



Published in final edited form as:

Prostate Cancer Prostatic Dis. 2018 June ; 21(2): 212–220. doi:10.1038/s41391-017-0001-1.

Phase II Prospective Randomized Trial of Weight Loss Prior to Radical Prostatectomy (PCAN-17-0128)

Susanne M Henning, PhD¹, Colette Galet, PhD¹, Kiran Gollapudi, MD¹, Joshua B. Byrd, MD¹, Pei Liang, PhD¹, Zhaoping Li, MD, PhD², Tristan Grogan, PhD³, David Elashoff, PhD³, Clara E. Magyar, PhD⁴, Jonathan Said, MD⁴, Pinchas Cohen, MD⁵, and William J. Aronson, MD^{1,6}

¹Department of Urology, David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California

²Center for Human Nutrition, David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California

³Statistics Core, David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California

⁴Department of Pathology, David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California

⁵USC Davis School of Gerontology, Ethel Percy Andrus Gerontology Center University of Southern California, Los Angeles, California

⁶VA Medical Center Greater Los Angeles Healthcare System

Abstract

BACKGROUND—Obesity is associated with poorly differentiated and advanced prostate cancer and increased mortality. In preclinical models, caloric restriction delays prostate cancer progression and prolongs survival. We sought to determine if weight loss (WL) in men with prostate cancer prior to radical prostatectomy affects tumor apoptosis and proliferation, and if WL effects other metabolic biomarkers.

METHODS—In this Phase II prospective trial, overweight and obese men scheduled for radical prostatectomy were randomized to a 5–8 week WL program consisting of standard structured energy-restricted meal plans (1200–1500 Kcal/day) and physical activity or to a control group. The primary endpoint was apoptotic index in the radical prostatectomy malignant epithelium. Secondary endpoints were proliferation (Ki67) in the radical prostatectomy tissue, body weight, body mass index (BMI), waist to hip ratio, body composition, and serum PSA, insulin,

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: http://www.nature.com/authors/editorial_policies/license.html#terms

Corresponding Author: William J. Aronson, MD, Department of Urology, University of California Los Angeles, Box 951738, Los Angeles, California 90095-1738, Telephone: 310-268-3446; FAX: 310-268-4858; waronson@ucla.edu.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed by the authors.

triglyceride, cholesterol, testosterone, estradiol, leptin, adiponectin, interleukin 6, interleukin 8, insulin-like growth factor 1, and IGF binding protein 1.

RESULTS—Twenty-three patients were randomized to the WL intervention and twenty-one patients to the control group. Subjects in the intervention group had significantly more weight loss (WL: -3.7 ± 0.5 kg; Control: -1.6 ± 0.5 kg; $p=0.007$) than the control group and total fat mass was significantly reduced (WL: -2.1 ± 0.4 ; Control: 0.1 ± 0.3 ; $p=0.015$). There was no significant difference in apoptotic or proliferation index between the groups. Among the other biomarkers, triglyceride and insulin levels were significantly decreased in the WL compared to the control group.

CONCLUSIONS—In summary, this short-term WL program prior to radical prostatectomy resulted in significantly more WL in the intervention *vs.* the control group and was accompanied by significant reductions in body fat mass, circulating triglycerides, and insulin. However, no significant changes were observed in malignant epithelium apoptosis or proliferation. Future studies should consider a longer term or more intensive weight loss intervention.

Keywords

Prostate cancer; clinical trial; apoptosis; weight loss; inflammation; Ki67

INTRODUCTION

Obesity is associated with poorly differentiated and advanced prostate cancer, increased risk of biochemical failure following radical prostatectomy and radiation therapy, and increased prostate cancer mortality (1–8). Multifactorial mechanisms may explain the link between obesity and the increased risk of advanced prostate cancer. Insulin metabolism, IGF-1, IGF binding protein, altered serum levels of sex hormones, pro-inflammatory cytokines, and adipokines may be involved (9–12). Visceral obesity may play an important role in the link between obesity and development of prostate cancer. One study among men in China showed that men in the highest quartile of waist-to-hip ratio had an almost 3-fold increased risk of developing prostate cancer (13). Another study described that central body fat mass was associated with increased high-grade prostate cancer (14). Likewise, increased periprostatic fat mass was associated with higher Gleason grade (15–17).

Whether weight loss (WL) has the potential to delay prostate cancer progression is of great interest. In preclinical studies, energy restriction is well-known to decrease prostate cancer progression and prolong survival in mouse models (18–21). The IGF-AKT pathway, cytokines and adipokines, and microvessel density/vascular endothelial growth factor (VEGF) gene expression play a role in the decrease of prostate cancer progression in mouse models (18, 19, 21). However, evidence from human studies is inconclusive (22). To examine if WL has the potential to slow the progression of prostate cancer, we designed a prospective randomized pre-prostatectomy trial to determine whether WL from a hypocaloric diet and increased physical activity results in anti-proliferative and pro-apoptotic effects on prostate cancer tissue histopathology. Other examined endpoints included weight change, body composition and fat depots, and concentrations of potential mechanistic

markers such as serum lipids, cholesterol, insulin, IGF-1, IGFBP-3, leptin, adiponectin, IL-6, IL-8, testosterone, and estradiol.

MATERIALS AND METHODS

Patient Eligibility and Recruitment

Participants were recruited from the urology clinics at the Veterans Administration Greater Los Angeles Healthcare System, UCLA, and Santa Monica UCLA from 2009 to 2013. Inclusion criteria included BMI of $> 25 \text{ kg/m}^2$, physical ability to undergo a physical activity intervention, and able to come to the VA Clinical Research Center for 7 study visits if randomized to the WL group. Subjects were ineligible if they had Gleason score $>4+5=9$, a history of receiving androgen deprivation therapy, antiandrogen therapy, finasteride, radiotherapy, or cryotherapy. Patients were also excluded if they had a history of diabetes and were receiving insulin, if they were taking weight loss medication or enrolled in a weight loss program, taking lycopene supplements, or had significant co-morbidities (i.e. cardiac, pulmonary, liver disease, and ongoing alcohol/drug abuse) or a cardiac pacemaker. The study was approved by the Institutional Review Boards at the VA and UCLA and registered with ClinicalTrial.gov (NCT#00475982).

Study Design

This was a randomized two-arm open label intervention study. All subjects signed informed consent documents prior to study entry. Subjects were randomized using a permuted block design to either a weight loss program or control group. After randomization, baseline weight, height, waist, hip circumference, and body composition by dual-energy X-ray absorptiometry (DEXA) (GE Lunar DEXA, Chicago, IL; maximum weight capacity 350 lbs) were determined, and fasting blood was collected. The control group proceeded with the scheduled radical prostatectomy. Within 3 days prior to radical prostatectomy, the control group had one additional visit to the clinical research center (CRC) for measurement of weight, height, waist, hip circumference, and fasting blood collection. Performance of a second DEXA scan in the control group prior to radical prostatectomy was added as a protocol modification after the beginning the trial, and therefore the first nine participants in the control group did not have an end of study DEXA scan. The control group was offered a free weight loss program after prostatectomy.

Subjects randomized to the WL group received one of two standard structured energy-restricted meal plans (1200 and 1500 Kcal/day) using commercially available meal replacements and portion-controlled foods. Patients were taught how to count portions and how to consume the recommended calories from commercial ready-made frozen dinners. Prescribed plans were based upon lean body mass as determined by DEXA. The goal of the meal plan was to provide a total calorie intake incorporating 500–800 calorie deficits per day. Subjects had weekly visits with the CRC dietitian for the first 4 weeks, and every 2-week visits for the following 4 weeks and received instruction on recipes, grocery shopping strategies, education on healthy food preparation, and preparation of meal replacements. Prior to each visit, subjects in the WL group completed a 3-day food record to promote compliance and as a tool to assist the dietitian with counseling. Subject's wives or life

partners were encouraged to attend and participate in the sessions. The goal for recommended diets was to contain 20–25% energy from fat, 15–20% from protein, and 50–65% from carbohydrates largely from fruits and vegetables with some whole grains. Fiber recommendations were a total of 25 grams/day from fruits, vegetables, legumes, and high fiber cereals.

Patients in the WL group were counseled on performing 1 hour of exercise/day including aerobic, resistance, and flexibility activities such as walking and stretching. As an exercise incentive, patients were provided pedometers (Omron HJ-112 Digital Premium Pedometer, Bannockburn, IL) and exercise logs to complete and results were reviewed with the dietitian at each visit. As shown by Bravata et al., the use of pedometers is associated with significant increase in physical activity (23). Following the 5 to 8-week weight loss intervention and within 3 days prior to radical prostatectomy, weight, height, and waist to hip ratio were measured, fasting serum for biomarker analysis collected, and a DEXA scan was performed.

Outcomes

The primary endpoint was apoptotic index in the radical prostatectomy malignant epithelium. Secondary endpoints were proliferation (Ki67) in the radical prostatectomy malignant epithelium, body weight, BMI, waist to hip ratio, body composition, and serum PSA, insulin, triglyceride, cholesterol, testosterone, estradiol, leptin, adiponectin, IL-6, IL-8, IGF-1, and IGFBP-1 levels.

Serum Analyses

Serum PSA, triglyceride, total cholesterol, LDL- and HDL-cholesterol, insulin, testosterone, and estradiol were measured by the UCLA clinical laboratory using standard laboratory methods. Serum leptin and adiponectin concentrations were measured using ELISA kits according to manufacturer instructions (Invitrogen, Carlsbad, CA) with coefficient of variation (CV) for leptin: Intra-assay CV 3.0–3.8% and inter-assay CV 3.9–4.6% (147–884 pg/mL), and adiponectin intra-assay CV 3.8–3.0% and inter-assay CV 5.2–2.8% (1.9–24.8 pg/mL). Serum IL-6 and IL-8 were quantified using ELISA kits from BD Biosciences (San Jose, CA) according to instructions with the following CV for IL-6: Intra-assay CV 4.1–10.8% (43.6–146.9 pg/mL) and inter-assay CV 10.9–7.9% (39.1–147.8 pg/mL) and IL-8: Intra-assay CV 4.2–5.5% (27.4–92.1 pg/mL) and 3.4–3.2% (27.2–99.9 pg/mL).

Plasma IGF-1 and IGFBP-1 concentrations were determined using a validated ‘in-house’ ELISA assay at the University of Southern California Aging Biomarker Service Core (Los Angeles, CA) with CV <10% (24).

Immunohistochemistry

Serial sections for immunohistochemical analyses were cut from archived paraffin embedded blocks with the largest cancer volume and with the Gleason grade corresponding to the grade on the final pathology report. Slides were stained for Ki67 (monoclonal mouse anti-human Ki67 antigen [Dako Omnis/Agilent, Santa Clara, CA]) and TUNEL (ApopTag® Plus Peroxidase In Situ Apoptosis Kit [Millipore, Temecula, CA]) (25) to assess proliferation and apoptosis, respectively. The areas of adenocarcinoma were circled by the

study pathologist (J.S.) Slides were digitized on a ScanScope AT (Aperio Technologies, Inc., Vista, CA) and morphimetric analysis performed with *Definiens'* Tissue Studio (Definiens Inc., Parsippany, NJ) to determine the percentage of Ki67 or TUNEL positive cells in a non-biased method. Briefly, using the pre-defined nuclear detection module and classification tool, positive and negative nuclei within each region of interest were identified. Thresholds were set to classify hematoxylin stain for negative nuclei and DAB stain for positive nuclei. The data were exported to Excel for further statistical analysis. The number of Ki67 or TUNEL-stained nuclei per total cells in the adenocarcinoma region was used to calculate the percent of positive stained cells (26). Scanning and analyses were performed through the Translational Pathology Core Laboratory, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA.

Statistical Analysis

A sample size of 65 subjects [no weight loss = 35, weight loss = 30] was estimated to provide 80% power to detect an effect size of 0.74 using a two group t-test with a 0.050 two-sided significance when comparing the apoptotic index (primary outcome variable) in the radical prostatectomy malignant epithelium between the WL and no WL groups. To put this effect size in context, a similar study looking at a nutritional intervention by Kim et al. observed an effect size of 1.81 on apoptotic index using a nutritional intervention with similar study characteristics (27). To account for a post-randomization attrition rate of up to 15% in the WL group, we planned to randomize 35 subjects to the WL group.

After 34 subjects fully completed the trial, an interim analysis was performed to evaluate the feasibility of finding a statistically significant difference between the groups for the primary outcome. A conditional power analysis demonstrated that, with enrollment of 65 participants, there was only a 0.9% chance of finding a significant difference in the apoptotic index between the treatment and control group. At this point, study enrollment was closed and secondary endpoint analyses were performed.

Baseline patient characteristics were compared between groups using mean \pm SD and frequencies. Secondary outcomes were measured both at baseline and prior to surgery and change from baseline to surgery was calculated. Within each group, changes from pre to post were calculated using the paired t-test. Next these changes were compared between control and WL intervention groups using the two sample t-test. For outcomes that had skewed distribution, a log transformation was implored prior to conducting the t-test. P values less than 0.05 were considered significant. Statistical analyses were carried out using IBM SPSS V24 (Armonk, NY). The data are presented as mean \pm SD or SEM where appropriate.

RESULTS

Baseline Characteristics

Twenty-three patients were randomized to the WL intervention and twenty-one patients to the control group. Seven patients in the WL group and three from the control group withdrew from the study with 34 patients completing the trial (Figure 1). The baseline

characteristics of the 34 patients that completed the trial are shown in Table 1. All participants were overweight or obese. In the WL group, 44% were overweight, 44% obese, and 12% morbidly obese at baseline, while, in the control group, 31% were overweight, 44% obese, and 25% morbidly obese. Sixty seven percent of patients in the control group and 69% in the WL group were taking statins. The mean PSA in the WL group was 6.8 ± 2.5 compared to control group 7.5 ± 8.0 (Table 1). There was no significant difference in age, race, ethnicity, statin use, Gleason Score, and disease stage between the two groups (Table 1).

Body Weight and Composition

The mean time from study enrollment until radical prostatectomy was 62 ± 19 days in the control group and 51 ± 16 days in the WL group. Although patients had significant WL in both groups, subjects on the WL intervention had more weight loss (-3.7 ± 1.9 kg) compared to the control group (-1.6 ± 2.3 kg) (Table 2). Patients in the WL group also had a greater decline in BMI (-1.2 ± 0.6) as compared to the control group. (-0.5 ± 0.7) (Table 2). The WL intervention group had a greater decrease in fat mass (WL group -2.1 ± 1.8 vs. control group 2.2 ± 6.2) and decrease in percent gynoid fat (WL group 1.4 ± 1.9 vs. control group 0.2 ± 1.3 , Table 2). There was a trend for a greater decrease in percent body fat in the WL group ($p = 0.06$) vs. the control group. No significant change was observed in lean body mass, percent trunk fat, and percent android fat between the groups.

Prostate Cancer Tissue Apoptosis and Proliferation

There was no significant difference in apoptotic index in radical prostatectomy tumor tissue (Primary Endpoint) as measured by TUNEL between the groups (Figure 2A). Likewise, there was no significant difference in the proliferation index as measured by Ki67 staining between the groups (Figure 2B).

Serum Lipid, Adipokine, Hormone, Cytokine, and IGF/IGFBP-1

During the intervention period, there was a significant 33% decrease in serum triglyceride from 208 ± 194 to 140 ± 79 mg/dL in the WL group, while triglycerides increased in the control group from 131 ± 51 to 138 ± 71 . Likewise, serum insulin levels decreased in the WL group from 17 ± 10 to 13.8 ± 7 and increased in the control group from 12 ± 7 to 14 ± 9 μ IU/mL. There was no significant difference in serum total cholesterol or HDL-cholesterol between the WL and control groups (Table 3). There was a significant between group difference in LDL-cholesterol levels with a decrease in the control group as compared to the WL group. There were no significant between group changes in adipokines, testosterone, estradiol, IL-6, IL-8, IGF-1, and IGFBP-1 levels.

DISCUSSION

Obesity is a well-established factor associated with increased risk and mortality of a number of human malignancies (28). Given the well-known impact of obesity on prostate cancer aggressiveness and mortality and the significant effect of caloric restriction on prostate cancer progression in preclinical models, there is strong evidence to support the conduct of clinical trials evaluating WL as a therapy for men with prostate cancer. Although the short-

term WL intervention in our trial did not impact apoptosis or proliferation in radical prostatectomy malignant epithelium, biomarker results from our trial and others suggest the potential for clinical benefit of WL for men with prostate cancer. For example, a significant reduction in percent body fat was observed over the course of the trial. Previous studies showed that central body fat mass was associated with increased high-grade prostate cancer (14). Likewise, increased periprostatic fat mass was also associated with higher Gleason grade (15–17). Iyengar *et al.* recently reviewed the pro-inflammatory and pro-carcinogenic effects of hyperadiposity on the tumor microenvironment, and discussed the link between chronic low-grade inflammation and hyperinsulinemia (29). Noteworthy, in the current study circulating insulin levels were also reduced in the WL group (–18% compared to +18% in the control group), and insulin is a known growth factor for prostate cancer.

A number of short-term clinical studies examined whether WL favorably modifies hormonal factors associated with prostate cancer progression. A small (n=11) short-term intensive WL intervention with a very low fat diet (<10% kcal from fat) in overweight and obese men was found to modify serum factors (IGF-1 decreased by 20%, IGFBP-1 increased by 53%, and insulin decreased by 25%) and decreased serum-stimulated growth of LNCaP cells was observed in an ex-vivo bioassay (30). It is noteworthy that patients lost more weight in this trial (4.2% WL over an 11-day period) as compared to our trial (1.5% WL in the control group and 3.7% WL in the treatment group), and in our trial IGF-1 and IGFBP-1 levels did not change. Given that the IGF axis may play a key role in the effects of weight loss on prostate cancer, it may be that the degree of weight loss in our trial was not adequate to affect tissue apoptosis. In another trial, Lin *et al.* reported that a 6-week low-fat, low-glycemic load diet resulted in significant WL (5.5%) and gene expression changes in 26 genes comparing biopsy tissue collected before and after diet intervention (31). In another small randomized trial, a 6-week caloric restricted diet in men with prostate cancer resulted in significant WL (–1.7%) and an increase in serum IGFBP-3 (+2.8%) compared to controls (WL +1%, IGFBP-3 –6.9%) (32). No significant changes in serum insulin, IGF-1 and adiponectin were observed (31). Heymach *et al.* conducted a controlled prospective randomized 4-arm pre-prostatectomy trial incorporating a low-fat diet and flax seed. They reported that WL significantly correlated with reduction in plasma VEGF levels, TNF-related apoptosis-inducing ligand (TRAIL) levels, and five other pro-inflammatory cytokines (33). Fabian *et al.* demonstrated a 10% weight loss along with a significant decrease in Ki67 staining in breast cancer tissue (34). Another preprostatectomy weight loss study is ongoing (35). These investigators reported 9% weight loss in the intervention group and 6.2% weight loss in the control group, but have not yet reported on changes in tumor biomarkers (36).

A number of mechanisms have been proposed linking obesity to advanced prostate cancer. As shown in animal studies, alterations in insulin metabolism, IGF-1, IGF binding protein, altered serum levels of sex hormones and pro-inflammatory cytokines, and adipokines might be involved (37, 38). The IGF axis is a frequently investigated target in prostate cancer since it plays an important role in cell proliferation, cell differentiation, apoptosis, and glucose and lipid metabolism (39). In a previous study by our group, long-term consumption of a low-fat/high-fiber diet, including soy for 6 months in prostate cancer patients following radical prostatectomy resulted in decreased serum IGF-1 compared with the consumption of the

USDA recommended diet (40). In the present trial, we did not find any change in IGF-1 or IGFBP-1.

In the current trial, we found a decrease in serum triglycerides, total cholesterol, and fat mass, which was expected with WL. A recent meta-analysis found that there was no relationship between serum triglyceride and prostate cancer risk (41). Although a decrease in fat mass may potentially result in a decrease of inflammatory cells in adipose tissue, we did not find any decrease in serum IL-6 or IL-8 levels.

Noteworthy, in our present trial, there was significant WL in the control group (-1.6 ± 2.3 kg). However, between group comparisons demonstrated significantly more WL in the intervention group (-3.7 ± 1.9 kg) as compared to the control group. Through the standard consenting process, research subjects are aware of general aspects of the control and intervention groups and often desire randomization to the intervention group. Our trial and others demonstrated that patients randomized in the control group often self-implement behavioral changes and, in this case, achieved WL (42). In our trial, the incremental difference in weight loss between the intervention and control group was relatively low at 2.1 kg. Weight loss in the control group also occurred in other studies (36). Consideration should be given to implementing active interventions in the control group to prevent WL. Future trials should also consider more intensive weight loss interventions to achieve a greater difference in weight loss between the treatment and control groups. In this regard, data from our trial may be useful for power calculations for future randomized WL intervention trials in men with prostate cancer.

A number of study designs may be appropriate for future WL intervention trials in men with prostate cancer. For example, men on active surveillance undergoing targeted same sight biopsies may be an ideal study population to undergo a long-term intervention. Another population to consider would be men on androgen deprivation for prostate cancer. Androgen deprivation is known to increase body fat, making this potentially an ideal population for future studies (43). In a prospective randomized trial incorporating diet and exercise, O'Neill *et al.* reported significant WL, reduction in total body fat, and improved functional capacity in men on androgen deprivation therapy, though they did not report on biomarkers related to prostate cancer progression (44).

There are several limitations to our study. Our trial was a short-term pre-prostatectomy trial, and a longer intervention may be required to observe tissue biomarker changes as a result of WL. Men in the study lost on average 0.5 kg per week. It appears that participants did not completely follow the dietary instructions since they should have lost more weight if eating a 1200 or 1500 kcal diet. The compliance measure in the present study was weight loss. We did not report food intake data and pedometer readings. This information may potentially be useful for designing future trials and evaluating compliance. A number of pre-prostatectomy dietary intervention trials incorporating dietary supplements such as fish oil and flax seed, and increased dietary intake of lycopene rich tomato sauce reported changes in tissue biomarkers, but WL without a specific focus on selected dietary nutrients may require longer term interventions (27, 45). In addition, our trial was offered to all overweight and obese patients undergoing radical prostatectomy at the VA and UCLA. Future research should

focus on selecting out specific patients more likely to respond to WL interventions based on inflammatory markers and thus incorporate “precision medicine” markers prior to enrollment.

CONCLUSION

In summary, our short-term WL program prior to radical prostatectomy resulted in significantly more WL in the intervention *vs.* the control group and was accompanied by significant reduction in body fat mass, circulating triglycerides, and insulin levels. However, there were no significant changes in malignant epithelium apoptosis or proliferation levels. Based on the known association of obesity and lethal prostate cancer, future longer-term or more intensive weight loss intervention trials are warranted to further examine if WL has therapeutic benefits in men with prostate cancer.

Acknowledgments

Grant sponsor: National Institute of Health P50CA92131 (WJA); Merit Review Award from the United States Department of Veterans Affairs. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government. Statistical analyses were supported by NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR001881 (TG/DE).

References

1. Moller H, Roswall N, Van Hemelrijck M, Larsen SB, Cuzick J, Holmberg L, et al. Prostate cancer incidence, clinical stage and survival in relation to obesity: a prospective cohort study in Denmark. *Int J Cancer*. 2015 Apr 15; 136(8):1940–7. [PubMed: 25264293]
2. Haque R, Van Den Eeden SK, Wallner LP, Richert-Boe K, Kallakury B, Wang R, et al. Association of body mass index and prostate cancer mortality. *Obes Res Clin Pract*. 2014 Jul-Aug;8(4):e374–81. [PubMed: 25091359]
3. Goris Gbenou MC, Peltier A, Schulman CC, Velthoven R. Increased body mass index as a risk factor in localized prostate cancer treated by radical prostatectomy. *Urol Oncol*. 2016 Jun; 34(6): 254.e1–6.
4. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol*. 2013 May; 63(5):800–9. [PubMed: 23219374]
5. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *Int J Cancer*. 2007 Oct 1; 121(7):1571–8. [PubMed: 17450530]
6. Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, et al. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*. 2007 Jan; 16(1):63–9. [PubMed: 17179486]
7. Stocks T, Hergens MP, Englund A, Ye W, Stattin P. Blood pressure, body size and prostate cancer risk in the Swedish Construction Workers cohort. *Int J Cancer*. 2010 Oct 1; 127(7):1660–8. [PubMed: 20087861]
8. Bonn SE, Wiklund F, Sjolander A, Szulkin R, Stattin P, Holmberg E, et al. Body mass index and weight change in men with prostate cancer: progression and mortality. *Cancer Causes Control*. 2014 Aug; 25(8):933–43. [PubMed: 24810654]
9. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med*. 2010; 61:301–16. [PubMed: 19824817]
10. Ho E, Boileau TW, Bray TM. Dietary influences on endocrine-inflammatory interactions in prostate cancer development. *Arch Biochem Biophys*. 2004 Aug 1; 428(1):109–17. [PubMed: 15234275]

11. Saglam K, Aydur E, Yilmaz M, Goktas S. Leptin influences cellular differentiation and progression in prostate cancer. *J Urol*. 2003 Apr; 169(4):1308–11. [PubMed: 12629349]
12. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr*. 2004 Sep; 92(3):347–55. [PubMed: 15469638]
13. Hsing AW, Deng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Benichou J, et al. Body size and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev*. 2000 Dec; 9(12):1335–41. [PubMed: 11142419]
14. Moran Pascual E, Martinez Sarmiento M, Budia Alba A, Broseta Rico E, Camara Gomez R, Boronat Tormo F. Central Body Fat Mass Measured by Bioelectrical Impedancimetry But Not Body Mass Index Is a High-Grade Prostate Cancer Risk Factor. *Urol Int*. 2016 Jul 6.
15. Bhindi B, Trottier G, Elharram M, Fernandes KA, Lockwood G, Toi A, et al. Measurement of periprostatic fat thickness using transrectal ultrasonography (TRUS): a new risk factor for prostate cancer. *BJU Int*. 2012 Oct; 110(7):980–6. [PubMed: 22372862]
16. Tan WP, Lin C, Chen M, Deane LA. Periprostatic Fat: A Risk Factor for Prostate Cancer? *Urology*. 2016 Dec; 98:107–12. [PubMed: 27592523]
17. Woo S, Cho JY, Kim SY, Kim SH. Periprostatic fat thickness on MRI: correlation with Gleason score in prostate cancer. *AJR Am J Roentgenol*. 2015 Jan; 204(1):W43–7. [PubMed: 25539273]
18. Kobayashi N, Barnard RJ, Said J, Hong-Gonzalez J, Corman DM, Ku M, et al. Effect of low-fat diet on development of prostate cancer and Akt phosphorylation in the Hi-Myc transgenic mouse model. *Cancer Res*. 2008 Apr 15; 68(8):3066–73. [PubMed: 18413778]
19. Mukherjee P, Sotnikov AV, Mangian HJ, Zhou JR, Visek WJ, Clinton SK. Energy intake and prostate tumor growth, angiogenesis, and vascular endothelial growth factor expression. *J Natl Cancer Inst*. 1999 Mar 17; 91(6):512–23. [PubMed: 10088621]
20. Buschemeyer WC 3rd, Klink JC, Mavropoulos JC, Poulton SH, Demark-Wahnefried W, Hursting SD, et al. Effect of intermittent fasting with or without caloric restriction on prostate cancer growth and survival in SCID mice. *Prostate*. 2010 Jul 1; 70(10):1037–43. [PubMed: 20166128]
21. Cho HJ, Kwon GT, Park H, Song H, Lee KW, Kim JI, et al. A high-fat diet containing lard accelerates prostate cancer progression and reduces survival rate in mice: possible contribution of adipose tissue-derived cytokines. *Nutrients*. 2015 Apr 09; 7(4):2539–61. [PubMed: 25912035]
22. Liss MA, Schenk JM, Faino AV, Newcomb LF, Boyer H, Brooks JD, et al. A diagnosis of prostate cancer and pursuit of active surveillance is not followed by weight loss: potential for a teachable moment. *Prostate Cancer Prostatic Dis*. 2016 Dec; 19(4):390–4. [PubMed: 27431498]
23. Bravata DM, Smith-Spangler C, Sundaram V, Gienger AL, Lin N, Lewis R, et al. Using pedometers to increase physical activity and improve health: a systematic review. *JAMA*. 2007 Nov 21; 298(19):2296–304. [PubMed: 18029834]
24. Muzumdar RH, Ma X, Fishman S, Yang X, Atzmon G, Vuguin P, et al. Central and opposing effects of IGF-I and IGF-binding protein-3 on systemic insulin action. *Diabetes*. 2006 Oct; 55(10):2788–96. [PubMed: 17003344]
25. Kobayashi N, Barnard RJ, Henning SM, Elashoff D, Reddy ST, Cohen P, et al. Effect of altering dietary omega-6/omega-3 fatty acid ratios on prostate cancer membrane composition, cyclooxygenase-2, and prostaglandin E2. *Clin Cancer Res*. 2006 Aug 1; 12(15):4662–70. [PubMed: 16899616]
26. Ong CW, Kim LG, Kong HH, Low LY, Wang TT, Supriya S, et al. Computer-assisted pathological immunohistochemistry scoring is more time-effective than conventional scoring, but provides no analytical advantage. *Histopathology*. 2010 Mar; 56(4):523–9. [PubMed: 20459559]
27. Kim HS, Bowen P, Chen L, Duncan C, Ghosh L, Sharifi R, et al. Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. *Nutr Cancer*. 2003; 47(1):40–7. [PubMed: 14769536]
28. Goodwin PJ, Chlebowski RT. Obesity and Cancer: Insights for Clinicians. *J Clin Oncol*. 2016 Dec 10; 34(35):4197–202. [PubMed: 27903158]
29. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and Cancer Mechanisms: Tumor Microenvironment and Inflammation. *J Clin Oncol*. 2016 Dec 10; 34(35):4270–6. [PubMed: 27903155]

30. Ngo TH, Barnard RJ, Tymchuk CN, Cohen P, Aronson WJ. Effect of diet and exercise on serum insulin, IGF-I, and IGFBP-1 levels and growth of LNCaP cells in vitro (United States). *Cancer Causes Control*. 2002 Dec; 13(10):929–35. [PubMed: 12588089]
31. Lin DW, Neuhaus ML, Schenk JM, Coleman IM, Hawley S, Gifford D, et al. Low-fat, low-glycemic load diet and gene expression in human prostate epithelium: a feasibility study of using cDNA microarrays to assess the response to dietary intervention in target tissues. *Cancer Epidemiol Biomarkers Prev*. 2007 Oct; 16(10):2150–4. [PubMed: 17932364]
32. Wright JL, Plymate S, D’Oria-Cameron A, Bain C, Haugk K, Xiao L, et al. A study of caloric restriction versus standard diet in overweight men with newly diagnosed prostate cancer: a randomized controlled trial. *Prostate*. 2013 Sep; 73(12):1345–51. [PubMed: 23775525]
33. Heymach JV, Shackelford TJ, Tran HT, Yoo SY, Do KA, Wergin M, et al. Effect of low-fat diets on plasma levels of NF-kappaB-regulated inflammatory cytokines and angiogenic factors in men with prostate cancer. *Cancer Prev Res (Phila)*. 2011 Oct; 4(10):1590–8. [PubMed: 21764858]
34. Fabian CJ, Kimler BF, Donnelly JE, Sullivan DK, Klemp JR, Petroff BK, et al. Favorable modulation of benign breast tissue and serum risk biomarkers is associated with > 10 % weight loss in postmenopausal women. *Breast Cancer Res Treat*. 2013 Nov; 142(1):119–32. [PubMed: 24141897]
35. Demark-Wahnefried W, Nix JW, Hunter GR, Rais-Bahrami S, Desmond RA, Chacko B, et al. Feasibility outcomes of a presurgical randomized controlled trial exploring the impact of caloric restriction and increased physical activity versus a wait-list control on tumor characteristics and circulating biomarkers in men electing prostatectomy for prostate cancer. *BMC Cancer*. 2016 Feb 05; 16:61. [PubMed: 26850040]
36. Fruge AD, Ptacek T, Tsuruta Y, Morrow CD, Azrad M, Desmond RA, et al. Dietary Changes Impact the Gut Microbe Composition in Overweight and Obese Men with Prostate Cancer Undergoing Radical Prostatectomy. *J Acad Nutr Diet*. 2016 Dec 14.
37. Mistry T, Digby JE, Desai KM, Randeve HS. Obesity and prostate cancer: a role for adipokines. *Eur Urol*. 2007 Jul; 52(1):46–53. [PubMed: 17399889]
38. Berger NA. Obesity and cancer pathogenesis. *Ann N Y Acad Sci*. 2014 Apr; 1311:57–76. [PubMed: 24725147]
39. Heidegger I, Massoner P, Sampson N, Klocker H. The insulin-like growth factor (IGF) axis as an anticancer target in prostate cancer. *Cancer Lett*. 2015 Oct 28; 367(2):113–21. [PubMed: 26231734]
40. Li Z, Aronson WJ, Arteaga JR, Hong K, Thames G, Henning SM, et al. Feasibility of a low-fat/high-fiber diet intervention with soy supplementation in prostate cancer patients after prostatectomy. *Eur J Clin Nutr*. 2008 Apr; 62(4):526–36. [PubMed: 17392697]
41. Ma HQ, Cui LH, Li CC, Yu Z, Piao JM. Effects of Serum Triglycerides on Prostate Cancer and Breast Cancer Risk: A Meta-Analysis of Prospective Studies. *Nutr Cancer*. 2016 Oct; 68(7):1073–82. [PubMed: 27618148]
42. Waters L, George AS, Chey T, Bauman A. Weight change in control group participants in behavioural weight loss interventions: a systematic review and meta-regression study. *BMC Med Res Methodol*. 2012 Aug 08; 12:120. [PubMed: 22873682]
43. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology*. 2004 Apr; 63(4):742–5. [PubMed: 15072892]
44. O’Neill RF, Haseen F, Murray LJ, O’Sullivan JM, Cantwell MM. A randomised controlled trial to evaluate the efficacy of a 6-month dietary and physical activity intervention for patients receiving androgen deprivation therapy for prostate cancer. *J Cancer Surviv*. 2015 Sep; 9(3):431–40. [PubMed: 25916660]
45. Demark-Wahnefried W, Polascik TJ, George SL, Switzer BR, Madden JF, Ruffin MT, et al. Flaxseed supplementation (not dietary fat restriction) reduces prostate cancer proliferation rates in men presurgery. *Cancer Epidemiol Biomarkers Prev*. 2008 Dec; 17(12):3577–87. [PubMed: 19064574]

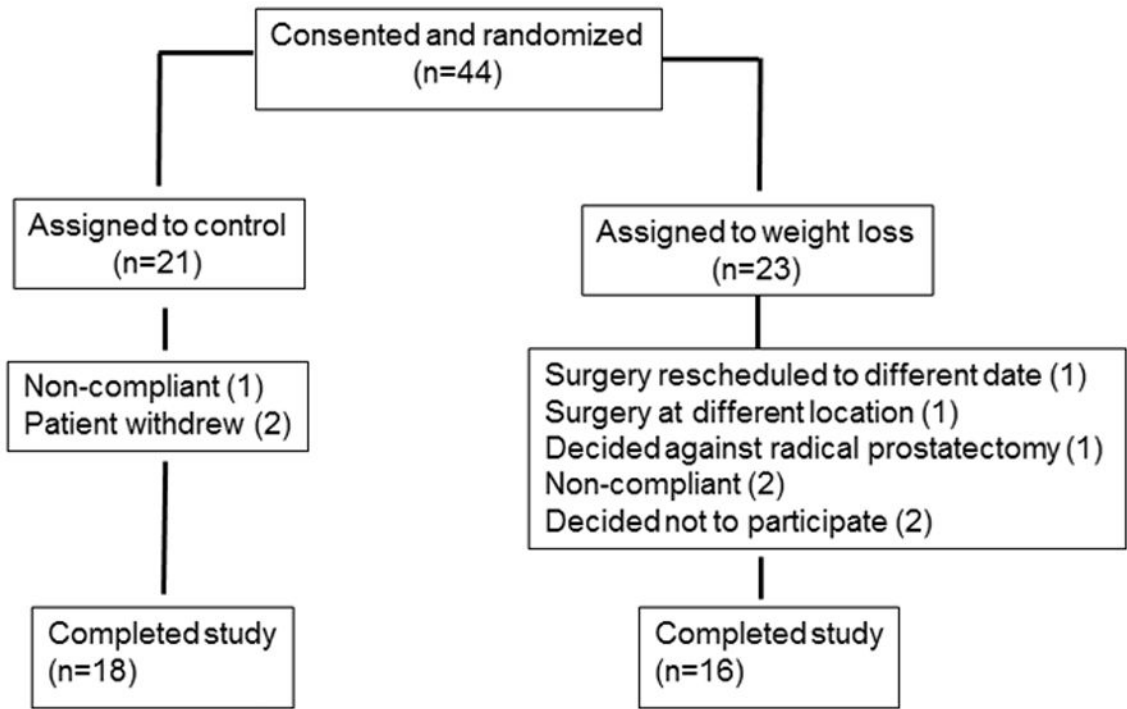


Figure 1.
CONSORT Diagram

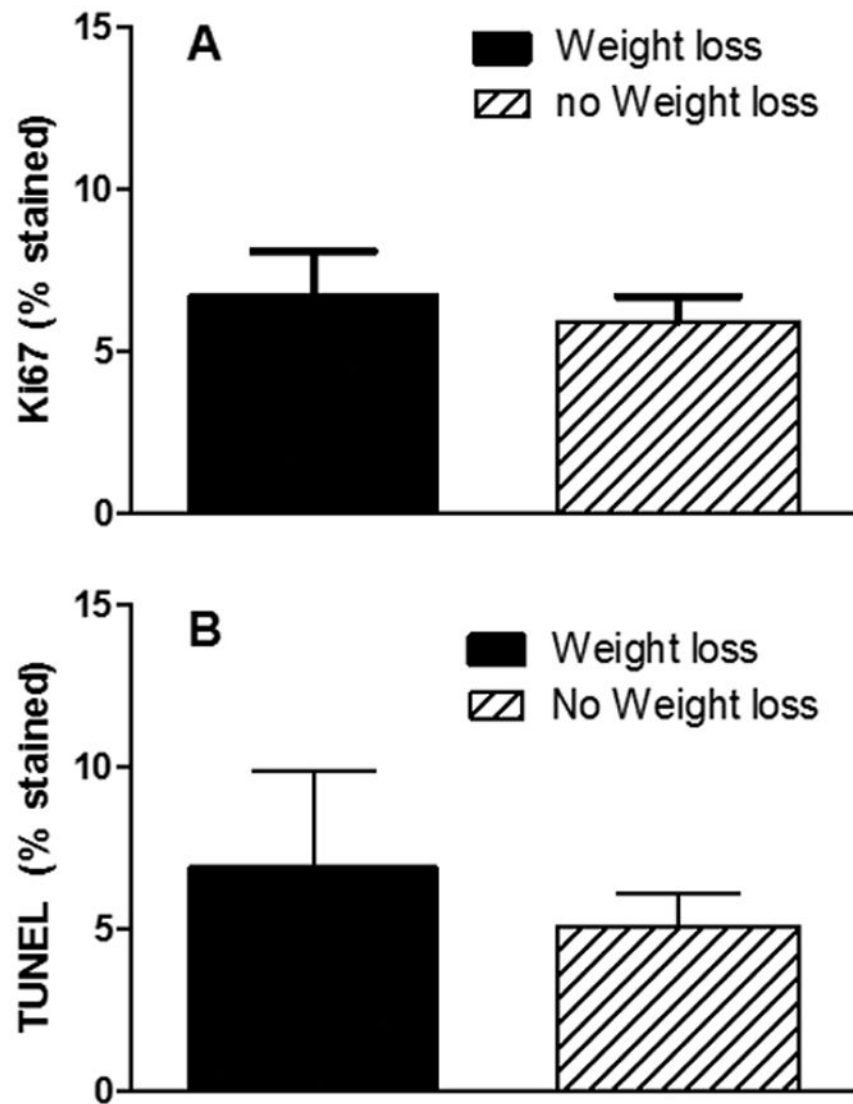


Figure 2. Effect of WL intervention on proliferation and apoptosis in tumor prostate tissue from post-intervention radical prostatectomy specimens. A) Ki67 staining and B) TUNEL. Data are presented as mean \pm SEM for each group (n = 18 control, n = 16 WL). Statistical significance was assessed using two independent sample t-test; p < 0.05.

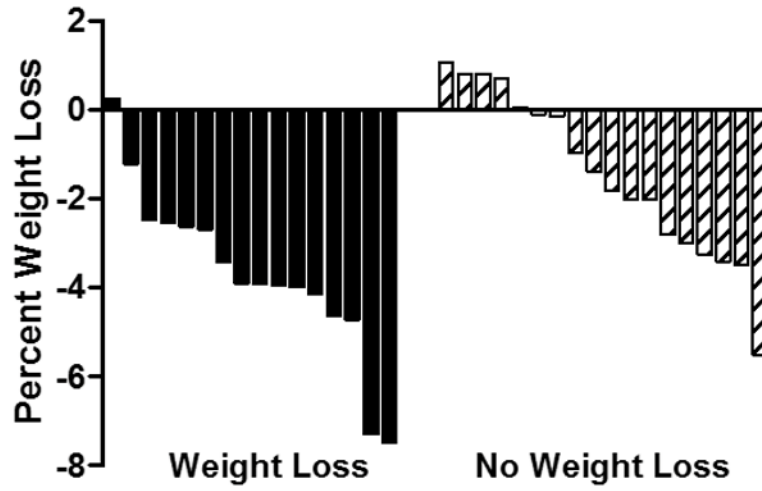


Figure 3.
Waterfall plot of weight loss (n = 18 control, n = 16 WL).

Table 1

Baseline characteristics of study participants

	Control (n = 18)	Weight Loss (n = 16)
Ethnicity		
Caucasian (No.)	14	11
Black American (No.)	3	5
Hispanic (No.)	1	0
Age (y), mean \pm SD	61.7 \pm 1.5	63.4 \pm 1.2
PSA (ng/mL; mean \pm SD)	7.5 \pm 1.9	6.8 \pm 0.6
BMI pre	31.7 \pm 1.1	32.9 \pm 1.5
Gleason sum at diagnosis (No.)		
6	6	4
7	8	9
8–9	4	3
No. of positive cores		
Mean \pm SD	3.0 \pm 2.9	2.8 \pm 3.0
Days in Study (d), mean \pm SD	61.7 \pm 4.2	51.3 \pm 3.9
Days in Study (d), range	33–96	29–89

Values presented as Mean \pm SEM or frequency.

Table 2

Changes in body composition

Study Outcomes	Control	WL	p-value
	Post-intervention minus pre-intervention	Post-intervention minus pre-intervention	
Weight (kg)	-1.6 ± 0.5	-3.7 ± 0.5**	0.007
BMI (kg/m ²)	-0.5 ± 0.2	-1.2 ± 0.6**	0.005
Waist (cm)	-0.4 ± 0.2	1.0 ± 0.3	0.113
Hip (cm)	-1.2 ± 0.7	-0.5 ± 0.45	0.390
Fat mass (kg)	0.1 ± 0.3	-2.1 ± 0.4*	0.015
Lean mass (kg)	-0.7 ± 0.4	-1.6 ± 0.6	0.304
Body fat (%)	0.4 ± 0.3	-0.9 ± 0.5	0.063
Trunk fat (%)	0.6 ± 0.4	-0.9 ± 0.7	0.125
Gynoid fat (%)	0.2 ± 0.4	-1.4 ± 0.5*	0.032
Android fat (%)	0.6 ± 0.3	-1.0 ± 0.8	0.156

Data represent mean ± SEM. N = 18 for control and n = 16 for WL group. Within each group the difference between baseline and end of intervention was evaluated using paired t-test;

* p 0.05,

** p<0.01.

Changes between groups were calculated using two independent sample t-test.

Table 3

Changes in metabolic and inflammatory biomarkers

Study Outcomes	Control	WL	p-value ^a
	Post-intervention minus pre-intervention	Post-intervention minus pre-intervention	
Triglyceride (mg/dL)	7.0 ± 9.3	-67.5 ± 30.1 *	0.019
Cholesterol (mg/dL)	-9.7 ± 5.9	-6.1 ± 6.1	0.672
LDL-Chol (mg/dL)	-11.2 ± 5.7	5.4 ± 5.2 *	0.041
HDL-Chol (mg/dL)	0.06 ± 1.4	-0.8 ± 1.0	0.639
Leptin (pg/mL)	22.6 ± 77.5	-141.2 ± 99.7	0.201
Adiponectin (pg/mL)	0.3 ± 0.6	0.06 ± 0.6	0.783
Leptin/Adiponectin Ratio	3.3±18	-23.6±62	0.147
Insulin (µIU/mL)	2.1 ± 1.6	-3.2 ± 1.9 *	0.035
Total Testosterone (ng/dL)	-22.4 ± 24.8	27.1 ± 19.8	0.135
Free Testosterone (ng/dL)	-4.6 ± 2.8	0.8 ± 1.1	0.083
Estradiol	-4.9 ± 2.2	-0.5 ± 3.7	0.307
IL-6 (pg/mL)	4.1 ± 3.0	0.1 ± 1.4	0.234
IL-8 (pg/mL)	-28.1 ± 16.3	33.7 ± 32.3	0.092
IGF-1 (ng/mL)	-3.1 ± 3.9	7.4 ± 1.8	0.186
IGFBP-1 (ng/mL)	-0.03 ± 7.4	2.2 ± 1.5	0.353

Data represent mean ± SEM. N = 18 for control and n = 16 for WL group. Within each group the difference between baseline and end of intervention was evaluated using Student's t-test.

* p < 0.05.

Changes between groups were calculated using two independent sample t-test.

^a lists p-values.