Examples of Funded Grants in Behavioral Research

Overview

The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let the Behavioral Research Program (BRP) post excerpts of their grant applications online.

About

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the research community. To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application), where applicable. In addition, we only include a copy of SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches).

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PI: WINTERS-STONE, KERRI M

Grant Number: 1 R01 CA222605-01A1

Title: Preventing Falls and Frailty in Prostate Cancer Survivors: GET FIT Prostate

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FOA Title: NIH Research Project Grant (Parent R01)

Organization: OREGON HEALTH & SCIENCE UNIVERSITY

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Role Category: PD/PI

Project Summary/Abstract

Based on recent findings from our team and others, we confirm initial reports that prostate cancer (PC) survivors treated with androgen deprivation therapy (ADT) are significantly more likely to fall and to become frail than PC survivors who do not receive this treatment or men without cancer, placing nearly half of all PC survivors at higher risk of fall-related fractures, other life-threatening injuries, disability and death. Currently, there are no evidence-based fall prevention strategies that specifically target PC survivors on ADT. The purpose of the proposed study is to determine and compare the efficacy of two very distinct types of exercise, tai chi versus strength training, to prevent falls specifically linked to ADT for prostate cancer. We will examine additional endpoints of frailty and physical function that are also worsened with ADT and contribute to the risk of falls and future disability. We propose a 3-group, single-blind, parallel design, randomized controlled trial in PC survivors treated with ADT (N=360) comparing 1) tai chi to 2) strength training against 3) a placebo control group of seated stretching exercise. Men will participate in supervised study programs 3x/wk for 6 months and will be followed for 6 more months after formal training stops. The specific aims of this study are to determine and compare the efficacy of both tai chi and strength training to 1) reduce falls and 2) lessen frailty (shrinking, weakness, slowness, exhaustion, and inactivity) and dysfunction (mobility, balance, self-report function) in PC survivors on ADT, 3) Determine whether or not the benefits of each intervention last after structured training stops and 4) Explore the patterns and predictors of men who respond best to each intervention. The proposed study is innovative in its approach because it applies two well-characterized fall prevention exercise programs (e.g., tai chi and strength training) to a new population just recently identified at high risk of falls and for whom the causes of falls and effective countermeasures remain unclear. This study is the very first attempt at a direct comparison of two known exercise modalities, each with distinct training properties, to reduce falls, frailty and dysfunction in PC survivors. The proposed project responds to an urgent research agenda in cancer survivorship that calls for developing appropriately targeted, effective, and sustainable exercise programs for cancer survivors and to NCI and IOM priorities to expand cancer care to prevent disability in older survivors. This study is relevant to public health because up to 45% of the 2 million PCS alive in the U.S. are prescribed ADT. Men on ADT can survive 16 years or longer, lengthening the time they grow susceptible to falls, frailty and dysfunction from aging and cancer treatment, yet there are no evidence-based therapeutic treatment options for these men. This study addresses this significant barrier in clinical practice by proposing a safe, low- cost, and scalable exercise-based approach. If the aims are achieved, an effective solution to prevent falls and reduce frailty associated with ADT will be readily available to clinical and rehabilitative practice. Importantly, this study would address a NCI Cancer Moonshot℠ goal to reduce cancer's debilitating side effects.

Project Narrative/Relevance

Nearly half of the 2 million prostate cancer survivors (PCS) in the U.S. were prescribed androgen deprivation therapy (ADT) that increases their risk of falls, frailty and dysfunction. The proposed study determines whether exercise can reduce falls, frailty and dysfunction in PCS on ADT impacting both survival and independence.

Specific Aims

Two million prostate cancer (PC) survivors are alive in the U.S. and nearly half (45%) will receive androgen deprivation therapy (ADT) to reduce tumor androgen exposure and slow down cancer progression[1-3]. While beneficial for cancer survival, significant treatment-induced side effects from ADT may lead to serious health consequences including falls, frailty, and dysfunction that contribute to morbidity and mortality.[4-9]

New findings from our team and others show that the rate of falls, including those resulting in injury, are 2-3 times higher among PC survivors who receive ADT compared to men who never receive this treatment or to otherwise healthy, older men. ADT is associated with muscle loss, weakness, and unsteadiness[10,11] that may underlie falls as well as frailty[5,8,12] which in turn place men at greater risk of death[13], dysfunction and disability[14,15]. Despite the high risk associated with ADT, no fall or frailty prevention strategies, especially exercise-based modalities, have been developed in this clinical population[7,15] and clinical guidelines are bereft of recommendations to manage these life-threatening consequences of treatment.

Exercise has been shown to offer symptomatic relief from side effects of cancer treatment and improve quality of life among cancer survivors, but the potential benefits of exercise to prevent falls and frailty associated with ADT are unknown[16]. This creates a major treatment barrier in the field of oncology care for PC survivors as both the incidence of falls and prevalence of frailty increase as a result of conventional treatment with ADT. This dilemma makes the patient-oriented clinical treatment decisions difficult for providers and prolongs patient exposure to the harmful downstream consequences of ADT. Thus, there is an urgent clinical need to identify and test non-pharmacologic, community-based fall and frailty prevention programs for this at-risk patient population.

To meet this urgent need, we propose a trial to compare the efficacy of 2 well-established, yet distinct types of exercise, tai ji quan (also known as "tai chi") vs. strength training, to prevent falls and frailty in PC survivors on ADT. Tai ji quan and strength training each reduce falls in older adults without cancer by targeting different mechanisms: balance control or muscle strength, respectively[17]. Since the precise reasons that ADT increases falls are not yet known, a rigorous head-to-head comparison of two traditional types of exercise that are grounded in the evidence from older adults without cancer must also be evaluated as a fall prevention strategy for PC survivors. A combined tai ji quan + strength program is not well supported by the literature and could hamper efforts to meet our overall goal to swiftly implement effective and practical exercise interventions that maximize quality of life for cancer survivors.

Thus, we propose a 3-group, single-blind, parallel design randomized controlled trial in PC survivors treated with ADT (N=360) to compare: 1) tai ji quan to 2) strength training and each to 3) a placebo (stretching) control group. Our placebo group serves as an attention control and minimizes drop out to ensure the scientific rigor of this first-of-its kind efficacy trial and is also ethical since stretching exercise has other health benefits (i.e., better sleep) that are unrelated to our study outcomes. Men will participate in supervised programs three times per week for 6 months, with a 6-month follow-up after formal training stops. Our specific aims and hypotheses are:

Primary aim: To determine and compare the efficacy of tai ji quan training and strength training in reducing the incidence of falls in PC survivors on ADT.

Hypothesis: Tai ji quan and strength training groups will each reduce the incidence of falls compared to a control group. The relative efficacy of each type of training to reduce falls is not yet known.

Secondary aim*:* To determine and compare the efficacy of tai ji quan training and strength training to reduce frailty and dysfunction in PC survivors on ADT.

Hypothesis: Tai ji quan and strength training groups will each reduce the prevalence of frailty and improve physical function compared to a control group. The relative efficacy of each type of training to reduce frailty and improve physical function is not yet known.

Tertiary aim: To determine how well the benefits of Tai ji quan and strength interventions persist over a 6-month period.

Hypothesis: Group differences in the primary outcome of falls, and secondary outcomes of frailty and physical function will remain for 6 months after the end of the supervised interventions.

Exploratory Aim: To explore the patterns and predictors of types of men (including host and treatment factors) who benefit most from tai ji quan and strength training.

Falls are the leading cause of injury-related death in older adults and result in direct medical costs over $30 billion a year[18]. The number of PC survivors will double within 20 years and there are no evidence-based programs to prevent falls, frailty and dysfunction in this newly identified at-risk group. The proposed study will identify exercise programs that are clinically effective, safe, and scalable in PC survivors on ADT and thus, fill a significant gap in knowledge, yield novel insights into non-pharmacological approaches to care for PC survivors and make a rapid and durable impact on the field of rehabilitation and on cancer survivorship – aligning our study with the NCI Cancer Moonshot[SM] goal to accelerate research to minimize cancer's debilitating side effects.

Research Strategy

SIGNIFICANCE

Falls, frailty and dysfunction lead to costly injuries, loss of independence and early death among older persons. Falls are associated with 90% of hip, 50% of vertebral, and 100% of wrist fractures[19] and can cause traumatic brain injury, internal organ damage, hospitalization, disability and death[20]. One-third of those who fall will require assistance with activities of daily living and over half (58%) of those requiring help will need it for more than 6 months[21]. A single fall increases the risk of future falls[20] and recurrent falls increase the rates of nursing home admission and mortality and poor quality of life[22,23] and may be a symptom of frailty and poor physical and mental health status[24,25]. Frailty is an overall weakened physiological state usually associated with advanced age. Fried proposed a Frailty Phenotype model of 5 criteria to measure frailty (Fig. 1) and demonstrated that older adults with at least 3 of the 5 frailty criteria were at increased risk of hospitalization, development of disability, falls and early death[26-34].

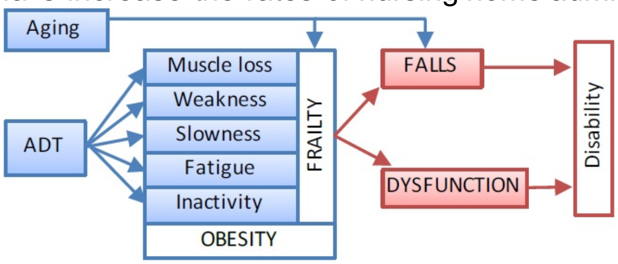


Fig. 1: Accelerated (obese) frailty from ADT and its consequences

Androgen deprivation therapy (ADT) for prostate cancer increases the risk of falls and frailty, even if treatment stops (Fig. 1). ADT is associated with muscle loss, weakness, fatigue, slowness, and inactivity[11,35,36] which are linked to falls in adults without cancer, and constitute the same elements of the Frailty Phenotype that predicts poor health outcomes[37]. Our data indicate that PC survivors whether treated currently or in the past with ADT, have a 5 to 6-times higher risk of recurrent falls and 9 to 10 times higher risk of frailty than men never on ADT[8]. Nearly half of all PC survivors are treated with ADT[3], placing millions of men at increased risk for these subsequently life-threatening side effects. <u>As the projected number of cancer survivors rises dramatically in a few decades, preventing excess falls, frailty, and dysfunction from ADT has become an urgent public health issue and a priority objective of the NCI Cancer Moonshot[SM]</u>.

PREMISE

Limitations and strengths of prior work: Recent evidence, including our data, indicates that PC survivors exposed to ADT are significantly more likely to report a history of falls, injurious falls, frailty and dysfunction compared to PC survivors never on ADT[4-9]. Currently, there is no non-pharmacologic and effective solution to the urgent problem of falls and frailty from ADT, leaving clinical practice bereft of knowledge to care for patients. However, studies, including published work from our group, on fall prevention in older adults suggest that exercise programs targeting gait, balance, strength, and functional tasks are most effective at reducing fall risk[38]. This proposed study builds on our years of solid work showing that tai ji quan reduces falls in older adults without cancer[39] or with Parkinson's disease[40] and that strength training reverses weakness and lessens disability in PC survivors on ADT[41]. <u>A major strength of the proposal is that both tai ji quan and strength training explicitly align with best practice recommendations for fall prevention</u> but the modalities are distinct, where strength training emphasizes muscle function and tai ji quan emphasizes balance[39,42,43]. Prior exercise research in PC survivors has not tested exercise modalities known to prevent falls in older adults with falls as a clinical endpoint[44], thus our direct comparison of strength training to tai ji quan in PC survivors on ADT is both scientifically rigorous and responds to an urgent clinical need. At this point, a combined tai ji quan + strength program is not supported by the literature nor even available in community settings, but based on findings from this study, could be considered in the future. We outline key details on scientific rigor in the *Approach* with attention to randomization, blinding, intervention fidelity, analysis, statistical power and sample size.

INNOVATION

Our head-to-head comparison of two exercise countermeasures to the newly uncovered threats of falls and frailty to PC survivors' is methodologically <u>robust</u>, cost and time effective, and the <u>first of its kind</u> to be conducted in any group of male cancer survivors. To our knowledge, this will be the <u>first study</u> to evaluate the impact of two distinct exercise interventions in PC survivors with either falls or frailty as intended clinical endpoints. We do not yet know whether ADT worsens age-related risk factors for falls and/or causes new problems, so well characterized approaches must be tested first. Including a follow-on period and identifying characteristics of responders to the interventions is also novel because we will be the first to evaluate outcomes that provide information about how to implement fall prevention programs in oncology practice.

We can also be the first to address a NIH charge to examine gender differences in clinical research (*NOT-OD-15-102*) in the context of falls among cancer survivors. Using data from the proposed trial in PC survivors and our recent trial in women cancer survivors (*R01CA163474)*[45] we could compare fall characteristics between men and women cancer survivors who receive distinctly different treatments for their cancers and determine whether or not they respond similarly to the same exercise approach to prevent falls.

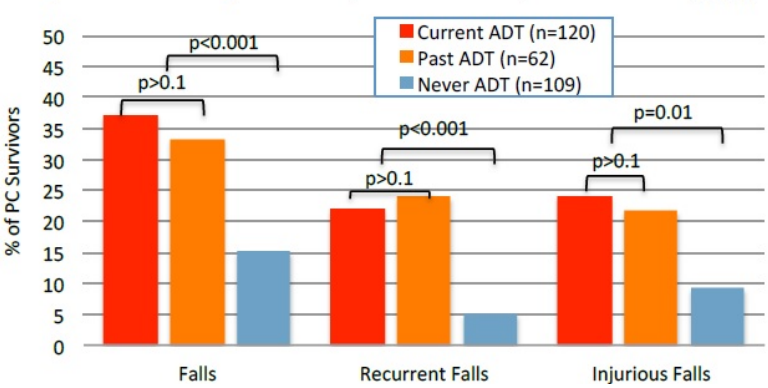
APPROACH

Justification and Feasibility for the Proposed Study

A well-designed, sufficiently powered trial that tests theoretically driven interventions has the best potential to provide clinical practice with evidence-based fall prevention strategies for PC survivors on ADT. The following section provides a succinct rationale for the proposed study based on preliminary data from our group and others and describes how our experienced team can successfully carry out the proposed work.

PC survivors prescribed ADT are more likely to fall and suffer a fall-related injury than men never on this treatment. Prostate cancer is the most common cancer in men and strikes predominantly in older age[46]. ADT is the principal systemic therapy in prostate cancer and is sole therapy or part of multi-agent therapy whenever systemic therapy is indicated. ADT serves as a component of therapy in many patients with newly diagnosed clinically localized intermediate or high-risk prostate cancer, in patients with a biochemical recurrence (e.g., rising prostate specific antigen (PSA) levels after surgery and/or radiation therapy), and in all patients with metastatic prostate cancer. Nearly half (45%) of all PC survivors will have received treatment with ADT to reduce tumor androgen exposure and limit cancer progression[1-3] but are then also exposed to the negative consequences of ADT for many years or the rest of their lives.

Fig 2. Fall rates among PC Survivors *(Winters-Stone et al, J Amer Geriatr Soc, 2017).*

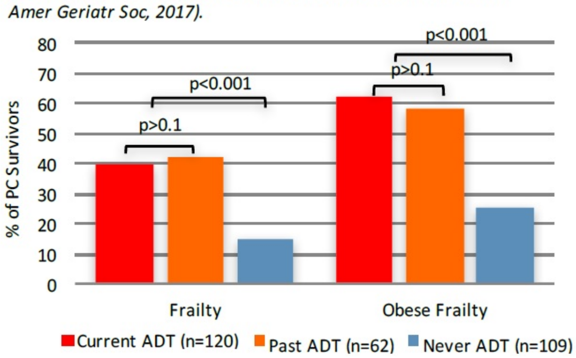


Recent clinical trials of new types of ADT drugs, e.g., enzalutamide, are the first to identify falls as a significant adverse event for men in the active treatment arm[6]. Across these trials, falls in enzalutamide treated men were more likely to result in an injury including fracture, joint injury and hematoma compared to men on placebo[4,6,7,47,48]. Notably, the studies identified increase fall risk with intensified ADT adding to evidence that falls are a consequence of hormonal therapy for prostate cancer. Though fall rates reported in these treatment trials appear low, this is likely due to the inconsistent tracking of falls in the EHR, in which 74% of falls may not be recorded when compared to patient fall diaries and/or recall[49]. We recently conducted a survey in a community-based sample of PC survivors (N=281) where we asked men about their physical health, including falls. We found that current or past ADT users were significantly more likely (p<0.001) to report a fall in the past year compared to PC survivors who had never taken ADT, even after adjusting for age and disease severity (Fig 2)[8]. Our findings are similar to the elevated fall rates reported recently by Wu and colleagues for Taiwanese PC survivors on ADT[9], which are 30%-50% higher among men on ADT compared to published fall rates in otherwise healthy older men[21,50-52]. Fall rates among current and past ADT users were nearly the same, suggesting little recovery from stopping treatment. A particularly striking finding was the high proportion of recurrent fallers (2+ falls) among men on ADT. Current and past ADT users were five times more likely to report recurrent falls than men not on ADT, who had recurrent fall rates comparable to the 6% reported for community-dwelling men[50]. Recurrent fallers are much more likely to experience a fall-related injury or death than one-time fallers. The number of injurious falls among men exposed to ADT in our sample was significantly higher compared to men never prescribed ADT (p=0.01), highlighting the urgency of addressing falls in ADT treated men.

Since falls are increased in PC survivors prescribed ADT compared to PC survivors on a placebo in an ADT treatment trial or to those who do not receive ADT as part of their treatment, side effects and symptoms associated with low testosterone must worsen established fall risk factors or cause new problems. In older adults, sarcopenia leads to muscle weakness that is linked to poor balance[53] and falls[54]. In PC survivors, ADT leads to muscle loss of 2% to 4% as soon as 6 months into treatment[36,55,56]. Using a test of lower body strength that is predictive of fall risk in older adults (e.g., timed chair stand[57]), we reported that PC survivors on ADT have chair stand times that are slow enough to place them at increased fall risk[41]. Instability is an independent risk factor for falls[58-60] and lower scores on balance tests in PC survivors on ADT[11], while likely associated with weakness, may also reflect an effect of ADT on stability that is independent of muscle loss[53]. For example, men on ADT are more likely to report symptoms of dizziness, vertigo and cognitive problems than men on placebo suggesting a potential effect of low testosterone on CNS functioning[6,61]. Reduced physical activity and fatigue are also common during ADT[28,29] and could further contribute to fall risk because each is associated with lower neuromuscular function. Clearly, there are many probable reasons why older PC survivors treated with ADT fall suggesting several targets for interventions – especially exercise, which we are well prepared to test.

ADT is also associated with frailty that is linked to injurious falls and dysfunction, further broadening the potential impact of this project. ADT may accelerate physical changes experienced by older adults that are conceptualized as frailty - a cycle of inactivity, slowing and weakening that cascades into falls, dysfunction and disability. The Frailty Phenotype is an approach to quantify frailty and is predictive of hospitalization, development of disability, and falls in older adults without cancer[27,62]. ADT is associated with the development of each frailty component, including loss of muscle mass,[10,36] weakness,[11] fatigue[63], slow walking speed[11,63] and inactivity[17,18] (Fig 1). <u>In our recent survey of PC survivors, current or past ADT users were three times more likely (p<0.01) to report being frail compared to men never on ADT (Fig 3)</u>[8]. Frailty is traditionally conceived as a wasting disorder, but since obesity is also linked to similar negative health outcomes similar to those seen with frailty, some have proposed an obese frailty phenotype, substituting obesity for low muscle mass[64]. Since ADT is also linked with excess fat gain[65], androgen deprived men may also be at risk for obese frailty. In our study, the odds of PC survivors having obese frailty were 19 times higher in ADT users compared to non-users. Men with any sign of frailty or obese frailty were 3-4 times more likely to report recurrent falls than men who weren't frail (p<0.01). Exercise could reduce frailty because it has been shown to improve individual frailty components in older adults without cancer[66,67]. <u>To date, there are no intervention trials in cancer survivors that have included either traditionally defined frailty or obese frailty as clinical endpoints</u>.

Fig 3. Frailty rates among PC Survivors *(Winters-Stone et al, J Amer Geriatr Soc, 2017).*



Currently, clinical practice has no effective solution to the rising problems of falls and frailty from ADT. Exercise may be the practical answer. (Aim 1 and 2): Current evidence for fall prevention in older adults, who fall for reasons related to old age, suggests exercise programs that target gait, balance, and strength, and functional tasks are most effective at reducing fall risk[38]. Both of our proposed interventions integrate these important training elements and align with best practice recommendations[68], but tai ji quan and strength training emphasize balance or strength, respectively. We do not know yet whether weakness or instability are primary drivers of ADT-related falls, but a head-to-head comparison of two distinct interventions will allow us to identify the mechanisms by which each intervention reduces falls. Findings from this trial will also further our understanding of whether and how two well-established exercise modalities could reduce frailty related to ADT, interrupting the downward trajectory toward disability and dependence and in turn, potentially delaying or avoiding hospitalization and premature death. The limited trials in PC survivors on ADT suggest that strength training could reverse weakness and lessen fatigue[69]; however, it is unclear whether changes in other frailty components may occur and whether changes in strength and fatigue are sufficient enough to shift frailty status. Tai ji quan consistently improves strength, gait and balance in older adults without cancer so this form of exercise could also lessen frailty[70,71] but, there are no studies of tai ji quan in PC survivors on ADT.

Strength training, when performed using functional lower body movements, builds muscle strength and challenges the neuromuscular mechanisms involved in maintaining upright balance. We conducted two controlled trials of functional strength training in PC survivors: 1) a 12-month RCT in PC survivors on ADT comparing strength training to a stretching control group (N=58) and 2) a 6-month RCT comparing partnered strength training in PC survivors and spouses to a usual care control group (N=64 couples). Retention in these training programs averaged 93% and adherence was 78%. Both trials used similar training programs and significantly increased maximal leg strength (17%-18%)[41,72]*. G*ains in muscle strength mediated training-related improvements physical function (p=0.016) and reductions in disability (p=0.018). Strength training improved chair stand time from a score that is indicative of increased fall risk (x score pre-intervention: 12.1 sec.) to a score below that threshold (x score post-intervention: 10.3 sec.)[41]. PC survivors who strength trained also reported engaging in significantly more physical activity and avoided gains in body fat compared to controls (P<0.01)[73]. These data show that strength training is safe and that men in our program get stronger, leaner, and become more active and independent– which also suggest that our strength training program might effectively reduce falls and frailty associated with ADT – hypotheses we will test in **Aims 1 and 2**. Our training program is based on a program we initially developed for women without cancer that has been successfully translated in community settings providing a model for future implementation in cancer survivors[74-76].

Tai ji quan is a series of individually choreographed movements linked in a continuous sequence, flowing slowly and smoothly from one movement to another[70] and is thus distinct from strength training that focuses on separate exercises for specific muscle groups. Used for centuries as a martial arts form, tai ji quan emphasizes 1) redistributing body weight to sufficiently overload and challenge postural control and 2) coordinating breathing and posture changes with mental concentration. We have conducted two controlled trials of tai ji quan exercise to reduce falls in older otherwise healthy community-dwelling adults and older adults with Parkinson's disease[39,40,77]. Compared to a stretching placebo group, six months of tai ji quan exercise significantly reduced falls in otherwise healthy adults (risk ratio=0.45, 95% CI: 0.30, 0.70) and in Parkinson's patients (Incidence Rate Ratio = 0.33; 95% CI, 0.16 to 0.71)40[40]. We also evaluated translation of the tai ji quan program into six community centers. The program had a 100% adoption rate and 87% reach into the target older adult population[78,79]. These data suggest that tai ji quan can reduce falls and is adaptable and efficacious in a clinical population and may be an effective strategy to prevent falls associated with ADT and could also reduce frailty by restoring mobility – hypotheses we will test in **Aims 1 and 2**. Though not current aim of the proposed trial, the effective translation of the program into the community setting demonstrates the potential translation of the program into clinical practice and community settings that support cancer survivors.

Understanding whether benefits from exercise persist long-term provides critical information for future implementation (Aims 3 and 4): To evaluate whether or not benefits from an intervention persist long term and how continued physical activity influences outcomes after a formal intervention stops, studies should include a follow-up measurement[80,81]. In our tai ji quan trial, balance improvements and reductions in falls from tai ji quan were sustained at 6 months after formal training stopped, possibly related to continued tai ji practice among 66% of participants[82]. In a 1-yr. follow-up study of a strength training trial we conducted in breast cancer survivors, women who continued to exercise maintained muscle strength better than women who stopped training[83]; but, we did not track falls in this study. Little is known about how long exercise benefits in PC survivors persist after a formal intervention stops nor about whether reductions in falls could be sustained without continued exercise. Careful monitoring of activity participation and measurement of physical performance after training stops allows the persistent effects of exercise training to be distinguished from maintenance effects of continued exercise participation. Our tertiary aim is designed to address whether and how benefits from exercise can be sustained long-term. Our project responds to an urgent research agenda in cancer survivorship calling for appropriately targeted, adaptive, effective, and sustainable exercise programs for all cancer survivors[81]. Thus, it is also important that we identify patterns and predictors of outcomes from the intervention so that we can use these data to revise the intervention and to properly define the target population. Our exploratory aim will use growth mixture modeling to explore the distinct types of men who benefit most from the interventions so that we can optimally translate effective programs for widespread dissemination and implementation.

The impact of the proposed study could be large because nearly half of all PCS may be treated with ADT[2] and median survival time following diagnosis for these older men is 16 years[46,84,85]. Our work provides a compelling scientific premise for the proposed trial by building on our prior work. We have the experience and expertise in working with the target cancer survivor population and we can recruit and implement our experimental and control exercise protocols. Our primary hypotheses are based on sound preliminary data indicating that falls and frailty are significantly elevated by exposure to ADT and that therapeutically-based fall prevention interventions have the potential for beneficial effects on the important endpoints of our investigation. The current trial focuses on PC survivors and we could later compare these data in relation to outcomes of our trial of exercise for prevention of falls associated with chemotherapy in women cancer survivors (R01CA163474). The results of our trial in women targets falls that are associated with chemotherapy that aims to kill rapidly growing cells throughout the body and thus cannot directly translate to androgen-deprived PC survivors. Since chemotherapy is cytotoxic it also kills cells in other organ systems producing a distinct fall risk factor profile, including central and peripheral nervous system toxicities that impact coordination and stability and hence, fall risk[86]. Chemotherapy is less commonly used in prostate cancer, thus our current trial provides little helpful information about which exercise type might best prevent falls associated with therapy that treats prostate cancer by suppressing androgens, i.e., ADT.

The proposed study addresses an unmet need by testing potentially low-cost, safe, scalable exercise-based solutions that could ultimately prevent or delay the falls and frailty linked to ADT. Each study intervention is based upon training programs for the general population of older adults created by members of our team and which have been implemented in community settings. Thus, our interventions could be readily translated into clinical practice using similar implementation methods (*see Li Biosketch and Gunter letter of support*). Identifying the type of exercise that best reduces frailty and dysfunction from ADT may also reduce disability risk, thereby prolonging independence and survival[87]. In 2011, the first generation of baby boomers turned 65 and the aging of this generation contributes to the projected doubling of cancer survivors by 2050[88]. Healthy People 2020 set a goal to reduce illness, disability and death caused by cancer[89] and the proposed study can make a significant contribution toward this goal.

Methods and Measures

Study Design and Rationale

To address study aims we propose the GET FIT Prostate trial (Group Exercise Training for Fall and Frailty prevention and functional Improvement from Treatment for Prostate cancer) - a single-blind, parallel group, randomized controlled trial comparing– 1) tai ji quan and 2) strength training against each other and vs. 3) a placebo control - over a 6-mos. supervised intervention (Aims 1 & 2) and 6-mos. follow-up (Aim 3). We considered expanding our current design by including a 4th group of combined tai ji quan + strength training, but felt little additional clinical insight would be gained by this approach. A combined condition raises concerns about dose variation because the volume of each strength and tai ji quan exercise need to be halved in order to maintain equal session length across groups. This untested training distribution creates a confounding effect of dose across groups and reduces the training stimulus from each exercise mode in a combined group by 50%, weakening the potential effectiveness of exercise training to prevent falls. A combined program might also hamper implementation since our interventions are based on training programs created by members of our team now implemented in community settings for older adults. These interventions are primed for translation to oncology care, whereas a combined program is not. For these reasons, it is logical to use the current experimental design and evaluate the results to determine whether a combined approach is warranted.

Setting

Trial activities will be coordinated centrally through Oregon Health & Science University (OHSU). Intervention will be offered at community sites serving different geographic regions of the Portland metro area and in other major population centers in the state of Oregon, including Salem, Eugene, and Bend. Since ADT is typically prescribed for 45% of PC survivors, we include regional sites to accrue a sample large enough to detect a change in our primary endpoint of falls. This sampling approach will also allow us to yield a more representative sample of PC survivors which will both enhance generalizability and increase translation of programs for future widespread dissemination. The PI and Co-I, Dr. Li, have conducted exercise trials using community facilities, including their current fall prevention trial in women and in Salem and Eugene. For Portland locations, testing will be conducted at OHSU and for regional exercise sites testing will occur at locations near the training facilities. We are able to conduct testing regionally because we are using electronic data capture systems, portable laboratory equipment for study measures and clinic-based assessments that all can be done in a non-laboratory setting. Oregon Research Institute, Salem Hospital and St. Charles Medical Center will serve as testing sites for the Eugene, Salem and Bend intervention sites, respectively (see **Letters of Support** and **Consortium**).

Sample

Eligibility. PC survivors treated with ADT and at risk for frailty comprise the target sample. We will not have lower or upper age limits since our data suggest falls associated with ADT are independent of age; however, we will stratify randomization to study group by age to ensure a between-group balance on this demographic variable. Men with chronic conditions that do not contraindicate participation in exercise are eligible, as are participants from the PI's prior trials. Specific inclusion and exclusion criteria are outlined in Table 1.

Table 1: Eligibility criteria plus rationale

Inclusion Criterion	Rationale
Diagnosed with histologically confirmed prostate cancer	We will not exclude men who have metastatic disease because the impact of exercise on falls may be most relevant for this group. Recent data, including ours, show that strength training is well tolerated and safe in men with metastatic disease.[41,90,91] In addition to stratifying on this criterion, we will repeat analyses considering these men separately to evaluate whether the efficacy of the interventions differ depending on disease severity.
1) currently on ADT for ≥6 months OR 2) not currently receiving ADT, but received ≥6-month course within the last 10 years	Based on our data, past ADT users are at similarly high risk of falls and frailty as men currently on ADT, thus we will enroll based on a history of ADT use. ADT is defined as either regular administration of an LHRH-receptor agonist + LHRH-receptor antagonist or orchiectomy. Current ADT users must have received or plan to receive ≥6 months of treatment. Past users of ADT must have received ADT for ≥ 6 months since the onset of significant muscle loss occurs after 6 months of ADT[56]. There are no published data on the time course of recovery of muscle mass after ADT cessation, but our data show that men receiving ADT within the last 10 years are at elevated fall risk.
Completed surgery, radiation or chemotherapy >3 mos.	Surgery and/or acute radiation or chemotherapy may reduce exercise tolerance, thereby lowering the dose of exercise received. Thus, we allow for 3 months of recovery to restore exercise capacity.
Meets criteria for having ≥1 component of traditional or obese frailty	Based on our preliminary data, we hypothesize that ADT leads to frailty which in turn places men at risk for falls and dysfunction; thus, we will target men who show signs of developing frailty as evidenced by having one or more of the frailty criteria (obesity or shrinking, slowness, weakness, inactivity, fatigue) as defined in the *Outcome Measures*
Exclusion Criterion	**Rationale**
Participating in strength training or tai chi 2+ times/wk	Tai ji quan or strength training may be most effective at preventing falls when men don't engage in these types of exercise. We will stratify randomization by total physical activity to avoid confounding when interpreting our outcomes.
Score <21 on MMSE[92]	Cognitive difficulties that may affect the ability to understand exercise instructions and participate safely.
Contraindication to exercise	Failure to meet the American College of Sports Medicine pre-participation screening criteria[93] and lack of physician clearance to participate in moderate intensity exercise training.

Power and Sample Size

We have powered the sample size based on our primary aim. In older adults, 20%-30% of community-dwelling elders are likely to fall within 1 year[20] and Li and others have reported a reduction in fall risk of 47% from 3[94] or 6[39] months of tai ji quan exercise. We are using an effect size for tai ji quan to power for both interventions because we have these data available from our prior work and effects sizes for strength training are similar to tai ji quan[95]. Our study will determine if strength training is as effective as tai ji quan. Using PASS 2008[96], based on a negative binomial regression model[97], at alpha = .05, the variance shared among the dummy vectors representing treatment (R^2=.25), and an estimate of the overdispersion parameter (Phi) of 2.5, a sample size of n=300 (n=100 per group) participants will provide 80% power to detect at least a 47% reduction in the fall incidence rate over six months by being in either of the 2 exercise groups versus control. To protect against an estimated attrition of ~17% during the intervention period, 120 participants will be randomized per group (total sample size: N=360). The attrition estimate is conservatively based on the highest attrition rate from our prior strength training trials in PC survivors (0% and 16% attrition in 6 and 12 month trials, respectively[41,72]). Though the total # of falls is the primary endpoint, the sample size of N=300 also provides sufficient power to detect differences between experimental and control groups on secondary outcomes of frailty and physical function. We and others' have data on the effect of exercise on individual components of frailty in PC survivors on ADT and self-report physical function. With a sample of N=100 per group we have a sufficient sample to detect a difference in 2.5% of lean body mass[98,99], a 4 sec. faster chair stand time[41,99], a 1.1 sec. faster gait speed[99], and a 9% difference in self-report physical function scores[41].

Recruitment
We have planned for a 40-month enrollment period (see **Timeline**) to recruit 360 men into the proposed study (9 participants/month). This enrollment rate is similar to that in our previous studies in PC survivors on ADT[90] and of women cancer survivors into a fall prevention study (N=466). Men will be enrolled into 8 waves of 45 men to maintain reasonable class sizes (15 men per class). Our primary recruitment strategy will be through the Oregon State Cancer Registry (OSCaR), which we have used for previous studies (see **Human Subjects**). Typically, 50%-80% of potential participants in our prior trials are respondents from OSCaR recruiting efforts. Current records indicate that there are 6112, 1217, 1120 and 909 living PCS who meet our age criteria in the cities of Portland, Salem, Eugene and Bend and who live within a 5-mile radius of each target community. Based on recent estimates of ADT use, we expect 45% of this pool to be current or past ADT users and of this group we expect ~25% to be ineligible because they have no sign of frailty and/or have a cognitive limitation or medical contraindications to exercise yielding 2062, 411, 378, and 308 men in each city, respectively (Total N=3159). In our prior studies, ~20% of eligible survivors enroll in exercise trials so using this estimate we could expect to enroll up to 630 men, far exceeding our target sample using the registry alone. Since PC disproportionately affects African American men, we also partner with the African American Health Coalition to recruit African American PC survivors into the trial (see **Letter of Support**). We will also recruit by clinician referral through OHSU Hospital (led by Co-Is Beer, Amling, and Hung), OHSU Community Oncology clinics that serve outer Portland area and distant sites including Salem Hospital and St. Charles Medical Center (see **Letters of Support**). Physicians have referred up to 15% of enrollees in past exercise studies. We will also use direct community recruitment using newspaper ads, radio, web and presentations at cancer organizations and conferences, which have yielded ~15%-20% of participants in past trials.

Randomization and Procedures
After phone screening, potentially eligible men will be scheduled for consent and baseline screening + possible further baseline testing in qualified men. To reduce bias we will to retain blinding of the research assistants who conduct the testing visits, by having the Project Director provide each participant with an envelope that contains his random group assignment *after* baseline testing is complete. Qualified men will be randomly assigned to 1 of 3 groups: 1) tai ji quan, 2) strength training or 3) stretching control. To avoid confounding and differential tolerance to exercise by ADT history, baseline frailty, and age, block randomization stratifying for timing of ADT (past or current (includes men with a prior hx of ADT use), baseline frailty (robust + prefrail vs. frail) and age (< vs. ≥75 years of age) will be done using EXCEL to generate random assignments from each block. We did not stratify by prior treatment with other modalities because we require sufficient recovery time prior to enrollment so that exercise tolerance is not affected. Assignment will be in random blocks of 6 to 9 within each wave (~42- 48 men) to facilitate even enrollment and to prevent the Project Director from predicting group assignment. Our unit of randomization is the individual participant (i.e., allocating each individual participant to intervention arms in turn using a randomly generated allocation sequence, see below) and past trials from our own group indicate no evidence of clustering effects (or location effects) due to community-based intervention implementation strategies. Further, while we run classes for each study arm at a single site, each exercise group comes at a different time reducing the threat of contamination across groups.

Retention of Participants and Adherence to Exercise Training
We have had excellent retention rates in prior exercise trials in PC survivors at 84%-100% for 1-year and 6 month randomized trials of strength training, respectively[72,90]. In our current GET FIT trial in women cancer

survivors, retention rates to the 6-month interventions average 94%. We have similarly strong adherence rates to supervised exercise classes, averaging 75%-81% for 6 and 12-month trials in PCS[72,90] and 75% in our current fall prevention study. These strong retention and adherence rates were achieved for exercise classes that were offered at a single hospital-based facility on set days and at set times, so we expect similar or better retention and adherence in the proposed trial. Retention and adherence strategies we have used before and will incorporate in the proposed study include the following: 1) free, close-in parking at exercise and testing locations, 2) $10 remuneration per testing visit to offset transportation costs. Participants are not specifically compensated for exercise participation, 3) allocation of every participant to an exercise program, including control group participants, and 4) offering exercise at a community location for easier travel to/from class, 5) encouragement of group cohesion by promoting social interactions among participants inside class, carpooling, buddy systems, etc. and, 6) regular review of exercise attendance logs by the Project Director with follow-up calls to participants who miss class for 2 weeks without prior notification.

Interventions

Participants in each study group will attend supervised 1-hr classes, 3 d/wk for 6 months. Certified exercise instructor(s) with 1+ years experience training older adults will be trained by the study team to lead classes. Class size will be limited to 15 participants per class so that enough individual attention is given to participants to ensure proper form and safety. To accommodate the small class size, we will have 3 sets of classes (1 per study program) per recruitment wave. For each wave, all 3 study programs will be held at each of the community sites (5 sites throughout the Portland metro area, 1 site each in Salem, Eugene, and Bend). Each intervention minimizes reliance on expensive equipment and emphasizes simple exercises based on functional movements. It is difficult to precisely equilibrate the total volume (intensity and duration) of exercise performed between experimental groups because the nature of each modality is so different. Both will be matched as closely as possible in progression from the low to high end of the range for moderate intensity over the first 3 months of the intervention. They will remain at a constant overload for the last half of the intervention. The initial volume of exercise progression across the study will follow progression outlines from our prior[41] and current work[45]. Instructors will work with the Project Director and Drs. Li and Winters-Stone on a monthly basis to refine individual participant efforts based on tolerance and to adjust training progression. The Project Director will meet weekly with instructors and communicate more frequently by phone and/or email.

<u>Strength Training:</u> Recommendations for improving muscle strength in older adults support the use of multiple- joint exercises for 1-3 sets per exercise at a weight that can be lifted 8–12 times[67]. Our strength training intervention uses <u>weighted vests</u> to apply resistance during lower body exercise - an innovative and safe method to maximize the effect of exercise on lower body musculoskeletal function**.** The strength training program used in this study is based on training programs that improved neuromuscular function (strength, gait, and balance) and reduced fall risk factors in our prior studies in women with[100,101] or without cancer[74,76] and in our recently completed trials in PC survivors on ADT[41,72,90]. Participants wear a weighted vest while performing exercises using <u>functional movement patterns that challenge balance</u> by using muscle groups and movement involved in everyday activities (chair rises, 90° squats, side-to-side squats, toe raises, lunges (forward, lateral, backward, walking), multi-directional step ups). The vest has multiple small pockets that each holds a ½-lb weight, so that the intensity of the exercise can be adjusted slowly. Pockets are distributed evenly around the torso in order to add resistance in an ergonomically efficient and safe way. Weighted vests allow men to perform functional exercises without safety risks related to balance disruption that can occur with handheld barbells and dumbbells.

<u>Tai ji quan:</u> The protocol contains an integrated exercise routine consisting of 8 purposeful movement forms and a set of therapeutic movements. This program was vigorously evaluated in 2 trials by Li et al[39,82], and subsequently in community settings[79] and with a clinical population[102]. Because the goal of the exercise is to assist patients in retaining postural control and stability, the protocol is specifically designed to challenge limits of stability and train gait patterns, as reflected in movements such as upright trunk positioning, displacement of body's center of mass over the weight-bearing leg, and step initiation, locomotion, and termination. The only resistance applied during tai ji quan will be the participant’s own body weight. The

early stage of the program (i.e., the first 12 weeks) emphasizes primarily learning and practicing single forms with multiple repetitions. The later stage focuses on performing individual forms to improve postural balance and movement locomotion and reviewing and practicing forms learned in previous sessions.

Stretching Control: Participants in the control group will attend a supervised flexibility program of the same total weekly duration as the experimental arms (e.g., 3, 60-min sessions per week). Control participants will perform a series of whole body stretching exercises, according to the ACSM guidelines for flexibility training[67], with a focus on developing and maintaining a healthy back. Stretching exercises will be performed in a seated or lying position that minimizes weight-bearing forces that might increase fitness or mobility. Many exercise trials in older adults, including ours, have used a stretching control condition and have shown no effect of this training on muscle strength[103]. Since the ACSM recommends “avoidance of inactivity” among cancer survivors to optimize quality of life[16] the increases in range of motion and sense of well-being from stretching may be viewed as a benefit for participants in this group. Men in this group will be asked to refrain from initiating new strength training or tai ji quan programs during their time in the study. Our prior exercise trial in PC survivors on ADT had a similar stretching control group and retention and compliance rates were similar as men in the strength training group[90]. In contrast, in our recent trial of partnered exercise in PC survivors and spouses, couples assigned to a usual care control group had greater attrition (25%) compared to the exercise group (0%); thus, the use of a placebo control group is an important feature of this study’s retention plan.

Quality control of intervention delivery

Delivery of 3 exercise programs at multiple sites introduces the potential for inconsistent delivery of study programs. We have taken the following steps to improve quality control over intervention delivery: 1) Exercise instructor training sessions for all instructors. A 2-day training workshop, led by Dr. Winters-Stone, Dr. Li, and the Project Director, will cover how to instruct each exercise protocol, training progression, safety considerations, and research conduct specific to the exercise program. Depending on the location of the exercise for a particular wave, training sessions will be held in Portland or at regional sites 2) Written guidelines will be provided for each instructor, in addition to hands-on training, that outlines the training protocols and overall study conduct to optimize delivery of the classes in a consistent fashion, 3) Rigorous oversight of class instruction. A primary role of the Project Director will be to oversee proper conduct of exercise classes, participant retention and exercise compliance. She will observe classes on a weekly basis over the first 3 months and monthly thereafter. She will work with instructors to minimize instructional differences across sites. Using this approach in our current fall prevention trial we have trained 7 instructors to deliver 15 study programs and have no differences across instructors on participant adherence or retention.

Participant safety during exercise

Any form of exercise carries a slight risk of injury. We have had no drop out from a study due to injury during training; however, as with any study in older adults, compliance has been affected by minor musculoskeletal complaints usually stemming from pre-existing orthopedic conditions. We take steps to reduce the risk of injury and other issues that might limit compliance, including: 1) required physician clearance for every enrolled participant and 2) monitoring and early care of musculoskeletal symptoms which may include slight adjustments in the training program (modifying intensity or select exercises) with a goal to maintain the overall training stimulus. Additional detail is provided in the **Human Subjects** section.

Six-month follow-up period

To evaluate the persistent effects of tai ji quan and strength training on falls and frailty, men will be followed for an additional 6 months after the 6-month supervised intervention stops. Men will continue to track their falls during the follow-up period using the same monthly reports employed in the intervention phase (see **Fall Surveillance** below). We recognize that men may wish to maintain their exercise habits after formal training stops and we will not discourage them from doing so. During the follow-up period, men will track their participation in home or community exercise programs in weekly logs that will be collected at the final testing appointment. Men will be called at 1 and 3 months during the follow-up period to provide early contact with them and to get verbal reports of their exercise logs. We will consider participation in community and/or home-based exercise in analysis for Aim 3 (see **Analysis Plan**) and will also repeat measures of frailty and function in order to better assess both the residual effects of the intervention programs among men who do not exercise in the follow-up period and the influence of continued exercise on outcomes after formal training stops.

Measures and Data Collection

Data on falls will be collected monthly while other measures will be collected at enrollment, 3- and 6-mos. (post- intervention), and 6 mos. after completion of the intervention (follow-up). A mid-study time point is included to detect early changes in frailty and function. Total time for performance testing and survey completion is ~2-2.5 hours. Men complete written surveys on a laptop computer at baseline and online for follow-up visits, unless they prefer to complete paper surveys (~5% of participants in our last intervention trial prefer paper over online). Staff reviews surveys for completeness and follows up with participants in person or by phone on missing data. In past trials we have had minimal participant complaints about the length of surveys, which are longer than in the proposed study, which we feel is due to the ease of completing surveys over time and at home when using an on-line system. As further evidence that our surveys rarely impose a significant burden on participants, the average completion rates for surveys, including monthly fall reports are 95%-98%.

Outcome Measures (Fig. 1)

Primary Endpoint: Falls

In this study, a fall is defined as unintentionally coming to rest on the ground or at some other lower level, not as a result of a major intrinsic event (e.g., stroke or syncope) or overwhelming hazard[22]. Falls over 6 months prior to baseline will be ascertained to characterize the sample and check for equality of randomization. Prospective assessment of falls will be done using the current gold standard of collecting monthly reports[104] returned by postal and/or electronic mail, an efficient (1-2 minute completion time) and effective method used by our team and others[39,86,105,106]. In two prior studies we obtained 98% of monthly fall reports over 6 months[45,86]. Participants will be provided with a monthly falls calendar to record falls when they occur, in order to reduce issues of recall and false negatives. Each participant that records a fall will be phoned to confirm that each fall meets the standard definition in order to reduce the risk of false positives, and to obtain information about the fall (e.g., how it occurred) and any resultant injury. An "injurious" fall is one that results in fractures, head injuries, sprains, bruises, scrapes, or serious joint injuries, or where the participant seeks medical care[22]. Of primary interest in the proposed study is the # of falls, with the # of injurious falls and medical care resulting from a fall being used for descriptive purposes of the study population.

Secondary Endpoint: Frailty will be measured using the components of the Frailty Phenotype[37]. The original 5 criteria of the phenotype (shrinking, exhaustion, low activity, slowness, and weakness) were limited to the measures available in the Cardiovascular Health Study[37]. The phenotype can now be measured more accurately with objective measures (e.g., lean body mass rather than self-report weight loss[107]). In this study, we will assess each frailty component using measures that will most accurately capture frailty criteria in the PC survivor population and where cutoff scores can be appropriately determined. A total frailty score will be calculated in the same manner as that of Fried: $\geq$3 criteria = frail; 1-2 criteria = prefrail; 0 criteria = robust. Since each variable is a continuous measure we will examine changes in each individual frailty component to determine how each intervention may shift frailty among our sample. Criteria are measured as follows:

1. *Shrinking*: Since weight gain is a common side effect of ADT capturing the loss of lean mass that the "shrinking" component of the Frailty Phenotype was intended to capture may be difficult by tracking weight loss alone. Rather, we will measure lean mass by bioelectric impedance analysis (BIA; Imp SFB7, ImpediMed, Inc., Australia). BIA has been recommended as a technique to measure sarcopenia in the elderly[108] and is as accurate and reliable[109,110] yet more practical than other types of body composition techniques such as DXA or skinfolds because it is portable and does not rely on extensive technician training and experience[111]. Cutoffs for sarcopenia have been established using BIA to determine a skeletal muscle index (SMI) calculated as BIA-predicted skeletal muscle mass adjusted by height-squared. We will use a cutoff score for moderate sarcopenia in men of $\leq$10.75 kg/m^2 based on criteria established using BIA measures from men aged 60+ in the NHANES II database[112]. Since obese, rather than traditionally defined frailty is an emerging concept and our data suggest obese frailty increases risk for falls even more than traditional frailty, we will calculate obesity frailty by

substituting BMI>30kg/m^2 for SMI and repeating analyses.

2. *Exhaustion*: We will use the self-reported score on SF-36 Vitality Scale which we have used to characterize exhaustion for frailty in cancer survivors[113] and which has established reliability[114], has been validated in cancer survivors as a fatigue measure[115] and has shown sensitivity to change in response to exercise in adult, older adult and clinical populations, including cancer[116-118]. We will use cutpoints of scores of less than 50.00 (normed) for PC survivors aged 50-64 years or scores less than 40.00 (normed) for PC survivors aged 65+ years. Cutpoints are lowest quartile of scale in general U.S. population[114]. Though not used in frailty assessment, but used to evaluate reductions in cancer-related fatigue from exercise[119], we can also consider changes in the fatigue subscale of the QLQC30 which could be more sensitive in PC survivors (see below).
3. *Low Activity*: Low activity will be measured by physical activity-related energy expenditure (METS), calculated from self-report physical activity. We will use Fried's original cutpoints for "low activity": <383 kcals per week spent in moderate-vigorous intensity activity measured by the 41-item Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire.[120] CHAMPS is a common and highly reliable[121] measure of physical activity in older adults, including our studies in cancer survivors[45,100,122,123]. We considered using accelerometry to track activity levels but this technique introduces considerable expense and personnel resources. Given our available resources we will be able to conduct a sub-study on 2 study waves (~100 men) to compare objective to self-report methods for tracking activity change over time.
4. *Slowness*: Walking speed will be measured as the fastest time of two 15' walks at a usual pace. Walks will be performed on an electronic gait mat to ensure accurate timing. We will use Fried's original cutpoints for "slowness" in older men of time $\geq$7 seconds for height $\geq$173 cm or time $\geq$6 seconds for height <173 cm. Test-retest correlations for average walk speed are strong: 0.72-0.93[124].
5. *Weakness*: In contrast to grip strength used by Fried in her original phenotype, lower body strength is more closely linked to falls, mobility, and dysfunction and can be easily obtained using well established timed chair stand test (seconds required to rise from chair 5 times)[125,126]. Chair stand time $\geq$12 seconds has been shown to predict a 2.4 increased risk of falls in older adults and we will apply this cutoff for "weakness"[57].

<u>Secondary Endpoint: Physical Function</u>: Physical function will be measured objectively (mobility, balance) and subjectively (perceived function by self-report).

Functional Mobility: The <u>Timed Up and Go (TUG) test</u> is a reliable[127] and widely accepted clinical measure of mobility that evaluates the time that it takes a person to rise from a chair, walk 3 m, turn around a cone and return and sit in the chair[128]. Slower TUG times are associated with an increased risk of falls[129] and disability[126]. Dr. Horak, a Co-Investigator, developed an instrumented version of the TUG test (iTUG; see **Equipment**) that incorporates wearable sensors to detect changes in mobility that are not apparent from the stopwatch TUG score.[130] The iTUG system can electronically capture individual elements of the TUG test at a very sensitive level to detect small changes over time and decrements in higher functioning patients that might be missed by a stopwatch time. TUG time is our main outcome, but we will examine additional information provided by the iTUG (e.g., segment time, step #) to understand which components of mobility ADT affects.

Functional Balance: <u>Postural sway</u> is a reliable[131] measure of how well a person can maintain their equilibrium during quiet standing. Increased sway indicates poor balance control and is associated with falls[128]. We will conduct a standard 30-second postural sway test to measure the sway area (m^2/s^3) and amount (m/s^2) and velocity (m/s) of sway during quiet standing with feet together and eyes closed using lightweight, inertial wireless sensors worn on the trunk[131]. Lateral sway velocity is the outcome of interest because it is a strong predictor of falls in older adults[132] and may detect changes in balance associated with cancer treatment[133].

Perceived Physical Function will be measured by self-report using the physical function subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; version 3, App. I), a cancer-specific measure and common in studies of PC survivors, including ours[41,134].

Descriptive and Process Measures

<u>Demographic variables</u> and cancer history and treatments will be measured at baseline by an in-house questionnaire. Measures that account for disease extent (presence or absence of metastatic disease), type of ADT (intermittent vs. continuous; use of next generation high potency agents) will be collected. Updated information will be collected at subsequent visits. Measures of weight and height will also be made.

Presence of chronic medical conditions that affect physical functioning will be measured by the Functional Comorbidity Index[135]. We have used the FCI before to describe the population and inform the exercise instructor about medical conditions that might affect physical ability. We will add two additional conditions to the list of 18 to capture vestibular problems and/or peripheral neuropathy that might affect exercise ability and predispose men to fall risk in excess of ADT so that we can control for this in analyses.

Exercise outside the exercise intervention could affect the fall and function outcomes in our study. In addition to using CHAMPS to measure physical activity for the frailty criterion and exercise participation during follow-up, we will also look at individual items to see whether participants significantly increase participation in other types of exercise in addition to their assigned study program.

Adherence. Adherence (% of prescribed sessions completed) will be tracked from attendance logs recorded by the exercise instructor. Adherence data will be used to describe the dose of exercise received by participants. It is expected that men will occasionally miss classes due to travel, illness, or other reasons, thus we must get an accurate estimate of received (exercise) dose in order to generalize our findings.

Acceptability of intervention and self-management of ADT side effects is useful information to guide future dissemination and implementation efforts. We will survey PC survivor's knowledge of and intent to manage ADT side effects[136] at baseline and assess satisfaction with each exercise program post-intervention[137].

Additional Measures of Interest

Fear of falling may impact a participant's confidence that he can safely engage in a study exercise program. This factor may also change across the intervention. Though this is not a major outcome in the proposed study, we feel it may provide important information about the population and intervention. To assess fear of falling we will use the Survey of Activities and Fear of Falling in the Elderly (SAFFE),[138] that has 11 items representing activities of daily living associated with fear of falling, mobility, and social activities. The SAFFE score is the average of item responses, with higher scores indicating greater fear of falling.

Perceived disability. Though not a specified endpoint for this trial disability and dependence upon others for daily tasks may result from frailty and dysfunction. If either experimental intervention reduces frailty and improves function it may also lower the risk for disability, so that PC survivors on ADT can remain more independent. We will measure perceived disability using the 16-item disability component of the Late-Life Function and Disability Instrument[139,140]. Scores range from 0-100, with higher scores indicating less disability.

Data Analysis Plan

All analyses will retain each participant in the group he was randomly assigned regardless of missing data or drop out status (i.e., intention to treat). We will track medical treatment changes and disease progression during the study to describe the sample or justify why participants exited the study. In the unlikely event of a large subgroup, these data could be used for exploratory subgroup analysis to suggest directions for future research. Age, timing of ADT (current vs. past), fall history at enrollment and baseline frailty will be considered as possible covariates in all analyses. Age and timing of ADT (past vs current) are included since they may affect exercise tolerance and/or responsiveness to exercise training; fall history is included because we want to examine the efficacy of the interventions to reduce falls in men with a fall history and prevent falls among men who have not recently fallen. Analyses will be conducted in Stata, R, and/or Mplus statistical software packages. Full information maximum likelihood estimation (FIMLE) will be used to estimate the models, as appropriate, because it is less biased and more efficient than other techniques for handling missing or incomplete data[141].

Aim 1: Compare the relative efficacy of tai ji quan and strength training to prevent falls*:* We will determine the efficacy of tai ji quan and strength training by comparing each of them to the control condition while adjusting for important covariates using negative binomial regression models which will analyze total number of falls per participant that occur from baseline to 6 months. A negative binomial regression was chosen over a Poisson regression for modeling the count data because of the overdispersion that is common with actual research data.[96,142] Intervention type will be entered into the model as 2 dummy variables, with the reference group being the control group. This will allow a comparison of the each of the intervention groups against control. *A second* model will be run with strength training as the reference category to compare the intervention groups to each other. In additional to standard ITT analysis, the impact of participants who drop out of the study on the falls outcome will be examined in a secondary data analysis. A significant incidence rate ratio (IRR) less than 1.0 for the dummy vector representing tai ji quan and/or strength training would provide support for the hypothesis that the respective intervention reduced the rate of falls compared to the control group.

Aim 2: To determine and compare the efficacy of tai ji quan training and strength training to reduce frailty and dysfunction*:* Each participant will be classified as frail, pre-frail or robust based on his total frailty score (see **Measures**). We hypothesize that the number of men classified as frail or pre-frail will decrease over the course of the study in the tai ji quan and strength training groups compared to control. Formal tests of frailty hypotheses will be conducted in a generalized mixed effects modeling framework as implemented in the R statistical computing environment.[143] Frailty category will be the multinomial dependent variable (with "robust" as the reference group) and study time point (0, 3 and 6 mos.), group (control as the reference group) and the group x time interactions will serve as predictors.[144] We will also run a second model with strength training as the group reference category to compare the two experimental groups to each other. Significant group x time interactions will indicate that the distribution of frailty between the groups (e.g., tai ji quan vs. control) is different across time. For significant interactions, additional contrasts testing for frailty differences will be examined to describe the pattern of change across time. Group differences across time in the continuous physical function and individual frailty measures will be tested in a linear mixed effects modeling framework[143] to estimate the trajectory of change in each dependent variable across time for each individual in each group, and then comparing the average trajectories across groups. The primary effect of interest is a cross-level interaction. Specific hypotheses about treatment group effects will be specified by adding dummy variables and hypotheses will be tested through group x time interactions (as above). We will also evaluate the practical significance of the interventions by summarizing results with respect to effect size.

Aim 3: Determine how well the benefits of each intervention persist after structured training stops: We will use the same modeling strategies described above for each outcome (i.e., negative binomial regression, multinomial/linear mixed effects models). However, we will perform the analyses piecewise, with a change point occurring at 6 months. Of particular interest is whether the observed effects for the treatment groups differ or remain the same after the change point. In addition, we will examine whether participation in exercise following the end of the intervention moderates the persistent effect of the intervention on study endpoints. We will categorize the type of exercise participants engaged in (i.e., walking/aerobic, strength training, tai ji quan, stretching) for at least 50% of the follow-up period. These categories will then be dummy coded and entered into the analyses outlined above, along with the product of these dummy vectors and treatment to represent the interaction. A significant coefficient for the product term would indicate that continued exercise modifies the effect of the intervention on falls, frailty, or physical function. This analysis will allow us to determine whether continued participation in an exercise program maintained improvements for an intervention group or a lack of participation caused a loss of improvements in an intervention group, and whether control participants who begin programs similar to the intervention programs improve in outcomes.

Exploratory Aim: Determine patterns and predictors of types of men who benefit the most. We will use a growth mixture modeling (GMM) approach using Mplus to explore there are distinct types of men (based on age, baseline frailty, cancer stage, ADT duration and timing, other treatments, etc.) who benefit most from the intervention(s). GMM is a type of clustering technique that can simultaneously handle longitudinal data and multiple measures to identify distinct subgroups of patients who have different responses to an intervention. For longitudinal outcomes (e.g., Aim 2), we will employ GMM to identify distinct patterns of change in subpopulations with varying response (growth) trajectories and unique variances reflecting homogenous within-trajectory growth. Patients will be assigned to the "most likely class" or pattern of change over time (e.g., men who improve most from an intervention) and follow-up analyses (e.g., multinomial regression) will be conducted to describe the demographic and clinical characteristics of patients who are classified into different subgroups.

Additional Analyses

Injurious falls: Though the proposed study is not powered to examine reductions in injurious falls from the intervention, we will conduct an additional analysis on this important outcome. An injurious fall is one that results in fractures, head injuries, sprains, or serious joint injuries, or in a participant seeking outside medical attention. We will conduct this analysis among the subsample that had at least 1 fall using logistic regression.

Mechanisms of intervention effects on falls: We can use strength and stability measures to identify the mechanism(s) by which each exercise approach may reduce falls, strengthening support for exercise as a fall prevention strategy. We will test 3 mediators, muscle strength (chair stand time) and stability (walk speed and postural sway) as possible mediators because both measures may be affected by each intervention and each possible mediator is a major risk factor for falls. Mediation of the intervention effect by changes in performance measures will be analyzed using Mplus. A manifest model will be tested with the dummy vectors representing tai ji quan and strength training as exogenous variables, change in strength and as endogenous variables (mediators), and number of falls over the intervention period as an endogenous variable (outcome). Significant indirect parameter estimates based on standard errors using the multivariate delta method from the treatment variables to number of falls through changes in strength and stability would provide support for mediation.

Potential moderators of sustained exercise after the intervention: Linear and logistic regression models will be used to explore different predictors (e.g., age, comorbidities, timing of ADT, etc.) of adherence to exercise after structured training stops.

Project Timetable

	Y1				Y2				Y3				Y4				Y5			
Development	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Finalize protocols, databases	X	X																		
Hire/train research assistants			X															X		
Hire/train exercise instructors			X			X				X				X						
Recruitment & initial testing																				
Recruit, enroll, baseline visit			W1		W2r	W3			W4r	W5		W6	W7	W8r						
Intervention and evaluation																				
Start 6-month intervention				W1		W2r	W3			W4r	W5		W6	W7	W8r					
Mid- & post-intervention visits				X	X	X	X	X	X	X	X		X	X	X	X				
6-month follow up visit						W1		W2r	W3			W4r	W5			W6	W7	W8r		
Data analysis & publication																				
Data cleaning and analysis							X	X	X	X	X	X	X	X	X	X	X	X	X	
Present and publish results																			X	X

Participants are recruited in 8 waves (W1, W2, …); "r" after wave abbreviation indicates a regional exercise site; Quarters are approximate time points

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