Dietary Fat Intake and the Fatty Acid Composition of the Peri-Prostatic Adipose Tissue in Obese and Overweight Patients with Prostate Cancer

By

© 2021

Cheryl Rajiv
B.Sc., Illinois State University, 2019

Submitted to the graduate degree program in Dietetics and Nutrition and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Master of Science.

_____

Chairperson: Jill Hamilton-Reeves, PhD, RD, CSO

_____

Susan Carlson, PhD

_____

Debra Sullivan, PhD, RD

_____

William Parker, MD

Date Defended: 13 April 2021

The thesis committee for Cheryl Rajiv certifies that this is the approved version of the following thesis:

Dietary Fat Intake and the Fatty Acid Composition of the Peri-Prostatic Adipose Tissue in Obese and Overweight Patients with Prostate Cancer

_____

Chair: Jill Hamilton-Reeves

_____

Graduate Director: Heather Gibbs

Date Approved: 6 May 2021

Abstract

Introduction

The periprostatic adipose tissue (PPAT) is adipose tissue that surrounds the surface of the prostate gland. The PPAT might play a role in the progression of prostate cancer (PCa), as it is made up of fatty acids that could be used by prostate cancer cells. Obesity is associated with poor PCa outcomes and is found to alter PPAT secretions. In this study we sought to identify the fatty acid composition of the peri-prostatic adipose tissue in obese and overweight patients with prostate cancer and understand its relationship with dietary fat intake.

Methods

PPAT biopsies were collected for fatty acid analysis from 21 participants in the WARRIOR study. The WARRIOR study was a randomized controlled trial that implemented a weight loss intervention in men with PCa. PPAT was examined through flame-ionization gas chromatography and results were compared to known standards to determine fatty acid composition. Mean, standard deviation, and range values for each fatty acid were used to describe the fatty acid content of the PPAT. Information on dietary fatty acid intake was collected through 24-hour recalls at two time points: baseline, and pre-surgery. Diet information was analyzed using the Nutrition Data System for Research (NDSR) database. Dietary fatty acid intake was compared to fatty acid content of the PPAT using Spearman's correlation coefficient values. Differences in the diet and the fatty acid content of the PPAT between the intervention and the non-intervention group were also analyzed.

Results

Adequate PPAT for fatty acid analysis was collected from 21 patients. Twenty-seven types of fatty acids were found in the PPAT. Oleic acid, palmitic acid, linoleic acid, stearic acid, myristic acid, and palmitoleic acid were found in high concentrations in the PPAT. Dietary intake of oleic acid, linoleic acid, and palmitic acid were higher than other dietary fatty acids. Other than a few exceptions, dietary intake of most fatty acids do not clearly correlate to fatty acid content of the PPAT . At baseline gadoleic acid ($r_s = 0.427$), oleic acid ($r_s = 0.399$), behenic acid ($r_s = -0.442$), and margaric acid ($r_s = -0.362$) intake correlated to the amount in the PPAT. At the pre-surgery timepoint, behenic acid ($r_s = -0.402$) and palmitoleic acid ($r_s = -0.376$) intake correlated to the amount in the PPAT.

Conclusion

The distribution of fatty acids in the PPAT seemed to follow a pattern with high amounts of oleic acid, palmitic acid, linoleic acid, stearic acid, myristic acid, and palmitoleic acid, and small concentrations of other fatty acids present. The relationship between dietary fatty acid intake andthe. composition of fatty acids in the PPAT seems to be unclear. Some fatty acids were found to have a fair correlation between diet and PPAT. Future research is required to better understand the relationship between diet and PPAT.

Acknowledgements

I would like to acknowledge and thank all who contributed to this thesis project. Dr. Jill Hamilton-Reeves conducted the parent study, advised the project, and acted as the committee chairperson. Misty Bechtel coordinated the study. Drs. Susan Carson, Debra Sullivan, and William Parker contributed as committee members and advised the project. Carrie Michel and Hilary Robertson conducted dietary recalls. Dr. Scott Sands conducted fatty acid analysis. Dr Prabhakar Chalise performed the statistical analysis. Caroline Rajiv edited the contents of the paper. I am indebted to them for all their support.

Table of Contents

Chapter 1: Introduction...……...….1

Chapter 2: Review of Literature……..... 4

2.1 Relationship between obesity and prostate cancer…….....5

2.2 Mechanisms linking obesity to the hallmarks of cancer growth and spread…..... 7

2.3 How can we disrupt the link between obesity and prostate cancer?..... 9

2.4 Dietary Fat and PCa…….....12

2.5 PPAT and PCa……12

Chapter 3: Methods……...… 17

3.1 Subject criteria…… 18

3.2 Ethics……... 18

3.3 Procedure…… 19

Chapter 4: Results……..... 22

Chapter 5: Discussion …….. 29

References ……..... 35

List of Figures

Figure 1. Comparison of the fatty acids in the PPAT and diet. 26

List of Tables

Table 1. Fatty Acid Composition of Periprostatic Adipose Tissue……. 23

Table 2. Relationship between baseline dietary fatty acid intake and the fatty acid composition of the periprostatic adipose tissue……. 24

Table 3. Relationship between pre-surgery dietary fatty acid intake and fatty acid composition of the periprostatic adipose tissue in PCa patients…… 25

Table 4. Dietary fatty acid intake differences in intervention and non-intervention groups…… 27

Table 5. Comparison of the fatty acid composition of the PPAT in the intervention and non-intervention group…….....28

Chapter 1: Introduction

Prostate cancer (PCa) is a leading health problem for men in the United States. PCa affects 1 in 8 men, and results in the death of 1 in 41 men (1). The fat around the prostate or the periprostatic adipose tissue (PPAT) plays a unique role in the progression of PCa. PPAT functions as an endocrine organ and secretes adipokines, chemokines, and other substances that affect PCa growth (2, 3). Additionally, the periprostatic adipose tissue secretes lipids which are used by PCa cells (4) indicating that fatty acids stored in the PPAT could play a role in the spread of PCa. Identifying the fatty acid composition of the PPAT in patients with PCa can be a useful strategy to explore this relationship. Only three studies to date have analyzed the fatty acid composition of PPAT in PCa patients. These studies found the fatty acid composition of PPAT from PCa patients correlated to markers of aggressive cancer (2); varied with ethno-geographic origin of patient (5); and was different from the fatty acid composition of benign prostatic hyperplasia patients (6).

Obesity is associated with poor PCa outcomes and altered PPAT. Obesity increases the incidence of aggressive PCa (7), mortality and biochemical recurrence of the cancer (8). Obesity also impacts the PPAT as it contributes to increased inflammation, alters hormone and adipokine levels (9), and stimulates PCa proliferation and angiogenesis (10). As previous research on the fatty acid composition of PPAT did not focus on men who were obese and overweight, identifying the fatty acid composition of PPAT in these patients with PCa will help provide information on whether increased adiposity alters the lipid content of the PPAT.

Additionally, the fatty acid composition of adipose tissue might reflect dietary intake of fat (11). When PPAT from African-Caribbean patients was compared to Caucasian patients, differences in monounsaturated, saturated, n-3 polyunsaturated and n-6 polyunsaturated fatty acids were found (5). These differences were attributed to high intake of sunflower and vegetable oil

commonly observed in African- Caribbean diets, which demonstrates that diet might affect the fatty acid composition of PPAT (5). Measuring the fatty acid profile of dietary fat intake and comparing it to the PPAT fat in patients with PCa could be an important first step to understand this relationship.

Overall, this project aimed to understand how diet and weight influences the composition of the PPAT. Studying this link could help in the development of novel PCa treatments in the future. The purpose of this study was to identify the fatty acid composition of the peri-prostatic adipose tissue in obese and overweight patients with prostate cancer and understand its relationship with dietary fat intake.

Research Questions:

1. What is the fatty acid composition of the periprostatic adipose tissue in obese and overweight patients with PCa?
2. How does the composition of fatty acids from the diet compare to the fatty acid composition of the peri-prostatic adipose tissue?

Chapter 2: Literature Review

Prostate cancer (PCa) involves the prostate, a gland located between the bladder and the seminal vesicles (12) . PCa is the most prevalent type of non-cutaneous cancer in American men (1). PCa affects 1 in 8 men, and results in the death of 1 in 41 men (1). In 2021, PCa is estimated to contribute to 26 % of new cancer cases, and 11% of cancer deaths in the United States (1). Established risk factors for prostate cancer include being over 40 years of age(1), African American descent (13), having a brother or father with the condition (14), inheriting mutations in the BRCA1 or BRCA2 genes (15, 16), or having Lynch syndrome (17). PCa is detected through elevated prostate-specific antigen (PSA) levels and digital rectal examinations and is confirmed through a biopsy (18). Screening for PCa is recommended at age 50, or before age 50 if at a higher risk (19).

The spread of PCa is also associated with excess weight gain and adiposity. Several studies have looked at the association between PCa and obesity.

2.1 Relationship between obesity and prostate cancer

Obesity is defined as having a body mass index ≥ 30 kg/m^2 (20) and is a condition prevalent in 42.4% of adults in the United States (21). Obesity is associated with an increased risk for endometrial, gastric, liver, colorectal, pancreatic, breast, esophageal, kidney, multiple myeloma, meningioma, ovarian, gall bladder, and thyroid cancers (22). The relationship between obesity and the incidence, progression, and recurrence of PCa has been studied.

2.1.1 Incidence of PCa

Early studies indicate that the incidence of PCa is not related to increased obesity. In a study of 135,000 Swedish construction workers, increased body size was linked to the higher mortality of PCa patients rather than incidence of the cancer itself (23). However, later studies found an

inverse relationship between obesity and the incidence of PCa mainly in men over the age of 70 (24) and men with localized PCa (25). These studies also implied that obesity could play a slight protective role in the development of PCa. (25).

Later studies found that obesity was related to the incidence of aggressive forms of PCa. PCa is characterized based on its assigned Gleason score and whether it is localized or advanced. A Gleason score is a grading system for PCa based on the biopsy of the prostate (26). A high Gleason score (>7) reflects high-grade cancer (26). Localized PCa stays contained in the prostate and has lower risk compared to advanced PCa which spreads outside the prostate (27). A large dose-response meta-analysis of forty-five studies found obesity to increase the risk of advanced and high grade PCa (28).

2.1.2 Mortality of PCa

Several studies found obesity was directly associated with increased PCa mortality rates (8, 23, 29, 30). A 20% increased risk of death from PCa was found with a 5 kg/m^2 increase in BMI (8). Obesity was associated with an increased risk of PCa specific mortality even after adjusting for clinical and pathological confounding variables (31).

2.1.3 Recurrence of PCa

Biochemical recurrence (BCR) occurs when PSA levels increase after the treatment of PCa reflecting cancer return (32). BCR occurs in 20-40% of patients within 10 years after RP (33). Obesity increases the risk of BCR (8, 34, 35). A 21% increased risk of BCR was found with a 5 kg/m^2 increase in BMI (8). The risk for BCR also doubled in men who gained weight (>2.2 kg) after RP surgery as compared to men who maintained a stable weight (35).

BCR is also related to the form of PCa treatment. Radical prostatectomy (RP) surgery, radiation therapy, and androgen deprivation therapy (ADT) are some treatment options for PCa (36). Higher incidence of BCR was observed in obese patients who underwent RP surgery and external beam radiation therapy (37).

2.2 Mechanisms linking obesity to the hallmarks of cancer growth and spread

Obesity affects each of the hallmarks of cancer pathways via tumor promoting inflammation, genomic instability, increased angiogenesis, increased invasion and metastasis, evasion of growth suppressors, cell death inducers, and immune destruction (38). However, the exact mechanisms by which obesity is related to the growth of PCa are not fully elucidated. Proposed mechanisms are mainly related to the presence of elevated insulin and insulin-like growth factor 1(IGF-1), and altered androgens and adipokine signaling (39).

2.2.1 Insulin and IGF-1

Obesity induces a state of increased circulating insulin (40) and IGF-1 (39). Increased circulating insulin is caused by chronic insulin resistance. When insulin binds to insulin receptors, it stimulates the extracellular-signal-regulated kinase (ERK) and the phosphatidylinositol-3 kinase (PI-3K) pathways (39). ERK and PI-3K are signal transduction pathways that stimulate cell growth and proliferation, which could lead to tumor development (39). Elevated insulin levels also inhibit the production of IGF binding proteins IGFBP-1 and IGFBP-2, where IGF-1 binds (39). As free IGF-1 cannot bind to these proteins, its mitogenic and apoptotic mechanisms favor tumor development (39). Two studies found increased tumor growth when hyperinsulinemia was induced in PCa mouse xenograft models (10, 41). Additionally, two meta-analyses found increased IGF-1 circulation was related to an increased PCa risk (42, 43). Insulin and IGF-I

receptors are present in prostate cancer cells which could in part explain one potential way that obesity leads to tumor development (44).

2.2.2 Androgens

Testosterone can be converted to dihydrotestosterone (DHT) through the enzyme 5α reductase or converted to the estrogen estradiol through the enzyme aromatase. PCa alters the function of the enzyme aromatase (45) and favors the formation of DHT. High DHT in the prostate is associated with increased PCa risk (46). An increased estradiol to testosterone ratio reduces the risk of aggressive PCa (47).

The enzyme aromatase is expressed in the adipose tissue. The accumulation of fat mass with obesity increases aromatase activity and increases the production of estradiol(48). Increased estradiol levels suppress the activity of gonadotropin-releasing hormones and reduce testosterone levels (48). Additionally, lower testosterone levels are typically found in men who are obese (49). Low testosterone levels are a risk factor for advanced PCa (50). However some studies show no relationship between testosterone levels (and other androgens) and the PCa risk (47), so the exact mechanisms behind the role of androgens are unclear.

2.2.3 Adipokines

The adipose tissue secretes several adipokines including leptin, adiponectin, and IL-6. Leptin is involved in energy homeostasis, angiogenesis, neuroendocrine functions, and several other mechanisms (51). Adiponectin has various cardio-protective and anti-inflammatory functions (52). The increase in adipose tissue with obesity leads to an increased expression and secretion of leptin and decreased secretion of adiponectin (53). Obesity alters the leptin-to-adiponectin ratio

and induces a state of low grade chronic inflammation as the functions of the adipokines are dysregulated (54). This low-grade chronic inflammatory state can lead to carcinogenesis (55).

Elevated serum leptin-to-adiponectin ratios were also found in patients with PCa (56). Elevated leptin levels increase the growth of PCa by increasing migration (57), proliferation (58), and decreasing the death of PCa cells (59). Adiponectin is protective against tumor-growth (39), so an increased leptin-to-adiponectin ratio due to obesity might play a role in PCa spread. In large studies, decreased adiponectin levels were associated with a lower risk of high-grade PCa (60, 61), while leptin did not affect PCa outcomes (61, 62).

Obesity also leads to increased serum IL-6 (63) levels which contribute to low-grade chronic inflammation and carcinogenesis (55). IL-6 has been found to be a growth factor for PCa cells in laboratory studies (64). Elevated serum IL-6 levels were found in patients with PCa that had metastasized to the bone (65). However, one population-based study found IL-6 levels did not correlate to an increased risk for aggressive PCa (62).

The different adipokines, androgens, and hormones affected by obesity play a role in contributing to PCa growth and spread.

2.3 How can we disrupt the link between obesity and prostate cancer?

Obesity is related to poor PCa prognosis and altered biological markers associated with PCa spread. Weight loss and weight maintenance to reduce obesity may be valuable for PCa patients. Promoting weight loss by improving diet and exercise patterns are plausible techniques that could improve PCa outcomes. Yet, limited studies have examined weight loss as a mechanism that impacts outcomes.

2.3.1 Weight loss interventions

Diet and exercise interventions help promote weight loss in PCa patients (66-68). A small study examined the role of diet interventions pre prostatectomy in eight obese men. Participants on a low fat and low glycemic load diet intervention lost weight when compared to the control subjects on a standard American diet (68). Diet and exercise interventions also facilitated weight loss in a large randomized controlled trial of elderly overweight and obese prostate, breast, and colorectal cancer survivors (67). Additionally, a pilot study found that a 12 week weight loss intervention in patients with non-metastasized PCa was successful and resulted in sustainable weight loss (66). Effective techniques used in these studies included providing telephone counseling, tailored education materials (67), nutritionist facilitated menu planning (68), and the use of group and individualized counselling sessions (66). These techniques can be used to help obese PCa patients lose excess weight.

2.3.2 Weight loss and PCa

While improved diet and exercise facilitate weight loss in PCa patients, it is unknown if it helps reduce the spread of cancer. Weight loss might help decrease cancer spread by reducing inflammation. A decrease in inflammatory markers such as IL-6 and leptin have been found with short-term weight loss interventions (69).

Two randomized controlled trials looked at facilitating weight loss in newly diagnosed obese patients with PCa, prior to RP surgery (70, 71). One study introduced a calorie restriction and aerobic physical activity program to the intervention group to facilitate a weight loss of 1 kg per week (70). The study found reduced leptin, but also increased testosterone and Ki67, a marker of tumor proliferation in the intervention group when compared to the control (70). While the study

presented a strong weight loss intervention, the study had a small sample size of 40 patients, and the control group also lost weight which might have impacted the outcomes (70). Another study introduced a six-week calorie restriction program based on the Diabetes Prevention program to the intervention group (65). The weight loss program resulted in an increase in insulin-like growth factor-binding protein 3 (IGFBP-3) in newly diagnosed PCa patients when compared to the control group (71). IGFBP-3 is a protein that binds IGF-1, a growth factor with increased circulation during PCa (42, 43). However, the study found no changes in serum insulin, adiponectin, and IGF-1 between the groups, which are other variables associated with PCa growth (71). This study had a short intervention period, had control participants who lost weight, and had a disproportional range of participant weights in the two groups which might have affected the outcomes (71).

A small study collected prostate tissue before the study and during RP surgery from eight men assigned to a low-fat and low glycemic diet intervention, and compared it to a standard American control diet (72). Differences in the gene expression of CXCR4, CXCL2, IGF-2, and other genes that play a role in tissue growth, and cell migration were observed in the intervention group but not the control (72). However, another study found the effects of weight loss on the expression of genes related to cancer spread to be inconsistent (70). This demonstrates that the effects of the weight loss on PCa biomarkers need to be further investigated in larger trials.

An additional area to be studied is whether weight loss can prevent the biochemical recurrence of cancer. Since obesity increases the risk of biochemical recurrence (8, 37), weight loss could be a potential mechanism to reverse the effects of increased adiposity. However, a study of this nature would have questionable feasibility due to the length and expense of conducting such a trial.

Overall, the effects of weight loss on the obesity altered markers of prostate cancer growth and spread demonstrates a promising technique to improve PCa outcomes.

2.4 Dietary Fat and PCa

The association between dietary fat intake and PCa is unclear. Some studies have found a relationship between increased dietary fat intake and PCa incidence (73, 74), while the relationship is not present in other studies (75, 76). Animal studies have found high-fat diets to increase PCa progression and tumor growth through mechanisms involving increasing fatty acid synthase expression (77), chemokine signaling (78), and IGF-1(78). However, this is less evident in human studies. A meta-analysis of 14 cohort studies found dietary fat intake did not increase the risk for advanced PCa (79). The type of dietary fat (saturated or unsaturated) is also not associated with PCa risk (79). Furthermore, data on the intake of omega-3 fatty acids and omega-6 fatty acids also demonstrate conflicting results regarding their role in PCa (80-84). Further research is required to better understand the role of dietary fatty acids and PCa.

2.5 PPAT and PCa

Periprostatic adipose tissue (PPAT) is a unique factor related to the spread of PCa. PPAT surrounds the prostate gland. The distribution of adipose tissue around the prostate is not uniform with the least amount of adipose tissue on the posterior surface (85). One exploratory study found increased PPAT thickness to correlate to high Gleason scores (86). Another study on men on active surveillance found the volume of periprostatic fat was associated with PCa progression (87). This suggests that PPAT might be involved in increasing PCa aggressiveness. As adipose tissue functions as an endocrine organ, PPAT is believed to contribute to the growth and progression of PCa tumors through its different secretions (3).

Increased expression of the adipokine IL-6 was found in PPAT, especially in patients with high Gleason scores (2). As limited inflammatory cells are found in PPAT, the adipocytes were associated with the expression of IL-6 (2). IL-6 mediates proinflammatory mechanisms that promote the progression of tumors which links PPAT to PCa growth and spread (2).

PCa cells use lipids for energy, signaling, and other functions (4). PCa cells can synthesize lipids or utilize lipids from their surroundings (4). PCa also alters the type of fatty acid-binding proteins (FABPs) found in the prostate. FABPs are involved in the intracellular transport and regulation of long chain fatty acids (88). There are more than ten different types of FABPs (89). A decreased expression of FABP-4 and FABP-5 (90, 91), and an increased expression of FABP-1 and FABP-2 were found in PCa cells when compared to noncancerous prostate cells (90). Metastatic PCa was found to result in an increased expression of the FABP12 gene which codes for a group of FABPs including FABP4, FABP9, FABP8, and FABP5 (92). This demonstrates an increase use of fatty acids by PCa cells. PPAT might serve as a source of fatty acids for PCa cells due to its relative proximity. Studying the fatty acid composition of PPAT can help provide a better understanding of the role PPAT in the tumor microenvironment.

2.5.1 Fatty acid composition of PPAT

Measuring the fatty acid composition of PPAT can be beneficial to understand PCa spread. Limited research has been conducted on this subject. When PPAT from PCa patients was compared to benign prostatic hyperplasia patients, differences were found in fatty acid composition (6). PCa PPAT had higher palmitic acid, arachidonic acid, and dihomo-gammalinolenic acid than the non PCa PPAT(6). Another study found the fatty acid composition of PPAT to be correlated with the extracapsular extension of PCa, but not Gleason scores (93). Extracapsular extension is a node of cancer metastasis beyond the tissue, which a sign of

aggressive cancer. When compared to subcutaneous adipose tissue, the PPAT from patients with extracapsular extension had higher monosaturated, and lower saturated fatty acids (93).

The fatty acid composition of PPAT also varies with the ethno-geographic origin of patients (5). PPAT collected from African-Caribbean patients with PCa was found to have less monounsaturated fatty acid, saturated fatty acid, n-3 polyunsaturated fatty acid and double the n-6 polyunsaturated fatty acid when compared to Caucasian patients (5). The researchers associated this difference in the fatty acid composition of PPAT to the high intake of sunflower oil and other vegetable oils found in African-Caribbean individuals (5). However, the study did not measure dietary intake of fat (5). Measuring the dietary intake of different fatty acids can help identify how diet influences the composition of PPAT.

The study also found low linoleic acid, and low eicosopentaenoic acid content in the PPAT were associated with less aggressive forms of PCa in African-Caribbean, and Caucasian participants respectively (5). Linoleic acid and eicosopentaenoic acid were found to alter the regulation of zinc finger enhancer binding protein (Zeb1) by reducing the entry of calcium into the cell in in vitro and ex vitro experiments (94). Zeb1 drives factors involved in cancer migration and invasion which can explain how linoleic acid and eicosopentaenoic acid were associated with less aggressive forms of cancer (94). Identifying the fatty acid composition of the PPAT, and the mechanisms through which it affects PCa growth can help generate new techniques to help patients with PCa.

2.5.2 Obesity and PPAT

Obesity influences PPAT. Altered PPAT genes were found in both PCa patients, and regular obese/overweight men (95). Altered genes in obese PPAT promoted tumor growth, providing an

optimal environment for PCa progression (95). Another study observed inflammation of the periprostatic white adipose tissue in both obese and non-obese PCa patients (9). The presence of crown-like structures which compose of dead adipocytes surrounded by macrophages indicated white adipose tissue inflammation (9). The periprostatic white adipose tissue inflammation was more prevalent in obese subjects, and was associated with more aggressive forms of PCa (9). Increased insulin, triglycerides, leptin, and decreased adiponectin levels were found in patients with periprostatic white adipose tissue inflammation (9). This could suggest a role in the hallmarks of cancer spread.

Additionally, when PPAT from obese patients was compared to non-obese patients it was found that PCa proliferation and angiogenesis was stimulated in obese patients more than non-obese patients (96). Proliferation assays were used to measure proliferation and angiogenesis (96). This demonstrates how obesity affects PPAT, and results in poor PCa outcomes. Identifying the fatty acid composition of PPAT in obese and overweight patients with PCA might better explain the relationship between obesity and cancer outcomes.

2.5.3 Weight loss and PPAT

Since obesity plays a role in altering PPAT and aggravating PCa, the question of whether decreasing obesity can have improved PCa outcomes arises. The effects of an estrogen treatment (known to reduce appetite), and calorie restriction treatment were studied in mice with periprostatic white adipose tissue inflammation (97). Both the estrogen and calorie restriction treatments were found to decrease weight, periprostatic white adipose inflammation, and pro-inflammatory secretions (97). This suggests a proposed role of weight loss in reducing PPAT inflammation and improving PCa outcomes. More human interventions are required to confirm

this association. These findings can help strengthen evidence for weight loss as a technique to reduce high-grade PCa or BCR in obese patients.

Chapter 3: Methods

The data for this study was derived from the WARRIOR study, a randomized controlled trial carried out at the University of Kansas Hospital (KU). The study assigned patients who were scheduled for RP surgery to a weight loss intervention or a control group. The participant's diets were assessed using dietary recalls. PPAT was collected from the patients during the RP procedure, and the fatty acid composition of the tissue was analyzed using flame-ionization gas chromatography (GC). The fatty acid composition of the PPAT was compared to dietary fatty acid intake at baseline and pre-surgery.

3.1 Subject criteria

The participants in this trial included men who were obese and overweight (BMI 25-45 kg/m^2), between 50 to72 years of age, newly diagnosed with PCa and scheduled for RP at stage T1 or T2. These patients were recruited by urologists and oncologists at the KU Urologic Clinic and KU Cancer Center. Exclusion criteria included a history of 5 alpha reductase inhibitors and radiation therapy, active cancer treatment or salvage therapy, castration-resistant PCa, evidence of metastasis or biochemical recurrence, and high-risk medical conditions like uncontrolled diabetes or kidney disease. Forty participants were recruited and were randomized into the intervention (n=20) and control group (n=20). The study took place between August 2017 and September 2020.

3.2 Ethics

The Human Subjects Committee and the Institutional Review Board at the University of Kansas Medical Center approved this study. Participation in this study was voluntary, and informed consent based on institutional guidelines was provided by all participants. The participants also consented to the use of leftover blood, tissue, and prostate sample for future research. Research

Electronic Data Capture (REDCap) was used to store the data, and a secure server was required to access the data. Health Insurance Portability and Accountability Act (HIPAA) regulations regarding data-privacy and security were followed. The study data was de-identified as the names of participants and medical record numbers were removed from study files in data processing steps. Access to the study data was restricted and password protected.

3.3 Procedure

The weight loss intervention focused on improving diet and physical activity to achieve ≥ 5% weight loss. The intervention lasted between 4 to 16 weeks, based on when the participants were scheduled for RP. Participants in the intervention group were on a calorie deficit of about 500 to 1000 kilocalories below energy needs and followed the Medifast® 5 & 2 & 2 meal plan. On this plan, they consumed five meal replacement products; two Lean & Green™ meals which consisted of lean protein, non-starchy vegetables, and healthy fat; and two healthy snacks. The participants were guided on achieving a goal of ≥150 minutes of intentional exercise a week and ≥10,000 steps/day. Participants in the weight loss intervention received weekly individualized coaching before their surgery targeting behaviors such as increasing physical activity, reducing portion sizes, and reducing eating out. Participants in the control group received the book, Dr. Walsh's Guide to Surviving Prostate Cancer" by Patrick C. Walsh and Janet Farrar Worthington and the American Institute for Cancer Research booklet, "Heal Well, A Cancer Nutrition Guide" at baseline.

3.3.1 Dietary intake analysis

Diet information was collected from both groups at baseline and one week prior to RP surgery through unannounced 24-hour dietary recalls. These 24-hour dietary recalls included information

from one weekday and one weekend. This information was collected through telephone interviews conducted by study dietitians using the multiple-pass interview approach. The multiple-pass interview approach uses five distinct passes to enable participants to recollect their food and beverage intake. In the first pass, the participant is asked to make a quick list of their food and beverage intake on the previous day. The participant reviews the list to ensure accuracy in the second pass. The third pass prompts the participant to provide detailed information about their meals including brand names, quantity consumed, and preparation methods. The participants are asked about their intake of commonly forgotten foods in the fourth pass. In the fifth pass, the recall is reviewed, and the participant confirms its completeness and accuracy. The participants also provided information about their dietary supplement intake. Nutrition Data System for Research (NDSR) was used to analyze the dietary information. NDSR provided data on the fatty acids consumed by participants though their diet and supplement intake. The average of the participant's fatty acid intake from the weekday and weekend diet recalls were used to estimate usual intake at baseline and pre-surgery timepoints.

3.3.2 PPAT fatty acid analysis

PPAT biopsies were collected during RP surgery. Chloroform and methanol were added to 10mg of the tissue, after which it was vortexed, filtered, centrifuged, and the upper phase was removed. The lower phase was prepared for thin-layer chromatography, after which the triglycerides were extracted and transmethylated. The samples were then prepared for flame-ionization gas chromatography. The 6890N GC system (Agilent Technologies, Santa Clara, CA) with a 100m fused silica capillary column (SP-2560, 0.25 mm i.d. x 0.2um film thickness, Supelco, Bellefonte, PA) was used to run the samples. Known standards (Supelco 37 component FAME mix, Cat.# CRM47885) were run concurrently in the GC system to identify fatty acid

methyl esters in the sample. Chemstation Open Lad CDS, version C.01.09 (Agilent Technologies) was used to analyze the samples.

3.3.3 Analysis of Data

Statistical analysis was conducted by the statistician Dr. Prabhakar Chalise. The fatty acid composition of the PPAT collected was determined though mean, standard deviation and range values. Differences between the fatty acid profile of the diet and fatty acid composition of the PPAT was analyzed through Spearman's rank correlation coefficient values at baseline, and pre surgery. Differences in the dietary intake of fatty acids, and the fatty acid composition of PPAT between the intervention groups were also measured.

Chapter 4: Results

4.1 Periprostatic Adipose Tissue Fatty Acid Analysis

PPAT biopsies were collected from 21 patients during radical prostatectomy surgery. At baseline, the study participants had an average BMI of 33.4, age of 60 years, PSA of 8.4 ng/mg, and a Gleason score of 7. There were 27 fatty acids found in the PPAT. Oleic acid, palmitic acid, linoleic acid, stearic acid, myristic acid, and palmitoleic acid composed of 87.11% of the fatty acids present in the PPAT (Table 1). Other fatty acids were present in small concentrations in the PPAT (Table 1).

Table 1. Fatty Acid Composition of Periprostatic Adipose Tissue

Fatty Acid	Fatty Acid Composition of PPAT (Mean area % of total fatty acids ± SD)	Fatty Acid Composition of PPAT (Range)
18:1 n-9 Oleic acid	41.09 ± 1.50	37.53 – 42.97
16:0 Palmitic acid	20.41± 1.22	17.98 – 22.46
18:2 n-6 Linoleic acid	17.02 ± 1.61	14.28 – 20.67
18:0 Stearic acid	4.68 ± 0.73	3.28 – 6.28
14:0 Myristic acid	2 .00 ± 0.3	1.57 – 2.71
16:1 Palmitoleic acid	1.91 ± 0.50	1.00 – 2.71
18:1 n-7 Vaccenic acid	0.93 ± 0.49	0.23 – 1.81
18:1t Elaidic acid	0.92 ± 0.20	0.60 – 1.30
18:3 n-3 Linolenic acid	0.81 ± 0.18	0.52 – 1.20
20:1 Gadoleic acid	0.49 ± 0.16	0.09 – 0.84
20:2 n-6 Eicosadienoic acid	0.42 ± 0.16	0.13 – 0.71
20:4 n-6 Arachidonic acid	0.31 ± 0.11	0.17 – 0.52
20:3 n-6 Dihomo-gamma-linolenic acid	0.29 ± 0.12	0.17 – 0.72
17:0 Margaric acid	0.26 ± 0.03	0.21 – 0.33
18:2t n-6 Linolelaidic acid	0.25 ± 0.12	0.07 – 0.48
22:4 n-6 Adrenic acid	0.22 ± 0.11	0.09 – 0.51
14:1 Myristoleic acid	0.21 ±0.04	0.11 – 0.28
22:5 n-3 DPA	0.18 ± 0.05	0.09 – 0.28
16:1t Trans-hexadecenoic acid	0.14±0.03	0.09 – 0.22
22:6 n-3 DHA	0.10 ± 0.05	0.05 – 0.20
18:3 n-6 GLA	0.09 ± 0.03	0.07 – 0.21
22:0 Behenic acid	0.06 ± 0.08	0.01 – 0.29
20:0 Arachidic acid	0.06 ± 0.04	0.02 – 0.19
22:5 n-6 DPA	0.04 ± 0.02	0.02 – 0.10
20:5 n-3 EPA	0.04 ± 0.02	0.01 – 0.10
24:0 Lignoceric acid	0.03 ± 0.02	0.01 – 0.07
24:1 Nervonic acid	0.02 ± 0.02	0.02 – 0.09

4.2 Relationship between diet and PPAT

Seventeen fatty acids consumed by study participants were present in the PPAT. At baseline and pre-surgery oleic acid, linoleic acid, palmitic acid, and stearic acid were consumed in large concentrations in the diet. Gadoleic acid (r_s = 0.427) intake, and oleic acid (r_s =0.399) intake at baseline had a fair correlation with their fatty acid content in the PPAT (Table 2). Additionally, behenic acid (r_s = -0.442) intake and margaric acid (r_s = -0.362) intake inversely correlated with the amount found in the PPAT (Table 2).

Table 2. Relationship between baseline dietary fatty acid intake and the fatty acid composition of the periprostatic adipose tissue

Fatty Acid	Dietary Fatty Acid intake (% of total intake of fatty acids) (1st Quartile, 3rd Quartile)	PPAT Fatty acid content (% of total fatty acids) (1st Quartile, 3rd Quartile)	Spearman's rank correlation coefficient (P-value)
14:0 Myristic acid	1.345, 3.935	1.780, 2.125	-0.024 (0.918)
14:1 Myristoleic acid	0.11, 0.244	0.183, 0.241	0.094 (0.685)
16:0 Palmitic Acid	18.108, 21.533	20.14, 21.24	-0.245 (0.282)
16:1 Palmitoleic acid	1.112, 2.167	1.567, 2.304	-0.283 (0.213)
17:0 Margaric acid	0.111, 0.292	0.235, 0.278	-0.362 (0.107)
18:0 Stearic Acid	7.313, 10.46	4.215, 4.945	-0.179 (0.435)
18:1 Oleic acid	32.297, 37.074	40.03, 42.45	0.399 (0.074)
18:2 n-6 Linoleic acid	16.661, 22.097	15.91, 17.80	0.012 (0.960)
20:0 Arachidic acid	0.177, 0.276	0.028, 0.073	-0.299 (0.188)
20:1 Gadoleic acid	0.313, 0.449	0.408, 0.589	0.427 (0.053)
22:0 Behenic acid	0.074, 0.138	0.028, 0.046	-0.442 (0.045)
20:4 n-6 Arachidonic acid	0.156, 0.326	0.239, 0.378	-0.208 (0.365)
20:5 n-3 EPA	0.014, 0.081	0.031,0.052	0.292 (0.199)
22:6 n-3 DHA	0.037, 0.198	0.065, 0.141	0.147 (0.526)
18:1t Elaidic acid	1.775, 3.105	0.767, 0.988	0 (1)
18:2t n-6 Linolelaidic acid	0.337, 0.574	0.160, 0.300	0.051 (0.825)
16:1t Trans-hexadecenoic acid	0.034, 0.087	0.132, 0.160	-0.045 (0.847)

Behenic acid (r_s = -0.402) and palmitoleic acid (r_s = -0.376) intake at the pre-surgery timepoint inversely correlated with the total percent area found in the PPAT (Table 3).

Table 3. Relationship between pre-surgery dietary fatty acid intake and fatty acid composition of the periprostatic adipose tissue in PCa patients

Fatty Acid	Dietary Fatty Acid intake (% of total intake of fatty acids) (1st Quartile, 3rd Quartile)	PPAT Fatty acid content (% of total fatty acids) (1st Quartile, 3rd Quartile)	Spearman's rank correlation coefficient (P-value)
14:0 Myristic acid	2.212, 3.83	1.780, 2.125	-0.169 (0.464)
14:1 Myristoleic acid	0.137, 0.243	0.183, 0.241	-0.299 (0.188)
16:0 Palmitic Acid	16.49, 21.138	20.14, 21.24	0.153 (0.506)
16:1 Palmitoleic acid	1.324, 1.953	1.567, 2.304	-0.376 (0.093)
17:0 Margaric acid	0.107, 0.214	0.235, 0.278	-0.210 (0.361)
18:0 Stearic Acid	7.235, 9.68556	4.215, 4.945	-0.210 (0.358)
18:1 Oleic acid	32.74, 37.308	40.03, 42.45	-0.060 (0.797)
18:2n6 Linoleic acid	18.38, 23.514	15.91, 17.80	0.009 (0.969)
20:0 Arachidic acid	0.163, 0.255	0.028, 0.073	-0.212 (0.357)
20:1 Gadoleic acid	0.302, 0.452	0.408, 0.589	-0.280 (0.219)
22:0 Behenic acid	0.103, 0.17	0.028, 0.046	-0.402 (0.071)
20:4n6 Arachidonic acid	0.158, 0.264	0.239, 0.378	-0.228 (0.321)
20:5n3 EPA	0.014, 0.035	0.031, 0.052	-0.083 (0.721)
22:6n3 DHA	0.031, 0.16	0.065, 0.141	0.074 (0.750)
18:1t Elaidic acid	1.617, 2.281	0.767, 0.988	-0.161 (0.487)
18:2t n-6 Linolelaidic acid	0.305, 0.481	0.160, 0.300)	0.265 (0.245)
16:1t Trans-hexadecenoic acid	0.05, 0.087	0.132, 0.160	-0.101 (0.664)

The fatty acids found in high concentrations in the PPAT included oleic acid, palmitic acid, and linoleic acid. Oleic acid, palmitic acid, and linoleic acid were also consumed in high concentrations by participants (Figure 1).

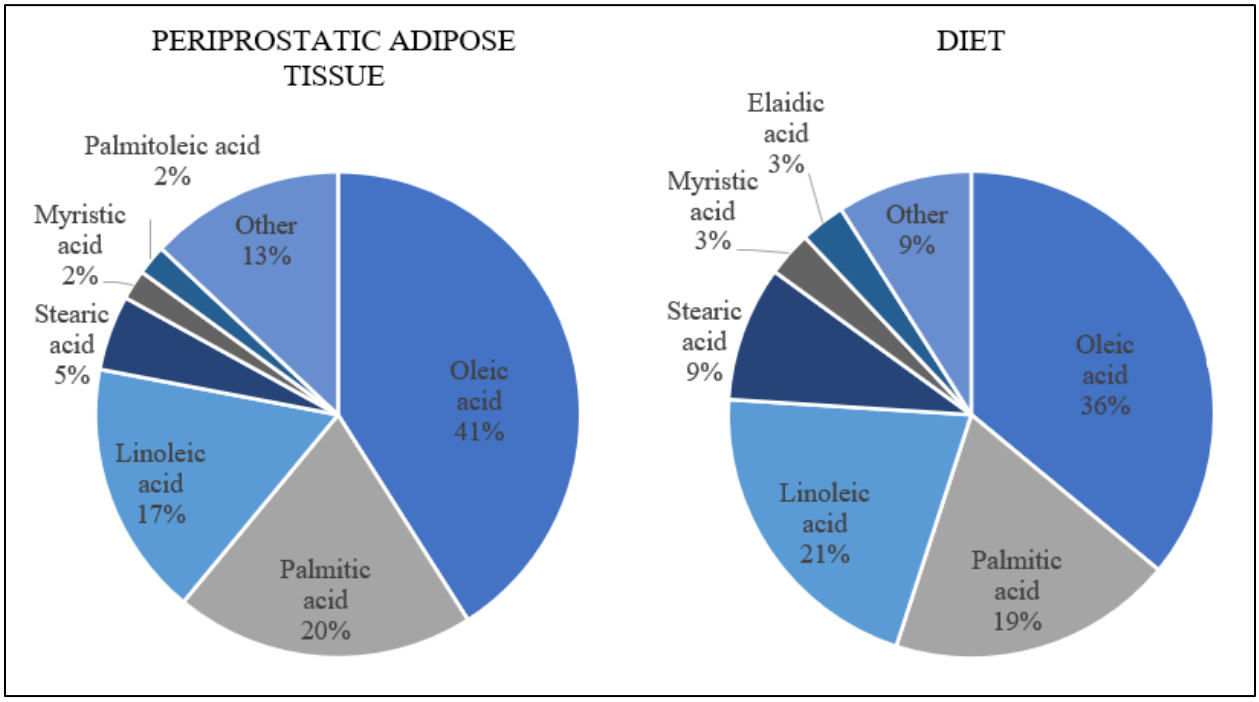

Figure 1. Comparison of the fatty acids in the PPAT and dietary intake of fatty acids at baseline (mean % of total fatty acids)

4.3 Changes between intervention groups

The study sample included 8 participants in the intervention group, and 13 participants in the non-intervention group. The differences in the dietary fat intake, and fat content of the PPAT between the intervention groups were analyzed. Consumption of myristic acid, palmitic acid, margaric acid, stearic acid, linoleic acid, arachidic acid, oleic acid, elaidic acid, and linolelaidic acid significantly decreased in the intervention group from baseline to pre-surgery (Table 4). There was minimal change in the consumption of fatty acids from baseline to pre-surgery in the non-intervention group (Table 4). Dietary intake of myristic acid, palmitic acid, margaric acid, stearic acid, linoleic acid, arachidic acid, behenic acid, oleic acid, linolelaidic acid, and trans-hexadecenoic acid were significantly different between the intervention and the non-intervention groups (Table 4).

Table 4. Dietary fatty acid intake differences in intervention and non-intervention groups

Fatty Acids	Intervention (n=8) (% of total dietary fatty acid intake)			Non-Intervention (n=13) (% of total dietary fatty acid intake)			Between arm changes
	Baseline Mean ± SD	Pre-surgery Mean ± SD	P_{within}	Baseline Mean ± SD	Pre-surgery Mean ± SD	P_{within}	$P_{between}$
14:0 Myristic acid	3.06 ± 1.08	2.94 ± 1.09	0.028	2.55 ± 1.168	2.96 ± 1.39	0.579	0.013
14:1 Myristoleic acid	0.21 ± 0.16	0.22 ± 0.1	0.195	0.18 ± 0.11	0.18 ± 0.11	0.579	0.374
16:0 Palmitic Acid	19.44 ± 2.78	18.51± 2.32	0.01	19.06 ± 3.49	18.89 ± 3.93	0.762	0.013
16:1 Palmitoleic acid	1.82 ± 0.88	1.85 ± 0.86	0.083	1.71 ± 0.82	1.75 ± 0.88	0.762	0.86
17:0 Margaric acid	0.26 ± 0.15	0.15 ± 0.09	0.003	0.19 ± 0.09	0.19 ± 0.09	1	0.016
18:0 Stearic Acid	10.04 ± 1.31	8.07 ± 1.48	0.003	8.58 ± 2.32	8.36 ± 2.37	0.801	0.013
18:1 n-9 Oleic acid	34.1 ± 3.27	34.67 ± 5.02	0.021	36.25 ± 6.25	34.47 ± 5.22	0.545	0.045
18:2n6 Linoleic acid	19.43 ± 3.38	21.27 ± 3.89	0.05	21.28 ± 7.39	22.1 ± 5.44	0.88	0.008
20:0 Arachidic acid	0.26 ± 0.07	0.19 ± 0.05	0.021	0.22 ± 0.12	0.2 ± 0.1	0.939	0.003
20:1 Gadoleic acid	0.43 ± 0.26	0.51 ± 0.42	0.13	0.58 ± 0.65	1.05 ± 2.47	0.579	0.14
22:0 Behenic acid	0.14 ± 0.11	0.13 ± 0.03	0.128	0.17 ± 0.26	0.21 ± 0.25	0.418	0.03
20:4n6 Arachidonic acid	0.21 ± 0.13	0.23 ± 0.09	0.279	0.24 ± 0.09	0.2 ± 0.1	0.336	1
20:5n3 EPA	0.23 ± 0.33	0.2 ± 0.29	0.156	0.1 ± 0.17	0.18 ± 0.58	0.608	0.169
22:6n3 DHA	0.29 ± 0.43	0.34 ± 0.54	0.636	0.19 ± 0.32	0.15 ± 0.39	0.798	0.547
18:1t Elaidic acid	3.44 ± 3.13	2.63 ± 1.29	0.028	2.93 ± 2.35	2.33 ±1.74	0.65	0.456
18:2t n-6 Linolelaidic acid	0.55 ± 0.25	0.43 ±0.11	0.015	0.45 ± 0.2	0.4 ±0.18	0.724	0.037
16:1t Trans-hexadecenoic acid	0.08 ± 0.04	0.07 ± 0.02	0.13	0.05 ± 0.03	0.07 ± 0.03	0.918	0.02

Docosapentaenoic acid n-3 [DPA] content of the PPAT was significantly different between intervention and non-intervention groups (p= 0.03, Table 5). Other fatty acids found in the PPAT did not differ based on the intervention group assigned to the participant (Table 5).

Table 5. Comparison of the fatty acid composition of the PPAT in the intervention and non-intervention group

Fatty Acid	Intervention group (Mean area % of total fatty acids ± SD)	Non-Intervention group (Mean area % of total fatty acids ± SD)	Between Group Differences (Pvalue)
14:0 Myristic acid	2.06 ± 0.33	1.97 ± 0.28	0.45
14:1 Myristoleic acid	0.23 ± 0.03	0.2 ± 0.04	0.18
16:0 Palmitic acid	20.06 ± 1.1	20.63 ± 1.28	0.21
16:1t Trans-hexadecenoic acid	0.14 ± 0.03	0.14 ± 0.03	0.8
16:1 Palmitoleic acid	2.1 ± 0.42	1.8 ± 0.52	0.22
17:0 Margaric acid	0.25 ± 0.03	0.27 ± 0.04	0.53
18:0 Stearic acid	4.51 ± 0.62	4.77 ± 0.79	0.8
18:1t Elaidic acid	0.92 ± 0.22	0.92 ± 0.2	1
18:1n9 Oleic acid	41.43 ± 1.26	40.88 ± 1.65	0.41
18:1n7 Vaccenic acid	0.83 ± 0.49	1 ± 0.49	0.56
18:2t n-6 Linolelaidic acid	0.21 ± 0.1	0.27 ± 0.13	0.49
18:2n6 Linoleic acid	16.84 ± 1.54	17.14 ± 1.7	0.51
20:0 Arachidic acid	0.06 ± 0.04	0.06 ± 0.05	1
18:3n6 GLA	0.11 ± 0.04	0.09 ± 0.02	0.18
20:1 Gadoleic acid	0.56 ± 0.18	0.45 ± 0.14	0.34
18:3n3 Linolenic acid	0.84 ± 0.21	0.79 ± 0.17	0.45
20:2n6 Eicosadienoic acid	0.45 ± 0.17	0.4 ± 0.15	0.66
22:0 Behenic acid	0.05 ± 0.02	0.07 ± 0.1	0.46
20:3 n-6 Dihomo-gamma-linolenic acid	0.31 ± 0.17	0.27 ± 0.08	0.72
20:4 n-6 Arachidonic acid	0.33 ± 0.11	0.3 ± 0.11	0.47
24:0 Lignoceric acid	0.03 ± 0.01	0.03 ± 0.02	0.82
20:5n3 EPA	0.04 ± 0.01	0.04 ± 0.02	0.24
24:1 Nervonic acid	0.01 ± 0.01	0.02 ± 0.02	0.51
22:4 n-6 Adrenic acid	0.24 ± 0.12	0.2 ± 0.1	0.45
22:5 n-6 DPA	0.05 ± 0.02	0.04 ± 0.02	0.22
22:5 n-3 DPA	0.21 ± 0.03	0.16 ± 0.06	0.03
22:6 n-3 DHA	0.12 ± 0.04	0.09 ± 0.05	0.11

Chapter 5: Discussion

In this study we analyzed the fatty acid composition of the PPAT. Gas chromatography analysis of the PPAT revealed several types of fatty acids present in the PPAT of patients with PCa. The fatty acid composition of the PPAT included saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) polyunsaturated fatty acids (PUFA), and trans fatty acids. The fatty acids found in high concentration in the PPAT included oleic acid, palmitic acid, linoleic acid, palmitoleic acid, and myristic acid. These fatty acids were also found in high concentration in other studies that analyzed the fatty acid composition of the PPAT (5, 6). This demonstrates that the distribution of fatty acids in the PPAT might follow a set pattern.

Despite the similarities between the fatty acid composition of the PPAT found in our study when compared to others studies, there were slight differences in the concentration of fatty acids. While Figuel et al. analyzed PPAT fatty acids, they found differences in the composition of the PPAT in relation to ethno-geographic origin. Their study looked at the composition of fatty acids in Caucasian, and African-Carribean PCa patients in France. The concentrations of MUFA and SFA in the PPAT in our study were similar to those found in African-Carribean patients with PCa (5). Additionally, the concentrations of certain SFA (14:0, 16:0, 17:0, 18:0, 20:0), and MUFA (18:1 n-9, 20:1), and PUFA (22:5 n-3) were lower in our study when compared to PCa patients in another study in Argentina (6). The concentrations of certain n-6 fatty acids (20:2 n-6, 20:3 n-6, 20:4 n-6) were higher in our study when compared to the those found in the studies in France and Argentina. As our cohort consisted of mostly white American participants (85%), differences in the concentration of fatty acids might be attributed to geographic differences. Also since other studies did not focus on patients who were obese, the different concentrations of fatty acids might be a result of altered adipose tissue function with obesity. Other confounding

variables like dietary fatty acid intake could influence the PPAT. While other studies that analyzed the fatty acid concentration of PPAT did not measure dietary intake of fatty acids, our study measured the dietary intake of fatty acids before RP surgery.

We measured dietary fatty acid intake to understand the relationship between diet and the PPAT. We compared dietary intake of fatty acids at baseline and one week before prostatectomy surgery with the fatty acid composition of the PPAT. We found that our participants had a higher intake of oleic acid, linoleic acid, palmitic acid, stearic acid, and myristic acid as compared to other dietary fatty acids. These fatty acids were also found in high concentrations in the PPAT. However, we found that the dietary intake of fatty acids did not strongly correlate to the fatty acid composition of the PPAT. Several fatty acids consumed in the diet were found in the PPAT, however the concentration of most fatty acids correlated poorly. Some exceptions were gadoleic acid, behenic acid, and palmitoleic acid. At baseline (4 to 16 weeks before surgery), dietary intake of gadoleic acid (20:1), and oleic acid (18:1 n-9) directly correlated to the amount in the PPAT, while intake of behenic acid (22:0) and margaric acid (17:0) inversly correlated to the amount in the PPAT. At the pre-surgery timepoint (one week before surgery), the intake of behenic acid and palmitoleic acid (16:1) inversely corelated to the amount found in the PPAT. The fatty acids that correlated are found in a variety of foods like animal products and oils. The exact functions of these fatty acids are unclear, and it is unknown if they have roles in PCa. Additionally, as the human body can synthesize most SFA and MUFA via de novo lipogenesis, the true impact of dietary fatty acid intake of SFA and MUFA on the composition of PPAT cannot be determined. The human body is unable to synthesize n-6, and n-3 PUFA however the dietary intake of these fatty acids did not significantly correlate to the amounts in the PPAT. Our study finds the impact of dietary fatty acid intake on the PPAT to be unclear.

The patients in this study were either a part of a weight loss intervention or a control group. The intake of myristic acid, palmitic acid, margaric acid, stearic acid, linoleic acid, arachidic acid, oleic acid, elaidic acid, and linolelaidic acid decreased from baseline to pre-surgery in the intervention group. This might be attributed to the weight loss intervention that was administered in these participants. The intervention focused on patients consuming a calore deficit and increasing intake of lean meats and healthy fats. These changes could have have resulted in decreased intake of the fatty acids from baseline to pre-surgery in the intervention group. Overall dietary intake of myristic acid, palmitic acid, margaric acid, stearic acid, linoleic acid, arachidonic, and behenic acid were significantly different between the intervention and the non-intervention group due to dietary changes implemented by the patients in the intervention group.

Weight loss might impact the biology of the PPAT, as one animal study found reduced PPAT inflammation and secretions with weight loss (97). However our weight loss intervention did not seem to impact the fatty acid composition of the PPAT. The composition of the peri-prostatic adipose tissue between the intervention and the non-intervention group was fairly identical. We only found a statistically significant difference in n-3 DPA content between the intervention and the non-intervention groups. However the n-3 DPA content in the intervention group was only 0.05% higher than the non-intervention group. As the weight loss intervention only lasted between 4-16 weeks, short term dietary changes do not seem to strongly influence the composition of the PPAT. While the effects of weight loss on the fatty acids in the PPAT are unclear, weight loss might impact different markers of inflammation and the secretions of the PPAT. This could be measured through immunohistochemistry and cell culture analysis.

Strenghts, Limitations, and Future Research

The role of the PPAT in PCa is a relatively novel area of research. Our study helps contribute to the limited literature on the fatty acid composition of the PPAT. We described the fatty acid composition of obese patients with PCa, and we were able to compare our findings with other studies. Our study also measured and analyzed the dietary intake of fatty acids. This has not been conducted in previous studies. Overall our study provided background information on the fatty acid concentration of PPAT and the role of diet in the PPAT.

The sample size is one of the limitations of this study. We only collected adequate adipose tissue for fatty acid analysis from 21 participants. Our findings would have to be confirmed in a larger study to better understand the relationship between adipose tissue and diet. We also collected diet information through 24-hour dietary recalls. Baseline data about a subject's diet during a specific timepoint can be generated by 24-hour dietary recalls. Since we found short term diet changes do not infuence the fatty acid composition of the PPAT, understanding habitual intake of fatty acids can help us understand the relationship between diet and PPAT. Measuring dietary intake of fatty acids through a food frequency questionnaire could have helped us better understand long term dietary intake of fatty acids. Finally, since the fatty acid composition of PPAT of healthy patients without PCa is difficult to obtain, we do not have a reference to compare our findings.

We found the role of diet and the fatty acid composition of the PPAT to be unclear. To better understand the relationship between diet and PPAT, future research should aim at assessing

habitual dietary intake of fatty acids in PCa patients, and comparing it to the PPAT in a larger cohort. Also, measuring plasma fatty acids, and understanding lipid secretions from the PPAT can help us better understand the role of fatty acids in PCa. Studying markers of inflammation in PPAT can also help us understand the role of adipose tissue in PCa. Additional areas for research include studying the functions of different fatty acids in PCa, understanding the effects of obesity on the PPAT, and studying how the PPAT impacts the hallmarks of cancer spread. This can help us better understand the relationship between diet, PCa, and obesity.

Conclusion

We described the fatty acid composition of the PPAT in overweight and obese patients with PCa. The distribution of fatty acids in the PPAT seemed to follow a pattern with high amounts of oleic acid, palmitic acid, linoleic acid, stearic acid, myristic acid, and palmitoleic acid, and small concentrations of other fatty acids present. The realtionship between dietary fatty acid intake and the the composition of fatty acids in the PPAT seems to be unclear. Some fatty acids were found to have a fair correlation between diet and PPAT, however future research is required to confirm our findings.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA: a Cancer Journal for Clinicians 2021;71(1):7-33.
2. Finley DS, Calvert VS, Inokuchi J, Lau A, Narula N, Petricoin EF, Zaldivar F, Santos R, Tyson DR, Ornstein DK. Periprostatic adipose tissue as a modulator of prostate cancer aggressiveness. J Urol 2009;182(4):1621-7. doi: 10.1016/j.juro.2009.06.015.
3. Laurent V, Guérard A, Mazerolles C, Le Gonidec S, Toulet A, Nieto L, Zaidi F, Majed B, Garandeau D, Socrier Y, et al. Periprostatic adipocytes act as a driving force for prostate cancer progression in obesity. Nature Communications 2016;7(1):10230. doi: 10.1038/ncomms10230.
4. Wu X, Daniels G, Lee P, Monaco ME. Lipid metabolism in prostate cancer. American journal of clinical and experimental urology 2014;2(2):111.
5. Figiel S, Pinault M, Domingo I, Guimaraes C, Guibon R, Besson P, Tavernier E, Blanchet P, Multigner L, Bruyère F, et al. Fatty acid profile in peri-prostatic adipose tissue and prostate cancer aggressiveness in African-Caribbean and Caucasian patients. Eur J Cancer 2018;91:107-15. doi: 10.1016/j.ejca.2017.12.017.
6. Careaga Quiroga VP, Sacca PA, Mazza ON, Scorticati C, Vitagliano G, Fletcher SJ, Maier MS, Calvo JC. Fatty acid composition of human periprostatic adipose tissue from argentine patients and its relationship to prostate cancer and benign prostatic hyperplasia. 2015.
7. Norat T, Vieira AR, Chan D, Aune D, Abar L, Navarro D, Vingeliene S. World Cancer Research Fund International Systematic Literature ReviewThe Associations between Food, Nutrition and Physical Activity and the Risk of Prostate Cancer. 2014.
8. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer prevention research (Philadelphia, Pa) 2011;4(4):486-501. doi: 10.1158/1940-6207.Capr-10-0229.
9. Gucalp A, Iyengar NM, Zhou XK, Giri DD, Falcone DJ, Wang H, Williams S, Krasne MD, Yaghnam I, Kunzel B, et al. Periprostatic adipose inflammation is associated with high-grade prostate cancer. Prostate Cancer Prostatic Dis 2017;20(4):418-23. doi: 10.1038/pcan.2017.31.
10. Venkateswaran V, Haddad AQ, Fleshner NE, Fan R, Sugar LM, Nam R, Klotz LH, Pollak M. Association of Diet-Induced Hyperinsulinemia With Accelerated Growth of Prostate Cancer (LNCaP) Xenografts. JNCI: Journal of the National Cancer Institute 2007;99(23):1793-800. doi: 10.1093/jnci/djm231 %J JNCI: Journal of the National Cancer Institute.
11. Field CJ, Angel A, Clandinin MT. Relationship of diet to the fatty acid composition of human adipose tissue structural and stored lipids. The American journal of clinical nutrition 1985;42(6):1206-20.
12. Society AC. Internet: https://www.cancer.org/cancer/prostate-cancer/about/what-is-prostate-cancer.html (accessed July 21 2020.
13. Odedina FT, Akinremi TO, Chinegwundoh F, Roberts R, Yu D, Reams RR, Freedman ML, Rivers B, Green BL, Kumar N. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infect Agent Cancer 2009;4 Suppl 1(Suppl 1):S2. doi: 10.1186/1750-9378-4-s1-s2.

14. Barber L, Gerke T, Markt SC, Peisch SF, Wilson KM, Ahearn T, Giovannucci E, Parmigiani G, Mucci LA. Family History of Breast or Prostate Cancer and Prostate Cancer Risk. Clin Cancer Res 2018;24(23):5910-7. doi: 10.1158/1078-0432.Ccr-18-0370.
15. Thompson D, Easton DF. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002;94(18):1358-65. doi: 10.1093/jnci/94.18.1358.
16. Kote-Jarai Z, Leongamornlert D, Saunders E, Tymrakiewicz M, Castro E, Mahmud N, Guy M, Edwards S, O'Brien L, Sawyer E, et al. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer 2011;105(8):1230-4. doi: 10.1038/bjc.2011.383.
17. Haraldsdottir S, Hampel H, Wei L, Wu C, Frankel W, Bekaii-Saab T, de la Chapelle A, Goldberg RM. Prostate cancer incidence in males with Lynch syndrome. Genet Med 2014;16(7):553-7. doi: 10.1038/gim.2013.193.
18. Kantoff PW, Taplin M-E, Smith MA. Clinical presentation and diagnosis of prostate cancer. Waltham, MA: UpToDate, 2020.
19. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, Brooks DD, Dash C, Guessous I, Andrews K, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin 2010;60(2):70-98. doi: 10.3322/caac.20066.
20. Obesity NAAftSo, Heart N, Lung, Institute B, Initiative NOE. The practical guide: identification, evaluation, and treatment of overweight and obesity in adults: National Institutes of Health, National Heart, Lung, and Blood Institute …, 2000.
21. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. 2020.
22. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the IARC Working Group. New England Journal of Medicine 2016;375(8):794-8.
23. Andersson SO, Wolk A, Bergström R, Adami HO, Engholm G, Englund A, Nyrén O. Body size and prostate cancer: a 20-year follow-up study among 135006 Swedish construction workers. J Natl Cancer Inst 1997;89(5):385-9. doi: 10.1093/jnci/89.5.385.
24. Bradbury BD, Wilk JB, Kaye JA. Obesity and the risk of prostate cancer (United States). Cancer causes & control : CCC 2005;16(6):637-41. doi: 10.1007/s10552-005-0383-6.
25. Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, Hurwitz P, Hollenbeck A, Leitzmann MF. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer 2007;109(4):675-84. doi: 10.1002/cncr.22443.
26. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU international 2013;111(5):753-60. doi: 10.1111/j.1464-410X.2012.11611.x.
27. John ME. Treating Localized Prostate Cancer: A Review of the Research for Adults. Edtion ed. Comparative Effectiveness Review Summary Guides for Consumers. Rockville (MD): Agency for Healthcare Research and Quality (US), 2005.
28. Norat T, Vieira AR, Chan D, Aune D, Abar L, Navarro D, Vingeliene S. World Cancer Research Fund International Systematic Literature ReviewThe Associations between Food, Nutrition and Physical Activity and the Risk of Prostate Cancer. 2014.

29. Fang X, Wei J, He X, Lian J, Han D, An P, Zhou T, Liu S, Wang F, Min J. Quantitative association between body mass index and the risk of cancer: A global Meta-analysis of prospective cohort studies. International journal of cancer 2018;143(7):1595-603. doi: 10.1002/ijc.31553.
30. Rodriguez C, Patel AV, Calle EE, Jacobs EJ, Chao A, Thun MJ. Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2001;10(4):345-53.
31. Vidal AC, Howard LE, Sun SX, Cooperberg MR, Kane CJ, Aronson WJ, Terris MK, Amling CL, Freedland SJ. Obesity and prostate cancer-specific mortality after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Prostate cancer and prostatic diseases 2017;20(1):72-8.
32. Tourinho-Barbosa R, Srougi V, Nunes-Silva I, Baghdadi M, Rembeyo G, Eiffel SS, Barret E, Rozet F, Galiano M, Cathelineau X, et al. Biochemical recurrence after radical prostatectomy: what does it mean? International braz j urol : official journal of the Brazilian Society of Urology 2018;44(1):14-21. doi: 10.1590/s1677-5538.Ibju.2016.0656.
33. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol 2004;172(3):910-4. doi: 10.1097/01.ju.0000134888.22332.bb.
34. Ho T, Gerber L, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL, Freedland SJ. Obesity, prostate-specific antigen nadir, and biochemical recurrence after radical prostatectomy: biology or technique? Results from the SEARCH database. Eur Urol 2012;62(5):910-6. doi: 10.1016/j.eururo.2012.08.015.
35. Joshu CE, Mondul AM, Menke A, Meinhold C, Han M, Humphreys EB, Freedland SJ, Walsh PC, Platz EA. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. Cancer prevention research (Philadelphia, Pa) 2011;4(4):544-51. doi: 10.1158/1940-6207.Capr-10-0257.
36. . Internet: https://www.cancer.org/cancer/prostate-cancer/treating.html (accessed 7/22/2020.
37. Hu MB, Xu H, Bai PD, Jiang HW, Ding Q. Obesity has multifaceted impact on biochemical recurrence of prostate cancer: a dose-response meta-analysis of 36,927 patients. Medical oncology (Northwood, London, England) 2014;31(2):829. doi: 10.1007/s12032-013-0829-8.
38. O'Flanagan CH, Bowers LW, Allott EH, Hursting SD. Molecular and metabolic mechanisms underlying the obesity–cancer link. Energy Balance and Obesity 2017;10.
39. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. J Annual review of medicine 2010;61:301-16.
40. Kim MK, Reaven GM, Kim SH. Dissecting the relationship between obesity and hyperinsulinemia: Role of insulin secretion and insulin clearance. Obesity (Silver Spring, Md) 2017;25(2):378-83. doi: 10.1002/oby.21699.
41. Freedland SJ, Mavropoulos J, Wang A, Darshan M, Demark-Wahnefried W, Aronson WJ, Cohen P, Hwang D, Peterson B, Fields T, et al. Carbohydrate restriction, prostate

cancer growth, and the insulin-like growth factor axis. The Prostate 2008;68(1):11-9. doi: 10.1002/pros.20683.
42. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet (London, England) 2004;363(9418):1346-53. doi: 10.1016/s0140-6736(04)16044-3.
43. Rowlands MA, Gunnell D, Harris R, Vatten LJ, Holly JM, Martin RM. Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. International journal of cancer 2009;124(10):2416-29.
44. Cox ME, Gleave ME, Zakikhani M, Bell RH, Piura E, Vickers E, Cunningham M, Larsson O, Fazli L, Pollak M. Insulin receptor expression by human prostate cancers. The Prostate 2009;69(1):33-40. doi: 10.1002/pros.20852.
45. Ellem SJ, Schmitt JF, Pedersen JS, Frydenberg M, Risbridger GP. Local aromatase expression in human prostate is altered in malignancy. J Clin Endocrinol Metab 2004;89(5):2434-41. doi: 10.1210/jc.2003-030933.
46. Platz EA, Giovannucci E. The epidemiology of sex steroid hormones and their signaling and metabolic pathways in the etiology of prostate cancer. J Steroid Biochem Mol Biol 2004;92(4):237-53. doi: 10.1016/j.jsbmb.2004.10.002.
47. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100(3):170-83. doi: 10.1093/jnci/djm323.
48. Williams G. Aromatase up-regulation, insulin and raised intracellular oestrogens in men, induce adiposity, metabolic syndrome and prostate disease, via aberrant ER-α and GPER signalling. Molecular and cellular endocrinology 2012;351(2):269-78.
49. Glass AR, Swerdloff RS, Bray GA, Dahms WT, Atkinson RL. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. J Clin Endocrinol Metab 1977;45(6):1211-9. doi: 10.1210/jcem-45-6-1211.
50. Schnoeller T, Jentzmik F, Rinnab L, Cronauer MV, Damjanoski I, Zengerling F, Ghazal AA, Schrader M, Schrader AJ. Circulating free testosterone is an independent predictor of advanced disease in patients with clinically localized prostate cancer. World Journal of Urology 2013;31(2):253-9. doi: 10.1007/s00345-012-0902-5.
51. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med 2010;152(2):93-100. doi: 10.7326/0003-4819-152-2-201001190-00008.
52. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006;116(7):1784-92. doi: 10.1172/jci29126.
53. Lee JM, Kim SR, Yoo SJ, Hong O, Son H, Chang S. The relationship between adipokines, metabolic parameters and insulin resistance in patients with metabolic syndrome and type 2 diabetes. Journal of International Medical Research 2009;37(6):1803-12.
54. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Molecular and cellular endocrinology 2010;316(2):129-39.
55. Pérez-Hernández AI, Catalán V, Gómez-Ambrosi J, Rodríguez A, Frühbeck G. Mechanisms linking excess adiposity and carcinogenesis promotion. Front Endocrinol (Lausanne) 2014;5:65. doi: 10.3389/fendo.2014.00065.

56. Siemińska L, Borowski A, Marek B, Nowak M, Kajdaniuk D, Warakomski J, Kos-Kudła B. Serum concentrations of adipokines in men with prostate cancer and benign prostate hyperplasia. Endokrynol Pol 2018;69(2):120-7. doi: 10.5603/EP.a2018.0006.
57. Huang CY, Yu HS, Lai TY, Yeh YL, Su CC, Hsu HH, Tsai FJ, Tsai CH, Wu HC, Tang CH. Leptin increases motility and integrin up-regulation in human prostate cancer cells. Journal of cellular physiology 2011;226(5):1274-82.
58. Somasundar P, Frankenberry KA, Skinner H, Vedula G, McFadden DW, Riggs D, Jackson B, Vangilder R, Hileman SM, Vona-Davis LC. Prostate cancer cell proliferation is influenced by leptin1. Journal of Surgical Research 2004;118(1):71-82.
59. Hoda MR, Popken G. Mitogenic and anti-apoptotic actions of adipocyte-derived hormone leptin in prostate cancer cells. J BJU international 2008;102(3):383-8.
60. Goktas S, Yilmaz MI, Caglar K, Sonmez A, Kilic S, Bedir S. Prostate cancer and adiponectin. Urology 2005;65(6):1168-72.
61. Li H, Stampfer MJ, Mucci L, Rifai N, Qiu W, Kurth T, Ma J. A 25-Year Prospective Study of Plasma Adiponectin and Leptin Concentrations and Prostate Cancer Risk and Survival. Clinical Chemistry 2010;56(1):34-43. doi: 10.1373/clinchem.2009.133272 %J Clinical Chemistry.
62. Baillargeon J, Platz EA, Rose DP, Pollock BH, Ankerst DP, Haffner S, Higgins B, Lokshin A, Troyer D, Hernandez J. Obesity, adipokines, and prostate cancer in a prospective population-based study. Cancer Epidemiology 2006;15(7):1331-5.
63. Roytblat L, Rachinsky M, Fisher A, Greemberg L, Shapira Y, Douvdevani A, Gelman S. Raised interleukin-6 levels in obese patients. Obes Res 2000;8(9):673-5. doi: 10.1038/oby.2000.86.
64. Okamoto M, Lee C, Oyasu R. Interleukin-6 as a Paracrine and Autocrine Growth Factor in Human Prostatic Carcinoma Cells in Vitro. Cancer Research 1997;57(1):141-6.
65. Shariat SF, Andrews B, Kattan MW, Kim J, Wheeler TM, Slawin KM. Plasma levels of interleukin-6 and its soluble receptor are associated with prostate cancer progression and metastasis. Urology 2001;58(6):1008-15.
66. Mohamad H, Ntessalen M, Craig LCA, Clark J, Fielding S, N'Dow J, Heys SD, McNeill G. A self-help diet and physical activity intervention with dietetic support for weight management in men treated for prostate cancer: pilot study of the Prostate Cancer Weight Management (PRO-MAN) randomised controlled trial. The British journal of nutrition 2019;122(5):592-600. doi: 10.1017/s0007114519001090.
67. Morey MC, Snyder DC, Sloane R, Cohen HJ, Peterson B, Hartman TJ, Miller P, Mitchell DC, Demark-Wahnefried W. Effects of Home-Based Diet and Exercise on Functional Outcomes Among Older, Overweight Long-term Cancer Survivors: RENEW: A Randomized Controlled Trial. JAMA 2009;301(18):1883-91. doi: 10.1001/jama.2009.643 %J JAMA.
68. Schenk JM, Neuhouser ML, Lin DW, Kristal AR. A dietary intervention to elicit rapid and complex dietary changes for studies investigating the effects of diet on tissues collected during invasive surgical procedures. Journal of the American Dietetic Association 2009;109(3):459-63. doi: 10.1016/j.jada.2008.11.026.
69. Reed JL, De Souza MJ, Williams NI. Effects of exercise combined with caloric restriction on inflammatory cytokines. Applied Physiology, Nutrition, and Metabolism 2010;35(5):573-82.

70. Demark-Wahnefried W, Rais-Bahrami S, Desmond RA, Gordetsky JB, Hunter GR, Yang ES, Azrad M, Frugé AD, Tsuruta Y, Norian LA, et al. Presurgical weight loss affects tumour traits and circulating biomarkers in men with prostate cancer. British Journal of Cancer 2017;117(9):1303-13. doi: 10.1038/bjc.2017.303.
71. Wright JL, Plymate S, D'Oria-Cameron A, Bain C, Haugk K, Xiao L, Lin DW, Stanford JL, McTiernan A. A study of caloric restriction versus standard diet in overweight men with newly diagnosed prostate cancer: A randomized controlled trial. Prostate 2013;73(12):1345-51. doi: 10.1002/pros.22682.
72. Lin DW, Neuhouser ML, Schenk JM, Coleman IM, Hawley S, Gifford D, Hung H, Knudsen BS, Nelson PS, Kristal AR. 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 Epidemiology Biomarkers & Prevention 2007;16(10):2150-4. doi: 10.1158/1055-9965.Epi-07-0154.
73. Fleshner N, Bagnell PS, Klotz L, Venkateswaran V. Dietary fat and prostate cancer. The Journal of urology 2004;171(2):S19-S24.
74. Liss MA, Al-Bayati O, Gelfond J, Goros M, Ullevig S, DiGiovanni J, Hamilton-Reeves J, O'Keefe D, Bacich D, Weaver B, et al. Higher baseline dietary fat and fatty acid intake is associated with increased risk of incident prostate cancer in the SABOR study. Prostate Cancer and Prostatic Diseases 2019;22(2):244-51. doi: 10.1038/s41391-018-0105-2.
75. Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, Johnsen NF, Tjønneland A, Linseisen J, Rohrmann S, et al. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 2008;87(5):1405-13. doi: 10.1093/ajcn/87.5.1405.
76. Wallström P, Bjartell A, Gullberg B, Olsson H, Wirfält E. A prospective study on dietary fat and incidence of prostate cancer (Malmö, Sweden). Cancer causes & control : CCC 2007;18(10):1107-21. doi: 10.1007/s10552-007-9050-4.
77. Huang M, Koizumi A, Narita S, Inoue T, Tsuchiya N, Nakanishi H, Numakura K, Tsuruta H, Saito M, Satoh S, et al. Diet-induced alteration of fatty acid synthase in prostate cancer progression. Oncogenesis 2016;5(2):e195. doi: 10.1038/oncsis.2015.42.
78. Huang M, Narita S, Numakura K, Tsuruta H, Saito M, Inoue T, Horikawa Y, Tsuchiya N, Habuchi T. A high-fat diet enhances proliferation of prostate cancer cells and activates MCP-1/CCR2 signaling. The Prostate 2012;72(16):1779-88.
79. Xu C, Han F-F, Zeng X-T, Liu T-Z, Li S, Gao Z-Y. Fat intake is not linked to prostate cancer: a systematic review and dose-response meta-analysis. PloS one 2015;10(7):e0131747.
80. Aronson WJ, Kobayashi N, Barnard RJ, Henning S, Huang M, Jardack PM, Liu B, Gray A, Wan J, Konijeti R. Phase II prospective randomized trial of a low-fat diet with fish oil supplementation in men undergoing radical prostatectomy. Cancer prevention research 2011;4(12):2062-71.
81. Brouwer IA, Geleijnse JM, Klaasen VM, Smit LA, Giltay EJ, de Goede J, Heijboer AC, Kromhout D, Katan MB. Effect of alpha linolenic acid supplementation on serum prostate specific antigen (PSA): results from the alpha omega trial. PloS one 2013;8(12):e81519.

82. Chua ME, Sio MCD, Sorongon MC, Dy JS. Relationship of dietary intake of omega-3 and omega-6 Fatty acids with risk of prostate cancer development: a meta-analysis of prospective studies and review of literature. Prostate cancer 2012;2012.
83. Williams CD, Whitley BM, Hoyo C, Grant DJ, Iraggi JD, Newman KA, Gerber L, Taylor LA, McKeever MG, Freedland SJ. A high ratio of dietary n-6/n-3 polyunsaturated fatty acids is associated with increased risk of prostate cancer. Nutrition Research 2011;31(1):1-8.
84. Lin P-H, Aronson W, Freedland SJ. Nutrition, dietary interventions and prostate cancer: the latest evidence. BMC Medicine 2015;13(1):3. doi: 10.1186/s12916-014-0234-y.
85. Hong H, Koch MO, Foster RS, Bihrle R, Gardner TA, Fyffe J, Ulbright TM, Eble JN, Cheng L. Anatomic distribution of periprostatic adipose tissue: a mapping study of 100 radical prostatectomy specimens. Cancer 2003;97(7):1639-43. doi: 10.1002/cncr.11231.
86. van Roermund JG, Hinnen KA, Tolman CJ, Bol GH, Witjes JA, Bosch JL, Kiemeney LA, van Vulpen M. Periprostatic fat correlates with tumour aggressiveness in prostate cancer patients. BJU international 2011;107(11):1775-9. doi: 10.1111/j.1464-410X.2010.09811.x.
87. Gregg JR, Surasi DS, Childs A, Moll N, Ward JF, Kim J, Daniel CR, Logothetis C, Bathala T, Davis JW. The Association of Periprostatic Fat and Grade Group Progression in Men with Localized Prostate Cancer on Active Surveillance. The Journal of Urology 2021;205(1):122-8.
88. Zimmerman AW, Veerkamp JH. New insights into the structure and function of fatty acid-binding proteins. Cellular and Molecular Life Sciences CMLS 2002;59(7):1096-116. doi: 10.1007/s00018-002-8490-y.
89. Chmurzyńska A. The multigene family of fatty acid-binding proteins (FABPs): Function, structure and polymorphism. Journal of Applied Genetics 2006;47(1):39-48. doi: 10.1007/BF03194597.
90. Das R, Hammamieh R, Neill R, Melhem M, Jett M. Expression pattern of fatty acid-binding proteins in human normal and cancer prostate cells and tissues. Clin Cancer Res 2001;7(6):1706-15.
91. Tölle A, Suhail S, Jung M, Jung K, Stephan C. Fatty acid binding proteins (FABPs) in prostate, bladder and kidney cancer cell lines and the use of IL-FABP as survival predictor in patients with renal cell carcinoma. BMC Cancer 2011;11(1):302. doi: 10.1186/1471-2407-11-302.
92. Liu RZ, Godbout R. An Amplified Fatty Acid-Binding Protein Gene Cluster in Prostate Cancer: Emerging Roles in Lipid Metabolism and Metastasis. Cancers (Basel) 2020;12(12). doi: 10.3390/cancers12123823.
93. Iordanescu G, Brendler C, Crawford SE, Wyrwicz AM, Venkatasubramanian PN, Doll JA. MRS measured fatty acid composition of periprostatic adipose tissue correlates with pathological measures of prostate cancer aggressiveness. Journal of Magnetic Resonance Imaging 2015;42(3):651-7. doi: 10.1002/jmri.24824.
94. Figiel S, Bery F, Chantôme A, Fontaine D, Pasqualin C, Maupoil V, Domingo I, Guibon R, Bruyère F, Potier-Cartereau M. A novel calcium-mediated EMT pathway controlled by lipids: An opportunity for prostate cancer adjuvant therapy. Cancers 2019;11(11):1814.
95. Ribeiro R, Monteiro C, Catalán V, Hu P, Cunha V, Rodríguez A, Gómez-Ambrosi J, Fraga A, Príncipe P, Lobato C, et al. Obesity and prostate cancer: gene expression

signature of human periprostatic adipose tissue. BMC Med 2012;10:108. doi: 10.1186/1741-7015-10-108.
96. Venkatasubramanian PN, Brendler CB, Plunkett BA, Crawford SE, Fitchev PS, Morgan G, Cornwell ML, McGuire MS, Wyrwicz AM, Doll JA. Periprostatic adipose tissue from obese prostate cancer patients promotes tumor and endothelial cell proliferation: A functional and MR imaging pilot study. Prostate 2014;74(3):326-35. doi: 10.1002/pros.22756.
97. Bhardwaj P, Ikeda T, Zhou XK, Wang H, Zheng XE, Giri DD, Elemento O, Verma A, Miyazawa M, Mukherjee S, et al. Supplemental estrogen and caloric restriction reduce obesity-induced periprostatic white adipose inflammation in mice. Carcinogenesis 2019;40(7):914-23. doi: 10.1093/carcin/bgz088.