Clinical Research Protocol

PALS: PROSTATE CANCER ACTIVE LIFESTYLE STUDY

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List of Abbreviations AND ACRONYMS

AAFQ	Arizona Activity Frequency Questionnaire
AE	Adverse event
AS	Active Surveillance
BMI	Body mass index
BUN	blood urea nitrogen
CI	Confidence Interval
CRF	case report form
DPP	Diabetes Prevention Program
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DXA	Dual x-ray absorptiometry
EDC	Electronic data capture
EPIC	Expanded Prostate Cancer Index
FDA	Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
GCP	Good Clinical Practice
GXT	Graded Exercise Treadmill test
HbA1C	Hemoglobin A1C
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Hazard Ratio
HRQOL	Health Related Quality of Life
ICF	informed consent form
ICH	International Conference on Harmonisation
IGF-BP3	Insulin like Growth Factor Binding Protein 3
IGF-1	Insulin like Growth Factor 1
IGF-1R	Insulin like Growth Factor 1 Receptor
IR	Insulin Receptor
IRB	Institutional Review Board
MAX-PC	Memorial Anxiety Scale for Prostate Cancer
NIH	National Institute of Health
PCPT	Prostate Cancer Prevention Trial
PE/DVT	Pulmonary embolism/deep venous thrombosis
PI	Principal Investigator
PCa	Prostate Cancer
PCSM	Prostate Cancer Specific Mortality
PSA	Prostate Specific Antigen
QOL	Quality of Life
RP	Radical Prostatectomy
RC	Research Coordinator
SAE	serious adverse event

PROTOCOL SYNOPSIS

TITLE	PALS: Prostate Cancer Active Lifestyle Study
SPONSOR	R01 CA184075-01A1
FUNDING ORGANIZATION	National Cancer Institute
NUMBER OF SITES	Fred Hutchinson Cancer Research Center
RATIONALE	Prostate cancer (PCa) is the most common cancer diagnosis in men today and the second leading cause of cancer-related mortality in men, accounting for almost 30,000 deaths annually. Obesity contributes to PCa-specific mortality (PCSM), increasing risk by 20-160%, but the causal mechanisms remain unknown. Men on Active Surveillance (AS), where low risk PCa patients are monitored with regular PSA blood tests, physical exams and prostate biopsies, provide an ideal population to study the effects of obesity on adverse outcomes in relation to a lifestyle intervention: (1) these men are cancer survivors not having had aggressive treatment, and may be more able and motivated to undergo a lifestyle intervention; and (2) they have intact tumors which allow for ongoing tumor tissue based analyses to be conducted. Despite their initial lower risk status, 50% of these patients will experience disease progression requiring active treatment. We hypothesize that obesity enhances tumor growth, leading to conversion of low-risk to high-risk disease. Thus, implementing a lifestyle intervention against obesity and understanding the biologic mechanisms linking obesity and PCa outcomes could have a profound effect on clinical practice through reducing overtreatment and its adverse side effects, reducing health care costs, and reducing patient anxiety. Identifying factors that may slow or prevent tumor progression in AS patients will have substantial clinical and public health impact by improving patient outcomes and reducing health cancer expenditures.
STUDY DESIGN	This is a randomized controlled trial to investigate the effects of a 6-month lifestyle intervention based on the Diabetes Prevention Program (DPP) on glucose regulation biomarkers, health related quality of life and pathologic features of follow-up biopsies in overweight and obese men with prostate cancer on Active Surveillance
PRIMARY OBJECTIVE	The study has the following primary **specific aims**: 1. To test whether the DPP lifestyle intervention (vs. control) improves serum fasting glucose; 2. To test whether the DPP lifestyle intervention (vs. control) improves serum biomarkers of glucose regulation (insulin, C-peptide, insulin-like growth factor-1 (IGF-1), IGF binding protein 3 (IGF-BP3) and adiponectin); 3. To test whether the DPP lifestyle intervention decreases the levels of insulin receptor or insulin-like growth factor-1 receptor (IGF-1R) in PCa tissue epithelium on follow-up prostate biopsy; 4. To test whether PCa patients randomized to the DPP lifestyle intervention sustain the lifestyle changes for at least 6 months after the end of the intervention period.
SECONDARY OBJECTIVES	The secondary objectives are to: 1. To evaluate whether the DPP lifestyle intervention improves health-related quality of life; 2. To evaluate whether the DPP lifestyle intervention effects on pathologic features of follow-up prostate biopsies.

NUMBER OF SUBJECTS	200
SUBJECT SELECTION CRITERIA: Inclusion Criteria	Inclusion Criteria: 1. histologically confirmed adenocarcinoma of the prostate, clinically localized, low or low-intermediate risk disease (T1C/T2a, Gleason≤7 (3+4), PSA < 20); 2. Primary treatment is AS with planned annual surveillance biopsies; 3. BMI≥25 kg/m2; and 4. Able to make the required dietary changes 5. Physically able to undertake an exercise program.
SUBJECT SELECTION CRITERIA: Exclusion Criteria	Exclusion Criteria: 1. Current, recent (<1 year), or planning to join a weight loss program, undergo weight loss surgery, or take appetite suppressants; 2. Steroid hormone (ADT) use within past 12 months; 3. Significant cardiovascular disease precluding an exercise program, including recent (within 6 months) myocardial infarction or stroke, pulmonary edema, myocarditis, pericarditis, unstable angina, PE/DVT, uncontrolled hypertension (SBP>200; DBP>110), uncontrolled arrhythmia, heart failure; or 4. Insulin dependent DM and/or metformin use. 5. MD confirmed cognitive impairment 6. Current alcohol or narcotic abuse
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 1 year **Treatment:** 6 months **Follow-up**: 6 months The total duration of the study is expected to be 4 years
PRIMARY ENPOINTS	**Primary Aims 1 and 2:** Compare change in fasting glucose, C-peptide, insulin, IGF-1, IGF-BP3, and adiponectin levels relative to baseline between the intervention and control arms. **Primary Aim 3:** We will test whether the change in expression of IR, IGF-1R, and AKT on prostate cancer epithelial cells from follow-up surveillance biopsy (6 months post-randomization) relative to 'baseline' (biopsy ~6 months prior to randomization). **Primary Aim 4:** We will test whether PCa patients randomized to the intervention arm are able to sustain the beneficial changes in weight and glucose regulation an additional 6 months after the active intervention.
SECONDARY ENDPOINTS	**Secondary Aim 1.** We will test whether the change in HRQOL, namely urinary and sexual QOL and bother, relative to baseline, differs between the intervention and control arms **Secondary Aim 2.** We will use a two-sample test of proportions to determine whether the proportion of participants with adverse pathology (Gleason upgrading, increase in number of positive cores, cores>50% positive) on follow-up surveillance biopsy differs between intervention and control arms.

STATISTICS Primary Analysis Plan	**Aims 1 and 2**: Global assessment of intervention effects will be evaluated using a two-sided t-test or Wilcoxon rank sum test if normality of the measurement is questionable (as determined by QQ-normal plots). Further analysis will quantify effects of patient age, BMI and other body composition measures on change in fasting glucose using linear regression. Differential effects between intervention and control arms will be quantified using interaction terms. All analyses will compare effects based on intention-to-treat. **Aim 3:** Global assessment of intervention effects will be evaluated using a two-sided t-test (or Wilcoxon rank sum test). Linear regression will be used to assess associations of IR, IGF-1R, and AKT expression with systemic measures of glycemic control at 6 months. **Aim 4:** We will follow the DPP research group characterization of sustained weight loss as maintenance of a 7% reduction in weight and sustained glucose regulation as maintenance within 5% of 6-month levels. Because not all participants will achieve 7% weight loss at 6 months, we 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.
Rationale for Number of Subjects	Our power calculations give the minimally detectable intervention effects for endpoints in Primary Specific Aims, setting two-sided alpha error at 5% and power at 80%. We have set a sample size of 100 in each of the intervention and control arms, based both on our overall evaluation of minimum detectable differences across the range of study endpoints and on a reasonable estimate of the number of men we can recruit. The sample size allows for a drop-out rate of 5%, and power calculations assume correlations of 0.70 between baseline and follow-up measures.

1 BACKGROUND

Obesity prevalence in the U.S. has risen dramatically over the past 20 years. Presently, more than one-third of adults are obese (body mass index (BMI) ≥ 30 kg/m^2) and among older men, approximately 40% are obese.[1] Obesity is linked with an increase in cancer-specific mortality and an estimated 14% of cancer deaths in U.S. men are due to obesity.[2] Epidemiologic studies have consistently associated obesity with an increased risk of prostate cancer (PCa) progression and PCa-specific mortality (PCSM).[2-18] In a study of 731 men with organ-confined, margin-negative PCa after radical prostatectomy (RP), the most obese men had a 4-fold increased risk of progression after adjusting for Gleason grade.[10] As shown in Table 1, obesity is associated with a 20% to 160% elevation in PCa-specific mortality. Pooled/meta analyses report that for every 5-point increase in BMI, there is a corresponding 20% increase in PCSM (95% CI 0.99-1.46) and conclude that "cumulative data is compelling for a strong positive association between obesity and fatal prostate cancer".[19] A 2011 Institute of Medicine Workshop on Obesity and Cancer Report noted: "evidence is building that obesity and weight gain are risk factors for poor outcome in prostate cancer".[20]

Table 1: Studies of Obesity and PCa-Specific Mortality

Study, year	No. Patients	Hazard Ratios (95% Confidence Intervals)			P trend
		BMI ≤ 25	BMI 26 – 29	BMI ≥ 30	
Andersson, 1997 [18]	2,368	1.00 (ref)	1.3 (1.0-1.7)*	1.4 (1.1-1.8)*	0.04
Calle, 2003 [2]	3,314	1.00 (ref)	1.1 (1.0-1.2)	1.2 (1.1-1.4)	< 0.001
Wright, 2007 [3]	9.986	1.00 (ref)	1.3 (0.9-1.8)	1.5 (0.9-2.3)	0.02
Efstathiou, 2007 [9]	945	1.00 (ref)	1.5 (1.0-2.3)	1.6 (1.0-2.7)	-- ^
Gong, 2007 [6]	752	1.00 (ref)	1.1 (0.6-2.3)	2.6 (1.2-5.9)	0.03
Ma, 2008 [16]	2,456	1.00 (ref)	1.3 (1.0-1.6)	2.0 (1.2-3.2)	< 0.001

* BMI (kg/m^2) quartiles used; ^ p Trend not provided

The mechanisms underlying the obesity-PCa progression relationship are unknown. However, a number of metabolic changes that occur in obese men may be responsible, including impaired glucose regulation and insulin resistance. Studies have shown that obesity is strongly associated with hyperinsulinemia[21] and weight loss both improves insulin sensitivity and prevents incident diabetes in high-risk individuals.[22]

The societal impact of PCa is significant, as the 2010 cost of care estimate was $11.9 billion.[23] The highest costs are during the first year after diagnosis, typically including treatment with either surgery or radiation.[24] However, there is growing awareness of overtreatment of men with low-risk PCa (the most common type of PCa) who are increasingly managed with active surveillance (AS). AS involves monitoring of the PCa with plans to intervene if the cancer progresses, thus avoiding expensive treatment with significant side- effects in a large proportion of men. AS has been shown to have lower 5-year costs compared to other PCa treatments with a potential net per-patient savings of $12,194 at 5-years.[25] Therefore, reducing progression on AS has the potential to have profound impacts on both an individual and societal perspective. Targeted weight reduction is a viable opportunity.

1.2 Dietary Studies in Prostate Cancer

Observational studies provide compelling evidence that dietary factors post-PCa diagnosis may affect disease progression. In the Health Professionals Follow-up Study, the consumption of specific food types by men with PCa was associated with disease progression suggesting that dietary intake can influence disease outcome.[26] Specifically, replacing 10% of energy intake after the diagnosis of PCa from carbohydrate with vegetable fat was associated with a significant reduction in the risk of PCSM (HR 0.71, 95% CI 0.51-0.98), whereas substituting 5% of saturated fat intake for carbohydrate significantly increased the PCSM risk (HR 1.30 95% CI 1.05-1.60).[27] A recent analysis of these men reported that men with a higher healthy lifestyle index (based on BMI, diet and physical activity) had a 40% reduction in the risk of lethal PCa (HR 0.61, 95% CI 0.42-0.88).[28] In a study of 1,560 men with PCa, those with the highest cruciferous vegetable intake post-diagnosis had a lower risk of disease recurrence.[29] Finally, patients with high vs. low saturated fat diets had a 2-fold increased risk of PCa recurrence (HR 2.0, 95% CI 1.2-3.2).[30]

Weight gain also increases the risk of progression after radical prostatectomy (RP).[15, 31, 32] In a study of 526 men, weight gain >1.5 kg/year between age 25 and PCa diagnosis was associated with a two-fold increased risk of recurrence vs. men who were weight stable (HR 2.3, 95% CI 1.1-5.1).[15] Similarly, among 359 men,

weight gain ≥2.5 kg the year before RP increased risk of PCa recurrence (HR 1.7, 95% CI 1.0-2.6).[31] Finally, in a study of 1,337 men, weight gain >2.2 kg between 5 years pre- and 1 year post-RP increased risk of recurrence nearly 2-fold (HR 1.9, 95% CI 1.1-3.3) vs. those who maintained their weight.[32] In addition to dietary changes, exercise also reduces the risk of PCSM, with men who do >3 hours of vigorous exercise per week having a 61% reduction in the risk of PCSM (HR 0.39, 95% CI 0.18-0.84).[33]

Studies in men with PCa have also demonstrated that dietary change leads to changes in serum markers that affect PCa cell growth.[34, 35] In a study of 12 men participating in a 6-month low-fat/high fiber diet with soy supplements, serum from participants was incubated with LnCaP PCa tumor cells and the intervention arm had a 20% inhibition of LnCaP cell growth ($p<0.05$) compared to the control arm.[34] In a second study of a vegan diet, moderate aerobic activity and stress management, LNCaP cell growth declined an average of 70% in the lifestyle intervention arm, compared to a 9% decline in the control arm ($p<0.001$).[35] In a study of 30 men undergoing a 3-month intensive nutritional and 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.[36] In summary, diet and dietary change post-PCa diagnosis can impact disease progression. Thus, a lifestyle intervention in men with PCa is timely, and studies identify glucose regulation as an important biomarker of this intervention effect.

1.3 Glucose Regulation and Prostate Cancer Outcomes

Preclinical and observational studies demonstrate that glucose regulation affects PCa outcomes.

Preclinical studies. Insulin and glucose are critical for cancer cell growth[37] and preclinical studies provide evidence of the role of glucose regulation in PCa.[38, 39] In one study, LnCaP tumor cells were injected and tumor growth was compared in mice with induced hyperinsulinemia through a high carbohydrate feeding to mice fed a low carbohydrate diet without resultant hyperinsulinemia.[39] After 9 weeks, the tumors in the mice with hyperinsulinemia were significantly larger than those tumors in mice without hyperinsulinemia ($p < 0.001$). In a second preclinical study, mice with LAPC-4 xenografts were fed either a western diet or a no carbohydrate diet. Tumor cell volume after 7 weeks was 33% lower in the mice fed the no carbohydrate diet.[38] These preclinical studies demonstrate the potential role of aberrant glucose regulation in PCa cell growth.

Several different cancers have been shown to overexpress the insulin receptor (IR),[40-43] including PCa.[44] The IR is structurally similar to the IGF-1 receptor (IGF-IR) and both are considered to be important in cancer. Activation of these receptors leads to mitogenic activity via RAS and MAPK and anti-apoptotic action through the AKT and mTOR pathway, with phosphorylated-AKT representing a measurable downstream signaling molecule for the IGF-IR and IR (Fig. 1)[45]. A study of 161 men undergoing RP for PCa found two-fold higher levels of IR staining on PCa cells compared to benign prostate cells.[44] This finding, combined with animal models demonstrating that dietary restriction in animals with PCa decreases expression of IGF-1R, IR and downstream signaling with phosphorylated-AKT (Table 2),[39] suggests that IR could be a target for therapy and tumor receptor expression/activation may serve as a biomarker of lifestyle modifications.

Human studies. Small studies have evaluated serum biomarkers of glucose regulation and PCa aggressiveness and cancer outcomes. In studies of men with diabetes undergoing RP, higher pre-RP HbA1C levels were associated with a greater risk of extracapsular disease and aggressive PCa.[50, 51] In an analysis of the control arm of the Prostate Cancer Prevention Trial (PCPT) by one of our investigators (MN), higher C-peptide (an insulin surrogate) levels were associated with an 88% increased risk of aggressive PCa.[52] In addition, longitudinal studies of men treated for PCa have found direct associations between markers of glucose regulation and PCSM.[16, 53] In one study, a higher mean fasting insulin level at diagnosis was found in those who died of PCa.[53] In the Physicians Health Study, PCa cases with the highest C-peptide concentrations (>2.7) had more than a 2-fold increased risk of PCSM (HR 2.4, 95% CI 1.3-4.3) vs. those with the lowest concentrations (<1.0).[16]

Table 2: Animal studies of diet and resultant PCa tissue receptor changes

Author, year	Diet	Receptor levels in diet arm
Narita, 2008[46]	Low fat	↓ IGF-1R
Powolny, 2008[47]	Caloric Restriction	↓ IGF-1R
Venkateswaran, 2007[39]	Low fat, low carb	↓ IR and ↓ phos-Akt
Kobayashi, 2008[48]	Low fat	↓ phos-Akt
Mavropoulus, 2009[49]	No carb	↓ phos-Akt

In previous studies, we determined that elevated glucose levels at PCa diagnosis independently predicted risk of recurrence. Men with PCa undergoing local therapy who had glucose ≥100 mg/dL at diagnosis had a 50% increased risk of recurrence (HR 1.5, 95% CI 1.1-2.0) vs. those with glucose level <100 mg/dL.[54] These findings are in line with results from studies in several other cancers, including breast, colon, liver and brain

cancers, which have also found that higher glucose levels are associated with a greater risk of tumor progression.[55-59] In summary, markers of glucose regulation may foreshadow PCa progression and glucose control may be a modifiable risk factor for PCa recurrence.

Considering the increasing prevalence of both obesity[60] and PCa, and the relationship of impaired glucose regulation with increased obesity and adverse PCa outcomes, a weight reduction lifestyle program to improve glucose regulation in PCa patients holds promise for reducing adverse PCa-specific outcomes. One of the most successful ways to lose weight is through a structured program of diet and exercise such as the Diabetes Prevention Program (DPP), which is individualized to take into account individual preferences and includes behavioral modifications that are important for dietary adherence.[61] AS patients represent an ideal population to study for this intervention. Cancer survivors on AS have untreated cancer which allows for comparisons of the intervention's effects on tumor tissue to be performed with repeat surveillance biopsies. Thus, the effect of the intervention on changes in cancer biomarkers can be ascertained. It would not be appropriate to delay definitive therapy for >6 months in men with higher risk PCa to obtain post-intervention tumor tissue. However, as AS patients have untreated cancer, they may be at a higher functional level since they are not recovering from surgery or radiation that could limit their abilities to fully participate in dietary and exercise interventions. Finally, as the men on AS do not have advanced disease, they are not suffering the consequences of metastatic disease and advanced therapy (androgen deprivation), which can influence metabolic biomarkers. Thus, men with PCa on AS offer a unique population in which to investigate a weight reduction intervention on biomarkers of tumor progression. Since 50% of men on AS progress to eventually requiring treatment,[62] a lifestyle modification that could delay or prevent this disease progression would represent a significant savings of heath care expenditures from surgery and other treatments as well as lowering morbidity and mortality in the patients requiring further treatment.

1.4 Diabetes Prevention Program

The DPP studied over 3,000 participants with elevated fasting glucose levels randomized to metformin, a 6-month lifestyle modification program or placebo.[22, 61] The goal of the lifestyle modification program was a 7% reduction in body weight through a structured dietary program and at least 150 minutes of weekly physical activity. The lifestyle intervention decreased incident diabetes mellitus (DM) by 58% vs. controls, while metformin reduced incident DM by 31%. Fasting glucose declined from a mean of 107 to 101 mg/dl in the lifestyle group whereas no change was seen in the placebo group. Long term follow-up of the DPP has demonstrated sustained weight loss at 10 years,[63] which 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[35], low glycemic[64] and prepared meals[65]). The results of the lifestyle intervention have also been found to be cost-effective and cost saving.[66, 67] A meta-analysis of weight loss studies based on the DPP lifestyle modification program consistently shows statistically significant and clinically relevant reductions in weight; however, the majority of participants in those studies were women and no studies to date have been conducted in older men with cancer.[68] Despite this, there are indications that older men may be an ideal population for the DPP lifestyle intervention. Older participants (≥60 years) 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, $p<0.001$).[69] The lifestyle intervention was more effective than metformin at weight loss with increasing age ($p=0.005$).[69] 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. [70] However, since only 20% of participants were older than 60 years of age, fewer than 1/3 of participants were men, and none of the participants had cancer, whether these results will have similar effects in a PCa population are unknown, but certainly these data provide evidence that the DPP intervention can succeed in this population. Thus, the DPP intervention offers a novel strategy to improve PCa patient outcomes and yield insights on biological pathways by which obesity may delay or prevent disease progression.

1.5 Active Surveillance (AS)

An emerging area of PCa management is AS. PCa will be diagnosed in over 200,000 men this year.[71] PCa is a cancer of older men (mean age at diagnosis of 67 years).[71] Because of the long natural history of PCa, many men will die of competing causes, the most common being cardiovascular disease. Considering the significant quality of life and functional side effects of PCa treatment, there is increasing pressure to reserve treatment for those most likely to experience PCa related morbidity and mortality. In AS, men with lower risk PCa are monitored regularly with PSA tests, physical exams and surveillance prostate biopsies. Men who

show evidence of disease progression (Gleason upgrading, increase in amount of cancer present) are recommended treatment (e.g., RP, radiation or androgen deprivation therapy) with curative intent.

Progression during AS occurs in 33% (range 14-49%) of patients at 5 years and 55% (range 40-59%) at 10 years,[62] suggesting that efforts to slow the growth of PCa while on AS are needed. In fact, delaying curative intervention in men with localized PCa remains a concern as men on AS who undergo delayed RP are found to have adverse features (pT3, Gleason ≥7 disease) on final pathology approximately 25% of the time.[72-74] Further, obese men represent an even greater risk population, as data have shown that obese men eligible for AS have an increased risk of upstaging (OR 4.2, 95% CI 1.7-10.6),[75] upgrading (OR 1.9, 95% CI 1.0-3.6)[76] and biochemical recurrence (HR 1.9, 95% CI 1.0-3.4).[13] In a recent study of men on active surveillance, a 5-point increase in BMI was associated with a 50% increased risk of pathologic progression (95% CI 1.1-2.1).[77] In a randomized study in 93 men on AS, the intervention arm was encouraged to eat a low-fat, plant based diet, to exercise and to participate in group support sessions, the proportion of men who progressed to require treatment within 2-years was greater in the control arm (13/49) compared to the intervention arm (2/43, $p<0.05$).[78] Mean weight loss was significantly greater in the intervention arm (4.5kg vs. 0kg, $p<0.001$). These findings support our theory that improving body weight in men on AS can positively influence PCa outcomes.

Men on AS have anxiety levels and mental health scores that are similar or worse compared to men treated with RP[79, 80, 81] However, men on AS can have improvements in their anxiety, as seen in a trial of dutasteride or placebo.[82] In that study, anxiety significantly declined over the course of the study in the dutasteride group compared to the placebo group ($p = 0.036$). Importantly, a study of lifestyle changes in men on AS demonstrated better mental and physical scores (from the generic HRQOL instrument, the Short Form 36 (SF-36)) in addition to sexual function compared to controls.[83] In a study of 30 men on AS undergoing a 3-month nutritional and lifestyle intervention, a 6.5 mean increase in mental component summary score was observed[36] along with decreased perceived stress. Analyses of the DPP have demonstrated HRQOL benefits with lifestyle intervention compared to placebo for health utility index and physical component summaries of the Short-Form-36 health survey.[84, 85] Therefore, the AS population represents a unique group of cancer survivors to study the effects of a lifestyle intervention.

2 STUDY RATIONALE

Obesity is associated with PCa recurrence and one potential mechanism is hyperglycemia and impaired glucose regulation, with both preclinical and observational data demonstrating this relationship. The DPP is a diet and exercise lifestyle intervention with a successful track record of improving glucose regulation, although it has not been extensively studied in an older male population with cancer. Men with PCa on AS represent an important group in which to test a lifestyle intervention. Approximately 50% of men on AS will experience disease progression requiring treatment and the associated complications/side effects. Thus, this study has the potential to improve overall survival and HRQOL in men by reducing PCa progression.

3 STUDY OBJECTIVES

3.1 Primary Objective

The study has the following primary **specific aims**:

1. To test whether the DPP lifestyle intervention (vs. control) improves serum fasting glucose;
2. To test whether the DPP lifestyle intervention (vs. control) improves serum biomarkers of glucose regulation (insulin, C-peptide, insulin-like growth factor-1 (IGF-1), IGF binding protein 3 (IGF-BP3) and adiponectin);
3. To test whether the DPP lifestyle intervention decreases the levels of insulin receptor or insulin-like growth factor-1 receptor (IGF-1R) in PCa tissue epithelium on follow-up prostate biopsy;
4. To test whether PCa patients randomized to the DPP lifestyle intervention sustain the lifestyle changes for at least 6 months after the end of the intervention period.

3.2 Secondary Objectives

We will also assess the following secondary aims:

1. To evaluate whether the DPP lifestyle intervention improves health-related quality of life;
2. To evaluate whether the DPP lifestyle intervention effects on pathologic features of follow-up prostate biopsies

4 STUDY DESIGN

4.1 Study Overview

This will be a 6-month, prospective, randomized trial in overweight (BMI = 25-29 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2) men with PCa (n=200) who have elected AS. Patients will be randomized to either:

1. Lifestyle intervention (a structured diet and exercise program based on the DPP); or
2. Control (oral and written information based on general U.S. dietary and physical activity guidelines).

Following randomization, men will be followed for 12 months, and the 12 month start and end dates will coincide with the yearly prostate biopsies that are part of routine clinical care for AS patients (thus no extra biopsies will be performed solely for the study; Fig. 3). Baseline and post-intervention (at 6 and 12 months) measures of glucose regulation will be compared along with BMI, physical activity, caloric intake, additional insulin related biomarkers, function and quality of life and pathologic endpoints.

Month 0	1	2	Month 3	4	5	Month 6	7	8	9	10	11	Month 12
PALS STUDY VISIT TIMELINE												
CLINIC VISIT 1			**CLINIC VISIT 2**			**CLINIC VISIT 3**						**CLINIC VISIT 4**
• Informed Consent • Blood draw • Height/weight • Waist/hip measures • Questionnaires • DXA scan • Exercise test • Meet with Nutritionist			• Blood draw • Weight • Waist/hip measures • Questionnaires			• Blood draw • Weight • Waist/hip measures • Questionnaires • Exercise test **Standard of care BIOPSY** • Tissue collection						• Blood draw • Weight • Waist/hip measures • Questionnaires • DXA scan
	PALS Lifestyle Intervention group only											
	PALS Sessions • Up to 11 one-on-one healthy eating instruction sessions • Up to 24 supervised exercise sessions						• Maintenance of healthy eating and physical activity					

5 CRITERIA FOR EVALUATION

5.1 Primary Endpoint

The primary endpoints for each of the primary aims are:

Primary Aim 1: change in fasting glucose levels relative to baseline between the intervention and control arms.

Primary Aim 2: change in fasting C-peptide, insulin, IGF-1, IGF-BP3, and adiponectin levels relative to baseline between the intervention and control arms.

Primary Aim 3: change in expression of IR, IGF-1R, and AKT on prostate cancer epithelial cells from follow-up surveillance biopsy (6 months post-randomization) relative to 'baseline' (biopsy ~6 months prior to randomization).

Primary Aim 4: will test whether PCa patients randomized to the intervention arm are able to sustain the beneficial changes in weight and glucose regulation an additional 6 months after the active intervention.

5.2 Secondary Endpoints

Secondary Aim 1. We will test whether the change in HRQOL, namely urinary and sexual QOL and bother, relative to baseline, differs between the intervention and control arms

Secondary Aim 2. We will use a two-sample test of proportions to determine whether the proportion of participants with adverse pathology (Gleason upgrading, increase in number of positive cores, cores>50% positive) on follow-up surveillance biopsy differs between intervention and control arms.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of localized prostate cancer who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. histologically confirmed adenocarcinoma of the prostate, clinically localized, low or low-intermediate risk disease (T1C/T2a, Gleason≤7 (3+4), PSA < 20);
2. primary treatment is AS with planned annual surveillance biopsies;
3. BMI≥25 kg/m^2; and
4. physically able to undertake a diet and exercise program

6.3 Exclusion Criteria

1. current, recent (<1 year), or planning to join a weight loss program or take appetite suppressants;
2. Steroid hormone use (ADT) within the past 12 months;
3. significant cardiovascular disease precluding an exercise program, including recent (within 6 months) myocardial infarction or stroke, pulmonary edema, myocarditis, pericarditis, unstable angina, PE/DVT, uncontrolled hypertension (SBP>200; DBP>110), uncontrolled arrhythmia, heart failure; or
4. 4) insulin dependent DM and/or metformin use.
5. MD confirmed cognitive impairment
6. Current alcohol or narcotic abuse

6.4 Study Specific Tolerance for Inclusion/Exclusion Criteria

Subjects who fail to meet one or more of the inclusion criteria or who meet any of the exclusion criteria will not be enrolled in this study. Waivers of any of the above study entry criteria will not be granted.

6.5 Screen Fail Criteria

Any consented patient who is excluded from the study before randomization is considered a screen failure. All screen failures must be documented with the reason for the screen failure adequately stated. Screen failures will not be re-screened for this study.

7 STUDY PROCEDURES

7.1a Recruitment from collaborating urology clinics

Clinic study staff will identify potential eligible participants from urologic clinics at the University of Washington, Valley Medical Center and the Veterans Affairs Seattle Puget Sound Heath Care System. Clinic study staff will pre-screen men to determine medical eligibility. Recruitment efforts will be targeted towards medically eligible men living in the greater Seattle area. All of our recruitment messages will outline the parameters of the project and will stress the time commitment necessary in order to participate. UW, Valley and VA clinic staff will approach eligible prospective participants to tell them about the study. Interested men will be provided a study brochure, and will be asked to sign consent to allow their personal contact information to be reported to FHCRC study staff for formal recruitment.

7.1b Recruitment from community urology clinics

If a patient from outside UW, Valley and VA contacts study staff directly about participating, PALS study staff will first obtain authorization (HIPAA) to allow access to the patients' medical records to confirm medical eligibility requirements are met before completing the final eligibility screening. FHCRC study staff will contact eligible and interested men by phone to further review the study procedures, and to conduct the final eligibility screening verbally. Men who meet all eligibility requirements and agree to participate will be scheduled to attend Visit 1 at the FHCRC Prevention Center clinic.

7.1c Recruitment from CSS

Direct case recruitment from CSS will follow the IRB-approved "Cancer Surveillance System Protocol for Direct Case Recruitment". Briefly, CSS will identify potential case participants and notify study staff. We will contact local urologists known to the study PI to first determine whether potential case patients meet the study eligibility requirements. Potential case patients who are known to not meet the study eligibility requirements will not be contacted. Potential case patients will be sent a 'Prior Notification' letter that describes the CSS, informs them that they are being invited to participate in PALS. Included with this letter is a letter from the PALS study team and a study brochure introducing the PALS study. After 10 days, if a potential case participant has not opted out of contact and there is no evidence to suggest that the prior notification letter could not be delivered; PALS study staff will contact the potential case participant. During this call, PALS study staff will introduce the PALS study, review study procedures and to conduct a verbal eligibility screen. Men who are interested in participating and meet the eligibility requirements will be asked to sign and return a HIPAA authorization to allow access to medical records to confirm medical eligibility. Once these procedures are complete, potential case participants will be schedule to participate in the study.

7.2 Consent

A waivers of HIPAA authorization has been obtained to allow the University of Washington and the Veterans Affairs Seattle Puget Sound Heath Care System urology clinic study staff to pre-screen patients for eligibility. Clinic study staff will obtain informed consent from medically eligible and interested men to allow their personal contact information to be sent to the FHCRC for recruitment into this study.

Men who self-refer to the study (from outside the VA/UW/Valley health care systems) or who are recruited via CSS will be asked to sign a HIPAA authorization to allow access to medical records to confirm medical eligibility to participate in PALS.

Eligible men will be asked to sign the study I consent to participate in the intervention trial at clinic visit 1. Participants who are recruited from UW/VA/Valley will also complete a HIPAA authorization to allow access to the medical information required to meet study objectives (Participants who self-refer to the study or who are recruited via CSS will already have signed the HIPAA authorization prior to Visit 1).

7.3 Randomization

Participants will be randomly assigned to either the intervention or control arm using a computerized program. In order to evenly distribute men to treatment arm, randomization will be blocked on BMI (25-29.9 or 30+) and age (<65years or 65+).

7.4 Intervention

***Intervention*.** The DPP intervention entails both a dietary program and an exercise component with goal based behavioral teaching. The goal is for participants to lose 7% total body weight over a 6 month time period at a pace of 1-2 pounds per week. Participants will be weighed at the start of each session. The program involves 16, 30-minute to one-hour sessions led by a dietitian over a 24-week period. Each session has a curriculum for the lifestyle coach/dietitian (http://www.cdc.gov/diabetes/prevention/recognition/curriculum.htm#3). These sessions are designed to help the patient adopt, and reinforce, lifelong skills for healthy living. The structured sessions provide training on nutrition, physical activity and behavioral self-management. Over the first 8 sessions, the focus is on teaching the fundamentals of energy intake modification and increasing energy output while learning self-monitoring skills. The last 8 sessions focus on the social, psychological and motivational hurdles to maintain these healthy lifestyle skills. During months 6-12, intervention participants will receive a monthly newsletter to keep them engaged in the study and actively trying to achieve or maintain their weight loss goal. These newsletters will build upon the diet instruction participants received during the first 6 months of the study.

Diet and exercise arm. The diet and exercise intervention is a caloric reduction program aimed at helping participants reduce total intake by 500-1000 calories/day, depending on one's initial body weight, with no more than 25% of calories from fat, and to expend at least 700 calories a week through exercise. The DPP teaches nutrition and behavior change skills: setting calorie and fat gram goals, counting calories of foods, self-monitoring, and coping with challenges to eating behavior changes. Several tools are provided, such as graphs for monitoring weight, participant worksheets, cooking and shopping for lower-fat eating, and etc. Participants

will attend 11 sessions with a study dietitian during the first 6 months of the study (once a week for 4 weeks, then every other week for 8 weeks, then once a month for 3 months) to receive diet and exercise instruction. If necessary, diet instruction can occur via telephone. During each session the dietitian will weigh the participant (or ask the participant to weigh themselves), collect and review calorie-count and physical activity journals, review the participant's dietary changes from the previous week and discuss any issues that may have arisen, providing appropriate behavioral counseling. The intervention will be individualized to the person's dietary preferences***.*** It is important to note that the DPP curriculum includes lessons related to compliance, retention and motivation.

Supervised exercise***.*** In addition, participants will complete up to 24 exercise sessions under the supervision of an exercise physiologist. The first two sessions will be one on one with the exercise physiologist to introduce exercises and provide teaching. The subsequent weekly visits will be supervised, but not one on one. If necessary, exercise instruction and supervision can via telephone. Many of the exercise sessions will coincide with the dietitian sessions.

Exercise test. All participants will undergo a submaximal graded exercise treadmill test (GXT) to 85% predicted heart rate reserve at baseline and at 6 months. The purpose of the GXT is to measure fitness level (predicted aerobic capacity), establish exercise heart rate for training, and ensure safety of exercise training. A screening questionnaire will be administered prior to the GXT to determine whether any contraindications to exercise testing are present. A brief heart and lung exam will also be conducted and the resting ECG reviewed. There will be physician on-call for all of these procedures.

Heart rate monitor. Participants randomized to the diet and exercise group will be asked to wear a heart rate monitor during exercise sessions for one week a month. They will be asked to put the monitor on prior to their daily exercise session. At the end of the exercise session (on average about 30 minutes) they will record the maximal heart rate that appears on the monitor screen. Men in the control group will not wear the heart rate monitor. This tool will allow participants to monitor their exercise intensity with an individual heart rate range, provided by the exercise physiologist based on the GXT, to stay in while they exercise. This will help to ensure that the participant exercises at an appropriate intensity level. We have chosen to use heart rate monitors because they measure kcals and time in activity directly as heart rate increases linearly with activity intensity. Heart rate monitors are also ideal to use for this intervention because they yield data on the time in specific heart rate zones during exercise and sedentary time. This approach will allow us to directly measure number of minutes/week (goal = 150 minutes/week) and whether individual goals are being met. The heart rate monitor data will be downloaded to the study database.

Compliance. Compliance to dietary and physical activity goals will be evaluated both formally and informally. The primary formal tool to assess overall study compliance will be participant weight loss; weight will be measured at each session (using a research scale and a standardized protocol) and if participants are meeting weight loss goals then compliance is achieved. Other formal compliance tools to assess compliance will include study dietitian-directed proactive check-ins and completion of a 3-day diet record (at 6 mo). At each intervention session the dietitian will review progress and any potential barriers, and individual dietary goals will be adjusted as needed.[104] Formal measures for adherence to physical activity goals will include reviewing heart rate monitor data and formal check-ins with the exercise physiologist. Informally, compliance to diet, physical activity and weight loss goals will be assessed by self-monitoring through logs and journaling.[111] In addition, global-study wide tailored messages with diet, physical activity and behavioral strategies content will be delivered by text message and e-blasts. This multi-tiered approach has been shown to maximize adherence and retention during intervention trials.[111]

Controls**.** Written information on standard healthy lifestyle recommendations will be provided along with a 20-30 minutes individual session with a dietitian including 1) US Dietary Guidelines (www.dietaryguidelines.gov); 2) Activity goal of 30 minutes of physical activity 5 days/week; and 3) Discussion of the health benefits of weight loss along with general behavior change suggestions for weight loss.

Follow-up Visits. All participants will come to the Fred Hutch Cancer Prevention Center for study visits at baseline (0), 3, 6 and 12 months. A description of the clinical assessments performed at each follow-up visit is provided below.

7.5 Clinical Assessments
Study visits will occur at baseline, 3, 6 and 12 months. During study visits, participants will undergo anthropometrics, fasting blood studies and/or complete physical activity, food diaries and HRQOL questionnaires. Assessments at 6 months will be used to evaluate the effectiveness of the intervention, and at 12 months will evaluate maintenance of the intervention.

Anthropometric Measurements. Height will be measured at baseline only, and weight, waist (1" above umbilicus), hip circumferences will be measured at baseline, 3, 6 and 12 months. Dual x-ray absorptiometry (DXA) using a GE Lunar iDXA will be obtained to measure overall percent body fat, lean mass and total bone density at baseline and 12 months.

Twelve-hour fasting blood. Fasting blood samples will be collected at baseline, and at 3, 6, and 12 months. Vacutainers will be labeled with participants' study ID and date, processed within 1 hour of collection and stored at -70ºC.

Prostate Tissue. As part of the consent to participate in this study, participants are asked to give permission to investigators to allow a) the collection of two extra prostate biopsy cores during their standard-of-care biopsy (UW and VA participants only), and b) access to pathology tissue from a pre-study biopsy (that was already collected as part of routine medical care for diagnostic purposes) to be used for this study (UW and VA participants only). For VA patients, separate consent allowing the collection of extra biopsy cores during a standard-of-care biopsy, and allowing access to biopsy tissue after used for diagnostic purposes will be obtained at the VAPSHCS by VA study staff on the day of their scheduled biopsy. For participants who are not patients at UW or the VA, since the collection of extra biopsy cores is not possible, they will be asked to sign a separate "Release of Information" allowing access to prostate biopsy tissue collected as part of their routine care. Tissue blocks, fixed in formalin and embedded in paraffin (standard for AS biopsies), will be sent to Dr. Colm Morrissey's laboratory. Participants will be enrolled on study so that the intervention calendar coincides with routine clinical care; no extra biopsies will take place outside of the routine clinical care. Tissue blocks will be cut and sections mounted on charged slides.

Questionnaires (see Appendix).

Food Diary. All participants will complete a 3-day food diary at baseline and 6 months. For men in the diet and exercise arm, the baseline food diary will be used together with information on the participant's body weight, age and usual physical activity level to calculate usual energy intake using the Nutrition Data Systems for Research (NDS-R, University of Minnesota Nutrition Coordinating Center, version 2012). The study dietitian will then compute the average calorie reduction needed to meet study goals individualized for each participant. This calorie level will be explained to each participant as incorporated into the DPP curriculum. At the end of the 6 month intervention, all participants will again complete a 3-day food diary to assess compliance.

Physical Activity. Physical activity will be assessed at baseline and 6 months with a self-administered administered physical activity questionnaire, the Arizona Activity Frequency Questionnaire (AAFQ) (see appendix). The AAFQ is a 59-item scannable questionnaire. The AAFQ has been validated in an eight-day doubly labeled water protocol to measure total energy expenditure.[113] It has been upgraded with the compendium of physical activity codes and MET intensities.[114] The AAFQ categorizes physical activity by leisure, recreational, household, and "other" activity categories. At randomization the AAFQ will assess participants' baseline activity level. These baseline data will inform the types of exercises that the exercise physiologist will prescribe for each participant to meet the intervention physical activity goal of >150 minutes/week of at least 700 kcal of physical activity.

Lifestyle. Demographics, lifestyle habits and family history of prostate cancer will be assed at baseline only. Self-assessments of Lower Urinary track symptoms will be completed by participants at baseline, 3, 6, and 12 months, and medication use will be completed at baseline, 6 and 12 months..

Quality of life. Self-administered quality of life (QOL) questionnaires will be completed by participants at baseline, 3, 6 and 12 months. We will assess the following: 1) anxiety related to PCa with the *Memorial Anxiety Scale for Prostate Cancer* (MAX-PC)[115] ; 2) PCa-specific QOL with the *Expanded Prostate Cancer Index* (EPIC) Short Form[116]; and 3) generic QOL with the extensively validated EQ-5D-5L,[118]

7.6 Outcomes

Serum Biomarkers.

Glucose. Plasma glucose concentrations will be measured in duplicate by an automated glucose oxidase method using SVR glucose test (Behring Diagnostics) Glucose assays will be performed in the Diabetes Research Lab.

Insulin. Insulin concentration will be determined using an immunoenzymatic assay as per manufacturer's instructions (Invitrogen). Insulin assays will be performed in the Diabetes Research Lab.

C-peptide. C-peptide is the cleaved sub-unit of pro-insulin. Levels will be quantified using a solid phase sandwich-type ELISA as per the manufacturer's protocol. The assay uses monoclonal antibodies directed against distinct epitopes of C-peptide (Beckman Coulter). C-peptide assays will be performed in Dr. Plymate's lab.

IGF-1. IGF-1 levels are quantified using a solid phase sandwich-type Enzyme Linked-Immuno-Sorbent Assay (ELISA) as per the manufacturer's protocol. The assay uses monoclonal antibodies directed against distinct epitopes of IGF-1 (R&D Systems). IGF-1 assays will be performed in Dr. Plymate's lab.

IGFBP-3. IGFBP-3 levels will be quantified using in vitro enzyme-linked immunoabsorbent assays following manufacturer's protocol (RayBiotech). IGFBP-3 assays will be performed in Dr. Plymate's lab.

Adiponectin. Adiponectin is quantified using in vitro enzyme-linked immunoabsorbent assays following manufacturer's protocol (RayBiotech). Adiponectin assays will be performed in Dr. Plymate's lab.

Tissue Biomarkers. pIR/IR, pIGF-IR/IGF-IR and pAKT/AKT protein expression will be assessed by IHC. Sections will be rehydrated and incubated with 3% H_2O_2, blocked with avidin/biotin blocking solution (Vector Laboratories Inc.) and then 5% goat serum. The sections will be incubated with either rabbit anti-IGF-1Rα (1:100; Santa Cruz Biotechnology), rabbit anti-phospho-IGF-1R (1:50; Abcam), mouse anti-insulin receptor (1:100; Santa Cruz Biotechnology), rabbit anti-phospho-insulin receptor (1:50; Abcam), rabbit anti-AKT, rabbit anti-phospho-AKT (1:50; Cell Signaling) or rabbit or mouse control IgG at the same concentration, washed and incubated with biotinylated secondary antibody (1:100; Santa Cruz Biotechnology), developed using the Vectastain ABC kit (Vector Laboratories Inc.) and stable DAB (Vector Laboratories), counterstained with hematoxylin, dehydrated, and mounted with Permount (Fisher). All staining will be performed in Dr. Plymate's laboratory. A research pathologist will score the staining and be blinded to intervention arm. Blind duplicates (5%) will be included. IHC staining intensity for each tissue section will be determined as follows: 0=no staining, 1=faint/present staining, 2=strong/intense staining. The percentage of staining cells is then estimated and a composite score calculated by multiplying mean intensity score and percent cells stained positively, and then dividing by number of cores taken.

Pathologic Features. Pathologic findings will be recorded from the baseline and post-intervention biopsies, including Gleason grade, number of cores taken (12 core biopsy is standard); number of cores with cancer, and the percentage of each core involved with cancer. Adverse pathology on surveillance biopsy will be indicated by any of the following: a ≥ 1pt increase in Gleason grade, an increase to > 50% of any one core involved with cancer, and/or an increase in the number of cores involved with cancer.

Intervention Sustainability. Participants will return to the clinic 6 months after the active intervention ends to assess whether they have continued to follow the lifestyle intervention on a long term basis. Additional measures of blood glucose, weight and quality of life will be assessed.

Quality of Life Outcomes.

Memorial Anxiety Scale for Prostate Cancer (MAX-PC). The MAX-PC will measure anxiety related to PCa.

MAX-PC contains subscales that assess general PCa anxiety, anxiety regarding PSA level, and fear of PCa recurrence.

EQ-5D-5L. The EQ-5D-5L is a generic QOL instrument. It is extensively validated and includes domains of mobility, self-care, activity level, pain/discomfort, and anxiety/depression.[118] EQ-5D-5L responses can be used to calculate health state utilities for health economic analyses.

Expanded Prostate Cancer Index (EPIC) Short Form. The EPIC will measures urinary and sexual function and bother.[116] EPIC survey results are transformed into summary scores scaled from 0-100, with a higher score indicating better QOL.

8 RISK / BENEFIT ASSESSMENT

Potential Risks

1. Participants may experience a little discomfort or have a temporary bruise from having blood drawn. Occasionally a participant may feel lightheaded or feel faint when having blood drawn.
2. There is a small risk of medical problems occurring during or after exercise testing.
3. The major risks of participating in this monitored program include fatigue, muscle soreness, and possible joint or skeletal injury or other unspecified medical events.
4. Some participants may feel that coming to clinic visits (including the nutrition and physical activity curriculum training sessions) may be inconvenient and/or burdensome.
5. Some participants may feel that the quality of life questionnaires about sexual and urinary function are embarrassing.
6. . Other potential risks are associated with the collection of personally identifiable and health information from the subjects, and the potential for (a) psychological harm if the subject learns they have a disease or medical condition they were previously unaware of; and (b) a financial and/or employment risk, as a breach of confidential information could make it harder for the subject to find health insurance, life insurance, or employment.

8.1 Protection Against Risks

In the event that this research activity results in an injury, medical treatment will be available, including first aid, emergency treatment and follow up care, as needed. All procedures involving blood collection, DXA, exercise testing and anthropometry will be done at the FHCRC Prevention Center Clinic. Trained staff will be available to assist should a medical emergency occur. An MD licensed in Washington State is the Prevention Center Director. Participants will be informed in the written consent form that payment for any such treatment must be provided by the individual and/or the individual's insurance company.

1. Blood draws are associated with certain physical risks such as bruising, fainting, or phlebitis. We will minimize these risks by making sure that all blood draws will be conducted by well-trained phlebotomists at the FHCRC Prevention Center. Subjects will be asked before the blood draw if they have experienced problems with blood draws in the past, and will be offered an opportunity to lie down during the procedure if they wish. In our experience, blood draws performed in this manner are well tolerated, and any side effects are minimal. Participants should be able to tolerate the loss of 10-20 cc of blood without negative health consequences.
2. We will screen participants so that only participants with no known heart conditions will be tested. Persons with a serious heart condition will not be eligible for this study. Participants may feel tired during or after the exercise test. Recovery generally occurs within 30 minutes. Participants will be continuously monitored and the test will be stopped at any time the participant asks (an emergency stop mechanism is available for subjects to use). A technician with Advanced Cardiac Life Support (ACLS) certification will be present at all times. In persons with an underlying heart condition, there is a slight (less than 1 chance in 1,000) risk of having a sudden heart attack and an even slighter (less than 2 chances in 10,000) risk of sudden death.
3. The risks associated with the exercise intervention will be reduced by proper warm-up/cool-down periods, instruction from a trained exercise specialist at a slow-paced progression which will be determined by the participants' current fitness level and careful monitoring by an exercise specialist. The exercise specialists will teach participants techniques to minimize joint or muscle injury. The risk of medical adverse events is greatly reduced by having all participants complete and pass an exercise test prior to entering the program.

4. We will make every effort to schedule participants to come to the FHCRC at times that are convenient for them. This includes all sessions with the study dietitian and exercise specialist.
5. Participants may choose to not answer any questions that make them feel uncomfortable or embarrassed.
6. To minimize the risk of breach of confidentiality s, we will make sure that all health information and records are labeled with a study identification number and initials. Personally identifiable information will be kept physically separate from any health information, and only one computer file will link the study identification number to the personally identifiable information such as name, address, telephone number, or e-mail address. Only the PI, study coordinator and study staff will have access to this password-protected file.
7. In the extremely rare and unexpected event of an emergency while subjects are attending to the Fred Hutch Prevention Center, a staff member and study staff will be on hand at all times throughout the visit to call for help as needed, and a physician will be on call. For complications arising among subjects that have left clinical facilities, subjects will be provided with the telephone numbers of the PI and the study coordinator, and will be encouraged to call with any problems at any time. Participants will be encouraged to call 911 in case a life-threatening emergency occurs; such an event is unlikely, and it would be extremely unlikely to be related to the study procedures.

8.2 Potential Benefits

Participants will be paid $100 upon completion of the study to help compensate for time and travel.

Participants will receive small study-branded gifts during the study in appreciation of their participation in the study. Below is the plan for distribution of these items:

	Intervention	Control
PALS squeeze apple and gel pack	Clinic visit 1	Clinic visit 4
PALS hat	Clinic visit 3	Clinic visit 4

The data generated from this proposed research study will provide essential information for the scientific community involved in making recommendations for optimal diet and physical activity regimens for men with prostate cancer undergoing active surveillance. This is an important area of research because if lifestyle factors can be shown to improve measures of glucose control, energy balance and subsequent health of prostate cancer patients, then it will have far reaching implications for the thousands of men undergoing active surveillance – hopefully demonstrating that lifestyle changes can prevent more invasive and life-altering procedures (i.e. radical prostatectomy). Thus, with minimal risk to study participants, we will generate data that will be beneficial to men with localized prostate cancer.

Overall, using this proposed study design, we have attempted to minimize any potential risks to study participants, whilst maximizing the amount of important scientific data that can be generated and ultimately shared with the scientific community and the general public.

8.3 Medical Monitoring

Jonathan Wright should be contacted directly at these numbers to report medical concerns or questions regarding safety.
Phone: 206-579-8922
Pager : 206-340-5071

9 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

9.1 Early Discontinuation of Study Treatment

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for early discontinuation of study treatment:

- Participant decision
- Adverse event
- Protocol violation
- Death

If a subject is discontinued from treatment due to a related adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

9.2 Withdrawal of Subjects from the Study

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. This may include subjects who withdraw from study treatment early and who decline to continue to come in for remaining follow-up visits or it may include subjects who completed treatment and decline to come in for remaining follow up visits.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Subjects who withdraw from the study should be encouraged to come in for a final visit.

9.3 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

10 DATA SAFETY MONITORING

Monitoring for data integrity and safety will be the responsibility of the investigators, the FHCRC Institutional Review Board, and a study Data and Safety Monitoring Committee, which will be established prior to recruiting any participants. The following will be included in the monitoring plan for the DSMC: safety of participants and volunteers, reporting of adverse events, validity and integrity of the data, enrollment rate relative to expectation, retention of participants and adherence to protocol, and data completeness.

10.1 Adverse Event Reporting

Adverse events for this study are expected to be very minimal since the diet and physical activity intervention activities have been safely used in many precious intervention studies without incident. Despite the low risk for adverse events, all study staff and investigators will carefully monitor and document any adverse events, which could include the following: bruising or fainting during the blood draws, injury from using the exercise equipment in the PHS Exercise Laboratory, injury from exercise at home (such as a fall) or a medical event during the treadmill test. All such adverse events will be reported to the Principal Investigator within 24 hours. Adverse event reporting to the IRO will occur within the required period of time depending on the nature and severity of the event.

10.2 Data Safety Monitoring Committee

The initial meeting of the DSMC will have primary focus on a review of the proposed study protocol and determination of stopping rules. Due to the low-risk nature of the intervention study, we expect the DSMC to review study progress each year. Informal rather than formal interim analyses will be performed, since the primary endpoints will not be determined until the end of the study. For each DSMC meeting, statistical reports will be prepared four weeks in advance. Tabulations of the distributions of the important variables will be inspected to detect outlying values. After the file has been thoroughly checked, tables and graphs of the data will be made and compared with the previous report. This check will identify major changes in the data that might be indicative of computational or processing errors. Tables will include data presented by study arm. These reports will include adverse events and participant drop-outs. The report will be mailed to members of the DSMC two weeks prior to the meeting.

11 STATISTICAL METHODS AND CONSIDERATIONS

Primary Aim 1. The primary analysis will compare change in fasting glucose level relative to baseline between the intervention and control arms. Global assessment of intervention effects will be evaluated using a two-sided t-test or Wilcoxon rank sum test if normality of the measurement is questionable (as determined by QQ-normal plots). Further analysis will quantify effects of patient age, BMI and other body composition measures on change in fasting glucose using linear regression. Differential effects between intervention and control arms will be quantified using interaction terms. All analyses will compare effects based on intention-to-treat.

Primary Aim 2. Additional analyses will compare changes in levels of C-peptide, insulin, IGF-1, IGF-BP3, and adiponectin relative to baseline measurements between the intervention and control arms. As in Aim 1, we will compare global and subgroup effects based on intention-to-treat analyses.

Primary Aim 3. We will test whether the change in expression of IR, IGF-1R, and AKT on prostate cancer epithelial cells from follow-up surveillance biopsy (6 months post-randomization) relative to 'baseline' (biopsy ~6 months prior to randomization, see Fig. 3) differs between intervention and control arms. Global assessment of intervention effects will be evaluated using a two-sided t-test (or Wilcoxon rank sum test). Linear regression will be used to assess associations of IR, IGF-1R, and AKT expression with systemic measures of glycemic control at 6 months. Exploratory analyses will also evaluate associations between adverse pathology, biomarkers of glycemic control and IR/IGF-1R/AKT expression.

Primary Aim 4. We will test whether PCa patients randomized to the intervention arm are able to sustain the beneficial changes in weight and glucose regulation an additional 6 months after the active intervention. We will follow the DPP research group characterization of sustained weight loss as maintenance of a 7% reduction in weight[17] and sustained glucose regulation as maintenance within 5% of 6-month levels. Because not all participants will achieve 7% weight loss at 6 months, we 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 Aim 1. We will test whether the change in HRQOL, namely urinary and sexual QOL and bother, relative to baseline, 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, SES, marital status, and baseline BMI. The minimally important difference for the HRQOL instruments will be a mean difference of at least 5 points.

Secondary Aim 2. We will use a two-sample test of proportions to determine whether the proportion of participants with adverse pathology (Gleason upgrading, increase in number of positive cores, cores>50% positive) on follow-up surveillance biopsy differs between intervention and control arms.

Table 4. Minimal detectable differences in serum and tissue biomarkers at 80% power, α=0.05 given a sample size of 200 (100 in each of the lifestyle intervention and control arms)

Biomarker	Baseline Mean (SD) or n (%)	*Minimum Detectable Difference (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%

11.1 Sample Size and Randomization

Our power calculations give the minimally detectable intervention effects for endpoints in Primary Specific Aims, setting two-sided alpha error at 5% and power at 80%. We have set a sample size of 100 in each of the intervention and control arms, based both on our overall evaluation of minimum detectable differences across the range of study endpoints and on a reasonable estimate of the number of men we can recruit. The sample size allows for a drop-out rate of 5%, and power calculations assume correlations of 0.70 between baseline and follow-up measures.

Table 4 gives the minimally detectable differences between treatment arms for serum and tissue biomarkers of glucose regulation. We have used a variety of data sources to complete these tables, attempting whenever possible to use data generated from human studies. For serum biomarkers of glucose regulation, we use data from our own pilot study and the PCPT,[133, 134] and for tissue expression of IR/IGF-R1 and AKT we use data from Cox et al.[15] The minimum detectable intervention effects range from 5.3% for serum glucose to 33.1% for insulin. Previous studies have shown that dietary change can induce the following intervention effects: 7% for fasting glucose, 40% for insulin and 2.2 % for adiponectin.[135 37] Our pilot study based on the DPP demonstrated an intervention effect of ↑9.7% for IGFBP3, ↓38% for insulin and ↓14% for C- peptide. Based on these observations, we will have good power to detect changes in all serum biomarkers of glucose regulation, consistent with those seen in other human intervention studies.

For expression of IR, IGF-1R and AKT on surveillance prostate biopsies, the minimum detectable intervention effects are 29.2%, 46.3% and 26.5%, respectively. Previous experimental studies in animals have

shown the following results: a low-fat/low-carbohydrate diet can reduce expression of IR; low-fat, or caloric restriction diets can reduce expression of IGF-1R by 40%; and low-fat and/or low-carbohydrate and no carbohydrate diets reduce expression of AKT by up to 60%.[7, 59-61] Based on these observations, we have very good power to detect changes in IR, IGF-1R and AKT expression on epithelial cells from PCa biopsies.

Table 5 indicates the minimal detectable differences in change, and the power to detect a 5-point change between arms for each QOL tool. For most HRQOL assessments, we have good power to detect the designated minimally important differences (5-points) in QOL scores. Analyses of the association between the intervention and adverse pathology are exploratory in nature; thus, power is limited for this endpoint. Based on our clinical experience, approximately 25% of patients have 'adverse pathology' on their follow-up biopsy. Given the sample size in this study, we will be able to detect a 15% difference between intervention and control arms in the proportion of participants with adverse pathology on follow-up biopsy.

Table 5. Power and MDD for QOL

QOL tool	Baseline Mean (SD)	Mean MDD	Power to detect 5-point difference in score
MAX-PC	14 (9)[136]	4.0	97%
EQ-5D	86 (15)[137]	6.7	63%
EPIC-Urinary bother	86 (14)[138]	6.3	69%
EPIC-Sexual bother	63 (23)[139]	10.3	32%

12 DATA COLLECTION, RETENTION AND CLINICAL MONITORING

12.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject who signs consent or treated with the study intervention or enrolled in the study.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic study forms OR study database when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected, but will be identified by a site number, subject number and initials.

The study staff is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the study staff. A copy of the CRF will remain in the study's files at the completion of the study.

12.2 Data Management Procedures

For this proposal we will adhere to all federal requirements to submit relevant publications to PubMed Central. We will present results from this study at national and international scientific meetings. We will collaborate with other investigators, both within and external to FHCRC to share data and knowledge as required by the NIH. For outside investigators wishing to use the data generated from this study, we will supply de-identified data. These data will be available approximately 12 months after the close of the intervention and after the submission of the primary manuscripts from this study. The costs for data transfer, including generation of data dictionaries and other documentation will be the responsibility of the investigator requesting to use the data. We are cognizant of and completely support the need to share data and resources with other investigators to maximize the NIH investment and prevent duplication of efforts. We welcome collaborations with outside investigators and those wishing to collaborate and use data will be asked to contact Dr. Wright directly.

12.3 Archival of Data

Databases are maintained with nightly backups and security updates.

12.4 Availability and Retention of Investigational Records

The study staff must make study data accessible to the IRB upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The study staff must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (e.g., patient files, signed informed consent forms, copies of CRFs, Essential Document and Study Reference Binders) must be kept secured.

12.5 Monitoring

Monitoring and/or auditing of this study will be performed by Fred Hutchinson Cancer Research Center according to the Institutional Data and Safety Monitoring Plan (DSMP).

12.6 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the IRB.

12.7 Protocol Amendments

Any amendment to the protocol will be written by the Investigator. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB is notified within five working days.

12.8 Institutional Review Boards

The protocol and consent form will be reviewed and approved by the IRB prior to study initiation. Serious adverse events regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the PI before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

12.9 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

During the course of the study, if modifications are made to the consent form that impact the subject, the subject will be re-consented as described above.

12.10 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

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