LCCC 1613: Feasibility Study of a Home-based Exercise Intervention Program for Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Androgen-Deprivation Therapy (ADT)

Principal Investigator
Erik D. Hanson, PhD
Assistant Professor, Exercise and Sport Science
Department of Exercise & Sport Science
315 Woollen Gym – CB # 8605 – UNC-CH
Chapel Hill, NC 27599
(Tel) 919-962-0816
(Fax) 919-962-0489
Email: edhanson@email.unc.edu

Co-Investigator(s)
Claudio Battaglini, PhD
Matthew Milowsky, MD
Young Whang, MD, PhD
Ethan Basch, MD
William Kim, MD
William Wood, MD, MPH
Mary Dunn, NP
Tracy Rose, MD
Rhonda Bitting, MD, Wake Forest

Biostatistician
Allison M Deal, MS
Lineberger Comprehensive Cancer Center
PO Box 7295
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-7295
Email: allison_deal@med.unc.edu

Sponsor: Lineberger Comprehensive Cancer Center
Funding Source: Physical Activity and Cancer Survivorship Pilot Grant (2016)
Version Date: October 23, 2019

--LCCC 1613: Feasibility Study of a Home-based Exercise Intervention Program for Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Androgen-Deprivation Therapy (ADT)

Principal Investigator
Erik D. Hanson, PhD
Assistant Professor, Exercise and Sport Science
Department of Exercise & Sport Science
315 Woollen Gym – CB # 8605 – UNC-CH
Chapel Hill, NC 27599
(Tel) 919-962-0816
(Fax) 919-962-0489
Email: edhanson@email.unc.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Erik Hanson

PI Signature: _____

Date: **October 23, 2019**

Version Date: October 23, 2019

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This single arm, multi-site pilot study aims to evaluate the feasibility of recruiting and adherence to a 12 week home-based exercise intervention to be conducted in men with metastatic castration resistant prostate cancer (mCRPC) receiving androgen deprivation therapy (ADT). Thirty patients will be enrolled, with the expectation that 20-25 will complete all follow-up measures.

The secondary objective of this study are to compare the changes in body composition (e.g., percent body fat, bone mineral content, lean mass), muscle strength, cardiovascular and overall physical function, and patient reported outcomes (quality of life (QoL), fatigue, depression) before and after the 12 week exercise intervention as a means of attenuating the declines in these outcomes typically seen with ADT. We hypothesize that exercise training will improve (post value > baseline value) strength and cardiovascular and physical function while body composition will remain unchanged. Finally, the effects of exercise on markers of inflammation and their relationship with changes in physical function and body composition will also be examined as exploratory outcomes. Data from this study will be used to determine feasibility (successfully able to recruit these individuals) and adherence to a home-based exercise intervention in men with mCRPC receiving ADT as well as the ability to refine the exercise intervention with plans to evaluate it in future larger trials in this population.

1.2 Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer among men and the second leading cause of cancer related deaths in men in the United States. An estimated 220, 800 men in the U.S will be diagnosed with prostate cancer in 2016 with an estimated 27,540 prostate cancer related deaths (Cancer Facts & Figures 2015). Since prostate cancer is stimulated to grow by the male hormone, testosterone, medications that shut off the normal production of testosterone referred to as ADT represent the first-line (primary) treatment for patients with advanced disease.

Unlike cancers arising from other organs such as lung and pancreas cancer, the life expectancy for patients with advanced prostate cancer is measured in years. Thus, side effects of treatment that impact on quality of life are extremely important to consider in men with prostate cancer. Loss of testosterone is associated with many side effects including those related to negative changes in body composition (increase fat mass, loss of muscle mass) (Galvao et al., 2008; Smith et al., 2002), male menopause symptoms including hot flashes, loss of sexual drive, osteoporosis, high cholesterol, cardiovascular disease and diabetes (Braga-Basaria et al., 2006; Smith et al., 2002, 2006), and severe fatigue. These side-effects, if not treated, may contribute to the development of other co-morbidities as well as lead to an inability to function at pre-cancer levels with the potential for a major impact on quality of life.) (Galvao et al., 2008; Smith et al., 2002)

1.2.1 Androgen Deprivation Therapy (ADT)

Primary ADT usually refers to surgical castration (orchiectomy) or medical castration using a gonadotropin-releasing hormone (GnRH) agonist or antagonist. The onset of ADT is associated with a number of adverse events, including loss of muscle strength, altered body composition, higher fatigue, poor physical function, and QoL (Galvao et al. 2008, Hanson and Hurley 2011). Prostate cancer that progresses on ADT is referred to as castration resistant, despite its continued reliance on androgens. This reliance is evidenced by the benefits reported with the androgen synthesis inhibitor, abiraterone acetate, and the potent androgen receptor inhibitor, enzalutamide, in metastatic CRPC (de Bono et al. 2011; Ryan et al. 2013; Scher et al. 2012; Beer et al. 2014). Based on these data, abiraaterone and enzalutamide represent the standard of care in men with mCRPC in the pre- and post-chemotherapy settings. However, additional androgen suppression beyond castration (sometimes referred to as androgen annihilation (Rove and Crawford 2013) or "super-castration" (Pezaro et al. 2013) may exacerbate the symptoms of primary ADT. For example, 7.5 months of abiraterone alone significantly decreased lean mass at 6 months by -4.3%, particularly in those with a body mass index (BMI) >30. While these additional castration agents (including but not limited to abiraterone and enzalutamide) are prolonging survival during mCRPC, it becomes increasingly important to examine ways to mitigate the ADT-related side effects such that both quantity and quality of life are maintained at the highest possible levels.

1.2.2 Exercise Training in Prostate Cancer

One possible remedy for the complications associated with ADT use in mCRPC patients is to prescribe exercise training. Exercise in men on primary ADT who were not yet castration resistant has been shown to improve muscle mass, strength, and physical function (Galvao et al. 2007, Galvao et al. 2010, 2009; Newton et al., 2009) but has yet to be examined as a potential complementary therapy in mCRPC. Specifically, Galvao and colleagues (2010) conducted a randomized controlled trial of twice weekly resistance (weights and abdominal crunches) and aerobic exercise (15-20 minutes of cycling and walking/jogging at 65 to 80% maximum heart rate) for 12 weeks versus usual care in men on ADT for at least 2 months prior to enrollment. The study reported significant differences between the two groups for muscle strength, lean mass, and several physical function tasks, all favoring the exercise group. Using the SF-36 QoL tool, significant improvements were reported for general health and fatigue, again favoring the exercise group. No adverse events were reported secondary to the exercise interventions, or to the testing procedures. More recently, a resistance training study in prostate cancer patients with bone metastases showed similar findings with gains in strength, physical function, and lean mass all favoring the exercise group (Cormie et al. 2013). No adverse events were reported in this study as well. Considering the current evidence of the positive effects of exercise in men with earlier stage prostate cancer and also those with more advanced disease, it is possible that the same benefits may also be achievable in mCRPC. Since many aspects of the proposed study are modeled after Galvao

and Cormie's earlier work in prostate patients, the safe use of and execution of the current protocol by mCRPC patients is highly expected. In addition, the American Cancer Society recently convened a group of experts to address physical exercise in cancer survivors (Schmitz et al. 2010). These guidelines recommend exercise in cancer survivors, including those with bone metastases provided appropriate support is available during exercise, and attention paid to issues such as balance (Rock et al. 2012).

In addition to these data, a systematic review of 10 studies evaluating the impact of exercise in prostate cancer patients undergoing ADT was recently published (Gardner et al 2013). The majority of study participants (>80%) did not have metastatic disease, although patients with non-bone metastases were included in some of the trials. The authors of this review concluded that exercise is safe in prostate cancer, and leads to similar benefits as those reported in otherwise healthy adults.

1.3 Purpose and Rationale

The purpose of our trial is to evaluate the feasibility and adherence to a home-based 12 week exercise intervention in mCRPC patients receiving ADT. We will also examine if a home-based exercise intervention can improve muscle strength, body composition, physical function, cardiopulmonary function fatigue, and patient reported outcomes (fatigue, depression, QoL). Finally, we will also explore the effects of the exercise training on biomarkers of inflammation-hormonal status and their potential association with changes in body composition, physical function, fatigue, depression, and QoL.

Most exercise studies in cancer patients have been conducted within exercise facilities, and ones conducted in prostate cancer report adherence rates >90%, (Galvao et al. 2006, 2009; Hanson et a. 2013), even in men with bone metastases (Cormie et al. 2013). However, this limits the benefits of exercise to individuals who live in close proximity to sites where these programs are offered. Recently, there are several reports on home-based exercise interventions. Findings from these studies have shown good adherence in addition to improvements in various outcomes such as cardiorespiratory function, fatigue, QoL and avoidance of weight gain and increases in body fat (Ligibel, et al. 2010; {Pinto, 2005 #78}, et al. 2007; Pinto, et al. 2005). This marks an important next step in expanding the number patients who can successful access exercise and is particularly relevant for advanced diseases (i.e. mCRPC) where patients may travel long distances to be seen in clinic but would not be able to regularly attend exercise training programs. As the North Carolina Cancer Hospital is a tertiary referral center, this limits the number of mCRPC patients who are local. The regimen to be used in the present study will include strength training and aerobic exercise 2-4x times per week, building up both components over time, following recommendations from the American College of Sports Medicine and utilizing a similar home-based exercise training program employed by Spector et al. (2014) in African America breast cancer patients. As relatively few studies to date have examined home-based

training program in more advanced disease states, feasibility programs are an important next step in expanding the outreach of exercise interventions. In addition, adaptations will be made throughout the training program to accommodate potential physical limitations and to account for the individual training response with the intent of maximizing feasibility and adherence and while simultaneously attempting to improve physical and psychological characteristics that are adversely affected during treatment for metastatic prostate cancer.

1.4 Future Work

Given the relative paucity of home based interventions in the mCRPC population, this work will determine if recruiting these men for exercise interventions is feasible. Moreover, it will also provide insight if the exercise adherence rates approach the levels seen in laboratory based exercise interventions. With this information in hand, the proposed project will provide the preliminary data to justify a randomized control trial to further investigate the role of home-based exercise in these patients. Finally, as future randomized control trials will likely need to be multi-site, similar projects are being developed at separate sites as parallel trials (Duke University, University of Alabama Birmingham) to demonstrate collaboration between these institutes and to be in position to generate the necessary accrurual numbers for the randomized trials.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To estimate the feasibility of a 12 week, home-based exercise intervention in mCPRC patients undergoing androgen deprivation therapy by reporting the percentage of patients who complete the pre/post exercise intervention testing.

2.2 Secondary Objectives

2.2.1 To report the level of adherence to the exercise intervention

2.2.2 To report the change in measurements of overall physical function (6 meter (m) usual and rapid walk, timed up and go, chair stands, and stair climb tests, 400m walk) in mCPRC patients before and after undergoing a home-based 12-week exercise intervention

2.2.3 To report the changes in patient reported outcomes including fatigue, depression and overall QoL in mCRPC patients before and after a home-based intervention

2.2.4 To report the change in total and regional lean, fat, and bone mass (e.g., upper limb, lower limb) in mCRPC patients before and after a home-based intervention

2.2.5 To report the changes in muscle function including muscle strength, endurance, and muscle architecture in mCRPC patients before and after a home-based intervention

2.2.6 To report the change in cardiopulmonary function (peak oxygen uptake) in mCRPC patients before and after a home-based intervention

2.3 Exploratory Objectives

2.3.1 To report changes in relevant biomarkers and immune function after exercise training, and explore the association of these changes with changes in physical function and lean mass. Biomarkers including but not limited to testosterone, lipid profile, PSA, stromal cell derived factor [SDF]-1α, IL-6, IL1β, IL-8 and IL-10 and IFN-γ cytokines will be explored. Immune function will be assessed by complete white blood cell counts and cell counts and function of specific subpopulations via flow cytometry.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subject must meet all of the inclusion criteria to participate in this study:

3.1.1 ≥18 years of age

3.1.2 Metastatic disease that has progressed despite castrate levels of testosterone (surgically or medically castrated, with testosterone levels of < 50 ng/dL) receiving ADT. This will be verified by assessing total testosterone levels within 4 weeks prior to enrollement.

3.1.3 No current chemotherapy

3.1.4 Patients may be receiving additional hormonal therapy agents including but not limited to antiandrogens (e.g. bicalutamide, enzalutamide) and CYP17 inhibitors (e.g. abiraterone).

3.1.5 Ability to engage safely in moderate exercise as determined by their treating physician

3.1.6 Not previously engaged in regular exercise training (<3 or more d/wk for > 30 min/d or <90 mins per week total including strength training, aerobic training, or walking) in the past 6 months

3.1.7 Access to a computer or a smart phone for syncing and uploading wearable activity data

3.1.8 Be able to speak and read English

3.2 Exclusion Criteria

All subjects meeting any of the exclusion criteria at baseline will be excluded from study participation

3.2.1 Any condition that causes severe pain with exertion

3.2.2 History of bone fractures

3.2.3 Active cardiovascular disease including any of the following:

- New York Heart Association (NYHA) Grade II or greater congestive heart failure
- History of myocardial infarction or unstable angina within 6 months prior to Day 1
- History of stroke or transient ischemic attack within 6 months prior to Day 1

3.2.4 Acute or chronic respiratory disease that is severe enough to compromise the ability of the participant to safely engage in exercise training protocol

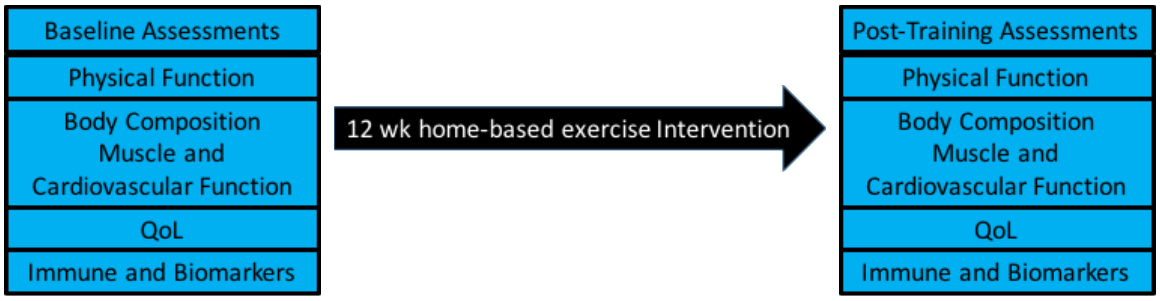
3.2.5 Acute or chronic bone/joint/muscular abnormalities compromising their ability to exercise

3.2.6 Neurological conditions that affect balance and, or muscle strength

3.2.7 Dementia, altered mental status or any psychiatric condition prohibiting the understanding or rendering of informed consent

4.0 STUDY PLAN

4.1 Schema



Participants with mCRPC receiving ADT will be recruited for involvement in a single-arm prospective 12-week exercise intervention study.

4.2 Recruitment of mCRPC patients receiving ADT

Thirty men with mCRPC receiving ADT will be recruited for this study and will engage in a home-based intervention. Men with mCRPC will be approached by their treating oncologist at UNC-Chapel Hill or Wake Forest and informed of the study. All patients who are interested in participating will be provided informed consent.

4.2.1 Overseeing Site

At UNC, recruiting prostate cancer patients undergoing ADT +/- additional hormonal therapies will be done in close collaboration and with the support of physicians (see co-investigators) from the UNC Lineberger Comprehensive Cancer Center (LCCC). In 2015, LCCC saw approximately 485 prostate cancer, of which ~125 were mCRPC. Over the past 3-year period, 124 men (16%) have enrolled in various cooperative group, pharmaceutical sponsored, or investigator-initiated studies. All eligible patients will be enrolled and track reasons for dropout, should they not complete all aspects of study.

4.2.2 Participating Sites

At Wake Forest, study activities will be led by Dr Rhonda Bitting, an Assistant Professor of Medicine in Hematology and Oncology and Alexander Lucas, PhD, a Research Fellow in the School of Medicine.

All patients from all sites will be requested to maintain their pre-study level of physical activity and diet (Appendix 0) during the duration of the study beyond the addition of the prescribed exercises. A 24 hour dietary recall the day before the baseline and post-training assessments will be completed to estimate total caloric intake at each time point and to help ensure that patients have eaten similarly prior to each testing session. This will help to ensure the validity of the secondary outcomes and also the testing assessments themselves. Physical activity levels will be screened during the introduction and consent process, with thresholds for inclusion defined in 3.1.6.

4.3 Exercise Intervention

The **exercise intervention** will consist of a combination of aerobic (cardiovascular exercise) and strength training (emphasis of the intervention) ~3 times per week for 12 weeks with each session lasting 1 hour. The home-based exercise intervention will begin with a low intensity walking and resistance (ie, strength) training, which progressed to follow the previously tested and successful home-based program demonstrated by Spector et al. (2014) [and designed by Co-Investigator Battaglini]. The combined aerobic and resistance training protocol will follow the guidelines set forth by the American College of Sports Medicine. The progressive standardized aerobic exercise plan will involve walking. Resistance training included upper, lower, and abdominal core strengthening exercises. Upper body strength exercises included lateral and front raises, wall or modified floor push-ups, chest press, bent row, arm curls, and triceps stretches. Lower body strength exercises included chair squats, chair leg raises, hamstring curls, and calf raises. The four core strengthening exercises were the bridge, crunches, reverse crunches, and obliques. Upper and lower body exercises will be done with elastic resistance bands. All exercises will be demonstrated to the participants during their initial exercise testing session. Participants will be also instructed to perform stretching exercises of major muscle groups after the walking component of their exercise program. Participants will be given an exercise training workbook that included

weekly exercise logs, the exercise training plan, illustrations of resistance exercises and stretches (Appendix 1). Participants will be given activity monitors to wear which will record heart rate, activity minutes and calories expended (these are small wrist watch-like devises that are easily operated). This information will be recorded by the participants and regularly synced with a computer so that weekly exercise totals (number of aerobic sessions, amount of time per session) along with the exercise intensity can be determined. To stimulate a training effect following recommendations from the American College of Sports Medicine, from week 1 to completion of the study, walking will be increased from 15 to 30 minutes and intensity from 40% to 65% of heart rate reserve. Therabands elastic bands will be used for the resistance training. Participants will be instructed to perform 12 to 15 repetitions per exercise beginning with the light- or medium-strength band and progressing to the heaviest strength band as ability permitted. Once a participant can comfortably complete 15 repetitions for all prescribed sets, they will increase resistance by moving up to the next band. The training volume increased from 1 set per exercise on week 1 to 3 sets by week 12 (see table below).

Week	Walking Sessions Per Week	Walking Sessions Minutes Per Week	Resistance Training Sets Per Week	Resistance Training Sessions Per Week	Target Heart Rate Reserve
1	2	15	1	1	40-50
2	2	15	1	2	40-50
3	3	20	2	2	50-60
4	4	30	2	3	50-60
5-6	4	22	2	3	50-60
6-8	4	25	2	3	55-65
10-12	4	30	3	3	55-65

To facilitate the engagement of the patients and to help with adherence, weekly contact will be made by a member of the research team. This will involve either a phone call, Skype, or an email contact, based upon the patient's preference. This follow up will allow for answering of any questions related to the study, including proper exercise technique, activity levels, or using/syncing the wearable device.

4.4 Study Measures

All testing procedures will be completed at baseline and 12 weeks after exercise training. All testing will be completed in a single baseline or post-training session lasting between 2-3 hours, including rest breaks. Pilot testing of the protocol has shown that these tests can be completed in this time frame. Standardized rest periods have been included and the testing order has been designed to allow for patients that meet the inclusion criteria to be able to perform all tests within a single session. The single session will also be more convenient for participants travelling longer distances to come to the UNC or Wake Forest Cancer Hospitals, which may help with the primary outcome (feasibility).

Testing Task	Time (mins)
Body Composition (DXA)	10
Ultrasound for Muscle Size/Quality	10
Muscle Function	40-50
Break (sitting)	10
Physical Function	30-40
Break (sitting)	5
Cardiopulmonary Testing	30
Total	**135-155**

Patient reported outcome questionnaires will be given out prior for the patients to complete at home and to bring into the respective testing sessions.

4.4.1 Physical Function

- **Overall functionality** will be assessed using standard simulated activates of daily living (Hanson et al. 2009, 2013), including the 6m usual and rapid walk tests, the timed up and go test, chair stands, and stair climb tasks and 400m walk test (Appendix 2).
- The short physical performance battery (5 chair stands, 8 foot usual walk, and side by side, tandem, and semi-tandem 10 second balance tests) will also determined (Guralnik et al. 1994).
- **Body Composition** to measure lean and fat mass and bone mineral density will be completed using dual-energy x-ray absorptiometry (DXA). Both total body and regional scans will be performed.
- **Muscle size and quality** of the quadriceps muscles will be measured using portable ultra-sound technology to determine cross-sectional area (size) and echo intensity (quality). The ultrasound CSA measurement will be performed on the right Vastus Lateralis via manual movement of the transducer slowly and continually from lateral to medial along an upper leg template suitable for each subject. The purpose of the template is to ensure precise measurement and reproduction of the same muscle area for the comparison of pre- and post-intervention CSA images. In the musculoskeletal mode of the device, gain and frequency will be standardized between tests and across subjects in order to optimize image quality. Depth will be adjusted between participants to ensure both deep and superficial fascia remain visible in the field-of-view. Hypoallergenic water-soluble transmission gel (1 - 2 oz.) will be applied to the skin to reduce possible near field artifacts and enhance acoustic coupling (Aquasonic 100, Parker Laboratories, Inc., Fairfield, NJ, USA). LogicView™ software (General Electric Company, Milwaukee, WI, USA) will be used to generate real-time panoramic cross-sectional images of the muscles. Three scans will be performed and an average of the three will be recorded in order to reduce the likelihood of technician error. Following each scan, each image will be reviewed to ensure appropriate image quality. If a scan is does not produce a clean image of CSA, additional

scans will be performed. All ultrasound imaging analyses will be performed using Image-J software (version 1.46r, National Institutes of Health, USA). Prior to analysis, each image will be individually scaled from area in pixels to centimeters using the straight-line function. CSA of VLs will be determined using the polygon function by selecting a region of interest that includes as much of the muscle as possible without any surrounding fascia.

- **Muscle function** in the forms of muscle strength, power, and endurance will be assessed using several different techniques. Upper and lower body muscle strength will be assessed on the chest press, knee extension, and leg press. Patients will be familiarized prior to undergoing baseline testing to minimize the risk of injury and to improve the validity of the testing outcome. Patients will complete sets of a single repetition with increasing resistance until they are no longer able to move the weight throughout the full range of motion (Hanson et al. 2009, 2013). The maximal amount of resistance lifted is their maximal strength. Muscle endurance will be determined using a repetitions test. Participants will complete as many consecutive repetitions as possible at 70% of their maximal strength for the chest and leg press (Hanson et al. 2013). The total number of successful repetitions will be used to determine endurance capabilities. Knee extensor muscle power, which is affected by both force and velocity, will be assessed on an isokinetic dynamometer. Patients will be asked to extend their leg as quickly as possible against a fixed resistance load to determine power and rate of force development (Appendix 3).
- **Cardiopulmonary function** (VO_2 peak) will be assessed using a graded exercise test on a treadmill. Patients will begin the test walking slowly on the treadmill and every two minutes, the grade and speed of the treadmill will be increased in a progressive manner until fatigue occurs. Respiratory gases will be collected throughout the test and analyzed using a metabolic cart to determine oxygen utilization and carbon dioxide production. The maximal oxygen uptake that is recorded will be used as a marker of aerobic fitness (Appendix 4).

4.4.2 Quality of Life (QoL)

QoL questionnaires will be completed at baseline and after exercise training.

- **Fatigue** (FACIT- Fatigue, Appendix 5). Fatigue will be measure using the FACIT-Fatigue, a 1 page form that uses a rating scale that goes from 0 (no fatigue) to 10 (severe fatigue). It assesses the patient's fatigue levels in the last 7 days. It also measures how usual activities, performing work, walking, relationship, and enjoyment of life are affected by fatigue.
- **Depression** will be measured using the Hospital Anxiety and Depression Scale (HADS; Appendix 6), a concise, self-administered 1 page form that categorizes anxiety and depression. The total score goes from 0-21, and scores are categorized from minimal to severe depression/anxiety.

- **QoL** will be measured using the Functional Assesment of Cancer Therapy-Prostate (FACT-P; Appendix 7). The FACT-P is composed of both multi-item scales and single-item measures. These include physical, social, emotional, and functional well-being, along with an assessment of prostate-specific health status. five functional scales, three symptom scales, a global health status / QoL scale, and six single items. All of the scales score from 0-4 and and a high scale score represents a higher response level.

  We recognize that any changes in QoL, depression, and fatigue will be difficult to attribute to exercise alone.

4.4.3 Laboratory Measures

Fasted blood draws will occur at baseline and after exercise training.

- **Select laboratory measures** (testosterone, lipid profiles, prostate specific antigen, stromal cell derived factor (SDF)-1α) and inflammatory markers (IL-6, IL-1β, IL-8, IL-10 and IFN-γ) will be measured using Enzyme-Linked Immunosorbent Assay (ELISA) from serum and plasma collected in the fasted, resting state at the beginning and end of the exercise intervention using analysis procedures appropriate for exercise studies (Hackney & Viru 2008). Any excess serum/blood remaining after protocol-dictated studies are complete will be destroyed.

4.5 Removal of Patients from Protocol

Participants will be removed from the study intervention if they indicate they no longer wish to participate and if they are not able to complete the exercise intervention due to disease/treatment complications. Additionally, subjects will be removed if their physician-oncologist request that their patient is excluded from the study for any medical or emotional concerns.

In case a patient decides to prematurely discontinue the protocol intervention, the patient should be asked if he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the study data collection forms.

4.6 Study Withdrawal

If a patient decides to withdraw from the study all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on study data collection forms.

5.0 EXPECTED RISKS/UNANTICIPATED PROBLEMS/DATA AND SAFETY MONITORING

5.1 Expected Risks

5.1.1 Exercise

There should be no psychological or physiological harm caused by the research, and thus this will not cause the patient any emotional or physical loss. In the unlikely event of injury during the fitness assessments and the exercise portion of this study, such as muscle distensions and joint trauma, medical professionals on the research team will provide the appropriate care. Also, due to the stringent criteria for participation in the study, only subjects deemed capable by their oncologists will be enrolled in the study.

5.1.2 Whole Body DXA Scan

The amount of radiation from exposure to a DXA scan is low, 0.008 mSv (0.8 mrem), equivalent to the radiation exposure everyone receives in one day from background radiation.

5.1.3 Ultrasound

There are no anticipated safety concerns associated with the use of ultrasound.

5.2 Unanticipated Problems

As defined by UNC's IRB, unanticipated problems involving risks to study subjects refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

5.3 Reporting

Any unanticipated problem that occurs during the conduct of this study and that meets **at least** the first two criteria listed in section 5.3 must be reported to the UNC IRB (overseeing site) using the IRB's web-based reporting system.

6.0 STATISTICAL CONSIDERATIONS

6.1 Study Design

This study will recruit patients with metastatic CRPC to undergo a home-based exercise intervention in order to establish feasibility in this patient population. Secondary objectives include evaluating its impact on changes in physical function, body composition, muscle function, cardiopulmonary function, fatigue, depression, quality of life, and biomarkers. Evaluations will be done at baseline and after the 12-week intervention. It is hypothesized that the exercise intervention will increase function relatively to baseline in these men.

6.2 Sample Size and Accrual

Previous exercise intervention studies have shown that attrition rates in healthy controls are between 20-30% (Hanson et al. 2009; Walts et al. 2008). Surprisingly, attrition rates are lower in prostate cancer patients on ADT at between 2-10% (Hanson et al. 2013; Galvao et al. 2006, 2011). However, prostate patients with bone metastases experienced higher drop out rates (25% (Cormie et al. 2013)). Because no study has examined the effects of exercise on metastatic CRPC patients, we want to confirm that patients will participate and complete pre/post study measures. We anticipate that recruiting 30 men should yield a final sample size of 20-25 subjects. The table below shows the percentage, along with exact 95% binomial confidence interval for possible results. If we retain 20/30 patients, our fesibility estimate will be 67%, with a 95% CI ranging from 47%-83%.

%	n/N	Estimate (95% CI)
50%	(15/30)	50.0% (31.3%,68.7%)
60%	(18/30)	60.0% (40.6%,77.3%)
67%	(20/30)	66.7% (47.2%,82.7%)
70%	(21/30)	70.0% (50.6%,85.3%)
80%	(24/30)	80.0% (61.4%,92.3%)
83%	(25/30)	83.3% (65.3%,94.4%)
90%	(27/30)	90.0% (73.5%,97.9%)
100%	(30/30)	100.0% (88.4%,100.0%)

For seconadary objectives comparing changes over time, a sample size of 25 will have 80% power to detect an effect size of 0.584 using a paired t-test with a 0.050 two-sided significance level. For example, for the 400m walk test - This effect size may be seen if the difference from pre to post if -5 seconds with a standard deviation is 8.56 seconds. If only 20 patients per group complete the post measures, there will be 80% power to detect an effect size of 0.66, which may be seen if the mean difference is 5.65 with a common standard deviation of 8.56.

Accrual of these patients will occur over the span of 24 months. Should sufficient recruitment (~30 men) not be obtained in that time period, the research team may conclude that exercise interventions in this population and setting appear not to be feasible.

6.3 Data Analysis Plans

Descriptive statistics including means, standard deviations, medians, ranges, and percentages, will be used to report on all measures at baseline and post intervention and changes in measures over time. Changes in continuous measures will be compared between groups using two group t-tests or Fisher's Exact tests for categorical variables.

Associations of changes in biomarkers with changes in physical function or body composition measures will be explored using correlation coefficients. Associations of other measures will be explored using two group t-tests for continuous and categorical variables or Fisher's Exact tests for two categorical variables.

As sample size permits, analyses will be repeated with stratification based on treatment type, treatment duration, or age. This will be purely exploratory.

All analysis will be performed by the statistician of record.

6.4 Data Management/Auditing

Data will be managed the PI and his designated staff, and it will be entered into an REDCcap database designed by the PI's staff, with input from the statistician of record. Co-investigators Lucas and Bitting at Wake Forest University will access REDCap for secure data entry. As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months, depending on the participation of affiliate sites.

7.0 STUDY MANAGEMENT

7.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, patient will be asked to give verbal consent so that the medical history screening can be completed over the

phone. At the initial visit, patients will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

7.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be placed on file at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form

7.3 Registration Procedures

All patients will be registered with Oncore™ by the Study Coordinator/PI. This will allow the cancer center to track accrual onto this important trial. Contact Paul Jones (paul_e_jones@med.unc.edu) for any questions on Oncore, and for Oncore training.

7.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

7.4.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by PI/UNC Research Personnel within five (5) business days of making the change.

7.4.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB as the overseeing site.

7.4.3 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the UNC IRB. According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

7.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

7.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring

logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

7.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

7.8 REFERENCES

1. Hanson, E.D., S.R. Srivatsan, S. Agrawal, K.S. Menon, M.J. Delmonico, M.Q. Wang, and B.F. Hurley, *Effects of strength training on physical function: influence of power, strength, and body composition.* J Strength Cond Res, 2009. 23(9): p. 2627-37.

2. Walts, C.T., E.D. Hanson, M.J. Delmonico, L. Yao, M.Q. Wang, and B.F. Hurley, *Do sex or race differences influence strength training effects on muscle or fat?* Med Sci Sports Exerc, 2008. 40(4): p. 669-76.

3. Hanson, E.D., A.K. Sheaff, S. Sood, L. Ma, J.D. Francis, A. Goldberg, and B.F. Hurley, *Strength Training Induces Muscle Hypertrophy and Functional Gains*

in Black Prostate Cancer Patients Despite Androgen Deprivation Therapy. J Gerontol A Biol Sci Med Sci, 2013. 68(4):490-8.

4. Galvao, D.A., K. Nosaka, D.R. Taaffe, N. Spry, L.J. Kristjanson, M.R. McGuigan, K. Suzuki, K. Yamaya, and R.U.Newton, *Resistance training and reduction of treatment side effects in prostate cancer patients.* Med Sci Sports Exerc, 2006. 38(12): p. 2045-2052.

5. Segal, R.J., R.D. Reid, K.S. Courneya, S.C. Malone, M.B. Parliament, C.G. Scott, P.M. Venner, H.A. Quinney, L.W. Jones, M.E. D'Angelo, and G.A. Wells, *Resistance exercise in men receiving androgen deprivation therapy for prostate cancer.* J Clin Oncol, 2003. 21(9): p. 1653-1659.

6. Galvao, D.A., D.R. Taaffe, N. Spry, D. Joseph, and R.U. Newton, *Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial.* J Clin Oncol, 2010. 28(2): p. 340-7.

7. Evans, E.S., C.L. Battaglini, D.G. Groff, and A.C. Hackney, *Aerobic exercise intensity in breast cancer patients: a preliminary investigation.* Integr Cancer Ther, 2009. 8(2): p. 139-47.

8. Evans E.S., Hackney A.C., McMurray R.G., Randell S.H., Muss H.B., Deal A.M., Battaglini C.L. *Impact of acute intermittent exercise on natural killer cells* in breast *cancer survivors.* Integr Cancer Ther. 2015 14(5):436-45.

9. Hanson E.D., Sakkal S., Baindur-Hudson S., Violet J., Battaglini C.L., McConell G.K., Hayes A. *Cytotoxic lymphocyte response to moderate intensity aerobic exercise in prostate cancer survivors*. Med Sci Sport Exerc. 2015. 47(5): S2659, 2015.

10. Battaglini, C.L., A.C. Hackney, R. Garcia, D. Groff, E. Evans, and T. Shea, *The effects of an exercise program in leukemia patients.* Integr Cancer Ther, 2009. 8(2): p. 130-8.

11. Warburton, D.E., C.W. Nicol, and S.S. Bredin, *Health benefits of physical activity: the evidence.* CMAJ, 2006. 174(6): p. 801-9.

12. Lakoski, S.G., N.D. Eves, P.S. Douglas, and L.W. Jones, *Exercise rehabilitation in patients with cancer.* Nat Rev Clin Oncol, 2012. 9(5): p. 288-96.

13. Galvao, D.A. and R.U. Newton, *Review of exercise intervention studies in cancer patients.* J Clin Oncol, 2005. 23(4): p. 899-909.

14. De Backer, I.C., G. Schep, F.J. Backx, G. Vreugdenhil, and H. Kuipers, *Resistance training in cancer survivors: a systematic review.* Int J Sports Med, 2009. 30(10): p. 703-12.

15. Loprinzi, P.D., B.J. Cardinal, K. Winters-Stone, E. Smit, and C.L. Loprinzi, *Physical activity and the risk of breast cancer recurrence: a literature review.* Oncol Nurs Forum, 2012. 39(3): p. 269-74.

16. Siegel, R., D. Naishadham, and A. Jemal, *Cancer statistics, 2012.* CA Cancer J Clin, 2012. 62(1): p. 10-29.

17. Hanson, E.D. and B.F. Hurley, *Intervening on the side effects of hormone-dependent cancer treatment: the role of strength training.* J Aging Res [Internet], 2011. Available from: http: //www.ncbi.nlm.nih.gov/pmc/articles/ PMC3034975/pdf/JAR2011-903291.pdf: p. doi: 10.4061/2011/903291.

18. Smith, M.R., F. Saad, B. Egerdie, P.R. Sieber, T.L. Tammela, C. Ke, B.Z. Leder, and C. Goessl, *Sarcopenia during androgen-deprivation therapy for prostate cancer.* J Clin Oncol, 2012. 30(26): p. 3271-6.

19. Galvao, D.A., N.A. Spry, D.R. Taaffe, R.U. Newton, J. Stanley, T. Shannon, C. Rowling, and R. Prince, *Changesin muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer.* BJU Int, 2008. 102(1): p. 44-7.

20. Basaria, S., J. Lieb, A.M. Tang, T. DeWeese, M. Carducci, M. Eisenberger, and A.S. Dobs, *Long-term effects of androgen deprivation therapy in prostate cancer patients.* Clin Endocrinol (Oxf), 2002. 56(6): p. 779-786.

21. de Bono, J.S., C.J. Logothetis, A. Molina, K. Fizazi, S. North, L. Chu, K.N. Chi, R.J. Jones, O.B. Goodman, Jr., F.Saad, J.N. Staffurth, P. Mainwaring, S. Harland, T.W. Flaig, T.E. Hutson, T. Cheng, H. Patterson, J.D. Hainsworth, C.J. Ryan, C.N. Sternberg, S.L. Ellard, A. Flechon, M. Saleh, M. Scholz, E. Efstathiou, A. Zivi, D. Bianchini, Y. Loriot, N. Chieffo, T. Kheoh, C.M. Haqq, H.I. Scher, and C.-A.-. Investigators, *Abiraterone and increased survival in metastatic prostate cancer.* N Engl J Med, 2011. 364(21): p. 1995-2005.

22. Smith, M.R., H. Lee, and D.M. Nathan, *Insulin sensitivity during combined androgen blockade for prostate cancer.* J Clin Endocrinol Metab, 2006. 91(4): p. 1305-8.

23. Kantoff, P.W., C.S. Higano, N.D. Shore, E.R. Berger, E.J. Small, D.F. Penson, C.H. Redfern, A.C. Ferrari, R. Dreicer, R.B. Sims, Y. Xu, M.W. Frohlich, P.F. Schellhammer, and I.S. Investigators, *Sipuleucel-T immunotherapy for castration-resistant prostate cancer.* N Engl J Med, 2010. 363(5): p. 411-22.

24. Lassi, K. and N.A. Dawson, *Emerging therapies in castrate-resistant prostate cancer.* Curr Opin Oncol, 2009. 21(3): p. 260-5.

27. Amaral, T.M., D. Macedo, I. Fernandes, and L. Costa, *Castration-resistant prostate cancer: mechanisms, targets, and treatment.* Prostate Cancer, 2012. 2012: p. 327253.

25. de Bono, J.S., S. Oudard, M. Ozguroglu, S. Hansen, J.P. Machiels, I. Kocak, G. Gravis, I. Bodrogi, M.J. Mackenzie, L. Shen, M. Roessner, S. Gupta, A.O. Sartor, and T. Investigators, *Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial.* Lancet, 2010. 376(9747): p. 1147-54.

26. Kantoff, P.W., T.J. Schuetz, B.A. Blumenstein, L.M. Glode, D.L. Bilhartz, M. Wyand, K. Manson, D.L. Panicali, R. Laus, J. Schlom, W.L. Dahut, P.M. Arlen, J.L. Gulley, and W.R. Godfrey, *Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer.* J Clin Oncol, 2010. 28(7): p. 1099-105.

27. Kucuk, O., E. Fisher, C.M. Moinpour, D. Coleman, M.H. Hussain, A.O. Sartor, G.S. Chatta, B.A. Lowe, M.A. Eisenberger, and E.D. Crawford, *Phase II trial of bicalutamide in patients with advanced prostate cancer in whom conventional hormonal therapy failed: a Southwest Oncology Group study (SWOG 9235).* Urology, 2001. 58(1): p. 53-8.

28. Tannock, I.F., R. de Wit, W.R. Berry, J. Horti, A. Pluzanska, K.N. Chi, S. Oudard, C. Theodore, N.D. James, I. Turesson, M.A. Rosenthal, M.A. Eisenberger, and T.A.X. Investigators, *Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.* N Engl J Med, 2004. 351(15): p. 1502-12.

29. Smith, M.R., *Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer.* Urology, 2004. 63(4): p. 742-745.

30. Smith, M.R., J.S. Finkelstein, F.J. McGovern, A.L. Zietman, M.A. Fallon, D.A. Schoenfeld, and P.W. Kantoff, *Changes in body composition during androgen deprivation therapy for prostate cancer.* J Clin Endocrinol Metab, 2002. 87(2): p. 599-603.

31. van Londen, G.J., M.E. Levy, S. Perera, J.B. Nelson, and S.L. Greenspan, *Body composition changes during androgen deprivation therapy for prostate cancer: a 2-year prospective study.* Crit Rev Oncol Hematol, 2008. 68(2): p. 172-7.

32. Levy, M.E., S. Perera, G.J. van Londen, J.B. Nelson, C.A. Clay, and S.L. Greenspan, *Physical function changes in prostate cancer patients on androgen*

deprivation therapy: a 2-year prospective study. Urology, 2008. 71(4): p.735-9.

33. Mauras, N., V. Hayes, S. Welch, A. Rini, K. Helgeson, M. Dokler, J.D. Veldhuis, and R.J. Urban, *Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity.* J Clin Endocrinol Metab, 1998. 83(6): p. 1886-1892.

34. Saigal, C.S., J.L. Gore, T.L. Krupski, J. Hanley, M. Schonlau, and M.S. Litwin, *Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer.* Cancer, 2007. 110(7): p. 1493-500.

35. Tsai, H.K., A.V. D'Amico, N. Sadetsky, M.H. Chen, and P.R. Carroll, *Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality.* J Natl Cancer Inst, 2007. 99(20): p. 1516-24.

36. Basaria, S., D.C. Muller, M.A. Carducci, J. Egan, and A.S. Dobs, *Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy.* Cancer, 2006. 106(3): p. 581-8.

37. Basaria, S., *Androgen deprivation therapy, insulin resistance, and cardiovascular mortality: an inconvenient truth.* J Androl, 2008. 29(5): p. 534-9.

38. Smith, M.R., *Osteoporosis and other adverse body composition changes during androgen deprivation therapy for prostate cancer.* Cancer Metastasis Rev., 2002. 21(2): p. 159-166.

39. Smith, M.R., W.C. Lee, J. Brandman, Q. Wang, M. Botteman, and C.L. Pashos, *Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer.* J Clin Oncol, 2005. 23(31): p. 7897-903.

40. Serpa Neto, A., M. Tobias-Machado, M.A. Esteves, M.D. Senra, M.L. Wroclawski, F.L. Fonseca, R.B. dos Reis, A.C. Pompeo, and A. Del Giglio, *A systematic review and meta-analysis of bone metabolism in prostate adenocarcinoma.* BMC Urol, 2010. 10: p. 9.

41. Martinez-Reig, M., L. Ahmad, and G. Duque, *The Orthogeriatrics Model of Care: Systematic Review of Predictors of Institutionalization and Mortality in Post-Hip Fracture Patients and Evidence for Interventions.* J Am Med Dir Assoc, 2012.

42. Galvao, D.A., D.R. Taaffe, N. Spry, D. Joseph, D. Turner, and R.U. Newton, *Reduced muscle strength and functional performance in men with prostate*

cancer undergoing androgen suppression: a comprehensive crosssectional investigation. Prostate Cancer Prostatic Dis, 2009. 12(2): p. 198-203.

43. Glover, E.I. and S.M. Phillips, *Resistance exercise and appropriate nutrition to counteract muscle wasting and promote muscle hypertrophy.* Curr Opin Clin Nutr Metab Care, 2010. 13(6): p. 630-4.

44. Hurley, B.F., E.D. Hanson, and A.K. Sheaff, *Strength training as a countermeasure to aging muscle and chronic disease.* Sports Med, 2011. 41(4): p. 289-306.

45. Segal, R.J., R.D. Reid, K.S. Courneya, R.J. Sigal, G.P. Kenny, D.G. Prud'Homme, S.C. Malone, G.A. Wells, C.G. Scott, and M.E. Slovinec D'Angelo, *Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer.* J Clin Oncol, 2009. 27(3): p. 344-51.

46. Hydock, D.S., C.Y. Lien, C.M. Schneider, and R. Hayward, *Effects of voluntary wheel running on cardiac function and myosin heavy chain in chemically gonadectomized rats.* Am J Physiol Heart Circ Physiol, 2007. 293(6): p. H3254-64.

47. Kyrdalen, A.E., A.A. Dahl, E. Hernes, E. Hem, and S.D. Fossa, *Fatigue in prostate cancer survivors treated with definitive radiotherapy and LHRH analogs.* Prostate, 2010. 70(13): p. 1480-9.

48. Petersen, A.M. and B.K. Pedersen, *The anti-inflammatory effect of exercise.* J Appl Physiol, 2005. 98(4): p. 1154- 62.

49. Vingren, J.L., W.J. Kraemer, N.A. Ratamess, J.M. Anderson, J.S. Volek, and C.M. Maresh, *Testosterone physiology in resistance exercise and training: the up-stream regulatory elements.* Sports Med, 2010. 40(12): p. 1037-53.

50. Winters-Stone, K.M., J. Dobek, L. Nail, J.A. Bennett, M.C. Leo, A. Naik, and A. Schwartz, *Strength training stopsbone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial.* Breast Cancer Res Treat, 2011. 127(2): p. 447-56.

51. Argiles, J.M., S. Busquets, and F.J. Lopez-Soriano, *The pivotal role of cytokines in muscle wasting during cancer.* Int J Biochem Cell Biol, 2005. 37(10): p. 2036-46.

52. Lira, F.S., A.S. Yamashita, J.C. Rosa, F.L. Tavares, E. Caperuto, L.C. Carnevali, Jr., G.D. Pimentel, R.V. Santos, M.L. Batista, Jr., A. Laviano, F. Rossi-Fanelli, and M. Seelaender, *Hypothalamic inflammation is reversed*

byendurance training in anorectic-cachectic rats. Nutr Metab (Lond), 2011. 8(1): p. 60.

53. Irwin, M.L., *ACSM's Guide to Exercise and Cancer Survivorship.* American College of Sports Medicine. 2012: Human Kinetics Publishing.

54. Hackney, A.C. and J. Dobridge, *Exercise and male hypogonadism: testerone, the hypothalamic-pituitary axis and physica exercise*, in *Male Hypogondal Disorders: Contemporary Endocrinology Series*, S. Winter, Editor. 2003, Humana Publishing. p. 314-333.

55. Urban, R.J., Y.H. Bodenburg, C. Gilkison, J. Foxworth, A.R. Coggan, R.R. Wolfe, and A. Ferrando, *Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis.* Am J Physiol, 1995. 269(5Pt 1): p. E820-E826.

56. Harris, W.P., E.A. Mostaghel, P.S. Nelson, and B. Montgomery, *Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion.* Nat Clin Pract Urol, 2009. 6(2): p. 76-85.

57. Galvao, D.A., D.R. Taaffe, N. Spry, D. Joseph, and R.U. Newton, *Acute versus chronic exposure to androgen suppression for prostate cancer: impact on the exercise response.* J Urol, 2011. 186(4): p. 1291-7.

58. Cuoco, A., D.M. Callahan, S. Sayers, W.R. Frontera, J. Bean, and R.A. Fielding, *Impact of muscle power and force on gait speed in disabled older men and women.* J Gerontol A Biol Sci Med Sci, 2004. 59(11): p. 1200-1206.

59. Newton, R.U., D.R. Taaffe, N. Spry, R.A. Gardiner, G. Levin, B. Wall, D. Joseph, S.K. Chambers, and D.A. Galvao, *A phase III clinical trial of exercise modalities on treatment side-effects in men receiving therapy for prostate cancer.* BMC Cancer, 2009. 9: p. 210.

60. Vincent, K.R. and R.W. Braith, *Resistance exercise and bone turnover in elderly men and women.* Med Sci Sports Exerc, 2002. 34(1): p. 17-23.

61. Galvao, D.A. and D.R. Taaffe, *Resistance exercise dosage in older adults: single- versus multiset effects on physical performance and body composition.* J Am Geriatr Soc, 2005. 53(12): p. 2090-2097.

62. Mangione, K.K., R.L. Craik, A.A. McCormick, H.L. Blevins, M.B. White, E.M. Sullivan-Marx, and J.D. Tomlinson, *Detectable changes in physical performance measures in elderly African Americans.* Phys Ther, 2010. 90(6): p. 921-7.

63. Temel, J.S., J.A. Greer, A. Muzikansky, E.R. Gallagher, S. Admane, V.A. Jackson, C.M. Dahlin, C.D. Blinderman, J. Jacobsen, W.F. Pirl, J.A. Billings, and T.J. Lynch, *Early palliative care for patients with metastatic non-small-celllung cancer.* N Engl J Med, 2010. 363(8): p. 733-42.

64. Rock CL, Doyle C, Demark-Wahnefried W, et al. *Nutrition and Physical Activity Guidelines for Cancer Survivors.* CA Cancer J Clin 2012. 62:242-274.

65. Cormie P, Newton RU Spry N et al. *Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases*. Prostate Cancer Prostatic Dis. 2013;16(4):328-335.

66. Mendoza TR, Wang XS, Cleeland CS, et al. *The rapid assessment of fatigue severity in cancer patients: Use of the Brief Fatigue Inventory*. Cancer. 1999;85:1186-1196.

67. Gardner JR, Livingston PM, Fraser SF. *Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review.* J Clin Oncol. 2014. 32(4):335-46.

68. Spector D, Deal AM, Amos KD, Yang H, Battaglini CL. *A pilot study of a home-based motivational exercise program for African American breast cancer survivors: clinical and quality-of-life outcomes.* Integr Cancer Ther. 2014. Mar;13(2):121-32.