exercise studies in this population have had at least 30% dropout (27, 28, 65). In comparison to the two studies that assessed 4-6 month post-intervention follow-up periods, our study compares rather favourably with Culos-Reed et al (24) and Bourke et al (28) reporting 42% and 64% attrition over this phase of study, respectively. To address attrition due to non-medical issues, we would recommend greater interaction between trainer and participants in order to forge a stronger bond and instil a greater level of responsibility to program participation and data collection. This may be achieved with more routine follow-ups in person or via phone/email/text-message, home visits to support exercise, or inducements to participate. That said, it should be considered that there may also be a proportion of the population that is simply not interested in continued participation in exercise, which is evidenced by studies showing that approximately 75% of men with

PCa do not meet physical activity guidelines (336, 338). Future studies should attempt to distinguish two types of attrition 1) loss of research participation that is tied to intent to discontinue exercise, and 2) loss of research participation is tied to discontinuation of research interest. This requires an examination of dropouts that is generally not ethical practice when participants are explicitly stating that they do not want to participate anymore. However, this may be circumvented with `exit interviews` that could provide useful for collecting insight on why participants withdrew from the study.

We were unable to use the physical activity logbooks due to poor completion by a majority of the participants. This prevented us from verifying physical activity volume provided by the GLTEQ, making it impossible to specifically assess compliance with the individualized exercise prescription or contamination between the two groups. Although logbooks can be useful tools in monitoring behaviour and progress, they are an extra (and possibly onerous) task that burdens the participant. Previous studies have also had to limit or omit the analysis of logbooks due to lack of completion or unusable data (494). One approach to quantifying physical activity that could be more palatable for certain participants is through the use of electronic communication via 'health-coaching' or 'electronic activity logs' that are contained within a mobile device, like a cell-phone, personal digital assistant, or tablet. An electronic recording device conceivably allows for easy, on-the-spot, data entry, that when paired with physiological monitoring devices (such as a heart rate monitor), can provide accurate and immediate information. This information could then be used to provide immediate feedback to participants regarding their exercise program. Our group is currently investigating whether or not electronic

health coaching software can improve exercise participation in heart failure and diabetic patients. Given the ubiquity of 'smart-phones', this approach may represent both a tool to enhance exercise participation/adherence and data collection/extraction.

Our predictive models for physical activity adherence were not empirically grounded. Each of the model variables (i.e. social support, exercise-induced feelings, and self-efficacy) that previously examined as independent determinants of exercise behaviour, however they have never been tested in combination. We were particularly interested in how these specific determinants might interact to influence exercise participation given their fairly stark distinction between each other but in summation do not necessarily represent an *established* theoretical framework. Our conceptual approach was that the aggregate effect of social influence, perceived-behavioural control/self-efficacy, and enjoyment of the activity would significantly contribute to the engagement of physical activity. Our exploratory analyses indicated that these had no influence on exercise participation, while age was likely the biggest factor. Future trials are required to further assess whether these individual components to exercise participation can collectively contribute to explained variance.

Due to limitations in financial resources, we were unable to conduct an analysis of the biomarkers for all participants at all time points. In the absence of sufficient funding for a complete sample analysis, we conducted assayed the first 13 subjects to complete assessments at baseline, 3 months, and 6 months from the AET and RET groups (n=26 total). This strategy was implemented to expedite the analysis with ambitions of securing additional funding for the balance of the assays. However, as funding was not secured

for the remaining samples our analysis of only the first 26 AET and RET participants is subject to selection bias via a training effect on behalf of the researcher. In this respect, our research may be criticized from the standpoint that the assessor's and researcher's skills or attitudes were not consistent over the course of the trial leading to participants in the early phases of the research project treated somewhat differently from participants in the later phases of the research. In retrospect, a better approach would have been to collect serum samples from all participants and then randomly select 13 from each group to comprise the samples for actual assay. This method will be utilized in future studies under similar circumstances.

In our study, neither the participants nor assessors were blinded to group allocation. In exercise research, blinding participants is virtually impossible without implementing some type of deception. In the present trial, it was unable to blind participants to which type of exercise they were completing because they needed to be aware of their specific exercise prescription. However, exemplary exercise intervention studies do maintain blinded outcome assessors to limit the risk of assessor bias. Blinding the outcome assessor (DSM) in the present trial was not feasible due to a lack of personnel resources. At the time of the study, there was no financial funding to support a blinded assessor and there was not graduate lab member with credentials and experience to conduct the fitness tests. Consequently, all assessments were completed by DSM who was also acting as the researcher and exercise physiologist. Given DSM's broad role in this research, the present trial may be criticized by having significant experimenter's bias. However, it may be argued that consistency in assessments (i.e. the same assessor

conducting all assessments) is a positive methodological characteristic. Given that the qualifications and credentials of our research team have become more aligned with clinical exercise physiology, blinding and maintaining consistency in assessors has been used in subsequent trials.

Finally, the booster sessions were poorly attended in contrast to previous home-based exercise programs in this population (24, 122). Participants cited various reasons for not attending, notably distance and travel time to the urban-based group exercise classes. Furthermore, due to resource constraints, it was not feasible to provide booster sessions specific to AET and RET, thereby introducing potential contamination during these sessions (although 2 sessions per month would not likely produce relevant changes in outcome measurement given the limited attendance). Whether or not booster sessions have a significant effect on program effect or adherence remains uncertain. Their intent, as implemented in this study and those by Culos-Reed et al (24, 122), were to support home-based exercise through group exercise that could assist in forming stronger exercise technique and competence as well as addressing barriers to ongoing participation. As previously mentioned, studies that specifically examine strategies to boost program adherence are needed, that would include an empirical assessment of the efficacy of booster sessions.

9.7 Study Strengths

The study's strengths should also be highlighted. First, the novel aspect of home-based AET versus RET provides important information regarding the acceptability,

safety, and efficacy of complementary exercise modalities as discussed earlier. To specifically reflect on the home-based nature of the exercise interventions, the value of assessing interventions with low institutional cost burdens that may contribute to sustained exercise participation cannot be understated. This is also consistent with preference for home-based, unsupervised exercise programs among many cancer survivors (468, 488). While our study cannot definitively determine whether AET is better or worse than RET in achieving a number of clinical outcomes, several within-group improvements suggest that either exercise modality is better than no exercise at all.

Second, outcomes were carefully selected for both direct comparison and as a strategic complement to earlier work in the field. This aspect of trial design has ensured that this research will contribute meaningful information to clinicians and researchers working to improve the overall wellbeing of men with ADT.

Third, to enhance participants' adherence to the exercise program, we provided exercise equipment and manuals to each group that would support exercise throughout the intervention period and afterwards. The cost of providing the exercise mat (~$25), stability ball (~$25), set of three resistance bands (~$10) and exercise manual (~$10) was approximately $70 per individual. The relatively low cost of materials that can provide a total-body workout and is dynamic to adjust intensity to the exerciser's ability have made the provision of this 'training' package a core component of the Survivorship Exercise Program. At present, the Survivorship Exercise Program employs a cost-recovery model that suggests a donation for participation in the program that goes towards covering the costs of the home-based exercise materials as well as general overhead costs. The

suggested donation amount is $100 and participants are free to donate as much or as little as they are comfortable with. No participant is obligated to donate and each participant receives the exercise program materials irrespective of donations. The donations allow the Survivorship Exercise Program to provide clinical care with home-based equipment for all participants with larger donations off-setting the costs of equipment for those that are not able to contribute.

Fourth, the 6-month post-intervention follow-up period represents the longest follow-up period from a structured exercise intervention for PCa patients to date. At the time of trial design, only Culos-Reed et al (24) conducted a post-intervention follow-up that was conducted 4 months after the end of the intervention. A recent study conducted by Bourke et al has also examined 6-month post-intervention physical activity and fitness effects while a telephone-based lifestyle intervention by Demark-Wahnefried et al (401, 402) assessed physical activity volume at 12-months post-intervention. Chronic exercise adherence in cancer populations is of critical significance and scientists in the field suggest that 6-months is an appropriate milestone to assess whether or not healthy lifestyle behaviours have been maintained (350). Although it may be resource intensive to extend a clinical trial to assess participation over the long-term, post-intervention follow-ups are a necessary aspect of research in this field to monitors, describe, and influence a permanent behaviour change.

Finally, we conducted both an intention-to-treat and per protocol analysis for most outcomes to respectively assess the effect of the exercise intervention as provided to all patients of the Prostate Centre at the PMH, and for those who complete the program as

per the parameters of the exercise prescription. These analyses provide efficacy for program implementation as well as modality-specific effects. Our recruitment rate of 32% is comparable to previous studies in this population but with approximately 70% of participants *not* willing to participate, greater effort must be directed towards improving motivation for exercise behaviour in this population.

9.8 Future Directions

The body of research investigating exercise for men with PCa is growing but additional studies are needed, to confirm ours and others' findings as well as explore new frontiers of research in clinical benefit, exercise maintenance, and program participation. Across PCa treatment populations, participants undergoing brachytherapy (many of whom are also undergoing ADT), chemotherapy, active surveillance, and radical prostatectomy) have received virtually no exercise-related information to base exercise recommendations or parameters. With minor treatment-specific adjustments, we have an opportunity (and likely an obligation) to extend our understanding of exercise-related benefit for all men with PCa that can be grounded in the evidence provided from ADT patients.

In addition to reaching PCa survivors undergoing a greater variety of treatments, it is also essential that we expand our investigation of exercise-related benefits to other clinical outcomes in PCa such as bone health, fracture incidence, disease recurrence/progression, and survival. Our findings and those from previous studies indicate that large sample sizes are needed to control for various for various confounding

factors (e.g. socioeconomic status, race/ethnicity, medical comorbidity, exercise motivations, past exercise behaviours) (55, 57). Contamination effects must also be closely monitored as participants may adopt exercise regimens that are not a part of their prescribed intervention. This will remain a challenge given the impossibility of blinding participants to their intervention arm.

It is also necessary to better understand the relevant factors contributing to physical activity initiation and chronic participation. Investigating the determinants of physical activity and more clearly defining the facilitators/barriers to participation may contribute to the development of more appealing interventions with better adherence rates. Embedding the intervention within a theoretical paradigm possibly offers a more cohesive perspective on the underlying determinants of health-related behaviour; however, the specific effect of adherence boosting strategies cannot yet be determined. The current body of literature contains numerous theory-based attempts at stimulating and enhancing exercise behaviours (77, 79)(72), but a new generation of research that tests interventions for exercise maintenance rather than exercise versus control or alternative modality is warranted. Optimizing long-term adherence will require innovative intervention strategies that are not only acutely beneficial, but convenient, attractive, and applicable across socioeconomic strata, geographic location, etc. Suggested strategies include: the incorporation of social supports, the provision of appropriate exercise equipment and instruction, motivation enhancement tools, satellite exercise facilities proximal to the patient's home, and home-based, self-directed exercise programs. Moreover, with research revealing that exercise is rarely discussed and

infrequently incorporated into standard PCa treatment (509-511) paired with findings that physicians maintain a strong influence on exercise behaviours of oncology patients (512), interventions aimed at improving physician discussion of exercise and/or referral to exercise programs is needed.

To date, assessment of home-based exercise adherence in PCa literature has only been assessed using logbooks, physical activity questionnaires, and attendance to biweekly group exercise booster sessions. The former two methods of assessment are subject to response and recall bias, and attendance at exercise classes does not necessarily reflect adherence to the home-based component of the exercise prescription. Furthermore, these assessments of exercise adherence cannot examine experiential aspects of program adherence from the patient's perspective that may be available from more open-ended approaches to data collection. Qualitative examination of the experience, motivation, and satisfaction of PCa patients participating in an exercise intervention has not previously been conducted. In response to this gap in the literature, we incorporated a qualitative analysis of the experiential aspects of program participation via semi-structured interviewing as a sub-study of the current trial (see Appendix N for the Semi-Structured Interview questions). Interviews were conducted following the formal intervention period (6 months) and before the post-intervention follow-up time point (12 months). The results of this sub-study have recently been reported in the Master's thesis of A. Kornblum (513). A detailed description of the qualitative interview procedures and adherence-related results are presented in Section 6. This post hoc element to the present trial represents the first qualitative assessment of the participation

experience for PCa in an exercise intervention which should be replicated and expanded on to derive nuances of participation not captured in standard paper-and-pencil and fitness tests.

10.0 Conclusion

Exercise has gained considerable attention as a behavioural approach to reducing many of the physical and psychosocial adverse effects associated with ADT for PCa. Our feasibility study demonstrates institutional and collegial capacity to conduct a large-scale research study with participation and adherence rates that are comparable to those in more established cancer-exercise research programs. Our data indicate that a full-scale two-arm RCT could be conducted safely and within approximately 3 years. However, given our observations regarding booster session attendance and attrition, modifications to this study's protocol for future studies should be considered. We provide a broad range of effect size and variance estimates for comprehensive statistical analyses (i.e. RM-ANOVA, multiple-linear regression) for a large-scale trial as well as more rudimentary analyses conducive to smaller research projects examining within group changes over varying intervention durations (i.e. paired-samples t-test). A direct result of this research project which will support, not only a main trial to examine this effect, but many trials in all facets of PCa and exercise research, is the conception and development of the Survivorship Exercise Program. The Survivorship Exercise Program is an ongoing, clinical-research initiative supported by the Prostate Centre and Princess Margaret Foundation to ensure that all men with PCa can be supported with lifestyle assistance while contributing to a greater understanding of the relationship between exercise and PCa management. Finally, while not the primary intent of this dissertation, hypothesis testing within the context of feasibility assessment yielded several interesting findings that must be considered with caution given the inadequate sample size. Of particular

note, it appears that the AET intervention was more effective at producing long-term, clinically significant increases in physical activity volume. Assessment of biomarkers, however, suggests that RET may be exclusively associated with anti-proliferative effects, while HRQOL and fatigue may be largely unresponsive to either AET or RET interventions in the home-based setting. Physical activity participation may be assessed indirectly in terms of observations of physical fitness changes in this population. Finally, although psychological determinants of physical activity were not associated with physical activity volume or fitness changes, exercise-induced feelings were routinely positively correlated with self-efficacy, which marks an area for further study because improving the enjoyment of the activity may elicit enhanced exercise adherence. Future exercise intervention trials must focus on strategies to improve participation and chronic adherence.

Table 1. Summary of Exercise Intervention Trials in Prostate Cancer

Authors	Sample	Design	Exercise Intervention	Participation and Adherence	Measures	Results
Interventions for PCa Patients Treated with Radical Therapy ± ADT						
Windsor et al, 2004 (66)	N=66 PCa patients treated with EBR; n=51 had early stage tumors (T1-T2); n=19 were treated with adjuvant ADT); mean age = 68.8 years.	RCT: home-based exercise (n=33) vs. standard care control (n=33)	Minimum of 3 sessions weekly for 4 weeks, unsupervised, home-based walking at 60-70% of estimated MHR for 30 minutes.	Participation Rate = 86% (n=11 refused); Adherence Rate = 100% (all patients in the exercise group recorded at least 90 minutes per week of AET at the recommended HR); Attrition Rate = 3%	BFI, modified shuttle walking test, RHR, exercise HR	Control group: increased fatigue scores from baseline to treatment completion (p=0.013), stable fatigue symptoms in the exercise group (p= 0.203); greater walking distance for the exercise group compared to the controls (p=0.0025) Adverse events were not reported.
Monga et al, 2007 (65)	N=21; localized PCa treated with EBR; mean age of AET group = 68.0; mean age of controls = 70.6	RCT: AET (n=11) vs. control (n=10)	3 sessions weekly for 8 weeks, supervised, facility based, walking at 65% of HRR for 30 minutes plus 5-10 minutes of warm-up and cool-down.	Participation Rate = 60%; Adherence Rate not reported; Attrition Rate = 30%	Bruce treadmill test; MSR; stand and sit test; PFS; FACT-P; BDI	Compared to controls, the intervention groups experienced significant improvements in cardiovascular fitness (p=0.006), lower extremity strength (p<0.001), flexibility (p<0.01), fatigue (p<0.001), physical wellbeing (p<0.001), social wellbeing (p<0.002), functional wellbeing (p=0.04), and overall HRQOL (p=0.006). Adverse events were not reported.
Segal et al, 2009 (21)	N= 121 PCa patients treated with EBR; n= 74 treated with adjuvant ADT; (n=96 participants had stage I or II disease; n=22 had stage III or IV disease; n= 3 had unassigned disease staging) mean age 66.3	RCT: RET (n=40) vs. AET (n=40) vs. wait-list controls (n=41)	3 sessions weekly for 24 weeks, supervised, facility based AET or RET for 15-45 minutes. AET group: exercises performed on elliptical, cycle ergometer, or treadmill at 50-75% of MHR RET group: 9 upper and lower body exercises (leg extension, leg curl, seated press, lat pull-down, overhead press triceps extension, bicep curls and modified curl-ups), 1 set of each exercise at 60% of 1RM, increased to 2 sets of 8 - 12 repetitions.	Participation Rate: 37%; Adherence Rate: RET = 88% (63 of 72 sessions); AET = 83% (60 of 72 sessions) (p=0.845). Attrition Rate = 9.9%	FACT-F; FACT-P; FACT-G; PSA; testosterone; haemoglobin; serum lipids (total cholesterol, LDL, HDL, triglycerides); upper and lower body muscular strength test; VO_2max (ramp protocol)	RET improved fatigue (p = 0.007), aerobic fitness (p = 0.034), upper (p < 0.001) and lower (p < 0.001) body fitness, and body fat percentage (p = 0.029). Compared to controls, AET improved aerobic fitness (p = 0.047) and body fat percentage (p = 0.033); trend towards improved fatigue (p = 0.060); trend of RET superior to AET in aerobic fitness. Three adverse events related to exercise, one serious (no fatalities)

Serda et al, 2010 (180)	N=33 PCa patients treated with RP (n=15), RP+ADT (n=2), EBR+ADT (n=1), or ADT-alone (n=15)	Uncontrolled trial; Pre/Post-test	2 sessions weekly for 24-weeks; 16 weeks under direct supervision + 8 weeks of autonomous exercise, all exercises were facility-based RET. RET consisted of 1-2 sets of 8-12 reps (50-70% of 8RM) of exercises targeting the quadriceps, pectorals, ischiotibials, deltoids, abdominals, biceps, triceps, back, and pelvic floor. Intensity was progressed incrementally.	Participation Rate: 78%; Adherence Rate: 93% (30 of 32 sessions); Attrition Rate = 8.3%	GLTEQ, aerobic fitness (mCAFT), pain (VAS), urinary incontinence (VAS), arterial pressure, 1RM of trunk and lower limbs, FACT-P, FACT-F, muscular endurance (standard load test), visceral adiposity (CT scan)	From baseline to post-test, improvements were observed for: BMI ($p=0.007$), WHR ($p=0.003$), WC ($p\leq0.001$), BF% (≤0.001), HRR ($p=0.02$), SBP ($p=0.001$), VO_2 peak ($p<0.001$), cardiovascular response to submaximal strength testing ($p\leq0.04$), FACT-P ($p=0.003$), urinary incontinence ($p<0.001$), and pain ($p<0.001$).
Interventions for PCa Patients Treated on Androgen Deprivation Therapy						
Segal et al, 2003 (120)	N = 155 PCa patients treated with ADT; n=75 with stage I or II disease; n= 51 with stage III or IV disease; n=29 had unassigned disease staging; mean age 67.9 years	RCT: RET program (n=82) vs. a waiting list control group (n=73)	3 sessions weekly for 12 weeks, supervised, facility-based RET at 60-70% of 1RM for 2 sets of 10-12 repetitions. RET program consisted of 9 upper and lower body exercises (leg extension, leg curl, seated press, lat pull-down, overhead press triceps extension, bicep curls and modified curl-ups)	Participation Rate = 30.6%; Adherence Rate = 79%; Attrition Rate = 12.9	FACT-F; FACT-P; standard load upper and lower body strength test; body weight, BMI, WC, subcutaneous skinfolds	RET participants reported less fatigue ($p=0.002$), higher HRQOL levels ($p=0.001$), better upper ($p=0.009$) & lower ($p<0.001$) body muscular fitness Adverse events were not reported.
Galvao et al, 2006, 2007 (29, 121)	N = 11; PCa patients treated with ADT (n= 5 on acute ADT $\leq$ 12 months; n= 6 on ADT > 12 months; mean duration = 1135.6 days)	Uncontrolled trial; Pre/Post-test	2 sessions weekly for 20 weeks of supervised, facility based RET (6-12RM for 2-4 sets) for 60 minutes/session. RT program consisted of 12 upper and lower body exercise (chest press; lat pull-down, seated row; shoulder press; biceps curl; triceps extension; leg extension; leg curl; squat; leg press; abdominal crunch; and back extension).	Participation Rate = (91 participants approached, n=10 refused, n=13 eligible, n=67 ineligible); Adherence Rate = not reported; Attrition Rate = 9%	1RM; muscle endurance test (maximum number of repetitions at 70% of 1RM); chair rise to standing; 6-m walk; 6-m backwards walk, stair climb; 400-meter walk; sensory organization test; DEXA, ultrasound, Hb, PSA, testosterone, GH, and cortisol.	Pre-post improvements in: upper body strength and endurance ($p<0.001$); functional performance ($p<0.05$); quadriceps muscle thickness ($p<0.05$) No adverse events related to exercise.

Carmack-Taylor et al, 2006 (30)	N=134; PCa patients treated with ADT (mean duration of ADT = 32.7 months); mean age 69.2 years	RCT: lifestyle program (n=46) vs. educational support group (n=51) vs. standard care (n=37)	Monthly group-based sessions for 6 months to increase unsupervised PA to 30 minutes of moderate intensity exercise for most days per week. To facilitate PA adherence, participants were taught cognitive-behavioural and exercise monitoring strategies.	Participation Rate = 22%; Adherence Rate = 64%; Attrition Rate = 15.7%	SF-36, CES-D, STAI, BPI, 6MWT, BMI, WC, HC, WHR, ISEL, 7-DPARQ, The Stage Motivational Readiness for Physical Activity, Processes of Change for Physical Activity Questionnaire, Decisional Balance for Physical Activity; Self-Efficacy Questionnaire	No significant effects were found in any of the outcome measures No adverse events related to exercise.
Culos-Reed et al, 2007 (24)	N = 31; PCa patients treated with ADT for a minimum of 6 months; mean age = 64.8 years Sub-sample (n=18) were followed up 4 months post-intervention; mean age = 65.7 years	Uncontrolled trial; Pre/Post-test	3-5 sessions per week for 12 weeks, unsupervised, home-based mixed modality exercise. 90 minute "Booster Sessions" held at 2-week intervals for group exercise, and to discuss progress, concerns, and foster/monitor adherence.	Participation Rate: not reported; Adherence Rate: 81% of participants attended 5 or 6 of 6 offered booster sessions; Attrition Rate: 0% at post-intervention; 41.9% at 4-month follow-up)	GLTEQ; RHR; 6MWT; hand-grip dynamometer test; MSR; EORTC-QLQ C30; FSS; BMI	Pre-post intervention improvements in strenuous/total PA ($p<0.01$) and functional capacity ($p<0.01$), resting HR ($p=0.03$), BMI ($p<0.01$) and fatigue ($p=0.05$) At 4 mos. post-intervention (n=18): decreased strenuous PA ($p=0.01$) and HRQOL ($p=0.04$) Adverse events were not reported.
Hansen et al, 2009(27)	N = 10; PCa patients; n=5 currently undergoing ADT vs. n=5 not undergoing ADT; mean age = 66.5 years	Non-randomized, non-controlled trial (pre/post-test and between groups analysis for men on ADT vs. not-on ADT)	3 sessions per week for 12 weeks, supervised, facility-based exercise. Progressively longer and intense high force eccentric cycle ergometry	Participation Rate = not reported; Adherence Rate = 100%; Attrition Rate = 38% (n=4 from the ADT group)	Quadriceps volume (via MRI); isometric quadriceps strength via dynamometry, Timed up and go test, 6MWT, FACT-P, FACT-F	ADT Group: improved 6MWT ($p=0.01$), isometric quadriceps strength (right leg: $p=0.03$, bilateral: $p=0.05$). Non-ADT Group: improved physical subscale of FACT-P ($p=0.03$), left quadriceps volume ($p=0.04$). No between group differences. No adverse events related to exercise.
Culos-Reed et al, 2010 (122)	N = 100 PCa patients receiving ADT for a minimum of 6 months, intervention group	RCT: Mixed-modality exercise (n=53) vs. waitlist control group	3-5 sessions weekly for 16 weeks of unsupervised, home-based mixed-modality exercise, home-based intervention. 90 minute "Booster Sessions"	Participation Rate = not reported; Adherence Rate = 77.8%; Attrition Rate = 34%	EORTC-QLQ C30; EPIC; FSS; CES-D; GLTEQ-LSI; RHR, BP, 6MWT, hand grip	Intervention improved PA levels ($p<0.004$), waist girth ($p<0.044$), and neck girth ($p<0.019$), and hormone symptoms (<0.074).

	mean age = 67.2, control group mean age = 68 years	(n=47)	held each week during intervention, and then monthly to the end of follow-up. Each session was designed to foster/monitor adherence, and consisted of group exercise, and discussion regarding progress and concerns.		dynamometer test, modified sit and reach, weight, BMI, WC, HC, WHR	Adverse events were not reported.
Galvao et al, 2010(23)	N = 57 PCa patients undergoing ADT (for minimum of 2 months); intervention group mean age = 69.5 years; control group mean age = 70.1 years	RCT: mixed modality exercise (n=29) vs. control (n=28)	2 sessions weekly for 12 weeks; facility-based, supervised exercise in small groups; AET = 15-20 minutes of cycling, walking, or jogging at 65-80% of HRM; RET = 2-4 sets of 6-12RM for chest press, seated row, shoulder press, triceps extension, leg press, leg extension, leg curl, and abdominal crunches.	Participation Rate = 58.8%; Adherence Rate = 94%; Attrition Rate = 5.3%	DEXA (total body and regional lean mass, fat mass, body fat percentage), 1RM for chest press, seated row, leg extension, and leg press, muscular endurance for chest press and leg press, chair sit-to-stand test, 6-m walking test, 400-m walking test, balance, falls self-efficacy, SF-36, EORTC-QLQ C30, testosterone, PSA, insulin, glucose, c-reactive protein, blood lipid profile	At 12 weeks the exercise group improved lean mass of the total body ($p=0.047$), upper limb ($p<0.001$), lower limb ($p=0.019$) and appendicular skeleton ($p=0.003$); chest press ($p=0.018$), seated row ($p<0.001$), leg press ($p<0.001$), leg extension ($p<0.001$), chest press muscle endurance ($p=0.041$), 6MWT ($p=0.024$), 6-m backward walk ($p=0.039$), c-reactive protein (($p=0.008$), and subscales of the SF-36 (general health: $p=0.022$; vitality: $p=0.019$; physical health composite: $p=0.02$) No adverse events related to exercise.
Bourke et al, 2011(28)	N = 50 PCa patients receiving ADT for a minimum of 6 months, intervention group mean age = 71.3 years, control group mean age = 72.2 years	RCT: Lifestyle intervention (exercise + dietary advice; n=25) vs. standard care (n=25)	12 week lifestyle intervention divided into two phases. Phase 1 (week 1-6): 2 sessions per week of supervised exercise including 30 minutes of AET (55-85% of HRM) plus 2 to 4 sets of RET exercises of upper and lower body plus one 30-minute session of unsupervised, home-based exercise. Phase 2 (week 7-12): 1 session per week of supervised training outlined in Phase 1 plus two 30-minute sessions of	Participation Rate = 64.1%; Adherence Rate: 95% of supervised sessions attended and 87% of unsupervised sessions completed; Attrition Rate: 14% at 12 weeks (post-intervention) and 64% at 6 month post-intervention follow-up	GLTEQ, FACT-F, FACT-G, FACT-P, submaximal aerobic fitness test, isokinetic and isometric dynamometry of the quadriceps, chair sit-to-stand test, BMI, IGF-1, IGFBP1, IGFBP-3, insulin, PSA, testosterone, free androgen index, SHBG	At 12 weeks, the lifestyle intervention group had improved PA volume (GLTEQ; $p<0.001$), total caloric intake ($p<0.005$) total, saturated, and monounsaturated fat intake ($p=0.005$, $p<0.001$, $p<0.001$), fatigue ($p=0.002$), aerobic fitness ($p<0.001$), chair sit to stand test ($p=0.001$) and isokinetic muscle strength ($p=0.033$) compared to usual care. At 6 month follow-up, the lifestyle intervention group maintained significant improvements compared to usual care for PA volume ($p<0.001$),

			unsupervised, home-based exercise Dietary advice was provided in group seminars for 15-20 minutes every two weeks and emphasized reduction in saturated fat and refined carbohydrate intake, increased fiber intake, and moderate consumption of alcohol.			fatigue (p=0.006), aerobic fitness(p<0.001), chair sit-to-stand test (p=0.001), isokinetic muscle strength (p=0.035). Adverse events were not reported.
Santa Mina et al, 2012(26)	N = 13 PCa patients receiving ADT or within 3 months of completing ADT, GBE group mean age = years, PT group mean age = 66.3 years	Randomized, non-controlled trial; GBE (n=6) vs. PT (n=7).	3 sessions per week for 8 weeks; supervised (group-based leader or personal trainer). 60 minute sessions with 5 minute warm-up, 25 minute RET, 25 minute AET, 5 minute cool-down. AET and RET exercises in both intervention arms were selected from a standardized list of exercises.	Participation Rate 24%; Adherence Rate = 91% and 88% in the PT and GBE groups, respectively; Attrition Rate = 23% (all dropouts, n=3, were from the GBE group)	PORPUS, FACT-P, FACT-F, directly measured VO_2 peak, grip strength, maximal upper and lower body strength (1RM), balance (Functional Reach Test), BMI, WC, body fat percentage, BMD (quantitative ultrasound of calcaneus)	Within group improvements for PT group included: resting systolic BP (p=0.033), body fat percentage (p=0.001), lower extremity 1RM (p=0.002); Between group differences were observed for upper body 1RM (GBE>PT, p=0.013) and lower body 1RM (PT>GBE, p=0.038) No adverse events related to exercise.

Legend: 6MWT – 6-minute walk test, 7D-PARQ = 7-day Physical Activity Recall Questionnaire, ADT = androgen deprivation therapy, AET = aerobic exercise training, BDI = Beck Depression Inventory, BFI = Brief Fatigue Inventory, BMI = body mass index, BP = blood pressure, BPI = Brief Pain Inventory, DEXA = dual energy x-ray absorptiometry, CES-D = Centre for Epidemiological Studies – Depression Scale, EBR = external beam radiation, EORTC-QLQ C30 = European Organization for the Research and Treatment of Cancer – Quality of Life Study Group, EPIC = Expanded Prostate Cancer Index, FACT-F = Functional Assessment of Cancer Therapy – Fatigue, FACT-G = Functional Assessment of Cancer Therapy – General; FACT-P = Functional Assessment of Cancer Therapy – Prostate, FSS = Fatigue Severity Scale, GH = growth hormone, GBE = group-based exercise, GLTEQ = Godin Leisure Time Exercise Questionnaire, Hb = hemaglobin, HC = hip circumference, HDL = high density lipoprotein, HR = heart rate, HRQOL = health-related quality of life, HRM = heart rate max, HRR = heart rate reserve, ISEL = Interpersonal Support Evaluation List , LDL = low density lipoprotein, m = meters, mCAFT (modified Canadian Aerobic Fitness Test), MSR = modified sit and reach, PA = physical activity, PFS = Piper's Fatigues Scale, PORPUS = Patient-Oriented Prostate Utility Scale, PSA = Prostate-specific antigen, PT = personal training, RCT = randomized controlled trial, RHR = resting heart rate, RM = repetition maximum, RP = radical prostatectomy, SF-36 = Short Form-36 Health Survey, SHBG = sex hormone binding globulin, STAI = State Trait Anxiety Index, WC = waist circumference, WHR = waist to hip rati

Table 2. Baseline Characteristics of Study Participants

Variable	AET (n=32)	RET (n=34)	P-value
Continuous Variables			
Age (years)	72.1 (8.9)	70.6 (9.5)	0.501
Charlson Comorbidity Score	0.31 (0.59)	0.41 (0.78)	0.565
Psychosocial Measures			
Fatigue – FACT – F	42.0 (8.4)	38.1 (12.1)	0.147
HRQOL – FACT-P	123.9 (17.3)	119.3 (19.6)	0.346
HRQOL – PORPUS	67.3 (11.5)	62.2 (10.4)	**0.085**
Physical Fitness			
Weight (kg)	88.6 (9.9)	87.0 (12.8)	0.557
WC (cm)	105.2 (9.6)	105.4 (11.0)	0.951
BMI (kg/m^2)	29.1 (3.4)	29.0 (4.0)	0.922
Chest Skinfold (mm)	35.6 (9.9)	35.3 (11.9)	0.895
Body Fat %	28.5 (5.6)	28.0 (7.4)	0.744
VO_2 – Relative (ml/kg/min)	25.0 (10.3)	28.4 (9.3)	0.169
Grip Strength (kg)	63.9 (14.3)	69.9 (11.9)	**0.081**
Physical Activity Volume (MET-hrs/wk)	19.5(19.4)	24.0 (36.1)	0.541
Psychosocial Correlates of Activity			
Self-Efficacy*	4.05 (0.21)	3.99 (0.21)	0.825
Social Support – Family	2.09 (0.17)	1.78 (0.16)	0.199
Social Support – Friends	1.8 (0.20)	1.5 (0.11)	0.192
Social Support – Total	1.97 (0.16)	1.71 (0.14)	0.236
Exercise-Induced Feelings	3.39 (0.16)	3.19 (0.20)	0.440
Biomarker Outcomes			
Leptin (μg/mL)	19.9 (13.2)	12.8 (9.3)	0.133
Adiponectin (μg/mL)	16.6 (6.1)	21.6 (10.0)	0.162
Leptin:Adiponectin	1.2 (0.87)	0.78 (0.81)	0.982
IGF-1 (ng/mL)	159.6 (55.2)	159.1 (51.2)	0.201
IGFBP-3 (ng/mL)	5582.7 (1514.3)	4360.5 (1370.9)	**0.050**
IGF-1: IGFBP-3	0.03 (0.002)	0.04 (0.005)	**0.078**

Table 2 (continued). Baseline Characteristics of Study Participants

Variable	AET (n=32)	RET (n=34)	P-value
Categorical Variables			
Caucasian	22 (69)	25 (74)	0.707
Married	19 (59)	26 (76)	0.412
Post-High School Education	22 (69)	22 (65)	0.528
Retired	18 (56)	24 (71)	0.562
Currently Smoking (no)	30 (94)	33 (97)	0.298
Gleason Score			
6-7	14 (44)	16 (47)	0.308
8-10	14 (44)	13 (38)	
Not Available	4 (13)	5 (15)	
T-Stage			
T1	4 (13)	6 (18)	0.881
T2	12 (38)	11 (32)	
T3	6 (19)	8 (24)	
T4	6 (19)	4 (12)	
Not Available	4 (13)	5 (15)	
Treatment			
LHRH-a alone	19 (59)	19 (56)	0.767
LHRH-a + anti-androgen	11 (34)	12 (35)	
Anti-androgen alone	2 (6)	3 (9)	

Data for continuous variables are presented as Mean (SD); p-value for between-group differences using independent sample t-test. Data for categorical variables are presented as Frequency (% of group); p-value for χ^2; LHRH-a = luteinizing hormone-releasing hormone agonist, ADT = androgen deprivation therapy; *the measure of self-efficacy for exercise was not implemented until partway through the study, thus not all participants have data at each time point and these data represent n = 21 from the AET group and n = 22 from the RET group.

Table 3. Baseline Characteristics of Dropouts and Non-Dropouts

Variable	Dropouts (n=22)	Non-Dropouts (n=44)	P-value
Continuous Variables			
Age (years)	74.2 (9.2)	69.8 (8.9)	0.067
Charlson Comorbidity Score	0.32 (0.65)	0.39 (0.72)	0.710
Psychosocial Measures			
Fatigue – FACT – F	40.9 (9.8)	39.6 (11.0)	0.650
HRQOL – FACT-P	122.8 (8.5)	121.1 (20.0)	0.746
HRQOL – PORPUS	64.4 (8.5)	65.2 (12.2)	0.806
Physical Measures			
Weight (kg)	91.3 (10.7)	86.0 (11.5)	0.077
WC (cm)	107.2 (9.8)	104.4 (10.5)	0.312
BMI (kg/m^2)	29.8 (3.1)	28.7 (3.9)	0.273
Chest Skinfold (mm)	34.3 (11.4)	36.0 (10.7)	0.564
Body Fat %	27.9 (5.9)	28.4 (6.9)	0.753
VO_2 – Relative (ml/kg/min)	23.5 (10.0)	28.5 (9.5)	0.052
Grip Strength (kg)	66.6 (16.3)	67.0 (11.6)	0.907
Physical Activity Volume (MET-hrs/wk)	29.1 (43.3)	18.6 (19.5)	0.181
Psychosocial Correlates of Activity			
Self-Efficacy*	4.08 (0.23)	3.99 (0.19)	0.734
Social Support – Family	2.09 (0.20)	1.87 (0.15)	0.400
Social Support – Friends	1.66 (0.20)	1.64 (0.14)	0.945
Social Support – Total	1.98 (0.18)	1.77 (0.13)	0.371
Exercise-Induced Feelings	3.45 (0.18)	3.24 (0.17)	0.457
Categorical Variables			
Caucasian	17 (77.2)	30 (68.2)	0.148
Married	16 (72.7)	29 (65.9)	0.239
Post-High School Education	15 (68.2)	41 (93.2)	0.277
Retired	13 (59.1)	29 (65.9)	0.169
Currently Smoking (no)	21 (95.5)	42 (95.5)	0.481
Gleason Score			
6-7	10 (45.5)	20 (45.5)	0.334
8-10	7 (31.8)	20 (45.5)	
Not Available	5 (22.7)	4 (9.1)	
T-Stage			
T1	2 (9.1)	8 (18.2)	0.805
T2	7 (31.8)	16 (36.4)	
T3	5 (22.7)	9 (20.5)	
T4	4 (18.2)	6 (13.6)	
Not Available	4 (18.2	5 (11.4)	
Treatment			
LHRH-a alone	13 (59.1)	24 (54.5)	0.644
LHRH-a + anti-androgen	6 (27.3)	17 (38.6)	
Anti-androgen alone	3 (13.6)	3 (6.8)	

Data for continuous variables are presented as Mean (SD); p-value for between-group differences using independent sample t-test. Data for categorical variables are presented as Frequency (% of group); p-value for χ^2; LHRH-a = luteinizing hormone-releasing hormone agonist, ADT = androgen deprivation therapy; *the measure of self-efficacy for exercise was not implemented until partway through the study, thus not all participants have data at each time point and these data represent n = 16 dropouts and n = 25 non-dropouts.

Table 4. Intention To Treat Analysis of the Effects of Aerobic Exercise Training and Resistance Exercise Training on Fatigue and Health-Related Quality of Life Outcomes in Prostate Cancer Patients Receiving ADT

	Baseline		3 Months		6 Months		12 Months		Main Effects (RM-ANOVA)		Group X Time Interaction
									Group	Time	
Variable	AET	RET	AET	RET	AET	RET	AET	RET	$F_{(df)}$ P	$F_{(df)}$ p	$F_{(df)}$ p
FACT-F	42.0 (1.5)	38.1 (2.1)	41.4 (1.4)	38.7 (1.7)	42.2 (1.3)	35.6 (2.2)	42.4 (1.4)	37.9 (2.2)	$2.86_{(1, 60)}$ 0.096	$0.149_{(2.2,132.26)}$ 0.880§	$0.98_{(2.2, 132.26)}$ 0.385§
FACT-P	123.9 (3.2)	119.3 (3.6)	124.4 (3.1)	118.6 (3.4)	124.2 (3.2)	117.4 (4.1)	125.5 (3.0)	119.0 (4.4)	$0.970_{(1,049)}$ 0.330	$0.196_{(1.831, 89.72)}$ 0.804§	$0.255_{(1.83, 89.72)}$ 0.756§
FACT-P – PWB	24.5 (0.86)	23.3 (0.94)	24.3 (0.86)	23.5 (0.83)	23.8 (0.77)	23.0 (0.95)	24.2 (0.74)	22.8 (1.01)	$0.951_{(1, 58)}$ 0.333	$1.513_{(3.0, 133.27)}$ 0.222§	$0.644_{(3.0, 133.27)}$ 0.548
FACT-P – SWB	22.9 (0.93)	20.7 (0.98)	22.7 (0.86)	20.6 (0.98)	22.6 (0.85)	20.2 (1.01)	22.9 (0.76)	20.9 (0.95)*	$3.65_{(1,58)}$ 0.06	$0.203_{(2.0, 116.19)}$ 0.817§	$0.532_{(2.0, 116.19}$ 0.589§
FACT-P – EWB	21.1 (0.53)	18.5 (0.84)	21.0 (0.53)	18.5 (0.71)	20.8 (0.59)	18.6 (0.78)	21.0 (0.56)	18.4 (0.87)	$7.30_{(1,58)}$ 0.009	$0.055_{(2.48, 143.97)}$ 0.983§	$0.036_{(2.48, 143.97)}$ 0.985§
FACT-P - FWB	22.7 (0.77)	20.2 (1.1)	22.3 (0.85)	20.6 (0.83)	22.4 (0.87)	20.9 (0.92)	23.0 (0.71)	20.2 (1.12)	$2.557_{(1,54)}$ 0.116	$0.537_{(1.96, 105.65)}$ 0.582§	$0.674_{(91.96, 105.65)}$ 0.509§
FACT-P - PSC	34.4 (1.1)	33.7 (1.1)	33.5 (1.01)	35.0 (0.72)	33.9 (0.99)	34.4 (1.0)	34.1 (1.1)	34.2 (1.05)	$0.271_{(1, 56)}$ 0.605	$0.055_{(2.23, 124.77)}$ 0.983§	$1.056_{(2.23, 124.77)}$ 0.357§
PORPUS	67.3 (2.0)	62.2 (2.0)	67.0 (1.2)	63.1 (1.9)	65.8 (2.1)	62.3 (2.2)	67.2 (2.0)*	64.5 (2.8)	$1.518_{(1,50)}$ 0.224	$1.345_{(2.51, 125.37)}$ 0.265§	$0.752_{(2.51, 125.37)}$ 0.501§

Intention-to-treat analysis (AET: n=32; RET: n=34); Data are presented as mean (standard error); PWB = physical wellbeing, SWB = social wellbeing; EWB = emotional wellbeing; FWB = functional wellbeing; PSC = prostate cancer-specific concerns; F (degrees of freedom) and p-values for between-factor, within-factor, and interaction analyses are reported for RM-ANOVA; * trend towards within-group change from 6 months ($p < 0.1$), †significant within-group change from baseline ($p \leq 0.05$); ‡significant within-group change from baseline ($p \leq 0.01$). Scales oriented to indicate improvement in wellbeing with increased score; § = analysis was conducted using Greenhouse Geisser's Correction for F-Statistic due to violation of Mauchley's test of sphericity.

Table 5. Intention to Treat Analysis of the Effects of Aerobic Exercise Training and Resistance Exercise Training on Physical Outcomes in Prostate Cancer Patients Receiving ADT

	Baseline		3 Months		6 Months		12 Months		Main Effects (RM-ANOVA)		Group X Time Interaction
									Group	Time	
Variable	AET	RET	AET	RET	AET	RET	AET	RET	$F_{(df)}$ (p)	$F_{(df)}$ (p)	$F_{(df)}$ (p)
Wt (kg)	88.6 (1.7)	87.0 (2.2)	87.0 (1.7)‡	87.2 (2.3)	87.7 (1.8)	87.0 (2.3)	88.2 (1.9)	87.5 (2.4)	$0.056_{(1, 63)}$ 0.814	$1.489_{(2.45, 189)}$ 0.225§	$1.489_{(2.45, 189)}$ 0.225§
WC (cm)	105.2 (1.7)	105.4 (1.9)	103.9 (1.7)‡	105.5 (1.9)	104.3 (1.7)	104.8 (1.8)	103.9 (1.7)†	104.6 (1.9)	$0.081_{(1, 62)}$ 0.776	$2.565_{(3, 186)}$ 0.056	$1.373_{(3, 186)}$ 0.252
BMI (kg/m^2)	29.2 (0.6)	29.0 (0.7)	28.7 (0.6)‡	29.1 (0.7)	28.9 (0.6)	29.1 (0.7)	29.1 (0.7)	29.2 (0.7)	$0.025_{(1, 63)}$ 0.874	$1.421_{(2.41, 151.52)}$ 0.243§	$1.027_{(2.41, 151.52)}$ 0.258§
Chest Skinfold (mm)	35.6 (1.8)	35.3 (2.0)	32.5 (1.7)†	34.2 (1.8)	33.5 (1.8)	33.7 (1.8)	33.2 (2.0)**	32.7 (1.9)**	$0.015_{(1, 62)}$ 0.901§	$4.813_{(1.99, 123.08)}$ 0.010§	$0.838_{(1.99, 123.08)}$ 0.434§
Body Fat %	28.5 (0.1)	28.0 (0.1)	27.1 (1.0)†	27.4 (1.2)	27.3 (1.0)	27.3 (1.2)	26.6 (1.1)†	26.1 (1.3)** •	$0.018_{(1, 61)}$ 0.895	$5.554_{(2.07, 126.36)}$ 0.004§	$0.512_{(2.07, 126.36)}$ 0.607§
VO_2 – (ml/kg/min)	25.1 (1.8)	28.4 (1.6)	28.1 (2.0)	29.1 (1.5)	27.9 (2.0)	30.5 (1.6)‡	28.2 (2.0)**	29.0 (1.8)	$0.640_{(1, 55)}$ 0.427	$2.655_{(2.32, 127.65)}$ 0.066§	$0.669_{(2.32, 127.65)}$ 0.536§
Grip Strength (kg)	63.9 (2.6)	69.6 (2.0)	64.2 (2.6)	68.1 (2.1)	64.5 (2.7)	68.9 (2.3)	65.0 (2.9)	68.5 (2.5)	$1.658_{(1, 61)}$ 0.203	$0.196_{(2.62, 159.97)}$ 0.876§	$0.270_{(2.62, 159.97)}$ 0.821§
PA Volume (MET-hrs/wk)	19.5 (3.5)	24.9 (6.4)	33.3 (6.6)†	24.7 (6.5)	36.3 (7.7)‡	26.7 (6.4)	33.4 (5.9)‡	26.5 (6.3)	$0.462_{(1, 61)}$ 0.499	$5.491_{(2.51, 152.89)}$ 0.003§	$3.122_{(2.51, 152.89)}$ 0.036§

Intention-to-treat analysis (AET: n=32; RET: n=34); Data are presented as mean (standard error); F (degrees of freedom) and p-values for between-factor, within-factor, and interaction analyses are reported for RM-ANOVA; * trend towards within-group change from 6 months ($p < 0.1$), †significant within-group change from baseline ($p \leq 0.05$); ‡significant within-group change from baseline ($p \leq 0.01$); • significant change from 6 months ($p \leq 0.01$); § = analysis was conducted using Greenhouse Geisser's Correction for F-Statistic due to violation of Mauchley's test of sphericity

Table 6. Per Protocol Analysis of Fatigue and Health-Related Quality of Life Outcomes in Prostate Cancer Patients Receiving ADT

	Baseline		3 Months		6 Months		12 Months		Main Effects (RM-ANOVA)		Group X Time Interaction
									Group	Time	
Variable	**AET (n=32)**	**RET (n=34)**	**AET (n=28)**	**RET (n=29)**	**AET (n=24)**	**RET (n=20)**	**AET (n=19)**	**RET (n=12)**	**F (df) (p)**	**F (df) (p)**	**F (df) (p)**
FACT-F	41.07 (1.95)	41.53 (2.86)	40.21 (1.95)	43.95 (1.73)	40.89 (1.81)	44.21 (1.99)	41.42 (1.91)	44.37 (2.25)	0.471 (1, 27) (0.498)	1.387 (3, 81) (0.253)	0.925 (3, 81) (0.418)
FACT-P	124.66 (4.77)	126.12 (3.78)	124.20 (4.90)	128.63 (3.15)	123.8 (4.78)	129.30 (3.65)	126.65 (4.21)	133.35 (2.82)	0.469 (1, 19) (0.502)	0.742 (1.59, 28.85) (0.450) §	0.360 (1.59, 28.85) (0.643) §
FACT-P – PWB	23.78 (1.28)	25.14 (1.02)	26.66 (1.35)	25.23 (0.62)	23.31 (1.09)	25.33 (0.87)	23.94 (1.04)	25.44 (1.00)	0.377 (1,24) (0.545)	0.006 (3,72) (0.999)	0.048 (3,72) (0.979)
FACT-P – SWB	23.01 (1.31)	22.65 (1.13)	22.60 (1.12)	22.89 (0.79)	22.49 (1.18)	22.31 (1.22)	22.94 (1.00)	23.69 (0.71)	0.466 (1, 25) (0.501)	0.095 (1.64,40.98) (0.874) §	0.882 (1.64,40.98) (0.403) §
FACT-P – EWB	21.16 (0.64)	19.87 (1.10)	21.29 (0.64)	19.73 (1.08)	20.89 (0.72)	20.33 (1.10)	21.18 (0.64)	20.46 (1.24)	1.006 (1,24) (0.326)	0.244 (3,72) (0.865)	0.501 (3,72) (0.683)
FACT-P - FWB	22.06 (0.98)	21.02 (1.69)	21.88 (1.21)	22.07 (1.16)	22.17 (1.21)	22.20 (1.35)	23.05 (0.94)	22.81 (1.45)	0.506 (1, 23) (0.484)	1.020 (1.78, 40.87) (0.362) §	0.536 (1.78, 40.87) (0.659) §
FACT-P - PSC	34.2 (1.26)	33.31 (1.89)	34.89 (1.26)	35.5 (1.06)	34.93 (1.35)	35.49 (1.52)	35.32 (1.55)	35.73 (1.43)	0.064 (1, 24) (0.803)	1.936 (3, 72) (0.131)	0.325 (3, 72) (0.808)
PORPUS	68.57 (3.13)	64.23 (2.83)	67.44 (2.71)	64.83 (3.46)	65.63 (3.28)	64.25 (3.67)	67.93 (2.96)	72.08‡* (3.61)	0.018 (1, 23) (0.894)	4.184 (3, 69) (0.009)	3.431 (3, 63) (0.022)

Per-protocol analysis; sample sizes for each within group analysis are presented; data are presented as mean (standard error); PWB = physical wellbeing, SWB = social wellbeing; EWB = emotional wellbeing; FWB = functional wellbeing; PSC = prostate cancer-specific concerns; F (degrees of freedom) and p-values for between-factor, within-factor, and interaction analyses are reported for RM-ANOVA; * trend towards a within-group change from 6 months ($p < 0.1$), †within-group change from baseline ($p \leq 0.05$); ‡within-group change from baseline ($p \leq 0.01$). Scales oriented to indicate improvement in wellbeing with increased score; § = analysis was conducted using Greenhouse Geisser's Correction for F-Statistic due to violation of Mauchley's test of sphericity.

Table 7. Per Protocol Analysis of Physical Fitness Outcomes in Prostate Cancer Patients Receiving ADT

	Baseline		3 Months		6 Months		12 Months		Main Effects (RM-ANOVA)		Group X Time Interaction
									Group	Time	
Variable	**AET (n=32)**	**RET (n=34)**	**AET (n=28)**	**RET (n=29)**	**AET (n=24)**	**RET (n=20)**	**AET (n=19)**	**RET (n=12)**	**F (df) (p)**	**F (df) (p)**	**F (df) (p)**
Wt (kg)	88.5 (2.0)	86.5 (2.4)	86.7 (1.9)‡	86.8 (2.6)	87.8 (2.2)	83.0 (3.0)	88.5 (2.4)	88.3 (3.7)	0.01 (1, 32) 0.921§	2.05 (2.3, 73.63) 0.129§	1.143 (2.3, 73.63) 0.336
WC (cm)	104.8 (1.9)	105.9 (2.2)	103.1 (1.8)‡	106.1 (2.1)	104.3 (2.2)	102.4 (2.3)	103.6 (2.4)†	105.3 (3.0)	0.15 (1, 32) 0.701	2.894 (3, 96) 0.039	1.022 (3, 96) 0.387
BMI (kg/m^2)	29.0 (0.7)	28.8 (0.8)	28.4 (0.7)‡	28.9 (0.8)	28.9 (0.8)	28.3 (1.1)	29.1 (0.9)	28.9 (1.1)	0.061 (1, 32) 0.807	2.152 (2.3, 73.57) 0.116§	1.052 (2.3, 73.57) 0.362§
Chest Skinfold (mm)	35.7 (2.0)	35.2 (2.2)	32.1 (1.9)†	34.0 (1.9)	34.0 (2.4)	36.8 (32.9)†	32.2 (3.0)	33.7 (2.3)	0.467 (1, 31) 0.499	2.461 (3, 93) 0.087	0.232 (3, 93) 0.818
Body Fat %	28.7 (1.2)	28.5 (1.4)	26.9 (1.1)†	27.8 (1.4)	27.3 (1.4)**	26.2 (1.7)**	25.1 (1.5)‡	25.3 (1.7)**	0.082 (1, 30) 0.777	5.483 (3, 90) 0.001	0.731 (3, 90) 0.536
VO_2 – (ml/kg/min)	28.1 (1.9)	27.5 (1.8)	30.4 (1.9)	28.3 (1.7)	31.1 (2.3)†	33.1 (2.0)‡	30.0 (2.6)	30.1 (3.6)	0.11 (1, 26) 0.743	2.876 (3, 78) 0.041	0.741 (3, 78) 0.531
Grip Strength (kg)	67.4 (2.6)	68.3 (2.1)	67.0 (2.8)	66.4 (2.1)	67.0 (3.4)	68.1 (2.8)	65.8 (3.6)	69.7 (4.0)	1.406 (1, 31) 0.245	0.605 (2.26, 7.2) 0.569§	0.155 (2.26, 7.2) 0.881§
PA Volume (MET-hrs/wk)	22.3 (4.0)	17.5 (3.2)	38.3 (7.4)†	18.3 (83.3.8)	43.5 (10.7)‡	23.9 (4.7)	34.3 (8.3)†	21.3 (4.5)	1.392 (1, 32) 0.247	2.714 (3, 96) 0.049	1.2 (3, 96) 0.314

Per-protocol analysis; sample sizes for each within group analysis are presented; data are presented as mean (standard error); F (degrees of freedom) and p-values for between-factor, within-factor, and interaction analyses are reported for RM-ANOVA; * trend towards a within-group change from 6 months ($p < 0.1$), †within-group change from baseline ($p \leq 0.05$); ‡within-group change from baseline ($p \leq 0.01$); • significant change from 6 months ($p \leq 0.01$); scales oriented to indicate improvement in wellbeing with increased score; § = analysis was conducted using Greenhouse Geisser's Correction for F-Statistic due to violation of Mauchley's test of sphericity.

Table 8. Subgroup Analysis of the Effects of Aerobic Exercise Training and Resistance Exercise Training on Biomarkers of Tumour Progression

	Baseline		3 Months		6 Months		Main Effects (RM-ANOVA)		Group X Time Interaction
							Group	Time	
Variable	**AET**	**RET**	**AET**	**RET**	**AET**	**RET**	**F (df) p**	**F (df) p**	**F (df) p**
Leptin (μg/mL)	19.9 (3.8)	12.8 (2.6)	14.9 (2.6)	13.6 (3.5)	20.6 (4.1)	12.1 (3.1)	$1.797_{(1, 23)}$ 0.446	$0.821_{/92, 46)}$ 0.446	$2.154_{/92, 46)}$ 0.128
Adiponectin (μg/mL)	16.6 (1.8)	21.6 (2.8)	16.1 (2.2)	21.1 (3.3)	16.1 (2.5)	20.5 (2.6)	$2.341_{(1, 22)}$ 0.140	$0.620_{(2, 44)}$ 0.538	$0.032_{(2, 44)}$ 0.969
Leptin:Adiponectin	1.2 (0.26)	0.78 (0.22)	1.08 (0.21)	1.04 (0.42)	1.6 (0.4)	0.88 (0.35)	$0.992_{(1, 22)}$ 0.330	$1.185_{(2, 44)}$ 0.315	$2.12_{(2, 44)}$ 0.132
IGF-1 (ng/mL)	159.6 (15.3)	159.1 (14.2)	169.7 (18.7)	138.3 (11.8)†	161.9 (12.7)	146.4 (13.7)	$0.796_{(1, 24)}$ 0.381	$0.221_{(1.53, 36.64)}$ 0.743§	$1.422_{(1.53, 36.64)}$ 0.252§
IGFBP-3 (ng/mL)	5582.7 (456.6)	4360.5 (380.2)	4770.4 (777.8)	4321.3 (334.3)	4259.8 (406.8)†	4887.9 (454.8)†	$0.424_{(1, 22)}$ 0.522	$0.877_{(2, 44)}$ 0.423	$3.338_{(2, 44)}$ 0.045
IGF-1: IGFBP-3	0.03 (0.002)	0.04 (0.005)	0.13 (0.09)	0.03 (0.005)	0.04 (0.01)†	0.03 (0.003)†	$1.188_{(1, 22)}$ 0.288	$1.084_{(1.01, 22.2)}$ 0.310	$1.148_{(1.01, 22.2)}$ 0.296

Subgroup analysis (AET: n=13; RET: n=13); data are presented as mean (standard error); F (degrees of freedom) and p-values for between-factor, within-factor, and interaction analyses are reported for RM-ANOVA; †within-group change from baseline ($p \leq 0.05$); ‡within-group change from baseline ($p \leq 0.01$); § = analysis was conducted using Greenhouse Geisser's Correction for F-Statistic due to violation of Mauchley's test of sphericity.

Table 9. Correlation Matrix for Physical Fitness Outcomes and Biomarkers at Baseline

	Weight	BMI	WC	BF%	PA Volume	VO_2	GS	IGF-1	IGFBP-3	Adiponectin	Leptin	Leptin: Adiponectin	IGF-1: IGFBP-3
Age (years)	-0.145	-0.157	0.000	-0.188	-0.076	-0.641‡	-0.556‡	0.047	0.196	0.316	-0.204	-0.146	-0.126
n	66	66	65	65	64	66	65	26	24	24	25	24	24
Weight (kg)	1	0.809‡	0.856‡	0.609‡	-0.137	-0.234*	0.089	0.027	-0.029	-0.471**	0.446**	0.531**	0.055
n		66	65	65	64	66	65	26	24	24	24	24	24
BMI (kg/m^2)		1	0.787‡	0.639‡	-0.122	-0.238*	0.036	-0.177	-0.214	-0.476**	0.480**	0.610†	-0.055
n			65	65	64	66	65	26	24	24	25	24	24
WC (cm)			1	0.654‡	-0.268**	-0.360†	-0.110	0.069	-0.154	-0.556†	0.480**	0.667‡	0.250
n				64	63	65	64	26	24	24	25	24	24
BF%				1	-0.262**	-0.029	-0.124	-0.121	-0.261	-0.523†	0.523†	0.606†	0.131
n					63	65	64	26	24	24	25	24	24
PA Volume (MET-hrs/wk)					1	0.292**	0.250**	0.210	0.277	-0.098	-0.065	-0.010	-0.162
n						64	63	26	24	24	25	24	24
VO_2 ($mlO_2/kg/min$)						1	0.474‡	-0.022	-0.192	-0.162	-0.182	-0.134	0.162
n							65	26	24	24	25	24	24
GS (kg)							1	-0.176	-0.394*	-0.029	-0.415**	-0.381*	0.134
n								26	24	24	25	24	24
IGF-1								1	0.517†	0.349*	-0.118	-0.109	0.462**
n									24	24	25	24	24
IGFBP-3									1	0.245	-0.065	-0.231	-0.450**
n										23	24	23	24
Adiponectin										1	-0.301	-0.598†	0.029
n											24	24	23
Leptin											1	0.833‡	-0.015
n												24	24
Leptin: Adiponectin												1	0.235
n													23

Pearson *r* correlations; n refers to number of participants in bivariate correlation analysis, BMI = body mass index, WC = waist circumference, BF% = body fat %, VO_2 = VO_2 peak; GS = grip strength; *p≤0.1; **p≤0.05; †p≤0.01; ‡p≤0.001

Table 10. Correlation Matrix for Change in Physical Outcomes from Baseline to 3 months

	ΔBMI	ΔWC	ΔBF%	ΔPA Volume	ΔVO_2	ΔGS	ΔIGF-1	ΔIGFBP-3	ΔAdiponectin	ΔLeptin	ΔLeptin: Adiponectin	ΔIGF-1: IGFBP-3
ΔWeight (kg)	0.999‡	0.441‡	0.183	-0.187	-0.110	-0.130	-0.223	0.073	0.140	0.602‡	0.334	-0.452**
n	65	64	64	62	63	63	26	24	24	25	24	24
ΔBMI (kg/m^2)	1	0.425‡	0.171	-0.181	-0.119	-0.145	-0.211	0.057	0.132	0.610‡	0.358*	-0.444**
n		64	64	62	63	63	26	24	24	25	24	24
ΔWC (cm)		1	0.243*	-0.372†	-0.024	0.051	-0.046	0.292	-0.087	0.411**	0.189	-0.456**
n			63	61	62	62	26	24	24	25	24	24
ΔBF%			1	-0.176	0.091	0.140	-0.311	-0.313	0.139	-0.109	-0.060	-0.067
n				61	62	62	26	24	24	25	24	24
ΔPA Volume (MET-hrs/wk)				1	0.340†	0.032	0.119	-0.017	0.139	-0.026	-0.040	0.117
n					61	60	26	24	24	25	24	24
ΔVO_2 ($mlO_2/kg/min$)					1	0.128	0.052	-0.087	0.154	-0.406**	-0.159	0.379*
n						61	26	24	24	25	24	24
ΔGS (kg)						1	0.138	-0.062	-0.093	-0.213	-0.253	0.043
n							26	24	24	25	24	24
ΔIGF-1 (ng/mL)							1	-0.161	-0.067	-0.048	0.175	0.573†
n								24	24	25	24	24
ΔIGFBP-3 (ng/mL)								1	-0.122	0.296	-0.029	-0.444**
n									23	24	23	24
ΔAdiponectin (μg/mL)									1	0.135	-0.250	0.052
n										24	24	24
ΔLeptin (μg/mL)										1	0.734‡	-0.565†
n											24	24
ΔLeptin: Adiponectin											1	0.099
n												23

Pearson *r* correlations; n refers to number of participants in bivariate correlation analysis, BMI = body mass index, WC = waist circumference, BF% = body fat %, VO_2 = VO_2 peak; GS = grip strength; *p≤0.1; **p≤0.05; †p≤0.01; ‡p≤0.001

Table 11. Correlation Matrix for Change in Physical Outcomes from Baseline to 6 months

	ΔBMI	ΔWC	ΔBF%	ΔPA Volume	ΔVO_2	ΔGS	ΔIGF-1	ΔIGFBP-3	ΔAdiponectin	ΔLeptin	ΔLeptin: Adiponectin	ΔIGF-1: IGFBP-3
ΔWeight (kg)	0.997‡	0.549‡	0.109	-0.156	-0.341†	-0.019	0.098	-0.179	-0.146	0.529†	0.526†	0.316
n	65	64	64	63	62	63	26	24	24	25	24	24
ΔBMI (kg/m^2)	1	0.532‡	0.095	-0.145	-0.35†	-0.035	0.078	-0.175	-0.142	0.517†	0.524†	0.297
n		64	64	63	62	63	26	24	24	25	24	24
ΔWC (cm)		1	0.339†	-0.178	-0.433‡	-0.052	0.228	-0.163	-0.044	0.267	0.226	0.432**
n			63	62	61	62	26	24	24	25	24	24
ΔBF%			1	-0.124	-0.034	-0.055	0.155	0.032	0.365*	-0.252	-0.529†	0.198
n				62	61	62	26	24	24	25	24	24
ΔPA Volume (MET-hrs/wk)				1	0.318†	-0.002	0.240	-0.075	-0.155	-0.132	-0.001	0.135
n					61	61	26	24	24	25	24	24
ΔVO_2 ($mlO_2/kg/min$)					1	0.044	0.142	0.045	0.087	-0.471**	-0.275	-0.133
n						60	25	23	23	24	23	23
ΔGS (kg)						1	0.156	-0.008	-0.065	0.323	0.249	0.090
n							26	24	24	25	24	24
ΔIGF-1 (ng/mL)							1	0.170	0.340	0.173	0.150	0.246
N								24	24	25	24	24
ΔIGFBP-3 (ng/mL)								1	0.200	-0.141	-0.024	-0.787‡
n									23	24	23	24
ΔAdiponectin (μg/mL)									1	-0.164	-0.292	-0.022
n										24	24	23
ΔLeptin (μg/mL)										1	0.773‡	0.311
n											24	24
ΔLeptin: Adiponectin											1	0.198
n												23

Pearson *r* correlations; n refers to number of participants in bivariate correlation analysis, BMI = body mass index, WC = waist circumference, BF% = body fat %, VO_2 = VO_2 peak; GS = grip strength; *p≤0.1; **p≤0.05; †p≤0.01; ‡p≤0.001.

Table 12. Correlation Matrix for Determinants of Exercise Outcomes at Baseline

	Charlson	EIF	SUP	SUPF	SUPFR	SE	PA	VO_2
Age	-0.015	0.073	0.011	-0.046	0.105	0.005	-0.076	-0.641‡
	66	59	62	63	62	41	64	66
Charlson	1	0.043	.043	-.043	-.069	-.30*	-.172	.07
		59	62	63	62	41	64	66
EIF		1	.273**	.248*	.257*	.534†	.143	.235*
			58	59	58	37	58	59
SUP			1	.979‡	.787‡	.339**	.056	.095
				62	62	41	61	62
SUPF				1	.644‡	.335**	.042	.068
					62	41	62	63
SUPFR					1	.258	.089	.164
						41	61	62
SE						1	.272*	.341**
							41	41
PA							1	.292**
								64

EIF = exercise-induced feelings; SUP = social support (total); SUPF = social support (family); SUPFR = social support (friends); SE = self-efficacy; PA = physical activity volume; VO_2 = VO_2 peak; *p<0.1; **p<0.05; †p<0.01; ‡p<0.001

Table 13. Correlation Matrix for Determinants of Exercise Outcomes at 3 Months

	Charlson	EIF	SUP	SUPF	SUPFR	SE	PA	VO_2
Age	-0.101	0.107	0.034	0.057	-0.011	-0.130	-0.096	-0.608‡
	55	48	51	52	52	51	52	52
Charlson	1	.055	-.104	-.164	.070	.151	-.238*	.075
		48	51	52	52	51	52	52
EIF		1	.415†	.404†	.331**	.490‡	.165	.243
			46	47	47	46	47	46
SUP			1	.978‡	.839‡	.294**	.021	.112
				51	51	49	50	49
SUPF				1	.709‡	.261*	-.007	.114
					51	50	51	50
SUPFR					1	.296**	.092	.093
						50	51	50
SE						1	.127	.303**
							51	49
PA							1	.383†
								50

EIF = exercise-induced feelings; SUP = social support (total); SUPF = social support (family); SUPFR = social support (friends); SE = self-efficacy; PA = physical activity volume; VO_2 = VO_2 peak; *p<0.1; **p<0.05; †p<0.01; ‡p<0.001.

Table 14. Correlation Matrix for Determinants of Exercise Outcomes at 6 Months

	Charlson	EIF	SUP	SUPF	SUPFR	SE	PA	VO_2
Age	-0.024	0.161	-0.022	-0.050	0.057	0.055	-0.199	-0.644‡
	41	39	41	40	41	37	41	40
Charlson	1	-.147	-.169	-.233	.059	.233	-.188	.103
		39	41	41	41	37	41	40
EIF		1	.195	.236	.015	.480†	.083	.205
			39	39	39	36	39	38
SUP			1	.961‡	.712‡	.221	.132	0.098
				41	41	37	41	40
SUPF				1	.489‡	.224	.137	.114
					41	37	41	40
SUPFR					1	.125	.068	.020
						37	41	40
SE						1	.165	.130
							37	36
PA							1	.389**
								40

EIF = exercise-induced feelings; SUP = social support (total); SUPF = social support (family); SUPFR = social support (friends); SE = self-efficacy; PA = physical activity volume; VO_2 = VO_2 peak; *p<0.1; **p<0.05; †p<0.01; ‡p<0.001.

Table 15. Correlation Matrix for Determinants of Exercise Outcomes at 12 Months

	Charlson	EIF	SUP	SUPF	SUPFR	SE	PA	VO_2
Age	-0.135	-0.084	-0.216	-0.125	-0.338	-0.130	-0.233	-0.699‡
	34	33	33	33	34	33	34	29
Charlson	1	.061	-.078	-.119	.038	-.065	-.054	-.164
		33	33	33	34	33	34	29
EIF		1	.092	.030	.184	.312*	.153	.130
			32	32	33	32	33	28
SUP			1	.956‡	.751‡	.334*	.017	.109
				33	33	32	33	28
SUPF				1	.523†	.303*	.033	.097
					33	32	33	28
SUPFR					1	.314*	-.026	.105
						33	34	29
SE						1	-.258	.029
							33	28
PA							1	.530†
								29

EIF = exercise-induced feelings; SUP = social support (total); SUPF = social support (family); SUPFR = social support (friends); SE = self-efficacy; PA = physical activity volume; VO_2 = VO_2 peak; *p<0.1; **p<0.05; †p<0.01; ‡p<0.001.

Table 16. Explained Variance in Regression Models for Determinants of Exercise and Control Variables at Each Time Point

Dependent Variable	Time point	n	R	R^2	Adjusted R^2	F	p	Coefficient Table
Physical Activity Volume	Baseline	41	0.417	0.174	0.041	1.309	0.286	17
	3 months	48	0.415	0.173	0.064	1.585	0.188	18
	6 months	39	0.305	0.093	-0.058	0.615	0.690	19
	12 months	29	0.445	0.198	0.037	1.232	0.324	20
VO_2 peak	Baseline	41	0.685	0.470	0.384	5.494	0.001	21
	3 months	48	0.753	0.568	0.507	9.448	<0.001	22
	6 months	39	0.726	0.528	0.446	6.476	<0.001	23
	12 months	29	0.713	0.508	0.385	4.132	0.01	24

Independent variables = social support, self-efficacy, exercise-induced feelings; Control Variables = age, exercise group;

Table 17. Model Coefficients for Physical Activity Volume at Baseline

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Self-Efficacy	4.178	4.293	.197	.973	.338
Social-Support	.673	4.405	.029	.153	.880
Exercise-Induced Feelings	3.621	3.927	.183	.922	.364
Age	-.519	.343	-.258	-1.513	.140
Exercise Group	-1.621	6.768	-.041	-.239	.812

Table 18. Model Coefficients for Physical Activity Volume at 3 Months

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Self-Efficacy	-1.391	4.853	-.050	-.287	.776
Social-Support	-8.162	7.589	-.180	-1.075	.289
Exercise-Induced Feelings	7.563	6.419	.219	1.178	.246
Age	-.446	.548	-.125	-.813	.421
Exercise Group	-22.818	9.748	-.362	-2.341	.025

Table 19. Model Coefficients for Physical Activity Volume at 6 Months

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Self-Efficacy	6.571	6.924	.190	.949	.350
Social-Support	5.062	11.150	.089	.454	.653
Exercise-Induced Feelings	-2.654	7.540	-.071	-.352	.727
Age	-.635	.765	-.147	-.830	.413
Exercise Group	-12.469	14.292	-.164	-.872	.390

Table 20. Model Coefficients for Physical Activity Volume at 12 Months

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Self-Efficacy	-8.597	4.983	-.356	-1.725	.097
Social-Support	-1.793	8.207	-.048	-.219	.829
Exercise-Induced Feelings	10.746	7.402	.299	1.452	.159
Age	-.910	.691	-.245	-1.317	.200
Exercise Group	-14.850	12.893	-.251	-1.152	.260

Table 21. Model Coefficients for VO_2 peak at Baseline

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Self-Efficacy	2.012	1.664	.196	1.209	.236
Social-Support	1.234	1.707	.109	.723	.475
Exercise-Induced Feelings	1.749	1.522	.183	1.149	.259
Age	-.542	.133	-.558	-4.077	.000
Exercise Group	2.721	2.623	.143	1.038	.308

Table 22. Model Coefficients for VO_2 peak at 3 Months

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Self-Efficacy	.448	1.098	.051	.408	.686
Social-Support	.469	1.756	.034	.267	.791
Exercise-Induced Feelings	4.488	1.696	.374	2.646	.012
Age	-.796	.128	-.726	-6.206	.000
Exercise Group	1.001	2.332	.051	.430	.670

Table 23. Model Coefficients for VO_2 peak at 6 Months

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Self-Efficacy	.132	1.223	.016	.108	.915
Social-Support	2.134	1.969	.154	1.084	.287
Exercise-Induced Feelings	2.254	1.331	.252	1.694	.101
Age	-.666	.135	-.642	-4.938	.000
Exercise Group	3.713	2.549	.200	1.456	.156

Table 24. Model Coefficients for VO_2 peak at 12 Months

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Self-Efficacy	-.724	1.601	-.078	-.452	.656
Social-Support	-1.272	2.562	-.092	-.496	.625
Exercise-Induced Feelings	1.641	2.423	.120	.677	.506
Age	-.998	.226	-.726	-4.416	.000
Exercise Group	1.713	4.013	.079	.427	.674

Table 25. Explained Variance in Regression Models for Determinants of Exercise and Control Variables for Program Adherence from Baseline to 24 weeks

Dependent Variable	n	R	R^2	Adjusted R^2	F	p
Physical Activity Volume (Δ from baseline to 6 months)	33	0.339	0.115	0.021	0.843	0.510
VO_2 Peak (Δ from baseline to 24 weeks)	33	0.393	0.154	0.019	1.141	0.360

Independent variables = social support, exercise-induced feelings; Control Variables = age, exercise group

Table 26. Model Coefficients for Change in Physical Activity Volume from Baseline to 6 Months

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Social-Support	-5.267	6.389	-.156	-.824	.417
Exercise-Induced Feelings	3.035	5.841	.101	.520	.608
Age	-.490	.737	-.126	-.665	.512
Exercise Group	-17.941	11.843	-.284	-1.515	.142

Table 27. Model Coefficients for Change in VO_2 Peak from Baseline to 6 Months

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Social-Support	-1.269	1.216	-.197	-1.044	.307
Exercise-Induced Feelings	-.015	1.111	-.003	-.014	.989
Age	.007	.141	.010	.052	.959
Exercise Group	4.017	2.306	.325	1.742	.094

Table 28. Power and Sample Size Calculations for Fatigue and HRQOL Outcomes

Primary Outcome	Observed Effect Size (partial η^2)	Observed Effect Size (*f*)	Observed Power	Sample Size Calculation for Observed Effect	Standard Deviation Used	MCID	Hypothesized Effect Size (*f*)	Sample Size for Hypothesized Effect†
Fatigue (FACT-F)	0.046	0.220	0.384	N=172	5.8 (120, 413)	3.5 points (120, 413)	0.30	N=78
HRQOL (FACT-P)	0.019	0.139	0.162	N=348	9.1 (120, 514)	5 points (120, 514)	0.15	N=92
HRQOL (PORPUS)	0.029	0.173	0.227	N=226	11.1 (425)	5 points (425)	0.23	N=134

Power and sample size calculations are based on a RM-ANOVA for between-groups analysis from baseline to 6 months using intention-to-treat approach; Observed Effect Size was derived from statistical output of SPSS; Observed Power reflects the power of the sample size of current analysis (AET: n = 32; RET: n = 34); † refers to sample size calculation using alpha = 0.05, Power = 0.80; a medium effect size was used as a conservative default when an MCID was not available, when the MCID and SD of the were available, they were used to calculate Cohen's d (d = MCID/SD) which was converted to Cohen's *f* using a reference table of effect sizes(515); Referent values for effect sizes using Cohen's *f*: 0.1 = small, 0.25 = medium, 0.4 = large.

Table 29. Power and Sample Size Calculations for Physical Fitness Outcomes

Primary Outcome	Observed Effect Size (partial η^2)	Observed Effect Size (*f*)	Observed Power	Sample Size Calculation for Observed Effect	Standard Deviation Used	MCID	Hypothesized Effect Size (*f*)	Sample Size for Hypothesized Effect†
Chest Skinfold (mm)	0.001	0.032	0.052	N=6668	NA	NA	0.25	N=110
Body Fat (%)	0.001	0.032	0.052	N=6668	7.1§ (21)	3%**	0.25	N=110
VO_2 peak (mlO_2/kg/min)	0.012	0.110	0.123	N=552	6.6§ (26)	3.5 mlO_2/kg/min‡	0.25	N=110
Grip Strength (combined - kg)	0.026	0.163	0.245	N=252	14.2 (26)	7 kg	0.25	N=110
Physical Activity Volume (MET-hrs/wk)	0.008	0.09	0.103	N=830	NA	9 MET-hrs/wk (110)	0.25	N=110

Power and sample size calculations are based on a RM-ANOVA for a between-groups analysis from baseline to 12 months using intention-to-treat approach; Observed Effect Size was derived from statistical output of SPSS; Observed Power reflects the power of the sample size of current analysis (AET: n = 32; RET: n = 34); † refers to sample size calculation using alpha = 0.05, Power = 0.80; a medium effect size was used as a conservative default when an MCID was not available, when the MCID was available and SD were available, they were used to calculate Cohen's d (d = MCID/SD) which was converted to Cohen's *f* using a reference table of effect sizes(515); §Segal et al's (21) previous assessment of RET effects over 6 months were used to provide SDs for a small-moderate effect size; **3% represents an approximate 10% reduction in total body fat percentage for someone overweight/obese (~30% body fat); ‡ MCID for relative VO_2 peak (mlO_2/kg/min) is generally understood to be 1 metabolic equivalent or 3.5 mlO2/kg/min; Referent values for effect sizes using Cohen's *f*: 0.1 = small, 0.25 = medium, 0.4 = large.

Table 30. Power and Sample Size Calculations for Biomarker Outcomes

Primary Outcome	Observed Effect Size (partial η^2)	Observed Effect Size (*f*)	Observed Power (n)	Sample Size Calculation for Observed Effect	Hypothesized Effect Size (f)	Sample Size for Hypothesized Effect†
Leptin (μg/mL)	0.072	0.28	0.250	N=88	0.25	N=110
Adiponectin (μg/mL)	0.096	0.33	0.310	N=66	0.25	N=110
Leptin:Adiponectin	0.043	0.21	0.159	N=152	0.25	N=110
IGF-1 (ng/mL)	0.032	0.18	0.137	N=204	0.25	N=110
IGFBP-3 (ng/mL)	0.019	0.14	0.096	N=348	0.25	N=110
IGF-1: IGFBP-3	0.051	0.23	0.181	N=128	0.25	N=110

Power and sample size calculations are based on a RM-ANOVA for between-groups analysis from baseline to 12 months using intention-to-treat approach; Observed Effect Size was derived from statistical output of SPSS; Observed Power reflects the power of the sample size of current analysis (AET: n = 13; RET: n = 13); † refers to sample size calculation using alpha = 0.05, Power = 0.80; for all biomarker assay sample size analyses, a medium effect size was used as a conservative default when an MCID because MCIDs have not yet been established; Referent values for effect sizes using Cohen's *f*: 0.1 = small, 0.25 = medium, 0.4 = large.

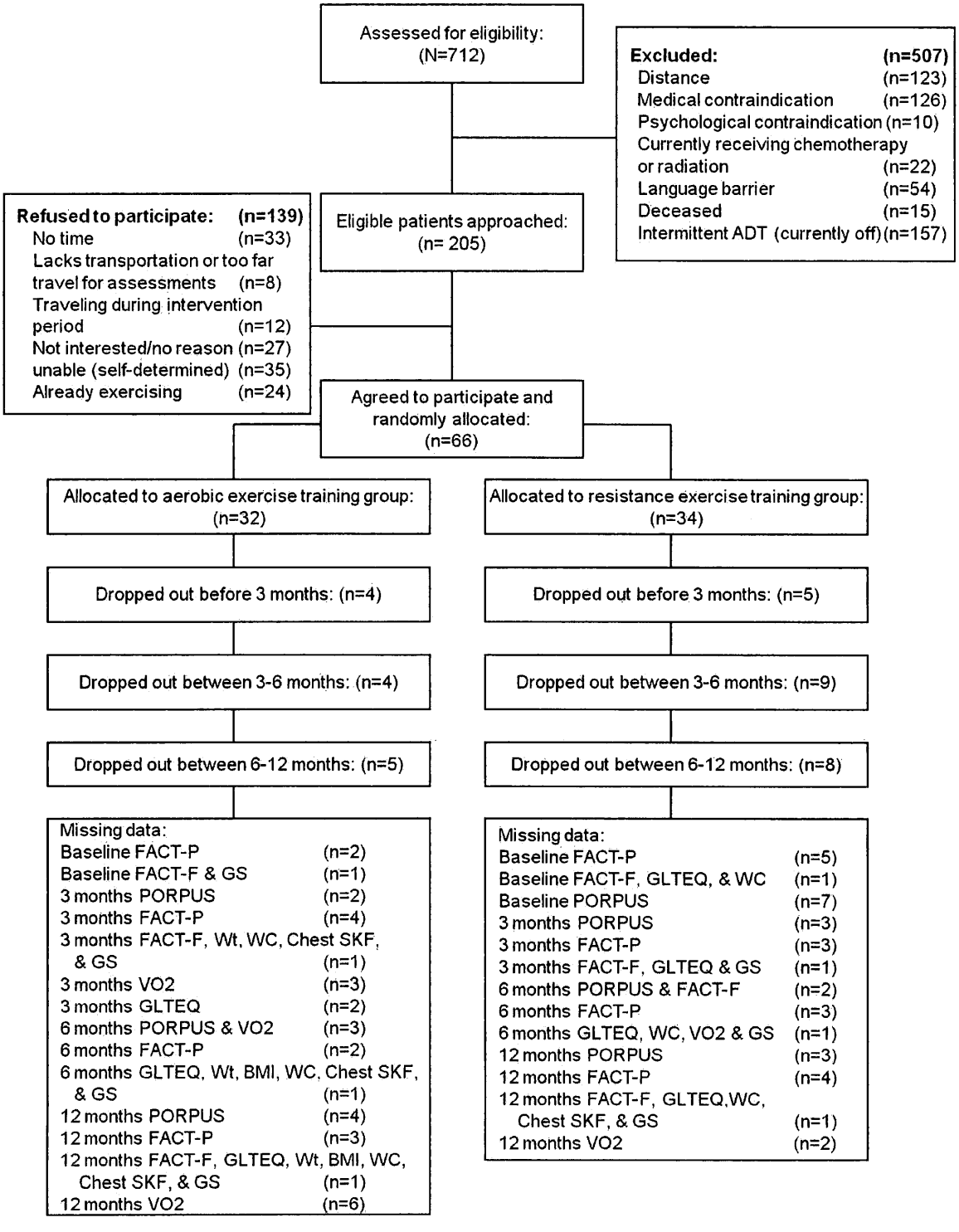

Figure 1. CONSORT Diagram

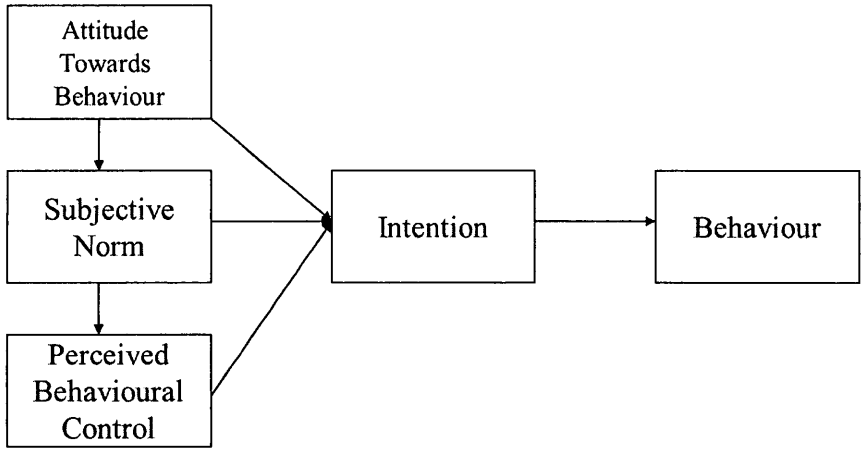

Figure 2. Theory of Planned Behaviour

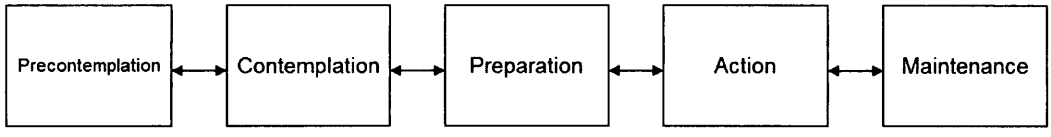

Figure 3. Transtheoretical Model (Stages of Change)

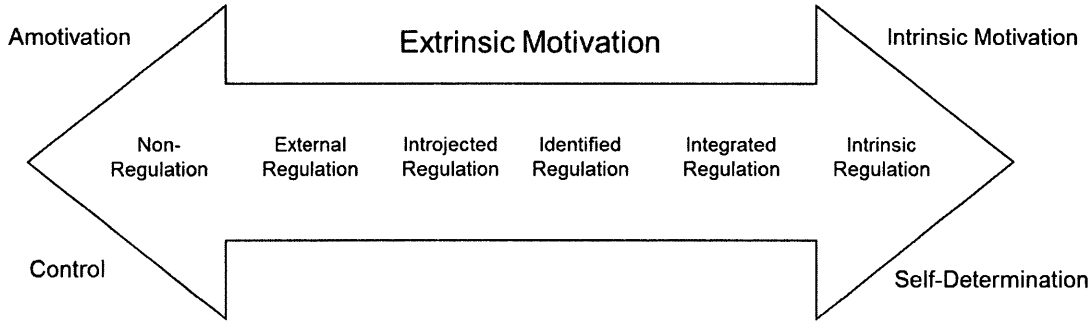

Figure 4. Self-Determination Theory

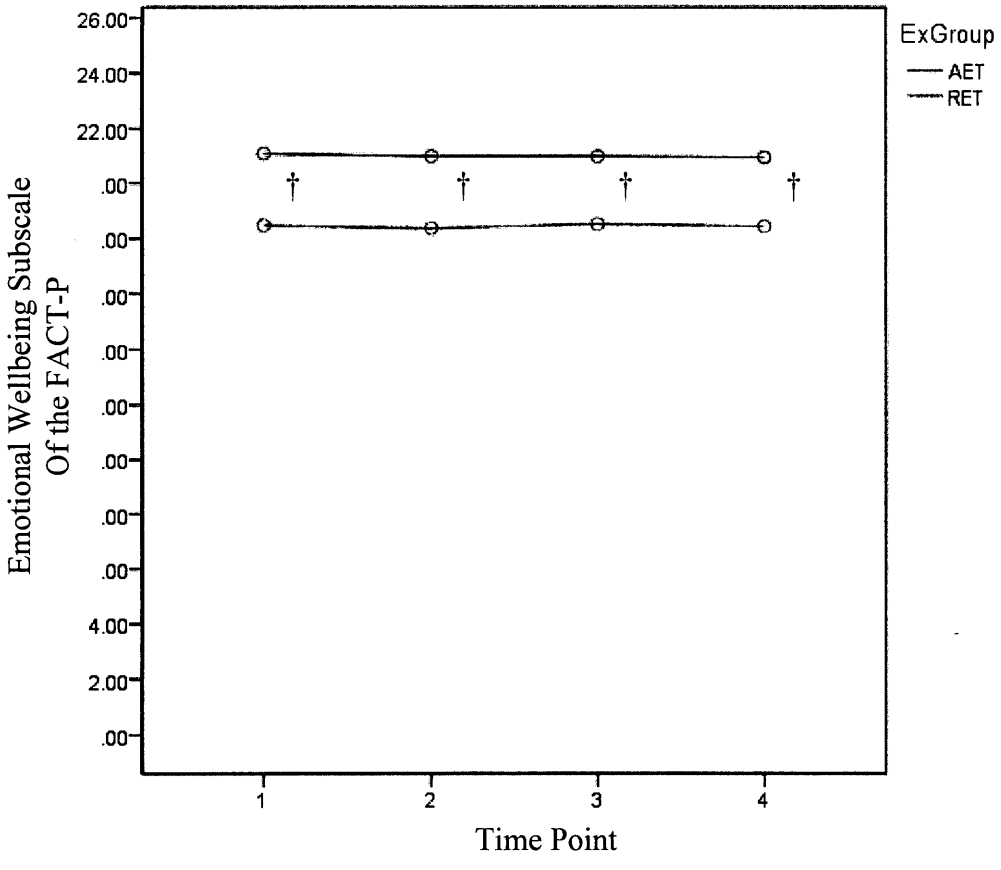

Figure 5. Intention to Treat Analysis of Emotional Wellbeing

Legend: Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 Months; main effect of Group: $F_{(2.51, 152.89)} = 7.302$, $p = 0.009$); †between-group difference, $p \leq 0.02$.

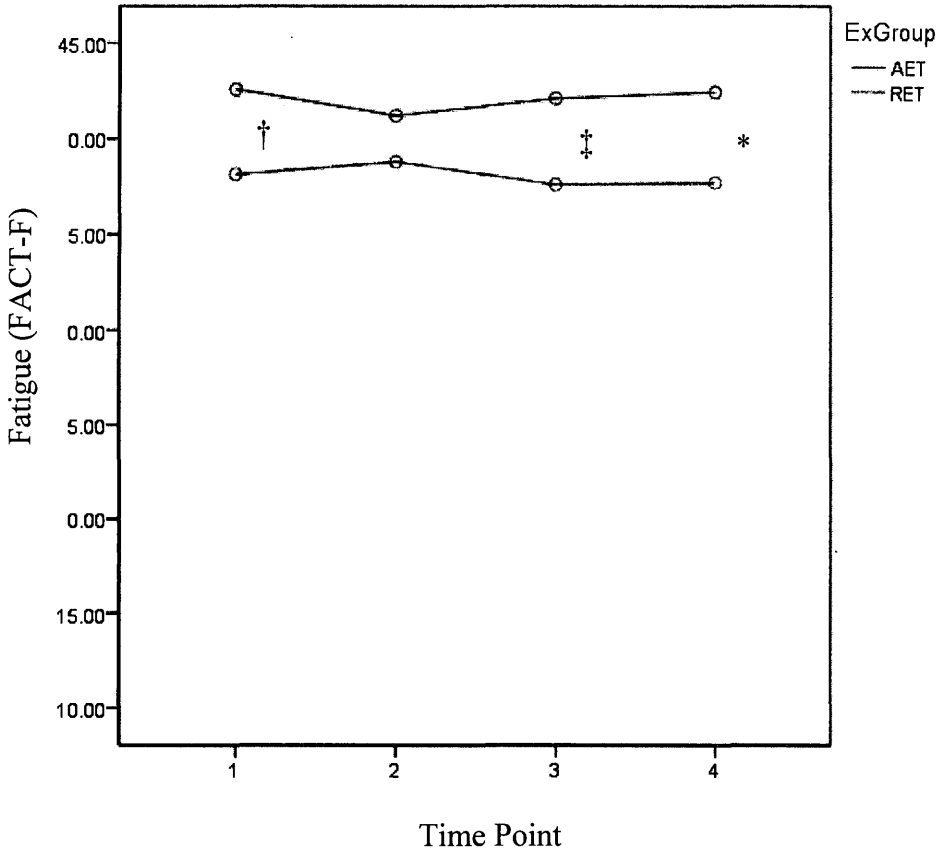

Figure 6. Intention to Treat Analysis of Fatigue

Legend: Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 Months; main effect of Group: $F_{(1, 60)} = 2.863$, $p = 0.096$); Between-group differences using simple effects analysis: † $p = 0.97$; ‡ $p = 0.092$; * $p = 0.084$

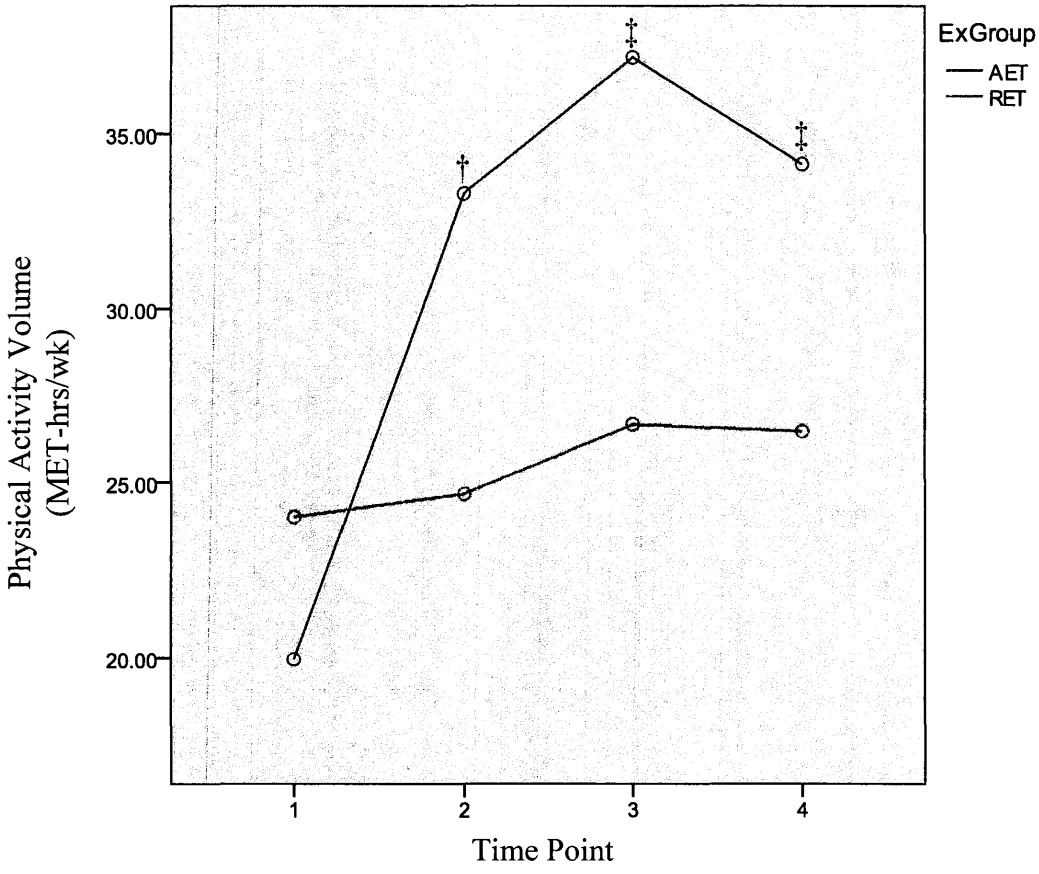

Figure 7. Intention to Treat Analysis of Change in Physical Activity Volume

Legend: Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 Months; main effect of Time: $F_{(2.51, 152.89)} = 5.491$, $p = 0.003$); †within-group change from baseline, $p \leq 0.01$; ‡within-group change from baseline, $p \leq 0.001$;

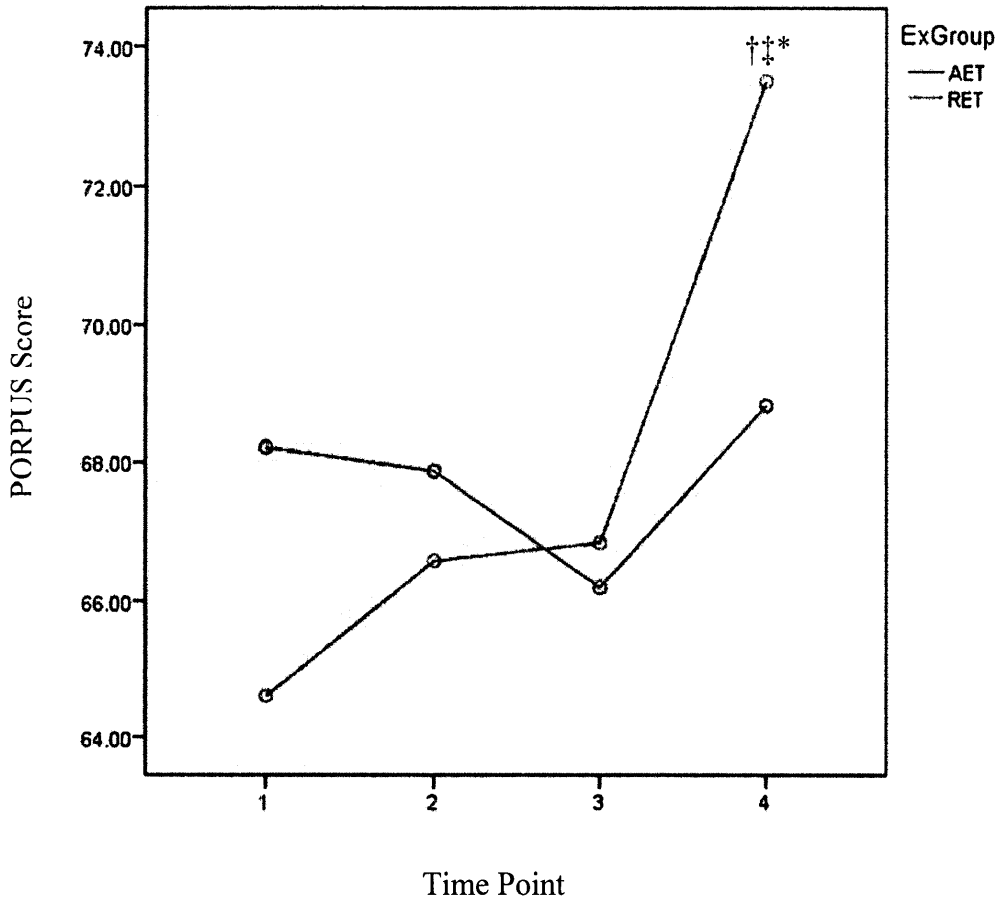

Figure 8. Per Protocol Analysis of Change in PORPUS Scores

Legend: PORPUS = Patient-Oriented Prostate Utility Scale; Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 months; main effect of Time: $F_{(3,69)} = 4.184$, $p = 0.009$; Group X Time interaction: $F_{(3, 69)} = 3.431$, $p = 0.022$; †within-group change from baseline, $p = 0.002$; ‡ = within-groups change from 3 months, $p = 0.014$; * within-group change from baseline, $p = 0.014$.

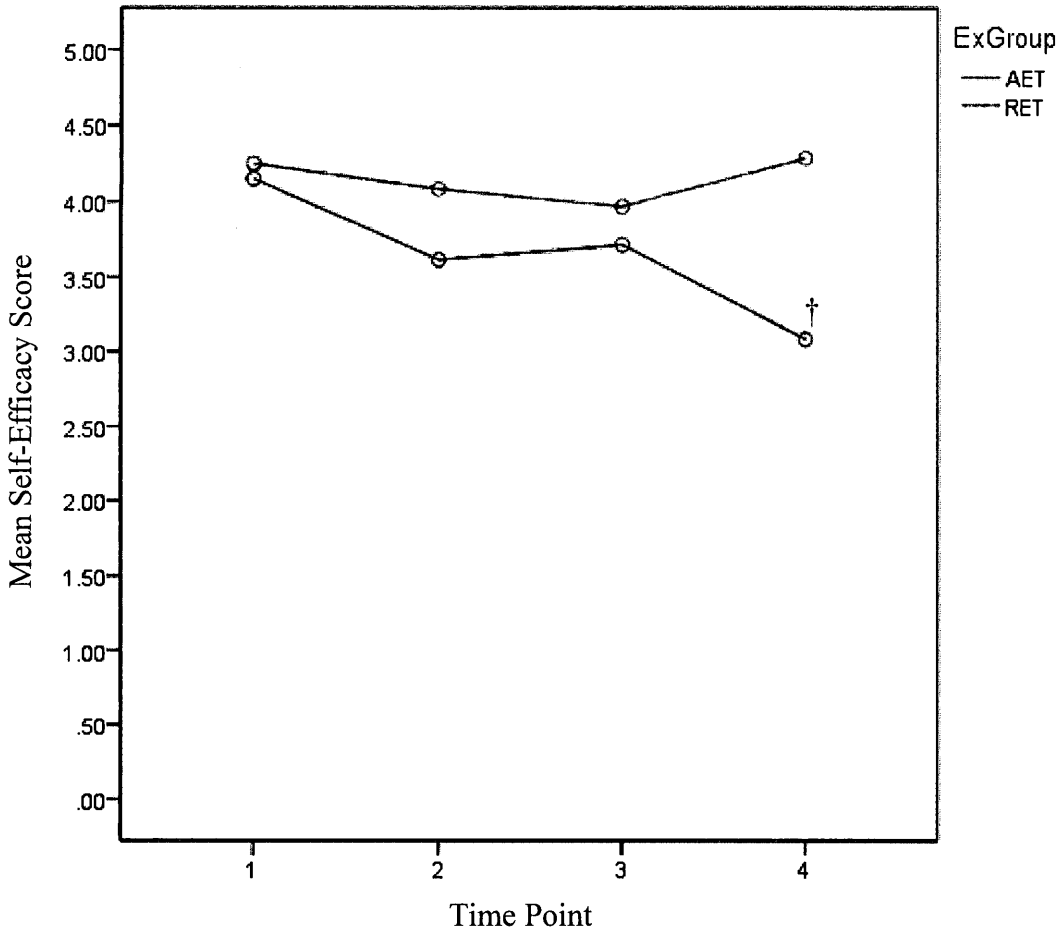

Figure 9. Change in Mean Self-Efficacy For Exercise Score Over Time

Legend: Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 Months; † within-group difference from baseline ($p = 0.014$)

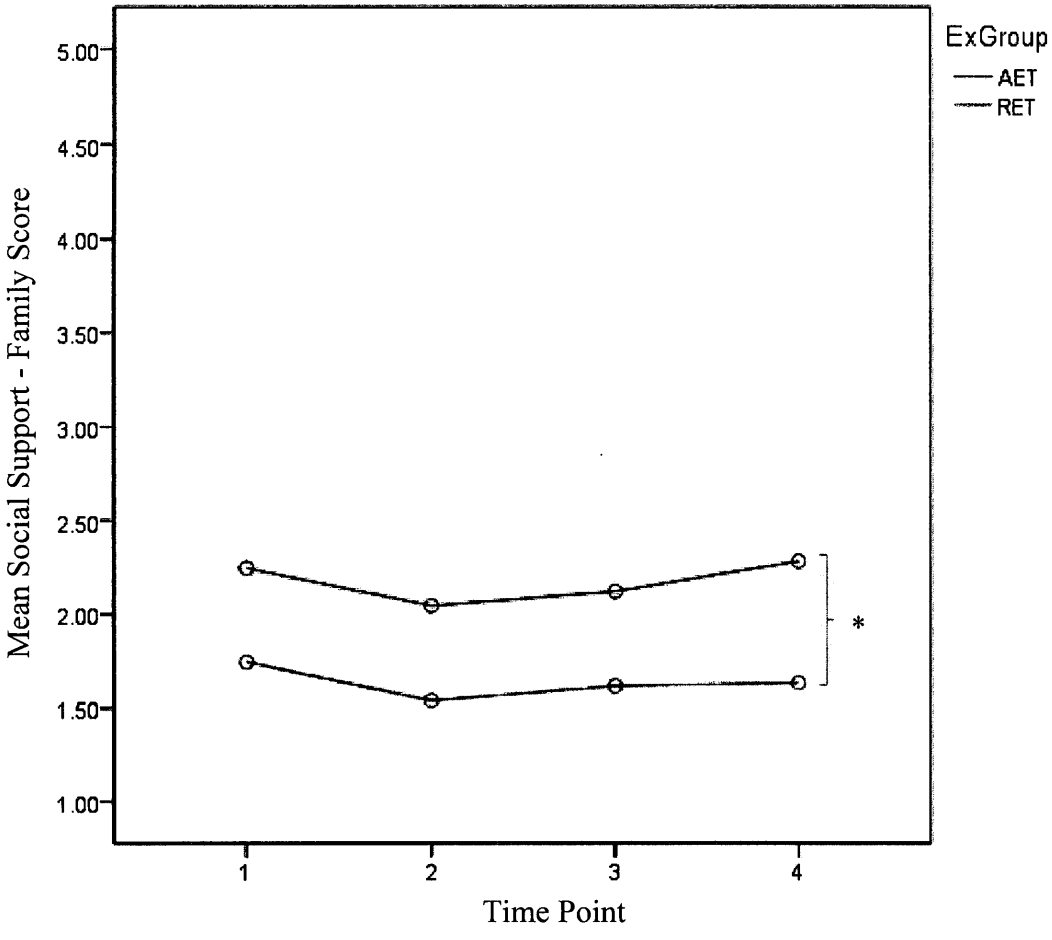

Figure 10. Change in Mean Score for Family Social Support For Exercise Score Over Time

Legend: Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 Months; * between-group difference (p = 0.037)

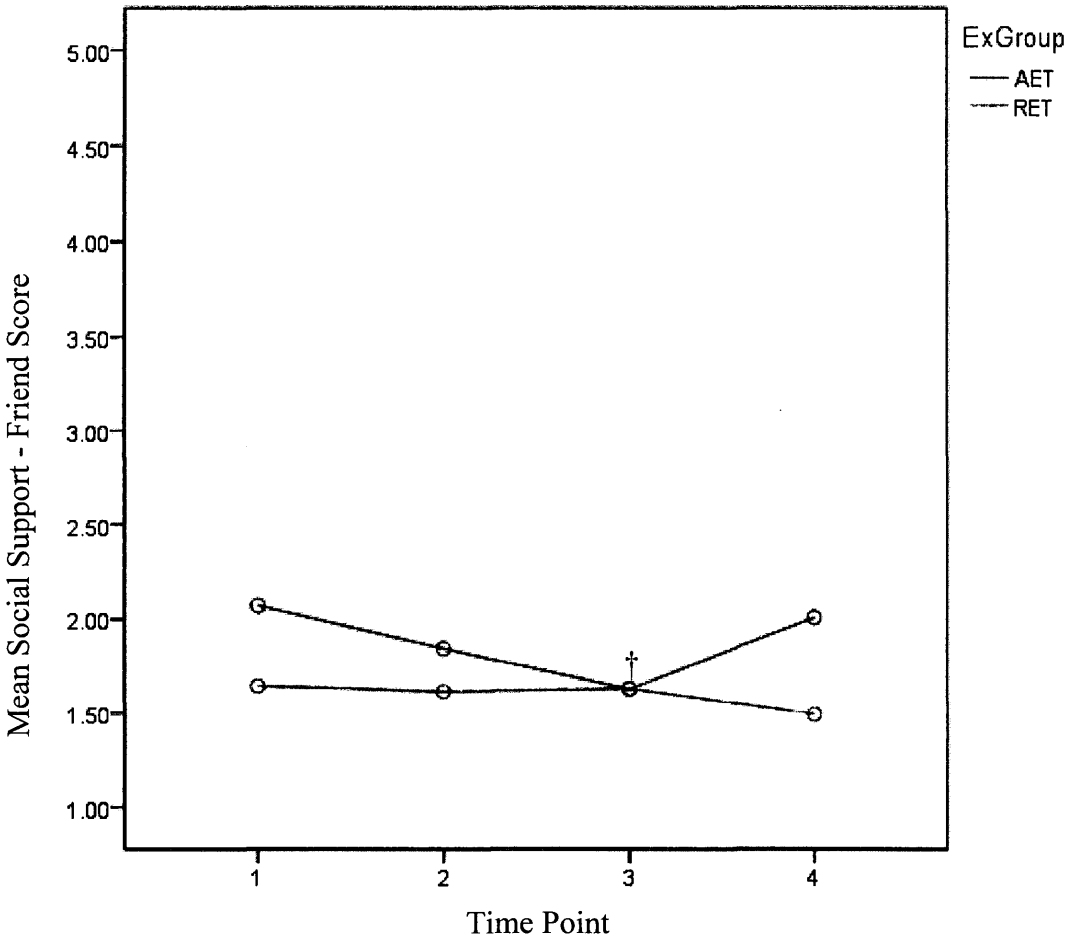

Figure 11. Change in Mean Score for Friend Social Support For Exercise Score Over Time

Legend: Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 Months; †within-group difference from baseline ($p = 0.043$).

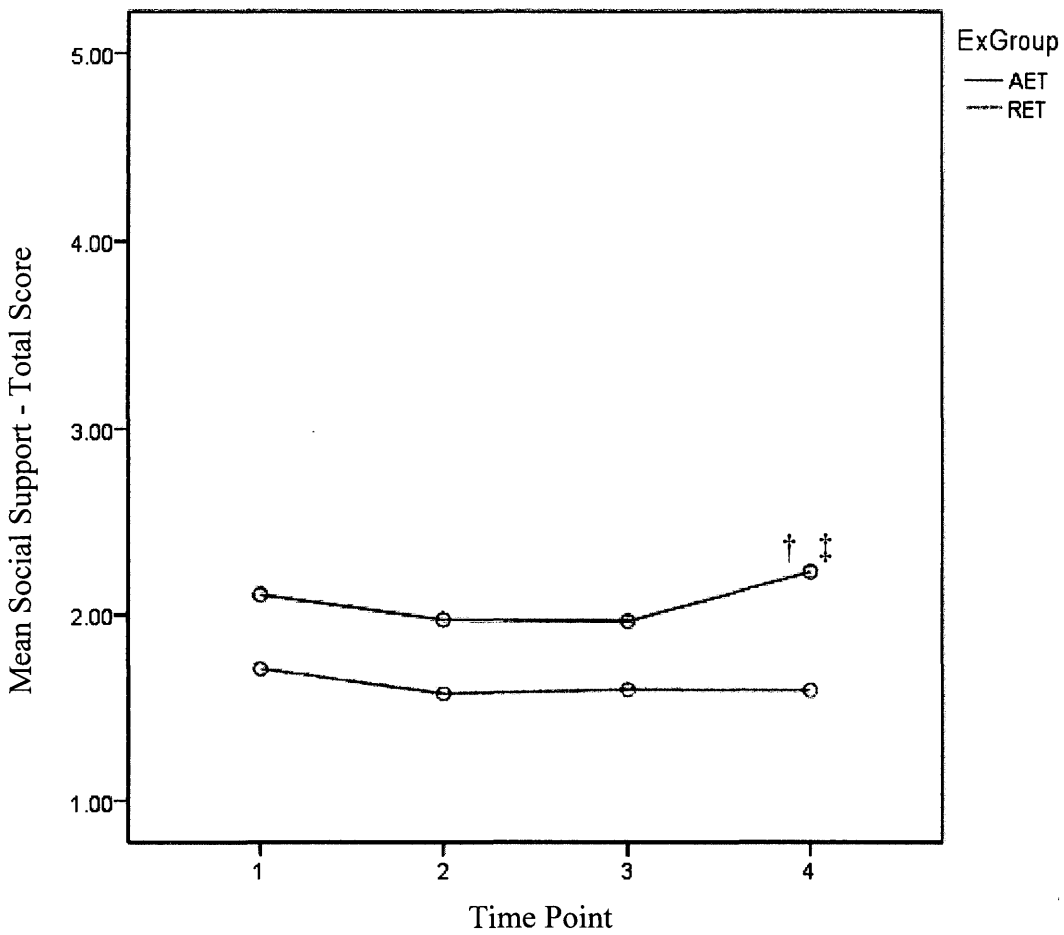

Figure 12. Change in Mean Score for Total (Friend + Family) Social Support For Exercise Score Over Time

Legend: Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 Months; † within-group difference from 3 months ($p = 0.027$); ‡ within-group difference from 6 months ($p = 0.03$).

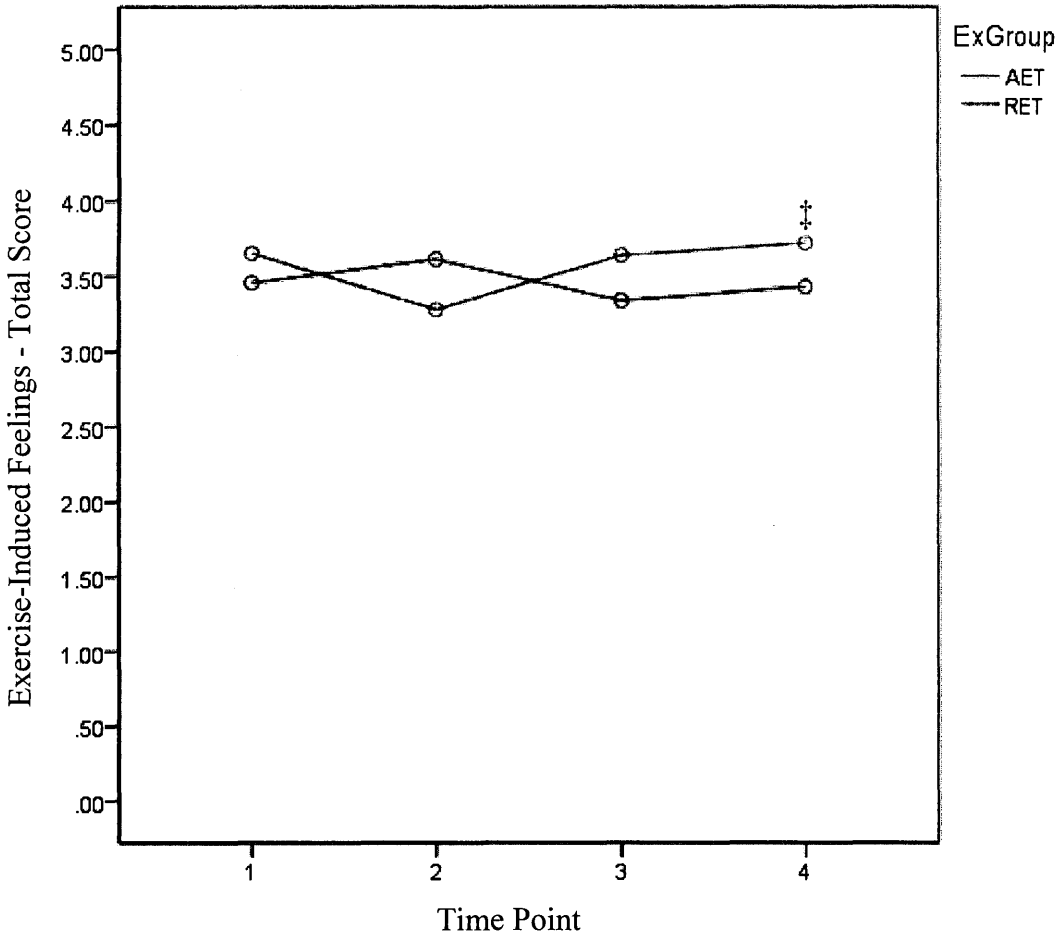

Figure 13. Change in Mean Score for Exercise-Induced Feelings Over Time

Legend: Time point 1 = Baseline; Time point 2 = 3 months; Time point 3 = 6 months; Time point 4 = 12 Months; ‡ within-group difference from 6 months ($p = 0.018$)

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Appendix A: Physical Activity Screening Form (PAR-Q)

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

→ **DELAY BECOMING MUCH MORE ACTIVE:**

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

Supported by: Health Canada Santé Canada

continued on other side...

Appendix B: Charlson Index

CHARLSON INDEX	OTHER
Cardiovascular	
☐ Myocardial Infarct	☐ Angina
☐ Congestive Heart Failure	☐ Hypertension
☐ Peripheral Vascular Disease	☐ Atrial Fibrillation
	☐ Hyperlipidaemia
	☐ Other:
Respiratory	
☐ Chronic Pulmonary Disease	☐ Asthma
	☐ Other:
Gastrointestinal	
☐ Peptic Ulcer Disease	☐ Diverticular Disease
☐ Mild Liver Disease	☐ Other:
☐ Moderate/Severe Liver Disease	
Endocrine	
☐ Diabetes	☐ Thyroid Disease
☐ Diabetes with End Organ	☐ Other:
Neurological	
☐ Cerebrovascular Disease	☐ Seizure Disorder
☐ Hemiplegia	☐ Other:
☐ Dementia	
Musculoskeletal	
☐ Connective Tissue Disease	☐ Arthritis
	☐ Osteoporosis
	☐ Other:
Genitourinary	
☐ Renal Failure, Chronic	☐ BPH
	☐ Other:
Hematology/Oncology	
☐ Localized Solid Tumour *Specify:*	☐ Other:
☐ Metastatic Solid Tumour *Specify:*	
☐ Lymphoma	
Infectious	
☐ HIV/AIDS	☐ Other:
Psychiatric	
	☐ Depression
	☐ Substance Abuse
	☐ Other Psychiatric
Miscellaneous	
	☐ Visual Impairment
	☐ Hearing Impairment
Other Comorbidities & Notes	

Appendix C: Consent to Participate in a Research Study

Title: **A Pilot Study of a Home-Based Exercise Intervention for Prostate Cancer Patients on Androgen Deprivation Therapy**

Principal Investigators: P. Ritvo, Ph.D.; S.M.H., Alibhai, MD (416-340-4800 ext 3203)

Co-Investigators: *A. Matthew, Ph.D; J. Trachtenberg MD, N. Fleshner; MD, M. Connor Ph.D.; & D. Santa Mina, Ph.D (Cand.)/CEP*

24-Hour Phone Number: 416-937-4567

You are being asked to take part in a research study. Before agreeing to take part in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks, and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you want to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor and/or study staff to explain any words you do not understand before signing this consent form. Make sure all your questions have been answered to satisfaction before signing this document. The principal investigators of this research study are Dr. Paul Ritvo and Dr. Andrew. Matthew. Mr. Daniel Santa Mina is the research coordinator and is also a graduate student at York University.

Background

Currently the standard of care for prostate cancer does not usually include exercise programming. However, recent studies have shown that exercise can help reduce some of the negative side-effects related to prostate cancer treatment, including hormone therapy. Specifically, some patients receiving hormone therapy (androgen deprivation), resistance training and/or aerobic exercise have demonstrated benefits throughout treatment. It is now important to compare the effects of different types of exercise to the standard care usually provided which does not include exercise programming. Thus, this study compares resistance training, aerobic exercise, and standard care (no exercise). Understanding the positive effects of exercise and the best approaches to exercise will assist in developing programs for patients in the future aimed at reducing the potential side-effects of hormone therapy.

Purpose

Several questions remain with respect to the appropriate type, intensity, duration, and frequency of exercise. This study aims to evaluate the effectiveness of two types of exercise, namely resistance training and aerobic exercise (e.g. walking, jogging, walking briskly), compared to standard care for patients undergoing hormone therapy for prostate

cancer. This study has a randomized controlled trial design in which 3 groups are compared: resistance exercise, aerobic exercise, and patients undergoing standard care (i.e. wait-list controls). Randomized means that the group you will be assigned to will be decided by chance, neither you nor the study doctor can choose which study group you will join. The patients in the standard care group will receive exercise information but no specific exercise instruction.

Study Visits and Procedures
We are recruiting 60 prostate cancer patients to take part in this study that will last 24-30 months. Should you agree to participate, you will be required to complete questionnaires, fitness and body composition assessments, and provide blood samples at 4 time points (baseline, at 12 weeks, and at 24 weeks).

Screening: The first study visit will be a screening visit and this will occur after your doctor explains this study to you (this may take place over the phone). You may contact the study coordinator immediately to discuss the study or the study coordinator may contact you if you tell your doctor you wish to participate. This screening visit will involve questions to help determine whether you can take part in this study.

Participation: Should you decide to participate, the study coordinator will schedule a time to conduct the baseline assessment. If you choose not to participate, we would ask you for your permission to collect information about your reason(s) for refusal. Refusing to be in the study will not affect your care in anyway.

Procedures: The study team needs to find out about your prostate cancer and your health history so they can see how well the exercise programs work. A baseline fitness assessment will be scheduled at the time of your screening visit to review your current levels of fitness and health. We will try to schedule these visits on the same dates as your other clinic appointments. You may be excluded from the study if your fitness level is found to be low.

The fitness assessments will be conducted by a certified exercise physiologist in a study office. The remaining questionnaires will be answered independently and will be mailed to the study centre (postage provided) or returned during clinic visits with your doctor. <u>All information gathered during the assessments will be kept strictly confidential.</u>

The measurements included in this study are:
- Prostate Specific Quality of Life Questionnaires (5 min)
- Fatigue Questionnaire (5 min)
- Anxiety and Depression Questionnaire (10 min)
- Body Composition (height, weight, waist girth, & skinfolds) (10 min)
- Treadmill Test (15 min)
- A Grip Strength Test (5 min)
- 10 ml blood sample (10 min)

Sample Questions: The type of questions you will be answering in the questionnaires:

- Please rate how often you experience a lack of energy
- Please rate your level of urinary frequency and urgency
- Using a list of descriptive statements, please describe the communication between yourself and your doctor.
- How often have worrying thoughts on your mind?

This baseline assessment will require you to complete a package of 5 questionnaires assessing prostate cancer and treatment related symptoms, a brief body composition assessment, a fitness test (treadmill walking test and/or step test), and a grip strength test. This visit will last approximately 60 minutes.

Semi-Structured Interview

To further understand your experience within this trial, we will be conducting a semi-structured telephone interview with you. During this interview you will be asked about your preference for your assigned group, factors that affected your participation and adherence, and your general experiences throughout the exercise program. The interview will be conducted at end of 24 weeks. The interview will take approximately 20-30 minutes.

Randomization: After your first assessment, you will be grouped into a resistance training exercise program or an aerobic exercise program for 24 weeks.

Exercise Program: Participants in the resistance and aerobic exercise groups will have a personalized, moderate intensity exercise program to be completed 3-5 times per week, for 60 minutes. Each exercise program is individually tailored to your current fitness level based on the fitness assessment. All exercise equipment will be provided to you free of charge, with no requirements to return any equipment at the end of the study. Participants in the exercise groups will receive instruction and demonstration of the exercises, intensity monitoring, completion of logbooks, and safety measures during exercise.

Booster Sessions: You will be required to attend 90 minute group-based 'booster sessions' every 2 weeks. Booster sessions include 60 minutes of group-based exercise and 30 minutes of group-based discussion to address motivation, barriers, and other issues related to your exercise program.

Follow-up Visits: You will be required to return to the study centre at the hospital 3 additional times after the baseline visit to complete the same measures as in your baseline visit. Your first follow-up visit will occur 12 weeks into the exercise program, the second visit will occur at the end of the exercise program (24 weeks), and the third visit will occur 24 weeks after the end of your exercise program.

Reminders:

- You should not conduct heavy physical activity on the day of your assessment
- You should not drink a caffeinated beverage before your visit
- You should not smoke before your visit
- You should not eat within 2 hours of your visit
- Tell your study team about anything that worries you
- Tell your study team about any changes to your treatments or medications
- Tell your study team if you change your mind about being in the study
- Ask your study team any questions related to the study and/or exercise program

Risks

The risks of experiencing a cardiac incident (heart attack, chest pain, etc.) involved in completing the physical assessments, questionnaires, and exercise program are extremely minimal (approximately 1/20000 or 0.00005%). All physical assessments will be conducted by a certified exercise physiologist using standardized protocols and clean equipment.

The fitness programs employed in this study are within the guidelines of recommended exercise frequency, duration, and intensity during prostate cancer and treatment, and have been used in previous studies. You will receive an information and education session on the appropriate exercise technique, intensity monitoring practice, and safety guidelines for your exercise program. You will be contacted by the exercise physiologist on a monthly basis to ensure that your program is being successfully maintained and so that any limitations, barriers, or problems may be addressed.

You will also be responding to questionnaires that have been used in numerous studies. There are minimal risks associated with answering these questions. You may refuse to answer any questions that you do not feel comfortable with.

Possible side effects of drawing blood include: faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection. A second attempt may be necessary to obtain blood if enough was not obtained the first time.

Skinfold measurements to assess body fat percentage have minimal risks. You may experience slight discomfort (like a pinch) while the skinfold is being measured.

Benefits

You may or may not receive any medical benefit from your participation in this study, although previous studies have shown some benefit for prostate cancer patients undergoing exercise treatment. Also, you may be interested in an exercise test to rate your own fitness level and body composition which may be an incentive for participation. This information will be provided to you. Additionally, information learned from this study may benefit other patients who are facing similar circumstances to your own.

Confidentiality
If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:

- name, address, date of birth
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area by the study doctor for 7 years. Only the study team or the people or groups listed in this document will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

Representatives of the University Health Network Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines.

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

If you decide to leave the study, the information about you that was collected before you left the study will still be used. No new information will be collected without your permission.

Presentation of Study Results
The final study research paper will be written without the use of any identifiable information to maintain the anonymity and confidentiality of the participants. Any publications (e.g. academic journals or media) arising from this study will also maintain the anonymity and confidentiality of the participants.

Participation
Your decision to participate is voluntary. You may decide not to be in this study, or to be in the study now, and then change your mind later. You may leave the study at any time without affecting your care. If you decide to participate, you can refuse to answer any questions you do not want to answer, or not answer and questionnaire question by saying "pass".

We will give you new information that is learned during the study that might affect your decision to stay in the study. You may also have access to the exercise physiologist if you

have any questions or concerns about your current physical activity and exercise programs.

This research study has been reviewed and approved for compliance with research ethics protocols by the Human Participants Review Subcommittee (HPRC) of York University and the Research Ethics Board at The University Health Network.

In Case You are Harmed in the Study (Compensation for Injury)
If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. The reasonable costs of such treatment will be covered by your health insurance for any injury or illness that is directly a result of participation in this study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You do not give up any of your legal rights by signing this consent form.

Expenses Associated with Participating in the Study
You will not have to pay for any of the procedures or exercise equipment/programming involved in this study. The exercise equipment that you will receive may remain with you permanently. You will not be reimbursed for any transportation, meals, time, or inconvenience related to this study, although we will try to schedule your visits you're your appointments to limit your trips to the hospital.

Questions
If you suffer any side effects or other injuries during the study, or you have general questions about the study, you may contact the Principal Investigators, Dr. Paul Ritvo at (416) 971-5100 extension 3203, Dr. Andrew Matthew at (416)-946-2332, or Daniel Santa Mina (Ph.D. candidate) at (416) 340-4800 extension 3957.

If you have any questions about your rights as a research participant, please call the Chair of the University Health Network Ethics Board or the Research Ethics Office at (416) 581-7849 or the Manager of the Office of Research Ethics at York University, 5th Floor, York Research Tower: (416) 736-5914. Contact with either of these offices will not affect your participation in this study.

Consent
I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study with the understanding that I may withdraw at any time without affecting my medical care. I have received a signed copy of this consent form. I voluntarily consent to participate in this study.

Participant's Name (print)	Participants Signature	Date
Name of person obtaining consent	Signature	Date

Appendix D: Reasons for Non-Participation Questionnaire

We are interested in understanding the reasons why you decided not to participate in the study so that we can improve the study protocol and increase future participation. There may be many reasons why you decided not to participate in the study. Please share with me which of these reasons apply to you.

1. **You do not believe in participating in any research studies.** Yes ☐ No ☐

   Please explain:

2. **You are too tired/fatigued to participate.** Yes ☐ No ☐

   Please explain:

3. **The length of this study (12 weeks) is too long.** Yes ☐ No ☐

   Please explain:

4. **The number of assessments is too many.** Yes ☐ No ☐

   Please explain:

5. **The length of the assessments is too long.** Yes ☐ No ☐

   Please explain:

6. **You do not see any personal benefit from participating in this study.** Yes ☐ No ☐

   Please explain:

7. **You do not like to exercise.** Yes ☐ No ☐

   Please explain:

8. **You find it difficult to exercise.** Yes ☐ No ☐

   Please explain:

9. **Your physician (either family physician or leukemia doctor) discouraged you from participating in this study.** Yes ☐ No ☐

   Please explain:

10. **A family member or friend discouraged you from participating in this study.** Yes ☐ No ☐

    Please explain:

11. **Are there any other factors that influenced your decision not to participate in this study?** Yes ☐ No ☐

    Please explain:

12. **Now that we have discussed the various reasons that may have contributed to your decision not to participate in this study, can you please tell me which of these reasons had the biggest influence on your decision to not participate in this study?**

    Please explain:

Appendix E: Booster Session Outline

Week 1: Maintaining an Active Lifestyle after Program Completion

- Logbook
- Plan of action

Week 2: Exercise in General

- Components of exercise
- Exercise guidelines (current national guidelines)
- FITT principle
- Monitoring intensity
- How to use the physical activity log: handout weekly activity log

Week 3: Goal Setting

- Specific, measurable, action, realistic, time: (SMART)
- Goal setting guidelines
- Planning for activity
- Set goals

Week 4: Behaviour Change

- Steps to change behaviour: awareness, management, reinforcement
- Steps in learning a new behaviour
- Personal plan of action

Week 5: Barriers & Relapse Prevention

- Identifying barriers
- Overcoming barriers
- Dealing with relapse
- Relapse planner

Week 6: Social Support

- Developing/maintaining support
- Spouse or partner support
- Children
- Friends or neighbours

Week 7: Monitoring Behaviour/Review

- Review weekly logs
- Check in on goals/discipline
- Activity variety

Week 8: Maintaining Motivation

- What is motivation?
- What motivates you?
- Who is a great motivator in your life?
- How are you similar/different to that person?
- How are you going to maintain motivation?
- Motivation tools

Week 9: Adapting your Fitness Program

- Guidelines for assessing and designing programs
- Review FITT
- Safe exercise techniques
- Common exercise concerns
- Warm up and cool down tips

Week 10: Personal Control

- What is control?
- Ways to maintain control
- Ways to let go
- Exercise control

Week 11: Self-Reward/Discipline & Attitude

- Self-esteem, self-talk, self-worth, positive attitude
- Types of rewards
- Principles of reinforcement
- Self-reward

Week 12: Home-based Exercise

- At home exercising
- How to maintain an at home exercise program

Appendix F: Functional Assessment of Cancer Therapy – Fatigue (FACT-F)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
1.	I feel fatigued.	0	1	2	3	4
2.	I feel weak all over.	0	1	2	3	4
3.	I feel listless ("washed out").	0	1	2	3	4
4.	I feel tired.	0	1	2	3	4
5.	I have trouble starting things because I am tired.	0	1	2	3	4
6.	I have trouble finishing things because I am tired.	0	1	2	3	4
7.	I have energy.	0	1	2	3	4
8.	I am able to do my usual activities.	0	1	2	3	4
9.	I need to sleep during the day.	0	1	2	3	4
10.	I am too tired to eat.	0	1	2	3	4
11.	I need help doing my usual activities.	0	1	2	3	4
12.	I am frustrated by being too tired to do the things I want to do.	0	1	2	3	4
13.	I have to limit my social activity because I am tired.	0	1	2	3	4

* These items comprise the 13-item fatigue scale

Appendix G: Functional Assessment of Cancer Therapy – Prostate (FACT-P)

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

	PHYSICAL WELL BEING	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
1.	I have a lack of energy.	0	1	2	3	4
2.	I have nausea.	0	1	2	3	4
3.	Because of my physical condition I have trouble meeting the needs of my family.	0	1	2	3	4
4.	I have pain.	0	1	2	3	4
5.	I am bothered by side effects of treatments.	0	1	2	3	4
6.	I feel ill	0	1	2	3	4
7.	I am forced to spend time in bed.	0	1	2	3	4

	SOCIAL/FAMILY WELL BEING	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
1.	I feel close to my friends.	0	1	2	3	4
2.	I get emotional support from my family.	0	1	2	3	4
3.	I get support from my friends.	0	1	2	3	4
4.	My family has accepted my illness.	0	1	2	3	4
5.	I am satisfied with family communication about my illness.	0	1	2	3	4
6.	I feel close to my partner (or the person who is my main support.) *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box☐ and go to the next section.*	0	1	2	3	4
7.	I am satisfied with my sex life.	0	1	2	3	4

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

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

	FUNCTIONAL WELL BEING	Not at all	A little bit	Somewhat	Quite a bit	Very much
1.	I am able to work (Include work at home).	0	1	2	3	4
2.	My work (Include work at home) is fulfilling.	0	1	2	3	4
3.	I am able to enjoy life.	0	1	2	3	4
4.	I have accepted my illness.	0	1	2	3	4
5.	I am sleeping well.	0	1	2	3	4
6.	I am enjoying the things I usually do for fun.	0	1	2	3	4
7.	I am content with the quality of my life right now.	0	1	2	3	4

	ADDITIONAL CONCERNS	Not at all	A little bit	Somewhat	Quite a bit	Very much
1.	I am losing weight.	0	1	2	3	4
2.	I have a good appetite.	0	1	2	3	4
3.	I have aches and pains that bother me.	0	1	2	3	4
4.	I have certain parts of my body where I experience significant pain.	0	1	2	3	4
5.	My pain keeps me from doing things I want to do.	0	1	2	3	4
6.	I am satisfied with my present comfort level.	0	1	2	3	4
7.	I am able to feel like a man.	0	1	2	3	4
8.	I have trouble moving my bowels.	0	1	2	3	4
9.	I have difficulty urinating.	0	1	2	3	4
10.	I urinate more frequently than usual.	0	1	2	3	4
11.	My problems with urinating limit my activities.	0	1	2	3	4
12.	I am able to have and maintain an erection.	0	1	2	3	4

Appendix H: Prostate Outcomes Record of Psychometric and Utility Self-Report (PORPUS)

Please circle the statement that comes closest to describing you in the last **two weeks.**

I. Pain and Disturbing Body Sensations (e.g. hot flashes, painful swelling of breasts, nausea)

1. No pain and no disturbing body sensations.
2. Mild pain or disturbing body sensations that do not limit any activities (e.g. work, social, sexual, sleep).
3. Moderate pain or disturbing body sensations that limit a few activities.
4. Moderate to severe pain or disturbing body sensations that limit some activities.
5. Severe pain or disturbing body sensations that limit many activities.

II. Energy

1. Very full of energy, lots of pep.
2. Fairly energetic, no limitation of activities (for example: work, social, sexual).
3. Moderate reduction in energy or pep that limits a few activities.
4. Generally low energy or pep that limits some activities.
5. No energy or pep at all. I feel drained, and many activities are limited.

III. Support From Family and Friends

1. Most of the time feel supported by my spouse, family and friends.
2. A fair amount of the time feel supported by my spouse, family and friends.
3. Occasionally feel supported by my spouse, family and friends.
4. Rarely feel supported by my spouse, family, and friends.

IV. Communication With Doctor (primary caregiver for prostate cancer, may be specialist or family doctor) Please check the statement that comes closest to describing you in the last two scheduled appointments

1. Always able to express my concerns to my Doctor and get all the information or advice I need.
2. Most the time, able to express my concerns to my Doctor and get all the information or advice I need.
3. Some of the time, able to express my concerns to my Doctor and get all the information or advice I need.
4. Rarely able to express my concerns to my Doctor and get all the information or advice I need.

Please circle the statement that comes closest to describing you in the last **two weeks.**

V. Emotional Wellbeing

1. Generally happy and free from worry, sadness, or frustration.
2. A little worry, sadness, or frustration.
3. Moderate worry, sadness, or frustration.
4. Quite a bit of worry, sadness, or frustration.
5. Extreme worry, sadness, or frustration.

VI. Urinary Frequency (need to pass urine frequently during the day or night) **and Urgency** (difficulty delaying urination after the urge is felt to urinate, ability to "hold it")

1. No urinary frequency or urgency.
2. A little urinary frequency or urgency does not interfere with sleep or other activities (for example: work, social); no need to plan ahead.
3. Some urinary frequency or urgency interferes with sleep or other activities; may need to plan ahead.
4. Quite a bit of urinary frequency or urgency; need to be near a bathroom most of the time.
5. Extreme urinary frequency or urgency; need to be near a bathroom always.

VII. Leaking Urine/ Poor Bladder Control

1. Never, under any circumstances leak urine or lose bladder control.
2. On rare occasions, leak urine or lose bladder control, does not interfere with any activities (for example: work, social, sexual, sleep).
3. Occasionally leak urine or lose bladder control, interferes with a few activities.
4. A moderate amount of the time, leak urine or lose bladder control, interferes with some activities.
5. Most of the time, leak urine or have poor bladder control, interferes with many activities.
6. Require a clamp, catheter, or collecting bag because of leaking urine or poor bladder control.

VIII. Sexual Function (problems with achieving / maintaining an erection)

1. Full erections sufficient for intercourse.
2. Erections sufficient for intercourse, but some reduction in firmness.
3. Erections sufficient for masturbation or foreplay only.
4. Erections, but not firm enough for any sexual activity.
5. No erections at all.

Please circle the statement that comes closest to describing you in the last **two weeks.**

IX. Sexual Interest / Drive

1. Normal amount of sexual drive and interest for you.
2. A little decrease of sexual drive or interest for you.
3. Moderate decrease of sexual drive or interest for you.
4. Substantial decrease of sexual drive or interest for you.
5. No sexual drive or interest.

X. Bowel problems: diarrhea, rectal discomfort (pain, burning or irritation) **or constipation.**

1. No diarrhea, rectal discomfort, or constipation.
2. Occasionally have diarrhea, rectal discomfort, or constipation.
3. Frequently have diarrhea, rectal discomfort, or constipation
4. Nearly always have diarrhea, rectal discomfort, or constipation.

Appendix I: Godin Leisure Time Exercise Questionnaire (GLTEQ)

For this next question, we would like you to recall your average weekly exercise over the past month. How many times per week on average did you do the following kinds of exercise over the past month?

When answering these questions please:

- Consider your average over the past month.
- Only count exercise sessions that lasted 15 minutes or longer in duration.
- Only count exercise that was done during free time (i.e., not occupation or housework).
- Note that the main difference between the three categories is the intensity of the exercise.
- Please write the times per weekly on the first line and the average duration on the second line.

a. STRENUOUS EXERCISE

(I.E.HEART BEATS RAPIDLY, SWEATING)

(e.g., running, jogging, hockey, soccer, squash, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling, vigorous aerobic dance classes, heavy weight training)

_____ Times/week _____ Avg. Duration (minutes)

b. MODERATE EXERCISE
(NOT EXHAUSTING, LIGHT SWEATING)

(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing.

_____Times/week _____ Avg. Duration (minutes)

c. MILD EXERCISE
(MINIMAL EFFORT, NO SWEATING)

(e.g., easy walking, yoga, archery, fishing, bowling, lawn bowling, shuffleboard, horseshoes, golf,
snowmobiling)

_____ Times/week _____ Avg. Duration (minutes)

Appendix J: Modified Exercise Induced Feeling Inventory –Chronic (mEIFI-C)

Thinking back over the past week, please describe how much you experienced the following feelings during physical activity/exercise, using the scale provided (none of the time → all of the time):

	Feeling	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1	Refreshed	0	1	2	3	4	5
2	Calm	0	1	2	3	4	5
3	Fatigued	0	1	2	3	4	5
4	Enthusiastic	0	1	2	3	4	5
5	Relaxed	0	1	2	3	4	5
6	Energetic	0	1	2	3	4	5
7	Happy	0	1	2	3	4	5
8	Tired	0	1	2	3	4	5
9	Revived	0	1	2	3	4	5
10	Peaceful	0	1	2	3	4	5
11	Worn-out	0	1	2	3	4	5
12	Upbeat	0	1	2	3	4	5

Appendix K: Self-Efficacy for Physical Activity Survey (SEPAS)

Whether you exercise or not, please rate how confident you are that you could really motivate yourself to do things like these consistently, *for at least 6 months*		I know I Cannot (1)	Maybe I Can (2)	(3)	(4)	I know I Can (5)	Does Not Apply (6)
1.	Get up early, even on weekends to exercise.	1	2	3	4	5	6
2.	Stick to your exercise program after a long, tiring day.	1	2	3	4	5	6
3.	Exercise even though you are feeling depressed.	1	2	3	4	5	6
4.	Set aside time for a physical activity program; such as, walking, swimming, biking, resistance training or other continuous activities for at least 30 minutes, 3 times per week.	1	2	3	4	5	6
5.	Continue to exercise with others even though they seem too fast or too slow for you.	1	2	3	4	5	6
6.	Stick to your exercise with others even though they seem too fast or too slow for you.	1	2	3	4	5	6
7.	Attend a party only after exercising	1	2	3	4	5	6
8.	Stick to your exercise program when your family is demanding more time from you.	1	2	3	4	5	6
9.	Stick to your exercise program when you have household chores to do.	1	2	3	4	5	6
10.	Stick to your exercise program even when you have excess demands at work.	1	2	3	4	5	6
11.	Stick to your exercise program when social obligations are very time consuming.	1	2	3	4	5	6
12.	Read or study les in order to exercise more.	1	2	3	4	5	6

Appendix L: Social Support for Physical Activity Questionnaire (SSPAQ)

Please indicate, by circling the appropriate number, whether your family has done or said the following:

		None				Very Often
1	Exercised with me	1	2	3	4	5
2	Gave me encouragement to stick with my exercise program	1	2	3	4	5
3	Changed their schedule so we could exercise together	1	2	3	4	5
4	Offered to exercise with me	1	2	3	4	5
5	Gave me helpful reminders to exercise	1	2	3	4	5
6	Planned for exercise on recreational outings	1	2	3	4	5
7	Discussed exercise with me	1	2	3	4	5
8	Talked about how much they like to exercise	1	2	3	4	5
9	Helped plan activities around my exercise	1	2	3	4	5
10	Asked me for ideas on how they can get more exercise	1	2	3	4	5
11	Took over chores so I had more time to exercise	1	2	3	4	5
12	Made positive comments about my physical appearance	1	2	3	4	5
13	Got angry at me for exercising	1	2	3	4	5
14	Criticized me or made fun of me for exercising	1	2	3	4	5
15	Gave me rewards for exercising	1	2	3	4	5

Please indicate, by circling the appropriate number, whether your friend has done or said the following:

		None				Very Often
1	Exercised with me	1	2	3	4	5
2	Offered to exercise with me	1	2	3	4	5
3	Gave me helpful reminders to exercise	1	2	3	4	5
4	Gave me encouragement to stick with my exercise program	1	2	3	4	5
5	Changed their schedule so we could exercise together	1	2	3	4	5

Appendix M: Demographic Questionnaire

ID#_____ Today's date: _____ _____ _____
Month Day Year

Please provide the following information:
(Please answer the question in the space provided or place a check in the appropriate box)

1. Address:
_____

2. Telephone Number:
(Home)_____(Alternate)_____

3. E-mail: _____

4. Your Date of Birth: _____ _____ _____
Month Day Year

5. Your Age: _____

6. Your Ancestry/Ethnicity:

- ☐ White/Caucasian
- ☐ Black/Afro-Caribbean/African
- ☐ Latino/Hispanic
- ☐ Arabic (e.g. Lebanon, Palestine)
- ☐ Ashkenazi Jewish
- ☐ South Asian (e.g. India, Pakistan)
- ☐ East Asian (e.g. China, Korea, Japan)
- ☐ South East Asian (e.g. Philippines, Vietnam)

Other: Please Specify:_____

7. What is your annual household income?

- ☐ less than $40,000
- ☐ $40,000-$80,000
- ☐ more than $80,000

8. What is your current marital status?

- ☐ Single (never married)
- ☐ Married (including common law)
- ☐ Widowed
- ☐ Separated
- ☐ Divorced

9. What is your highest level of education?

- ☐ Less than high school
- ☐ High school graduate
- ☐ Community college/ trade school graduate
- ☐ University graduate
- ☐ Graduate university degree
- ☐ Other_____

9. Are you now working?

- ☐ No, retired
- ☐ No, but looking for job
- ☐ Yes, part-time
- ☐ Yes, Full-time

10. Do you currently smoke cigarettes?

- ☐ No
- ☐ Yes (Please specify frequency: ____/day)

11. Are you presently taking any medication?

- ☐ No
- ☐ Yes (Please specify type and dose)

_____

12. When were you first diagnosed with prostate cancer? __ __ / __ __ __ __
(month) (year)

13. What treatment(s) did you receive? (Please check all that apply)

- ☐ Radical Prostatectomy (Surgery)
- ☐ Radiation Therapy / Brachytherapy
- ☐ Hormone Therapy
- ☐ Watchful waiting
- ☐ Other:_____(Please specify)

14. What is your current hormone therapy treatment regimen?
(Please check as many as apply)

Medication(s) _____ frequency:_____; planned duration: _____

Medication(s) _____ frequency:_____; planned duration: _____

Thank you for completing this questionnaire.

Appendix N: Semi-Structured Qualitative Interview

Goal: To develop an improved exercise program and to get a representation of participant experiences and perspectives. Specifically, we want to know about their: a) level and reasons for adherence (or non-adherence); b) their general enjoyment/satisfaction with the program (i.e. strengths and weaknesses); and c) the benefits/setbacks associated with the program. *ALWAYS ASK IF THERE IS ANYTHING ELSE YOU WANT TO ADD.*

Survey Questions (short answer; yes/no):

- Were you assigned to resistance exercise training or aerobic exercise training?
- Was this your preference? Please explain why.
- On average, how many days per week did you exercise (frequency)? (days/week)
- On average, how intense (hard) did you exercise on a scale of 0-10 (to being maximal effort)?
- On average, how long were your exercise sessions? (minutes)
- Depending on what exercise program you were assigned to, did you or did you not add other forms of exercise? (If yes, what did you do? why did you take up other forms of exercise?)

"Now I want to ask you about your <u>adherence</u> or <u>compliance</u> to the exercise program"

- We know that people exercise for many different reasons. Can you tell us why you like to exercise?
- Some things make exercise easy to do.
    - What helped you to exercise using our exercise program (adherence)?
- Some things make exercise difficult to do. What prevented you from exercising in our program?
- Group-based exercise classes can be useful for teaching exercise, and improving motivation and adherence.
    - Did you attend the group-based booster sessions? Why/why not?
    - What would make you more likely to attend a booster session? Or Continue attending?
- The benefits of exercise are only maintained with consistent/routine exercise. As a program, how can we support adherence to exercise? (I.e. what would you suggest we do to keep people exercising?)
- Are you continuing to exercise? What has helped you continue to exercise after the program?
- Do you intend to keep exercising? Please explain why? How?

"Now I want to ask you about the <u>strengths and weaknesses of the exercise program</u>"

- As a new program offered at the Prostate Centre, we are continually trying to improve the patient experience. The exercise program is a new component of the Prostate Centre and we would like your feedback on how to improve the program.
- Can you identify some strengths and weaknesses of the program for promoting and maintaining exercise. *(Allow for respondent to provide answers, then use the prompts below).*
    - Location/office setting? (professional? Appropriate?)
    - Convenience (home-exercise, facility-based boosters, equipment, manual, staff)

    - Did you understand the manual (did you read it? Was it helpful? Use the logbook? How often did you refer to the manual?)
    - E-mails/calls (did you prefer emails or telephone calls? Frequency? Timing?)
    - Exercise technique (did you feel prepared to conduct your exercises? Were you comfortable increasing the intensity on your own? Did you have enough support from the manual/staff to address any concerns?)
    - Booster sessions (did you like the format? How would you improve?)
- If you were to design the program…
    - What would you do to make it better?
    - What did you not like?

"Now I want to ask you about some of the <u>outcomes of the study</u>, in terms of any benefits or setbacks that you may have experienced"

- How do you feel physically after participating in the exercise program? (strength changes, body weight? Body image? Fat? Energy? Endurance?, etc.)
- How do you feel mentally after participating in the exercise program? (attention, mental clarity, etc.)
- How do you feel emotionally after participating in the exercise program? (positive/negative mood, anxiety, depression, happiness, sadness)
- How would you compare your overall quality of life from the beginning to the end of the exercise program?

How has your lifestyle changed as a result of participating in this program? (has your diet changed? More time outdoors? More/ease-of daily activity? Sleeping habits?