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Randomized Trial Evaluating the Role of Weight Loss in Overweight and Obese Men with Early Stage Prostate Cancer on Active Surveillance: Rationale and Design of the Prostate Cancer Active Lifestyle Study (PALS)

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Abstract

Active surveillance (AS) is increasingly used to monitor patients with low-risk prostate cancer; however, approximately 50% of AS patients experience disease reclassification requiring definitive treatment and little is known about patient characteristics that modify the risk of reclassification. Obesity may be one of the major contributing factors.

The Prostate Cancer Active Lifestyle Study (PALS) is a clinical trial evaluating the impact of weight loss among overweight/obese (Body Mass Index (BMI) > 25 kg/m^2) men with clinically localized prostate cancer on AS. Two hundred participants will be randomized to either the PALS intervention, a 6-month structured diet and exercise program adapted from the Diabetes Prevention Program followed by 6 months of maintenance, or control (general diet and physical activity guidelines delivered in a single session). The PALS intervention involves one-on-one instruction with a registered dietitian and exercise physiologist to achieve the study goal of loss of 7% of baseline weight. Participation is coordinated so that the 6-month time point coincides with the participants' standard-of-care AS prostate biopsy. Primary outcomes will evaluate the intervention effects on circulating and tissue markers of glucose and insulin regulation, health-related quality of life and pathologic upgrading on follow-up prostate biopsies. Additional analyses will determine whether changes in weight and glucose regulation can be sustained for 6 months after the end of instruction. Findings from this trial may have wide reaching implications for men diagnosed with clinically-localized prostate cancer by providing an active lifestyle-based approach to improve prostate cancer patient outcomes.

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Keywords

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INTRODUCTION

Prostate cancer (PCa) is the most common cancer diagnosis among men, with over 164,000 men diagnosed in the United States in 2017.(1) Due to widespread prostate-specific antigen (PSA) screening, approximately 50% of men diagnosed with PCa present with clinically low-risk disease.(1) Increasingly, men with low-risk PCa are managed with active surveillance (AS), where patients are monitored via PSA blood tests, physical exams and surveillance biopsies with definitive treatment undertaken if evidence of disease reclassification (i.e. increase in PCa volume or aggressiveness).(2) Considering the significant quality of life and functional side effects associated with PCa interventions such as surgery and radiation, the goal of AS is to minimize treatment- related side effects in those least likely to experience PCa-related morbidity and mortality. Despite their initial lower risk status, roughly 50% of men on AS will experience disease reclassification requiring active treatment(3).

It is well established that being overweight/obese and weight gain are risk factors for poor PCa outcomes.(4) Epidemiologic studies have consistently associated obesity with an increased risk of PCa progression and PCa-specific mortality(5–12) and an increased risk of recurrence after definitive treatment(13). Increasing evidence also identifies being overweight/obese as a predictor of poorer prognosis for men on AS. Several studies have suggested that overweight/obese men with low-risk PCa who are otherwise good candidates for AS but chose instead to undergo immediate radical prostatectomy were more likely to experience upstaging and upgrading than normal weight men.(10, 14–16) Furthermore, among men on AS, obese men have a greater than 2-fold increased risk of pathologic progression compared with normal weight men(17, 18), suggesting that obesity may be a modifiable risk factor for PCa progression.

The causal mechanisms underlying the obesity-PCa progression relationship are unclear; though obesity-induced metabolic changes, including impaired glucose regulation, may be responsible.(19–21) Several lines of evidence suggest the importance of glucose regulation in PCa progression, including animal models of hyperinsulinemia and high glucose feeding(22, 23), observational human studies showing hyperglycemia and hyperinsulinemia are associated with worse PCa outcomes(19, 20, 24, 25), and tissue level evidence of overexpression of the insulin receptor on PCa cells(26, 27). These data support the notion that improved glucose regulation in men with PCa may reduce the risk of PCa progression and its associated morbidity and mortality.

To test the potential impact of weight loss and improved glucose regulation on men with low-risk, localized PCa, we developed the Prostate Cancer Active Lifestyle Study (PALS). PALS is a phase III, randomized clinical trial evaluating the effects of a diet and exercise program to promote weight loss among overweight/obese men (body mass index (BMI) ≥25

kg/m^2) on AS. This novel trial will enhance our understanding of the biologic mechanisms linking obesity and PCa outcomes. The overall goal is to test the effect of a weight loss intervention on serum and tissue markers associated with PCa mortality. Findings from this study may have wide-reaching implications for improving both the overall and disease-specific outcomes in men diagnosed with clinically localized PCa, and provide an alternative, non-invasive approach for men with low-risk PCa on AS.

2. Research Design and Methods

Overview

PALS is a randomized, phase III clinical trial of a diet and exercise lifestyle intervention vs general healthy lifestyle recommendations among men with low-risk PCa on AS. The trial is funded by the National Cancer Institute and is registered at clinicaltrials.gov (NCT02454517). As a clinical trial, a data safety monitoring board (DSMB) consisting of clinical, statistical and epidemiologic experts, has been selected to oversee trial progress. The DSMB meets annually to assess the safety and efficacy of the intervention. The study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board and the Veteran's Administration Puget Sound Health Care System Institutional Review Board and all participants are asked to provide written informed consent for participation.

Eligibility and exclusion criteria

Eligible men have histologically-confirmed, clinically-localized low or low-intermediate risk adenocarcinoma of the prostate (defined as stage T1c/T2a, Gleason grade group 1 (3+3) or 2 (3+4), and PSA < 20 ng/ml) and have elected AS as primary treatment. Additionally, eligible patients must be overweight or obese (defined as BMI ≥ 25 kg/m^2), able to make the required dietary changes, and physically able to undertake an exercise program.

Exclusion criteria include enrollment in a structured weight loss program (e.g. Weight Watchers® or Jenny Craig®) within the previous 12 months, planned weight loss surgery, use of appetite suppressants, use of androgen deprivation therapy within the previous 12 months, insulin dependent diabetes mellitus, use of metformin, and alcohol or narcotics abuse. Additional exclusion criteria limit participation to men without significant cardiovascular disease that would preclude participation in an exercise program (defined as a history of myocardial infarction or stroke within the previous 6 months, pulmonary edema, myocarditis, pericarditis, unstable angina, pulmonary embolism or deep vein thrombosis, uncontrolled hypertension (systolic and diastolic blood pressure above 200 and 110, respectively), uncontrolled arrhythmia, or heart failure).

Recruitment

Potential participants are identified in two different ways. (1) At collaborating University of Washington clinical sites (University of Washington Medical Center (UWMC), Valley Medical Center and the Seattle Puget Sound Veterans Affairs Heath Care System), clinic staff pre-screen urology clinic patients to determine medical eligibility. Eligible patients are approached during their clinic visit to introduce the study. Interested men are contacted by study staff to finalize recruitment into the study. (2) The Cancer Surveillance System (CSS)

of Western Washington Surveillance Epidemiology and End Results (SEER) program, which collects population-based data on cancer incidence and survival in 13 counties in western Washington State, is also used to identify potentially eligible men who have newly-diagnosed PCa and meet the clinical eligibility criteria (grade group 1 or 2, clinical T-stage≤T2a, PSA<20 ng/ml). Men identified via CSS are sent a prior notification mailing that introduces PALS, states the mission and purpose of the CSS, to informs men how to "opt out" of being contacted by study staff. Men who have not opted out within 10 days are then called by study staff and approached about participating in PALS.

PALS intervention

The PALS intervention is based on the Diabetes Prevention Program (DPP), an evidence-based lifestyle intervention that combines structured curriculum on nutrition and physical activity with goal-based behavior instruction to achieve weight loss(28), with modifications to condense the delivery of the intervention and tailor the materials to older men. The overall PALS lifestyle intervention goal is a 7% reduction in baseline. Weight loss of 7% has been shown to significantly decrease fasting glucose levels(29), reduce the risk of incident diabetes mellitus(29)(28), was sustainable over 10 years(30), and reduces the risk of cardiovascular disease(31). Weight loss is to be met via a reduction in caloric intake and an increase in physical activity. Participants are provided an individualized calorie goal, representing a reduction in total energy of 500 to 1000 calories/day, depending on the participants' starting body weight. The physical activity goal for all participants is 150 minutes per week of moderate to vigorous exercise. To help participants achieve moderate to vigorous intensity during exercise, they are provided an individualized target heart rate range, which is equivalent to 70 to 85% of their peak heart rate reached during the baseline submaximal exercise test.

The PALS intervention is delivered via a registered dietitian, who has received formal DPP training, and an exercise physiologist. The instructional materials are covered in a total of 11 sessions (Table 1). During the first 6-months of the trial participants meet one-on-one with the dietitian weekly for the first 4 weeks, then once every other week for 8 weeks, then once a month for the remaining 3 months. Concurrent with the first two dietitian sessions, participants also complete one-on-one instruction with the exercise physiologist. Thereafter, participants are invited to complete weekly supervised exercise sessions (overseen by the exercise physiologist, but no one-on-one instruction is provided). Nutrition sessions last between 30 and 60 minutes and one-on-one exercise instruction sessions lasts 60 minutes, both of which follow a prespecified curriculum (Table 1). At the beginning of each session, participants are weighed, and their progress reviewed by the dietitian and exercise physiologist. During each session the PALS intervention materials are reviewed, and individualized information is provided to help participants achieve study goals and stay motivated. Participants are asked to record their daily dietary intake and physical activity daily using a "Keeping Track™" booklet.

To support their progress in the intervention, participants receive a PALS binder containing the diet and exercise curriculum. Men are provided a 'punch card' to promote attendance of weekly supervised exercise sessions (months 1 – 6) at the Fred Hutchinson Cancer Research

Center Prevention Clinic's exercise facility. Participants also receive several tools to assist in achieving the PALS weight loss and physical activity goals, including a heart rate monitor (Polar Ft1®), Calorie King® book to tally the calorie and fat content of foods they eat, and measuring cups and spoons. In addition to the standardized curriculum, a "toolbox" approach is used to tailor the intervention to optimize behavior change for individual participants.(32) Examples of some toolbox topics include exercising in inclement weather, wearing appropriate footwear, healthy snack choices, making healthier food choices, and choosing healthier fats.

General healthy lifestyle (control)

Men assigned to the control arm receive general instruction on a healthy lifestyle during the baseline visit. This instruction reviews the United States Dietary and Physical Activity Guidelines for Americans(33, 34) and includes discussion of the health benefits of weight loss. At the end of their participation in the 12-month study, men assigned to the control arm will receive the PALS intervention materials as a notebook but they will not receive a full delayed intervention with specific, individual instructional sessions.

Data Collection

Both intervention and control participants complete 4 clinic visits over the 12- month study, which are scheduled at baseline, 3, 6 and 12 months. Participation in the study is coordinated so that the 6-month PALS clinic visit coincides with the participants' planned AS prostate biopsy (Figure 1). Pre-intervention biopsy tissue will be acquired from stored pathologic specimens from the most recent pre-study biopsy. Data and specimens collected at all clinic visits include anthropometric measures, fasting blood, and self-administered questionnaires on quality of life (Table 2). A 3-day food record and sub-maximal exercise tests are completed at baseline and 6 months, and a dual X- ray absorptiometry scan (DXA) is completed at baseline and 12 months. Participants who have abnormal results on the sub-maximal exercise test are required to receive clearance to participate from their physician. All intervention instruction and clinic visits are conducted in the Prevention Center at the Fred Hutchinson Cancer Research Center in Seattle, WA.

Outcomes

The primary outcomes of PALS include changes in glucose regulation from baseline (fasting glucose, C-peptide, insulin, Insulin like Growth Factor (IGF-1), IGF binding protein 3 and adiponectin) and changes in expression of insulin receptor, IGF-1 receptor and phosphorylated-AKT in PCa epithelial cells at 6-months. Selected blood- based biomarkers of glucose regulation have been found to be associated with PCa aggressiveness and outcomes. (19–21, 24, 25, 35)) The tissue-based markers of glucose regulation selected have been shown to be overexpressed in prostate cancer(26), found to be responsive to dietary restriction among animals with PCa(22, 36–39), or are a downstream signaling molecule for the IGF-1R and IR(40). An additional primary outcome is to evaluate whether patients randomized to the intervention arm are able to sustain the beneficial changes in weight loss and glucose regulation 6 months after the active intervention.

Secondary outcomes include several aspects of health-related quality of life (QOL), specifically PCa-related anxiety (measured by the Memorial Anxiety Scale for Prostate Cancer (MAX-PC)(41), urinary and sexual function and bother (measured by the Expanded Prostate Cancer Index (EPIC) short form-26)(42), and general quality of life (measured by the EQ-5D-5L)(43). Additional secondary outcomes include adverse pathology (defined as Gleason upgrading, increase in number of positive cores, greater than 50% positive cores) on follow-up biopsy.

Data Analysis

Adaptive randomization is used to assign participants by baseline age (<65 and ≥65 years) and BMI (<30 vs. ≥ 30 kg/m^2) to either the PALS lifestyle intervention or control arm. This design randomizes participants using an algorithm that minimizes treatment imbalances within each baseline age and BMI subgroup.(44) The total expected sample size is 210 men, which includes an anticipated 5% drop out in each arm.

Primary analyses will compare changes in circulating and tissue markers of glucose and insulin regulation between the intervention and control arms. Global assessment of the intervention effects will be evaluated using a two-sided t-test (or Wilcoxon rank sum test if normality of the measurement is questionable). Further analysis will quantify effects of patient age, BMI and other body composition measures on change blood and tissue measures. Differential effects between intervention and control arms will be quantified using interaction terms. Effects of missing data will be investigated using extreme case analysis. All analyses will be based on intention-to-treat principles.

To test whether PCa patients randomized to the intervention arm can sustain the beneficial changes in weight and glucose regulation an additional 6 months after the active intervention, sustained weight loss will be characterized as maintenance of a 7% reduction in baseline weight(30), and sustained glucose regulation as maintenance within 5% of 6-month levels. Because not all participants will achieve 7% weight loss at 6 months, analyses will look in the subset of participants who did and did not achieve this goal both separately and combined. A one-sample test of proportions will be used to determine whether the proportion of participants that are able to sustain lifestyle changes differs from zero.

Secondary analyses will test whether changes in PCa-specific QOL differs between the intervention and control arms. Intervention effects will be evaluated using a two-sided t-test, and models will be adjusted for age, socioeconomic status, marital status, and baseline BMI. An additional secondary analysis will evaluate whether the proportion of participants with adverse pathology (Gleason upgrading, increase in number of positive cores, increase in the number of cores with >50% positive involvement) on follow-up surveillance biopsy differs between intervention and control arms using a two-sample test of proportions.

Allowing for a drop-out rate of 5% and assuming correlations 0.70 between baseline and follow-up measures, the final sample size of 100 men in each arm provides 80% power to detect differences in changes in serum glucose regulation biomarkers between arms ranging from 5.3% for glucose to 33.1% for insulin with a 2-sided alpha of 0.05 (Table 3). Similarly,

for changes in tissue markers of glucose regulation, the minimum detectable differences in expression of markers range from 26.5% for AKT to 46.3% for IGF-1 receptor (Table 3).

DISCUSSION

Obesity is a well-established risk factor for the incidence of aggressive PCa and for PCa mortality.(5–12) More recently, obesity has also been identified as an independent risk factor of poor outcomes among men on AS. In two separate cohorts of men with low-risk PCa on AS, obesity was associated with significant increases in risk of pathologic progression.(17, 18) In addition, one of these studies also reported that obese men were also more likely than normal weight men to initiate active treatment for their PCa (HR=1.8; 95%CI, 1.0–1.9; p=0.08).(17) Furthermore, patient BMI is used an independent clinical variable in calculators designed to estimate risk of progression on subsequent biopsy among men using AS to manage PCa (https://canarypass.org/pass-risk-calculator, manuscript in preparation). Despite this observational evidence, clinical trial data are lacking as to whether weight loss after diagnosis will improve outcome.

Lifestyle interventions in patients who choose AS is an emerging area of research with potential to yield insights on biological pathways underlying disease progression, though few studies have been conducted to date. The Prostate Cancer Lifestyle Trial (PCLT), a 1-year trial evaluating an intensive lifestyle intervention (vegan diet supplemented with soy, fish oil, vitamin E, selenium and vitamin C, 3 hours weekly moderate exercise, and 1 hour daily stress management) among 90 men with low-risk PCa on AS, reported LNCaP cell growth declined an average of 70% in the lifestyle intervention arm, compared to a 9% decline in the control arm ($p<0.001$).(45) In a study of 30 men undergoing a similar 3-month intensive lifestyle intervention, which achieved a mean 2.6 unit decline in BMI, changes in gene expression from pre- and post- intervention prostate biopsies included down-regulation of IGF-1R genes.(46) In addition, the Men's Eating and Living (MEAL) study, a 6-month randomized trial, evaluated a behavior telephone-based intervention to increased vegetable (particularly cruciferous and tomato) intake, compared to control, among nearly 500 men on AS.(47) Preliminary analyses from this study have reported significant increases in the daily number of servings of vegetables consumed and in plasma carotenoid levels concentrations, although no significant differences in the rate of PCa progression between intervention and control groups.(48) No trials to date have specifically targeted weight loss and underlying glucose regulation mechanisms through diet and exercise among men on AS. Evaluating the effects of a lifestyle intervention among PCa survivors on AS also provides a novel approach to studying the biological pathways by which obesity may delay or prevent disease progression. Men with PCa on AS have untreated cancer and undergo routine surveillance biopsies, which allows the use of repeat biopsies to investigate the intervention's effects on tumor tissue and cancer biomarkers.

Men with PCa on AS represent an important group in which to test a lifestyle intervention. The growing concern of over-diagnosis and over-treatment of more indolent PCa(49) has led to a substantial increase in men choosing AS. However, patient acceptance of AS for primary treatment remains low and approximately 50% of men on AS will experience disease progression requiring treatment.(3) Of concern for patients is the anxiety about

doing “nothing” for their PCa. The PALS intervention has the potential to provide both patients and providers with an active yet non-invasive therapy to improve PCa patient outcomes.

The use of the DPP as the basis of the PALS intervention has several strengths. First, the DPP has a proven track record of weight loss and improved glucose regulation among a pre-diabetic population(29), and long-term follow-up has demonstrated sustained weight loss at 10 years(30). This is an important consideration as other studies of dietary interventions in men with PCa have used diets that are difficult to maintain over the long-term (e.g. vegan(45), low-glycemic(50) and prepared meals(51). Although the DPP has not previously been studied in cancer survivors, there are data to suggest that older men may be an ideal population for the DPP lifestyle intervention. (52) In the primary trial, older participants (≥60 yrs) compared to younger groups (25–44 yrs and 45–59 yrs) had the greatest weight loss (mean −6.4 kg vs. −4.1 and −5.0 kg respectively, $p<0.001$) and more commonly met the exercise goal (48% vs. 34% and 38% respectively, $p<0.001$).(52) In addition, compared to women, men lost more weight ($p<0.01$) and performed higher levels of physical activity ($p<0.05$) in the lifestyle intervention.(53) Lastly, if successful, expanding the delivery of the PALS program to PCa patients within the general community would be extremely feasibly as many community-based organizations, including hospitals, medical centers and YMCA’s across the nation already deliver the DPP lifestyle intervention program.

Conclusion

With the growing recognition that many men with lower-risk PCa features do not require definitive treatment and can instead be monitored through AS protocols, it becomes imperative to identify modifiable risk factors for reducing the rate of disease progression in these men. A lifestyle modification that could delay or prevent disease progression would represent a significant savings of health care expenditures from treatments such as surgery and radiation, as well as lowering morbidity and mortality in the patients requiring further treatment. Findings from this study may have wide reaching implications in improving both the overall and disease-specific outcomes in men diagnosed with clinically-localized PCa, and provide an alternative approach of an active lifestyle for AS.

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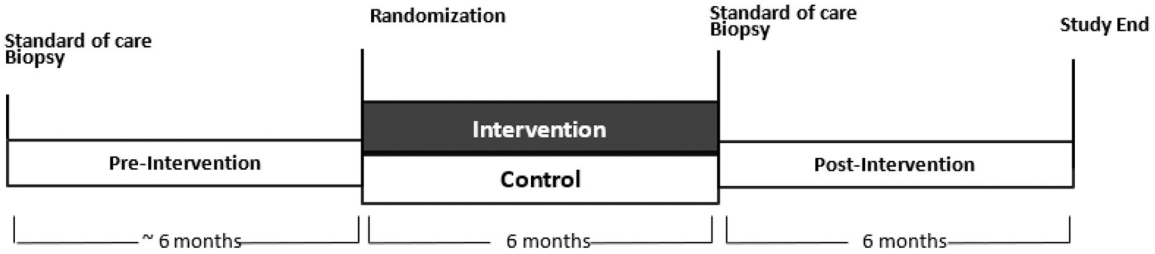

Figure 1.
PALS study Schema

Table 1.

PALS Lifestyle Intervention Curriculum

Week	Topic	Objectives
0	Introduction to PALS	• Overview of the PALS intervention program • Introduce study goals and self-monitoring
1	Be a Fat and Calorie Detective (part 1)	• Review individual fat, calorie and physical activity goals • Learn how keep track of fat and calories
	Move Those Muscles	• Learn how to increase physical activity in a safe and gradual way
2	Be a Fat and Calorie Detective (part 2)	• Learn 3 ways to eat less fat and fewer calories
	Jumpstart and Strengthen your Physical Activity	• Learn the F.I.T.T. principles (frequency, intensity, type of activity and time) as related to the activity goal. • Learn to incorporate strength training and intensity in workouts • Learn how to use heart rate monitor
3	Healthy Eating	• Learn how eating less fat/calories fit into the overall context of healthy eating • Learn to use MyPlate model to improve diet quality
4	Four Keys to Healthy Eating Out	• Learn the four principles for healthy eating out: planning ahead, assertion, stimulus control, and healthy food choices.
6	Tip the Balance	• Discuss how healthy eating and being active are related in terms of calorie balance and weight loss
8	Take Charge of What's Around You	• Learn about food and activity cues and ways to change them
10	Problem Solving	• Learn to use the five steps to problem solving to overcome weight loss, physical activity and healthy eating challenges
13	The Slippery Slope of Lifestyle	• Identify things that cause slips from healthy eating or being active • Learn to talk positive to negative thinking • Discuss strategies to get back on track after a slip
16	Make Social Cues Work for You	• Discuss ways to change problem social cues and add helpful social cues
20	You Can Manage Stress	• Discuss was in which stress is a barrier to making healthy changes in eating and exercise behaviors. • Identify ways to manage, reduce and prevent stress
24	Ways to Stay Motivated	• Renew the participants' commitment to the PALS program • Learn the importance of maintaining self-monitoring, healthy eating and physical activity for long-term success.

Table 2.

Data and specimen collection in PALS

	Pre-study	Baseline	3 months	6 months	12months
Fasting Blood Draw		X	X	X	X
Anthropometrics		X	X	X	X
QOL		X	X	X	X
Lifestyle Questionnaire		X			
3-day Food Record		X		X	
Physical Activity Questionnaire		X		X	X
Medication use		X		X	X
DXA scan		X			X
Exercise test		X		X	
Standard of care Biopsy	X			X	

Table 3.

Minimal detectable differences (MDD) in serum and tissue biomarkers at β=80%, α=0.05 given a sample size of 200 (100 each in intervention and control arms)

Biomarker	Baseline Mean (SD) or n (%)	*MDD*	
		Mean	% of mean
Primary Aim 1 - Serum			
Fasting glucose, mg/dL	106.3 (12.6)	5.6	5.3%
Primary Aim 2 - Serum			
C-peptide, ng/mL	1.7 (1.2)	0.54	31.6%
Insulin, pmol/L	138.0 (102.0)	45.7	33.1%
IGF-1, ng/mL	232.7 (75.4)	33.8	14.5%
IGF-BP3, ng/mL	4317.6 (975.2)	436.5	10.1%
Adiponectin, ug/mL	6.1(3.9)	1.8	29.0%
Primary Aim 3 - Tissue			
Insulin receptor	30 (34)	13.9	29.2%
IGF-1 receptor	112 (80)	32.7	46.3%
AKT	128 (83)	33.9	26.5%