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## 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<sup>1-3</sup>. 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.<sup>4-9</sup>

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<sup>10,11</sup> that may underlie falls as well as frailty<sup>5,8,12</sup> which in turn place men at greater risk of death<sup>13</sup>, dysfunction and disability<sup>14,15</sup>. Despite the high risk associated with ADT, no fall or frailty prevention strategies, especially exercise-based modalities, have been developed in this clinical population<sup>7,15</sup> 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<sup>16</sup>. 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<sup>17</sup>. 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<sup>18</sup>. 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<sup>SM</sup> goal to accelerate research to minimize cancer’s debilitating side effects.



























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			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
<b>Development</b>																				
Finalize protocols, databases	X	X																		
Hire/train research assistants			X															X		
Hire/train exercise instructors			X		X				X				X							
<b>Recruitment &amp; initial testing</b>																				
Recruit, enroll, baseline visit			W1		W2r	W3			W4r	W5		W6	W7	W8r						
<b>Intervention and evaluation</b>																				
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	X	X				
6-month follow up visit					W1		W2r	W3				W4r	W5			W6	W7	W8r		
<b>Data analysis &amp; publication</b>																				
Data cleaning and analysis						X	X	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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