2020

Exercise and nutrition induced weight loss for prostate cancer patients

Rebekah Louise Wilson
Edith Cowan University

Exercise and nutrition induced weight loss for prostate cancer patients

This thesis is presented for the degree of

Doctor of Philosophy

Rebekah Louise Wilson

Edith Cowan University

School of Medical and Health Sciences

2020

DEDICATION

In loving memory of my best friend Kimberley Kareena Bryant

5th June 1991 – 4th January 2018

ABSTRACTS

THESIS ABSTRACT

This thesis encompasses six main chapters - two reviews and four experimental chapters, in addition to a general introduction and discussion. Review 1 (Chapter 2) is a discussion of the negative impact of obesity on prostate cancer prognosis and common prostate cancer treatments. Review 2 (Chapter 3) is an evaluation of the current literature examining prostate cancer patients receiving androgen deprivation therapy (ADT) and how exercise and nutrition interventions can be used to induce fat loss, while preserving or improving lean mass. Study 1 (Chapter 4) is an examination of the efficacy of a weight loss program in altering body composition in overweight and obese prostate cancer patients scheduled for a robot assisted radical prostatectomy. Study 2 (Chapter 5) is an examination of the efficacy of a 12-week weight loss intervention to reduce fat mass and maintain lean mass in obese prostate cancer patients receiving ADT, with quality of life outcomes reported in an accompanying chapter (Chapter 6). Finally, study 3 (Chapter 7) is an investigation of the effect of a 12-week self-managed home-based exercise and nutrition program on body composition, physical function, and quality of life in obese prostate cancer patients receiving ADT who had previously completed a 12-week weight loss program.

CHAPTER TWO ABSTRACT

Title: A review of the relationship between obesity and prostate cancer

There is accumulating evidence demonstrating obesity to have a negative impact on prostate cancer. Although not associated with prostate cancer incidence, overweight and obese patients are at increased risk of exacerbated treatment side effects, progressing to advanced cancer stage, recurrence, development of obesity-related comorbidities, and all-cause and prostate cancer-specific mortality. The exact physiological mechanisms associated with obesity and poor prostate cancer prognosis are largely unknown; however, an increased inflammatory environment and metabolic irregularities associated with excess fat mass are commonly suggested. As such, a reduction in fat mass may prevent or slow down prostate cancer progression and improve a patient's risk profile. Therefore, the overall aim of this review was to present and discuss: 1) the association between obesity and poor prostate cancer prognosis; 2) the potential physiological mechanisms linking obesity and prostate cancer progression; 3) the effect of obesity on treatments for prostate cancer; and 4) the potential for weight loss strategies to improve outcomes in patients with prostate cancer. The findings of this review describe consistent epidemiological and clinical evidence on the association between obesity and prostate cancer progression and mortality. Although caution is warranted due to limited research, weight loss strategies using exercise and nutrition interventions may improve the risk profile of obese prostate cancer patients.

CHAPTER THREE ABSTRACT

Title: Using exercise and nutrition to induce fat loss while preserving lean mass in prostate cancer patients receiving androgen deprivation therapy: a narrative review.

Fat mass gain and lean mass loss are common side effects for patients with prostate cancer receiving androgen deprivation therapy (ADT). Excess fat mass has been associated with an increased risk of developing comorbidities such as cardiovascular disease and type 2 diabetes, prostate cancer progression, and all-cause and cancer-specific mortality. Lean mass is the predominant contributor to resting metabolic rate with any loss impacting long-term weight management as well as physical function and frailty. Consequently, reducing fat mass and preserving lean mass, may improve a patient's quality of life, risk of disease progression, and comorbidity development. Exercise and nutrition interventions are common strategies utilised to reduce fat mass and preserve or increase lean mass in addition to improving chronic disease risk factors in the non-cancer population. In men with prostate cancer on ADT, exercise and nutrition interventions lead to improvements in quality of life, physical function, and fatigue; however, effects on body composition have been variable. Fat mass loss in particular has been rarely targeted despite the known relationship ADT-induced fat gain has with poor patient outcomes. Therefore, the aim of this review was to provide a descriptive overview of exercise and nutrition interventions in prostate cancer patients on ADT and their effect on fat and lean mass. The findings of this review demonstrate fat mass gain and lean mass loss are side effects of ADT that might be prevented or reversed with the implementation of an exercise and nutrition intervention. However, the specifics and combinations of exercise and nutrition interventions are yet to be determined in future studies.

CHAPTER FOUR ABSTRACT

Title: Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer.

Obesity in prostate cancer patients is associated with poor prostate-cancer specific outcomes. Exercise and nutrition can reduce fat mass; however, few studies have explored this as a combined pre-surgical intervention in clinical practice. This study examined the efficacy of a weight loss program for altering body composition in prostate cancer patients prior to robot assisted radical prostatectomy (RARP). A retrospective analysis of 43 overweight and obese prostate cancer patients, aged 47 to 80 years, who completed a very low-calorie diet (~3000-4000 kJ) combined with moderate-intensity exercise (90 minutes/day) prior to RARP. Whole body and regional fat mass (FM) and lean mass (LM) were assessed by dual x-ray absorptiometry pre- and post-program. Body weight, waist circumference, and blood pressure were assessed weekly, with surgery-related adverse effects recorded at time of surgery and follow-up appointments. With a median of 29 days (IQR: 24-35 days) on the program, patients significantly ($p < 0.001$) reduced weight (-7.3 ± 2.9 kg), FM (-5.0 ± 2.6 kg), percent body fat (-3.1 ± 2.5 %), trunk FM (-3.4 ± 1.8 kg), LM (-2.4 ± 1.8 kg), and appendicular LM (-1.2 ± 1.0 kg). Lower weight, FM, percent FM, trunk FM, and visceral FM were associated with less surgery-related adverse effects ($r_s = 0.335$ to 0.468, $p < 0.010$). Systolic and diastolic blood pressure were reduced ($p < 0.001$) by 15 ± 22 and 8 ± 10 mmHg, respectively over the weight loss intervention. Undertaking a combined low-calorie diet and exercise program for weight loss in preparation for RARP resulted in substantial reductions in FM, with improvements in blood pressure, that may benefit surgical outcomes.

CHAPTER FIVE ABSTRACT

Title: Weight loss for obese prostate cancer patients on androgen deprivation therapy.

Excess fat mass (FM) contributes to poor prostate cancer (PCa) prognosis and comorbidity. However, FM gain is a common side effect of androgen deprivation therapy (ADT). We examined the efficacy of a 12-week weight loss intervention to reduce FM and maintain lean mass (LM) in ADT-treated obese PCa patients. Fourteen ADT-treated obese PCa patients (72 ± 9 years, 39.7 ± 5.4 % body-fat) were recruited for a self-controlled prospective study, with 11 completing the 6-week control period, followed by a 12-week intervention comprising 300 minutes/week of exercise including supervised resistance training and home-based aerobic exercise, and dietitian consultations advising a daily energy deficit (2100 – 4200 kJ) and protein supplementation. Body composition was assessed by dual x-ray absorptiometry. Secondary outcomes included muscle strength (1RM), cardiorespiratory fitness (VO_{2max}), and blood biomarkers. There were no significant changes during the control period. Patients attended 89% of supervised exercise sessions and 100% of dietitian consultations. No changes in physical activity or energy intake were observed. During the intervention, patients experienced significant reductions in weight (-2.8 ± 3.2 kg, $p = 0.016$), FM (-2.8 ± 2.6 kg, $p < 0.001$), and trunk FM (-1.8 ± 1.4 kg, $p < 0.001$), with LM preserved (-0.05 ± 1.6 kg, $p = 0.805$). Muscle strength (4.6 - 24.7 %, $p < 0.010$) and VO_{2max} (3.5 ± 4.7 $mL \cdot min^{-1} \cdot kg^{-1}$, $p = 0.041$) significantly improved. Leptin significantly decreased (-2.2 [-2.7 - 0.5] ng/mL, $p = 0.016$) with no other changes in blood biomarkers such as testosterone and lipids ($p = 0.051 – 0.765$); however, CRP ($r_s = -0.670$, $p = 0.024$) and triglycerides ($r = -0.667$, $p = 0.025$) were associated with individual changes in LM. This study shows preliminary efficacy for an exercise and nutrition weight loss intervention to reduce FM, maintain LM, and improve muscle strength and cardiorespiratory

fitness in ADT-treated obese PCa patients. The change in body composition may impact blood biomarkers associated with obesity and PCa progression, however, further research is required.

CHAPTER SIX ABSTRACT

Title: Quality of life outcomes in obese men with prostate cancer on androgen deprivation therapy undergoing planned weight loss.

Exercise and nutrition interventions have been established as a viable strategy to mitigate or improve androgen deprivation therapy (ADT)-related reductions in quality of life (QoL) in men with prostate cancer. Here we examine the effect of an exercise and nutrition-based weight loss intervention on QoL in obese prostate cancer patients undertaking ADT. Fourteen ADT-treated obese prostate cancer patients aged 72 ± 9 years with a body fat percent of 39.7 ± 5.4 % were recruited for a self-controlled prospective exercise and nutrition weight loss study. Eleven patients completed the full study program, including a 6-week control period followed by a 12-week intervention comprising 300 minutes/week of exercise including supervised resistance training, home-based aerobic exercise, and dietitian consultations advising a daily energy deficit (2100 – 4200 kJ) with post-exercise protein supplementation. General health-related QoL and prostate cancer-specific QoL were assessed using the SF-36 and EORTC QLQ-PR25 questionnaires, respectively. Patients experienced a significant reduction in body weight (-2.8 ± 3.2 kg) during the intervention, predominantly through fat loss (-2.8 ± 2.6 kg) while lean mass was preserved (-0.05 ± 1.6 kg). Improvements in muscle strength and cardiorespiratory fitness were also observed. There were no significant changes in the 8 domains of general health-related QoL by the SF-36 ($p = 0.142$ - 0.902) and the physical and mental component summary scores ($p = 0.757$ and 0.922, respectively). No changes were observed in urinary, bowel, and sexual activity domains of the QLQ-PR25 ($p = 0.072$ – 0.913), however, a decrease in hormone treatment symptoms approached statistical significance ($p = 0.059$). These preliminary findings indicate that general health-related and prostate cancer-specific QoL are

maintained in obese patients on ADT while undertaking an exercise and nutrition-based weight loss intervention.

CHAPTER SEVEN ABSTRACT

Title: A home-based exercise and nutrition program preserves body composition and physical function in obese prostate cancer patients on androgen deprivation therapy.

Supervised exercise and nutrition interventions in men with prostate cancer can improve or preserve body composition, physical function, and quality of life, which are negatively impacted when receiving androgen deprivation therapy (ADT). It is unclear whether these benefits are retained following a transition to self-management after a period of supervision while remaining on ADT. Accordingly, this study examined the effect of a 12-week self-managed, home-based exercise and nutrition program on body composition, physical function, and quality of life in obese prostate cancer patients on ADT following a 12-week supervised weight-loss program. Fourteen obese men with prostate cancer (48 - 84 years, 39.7 ± 5.4% body-fat) on long-term ADT (> 6 months) were initially recruited to undergo a 6-week control period followed by a 12-week exercise and nutrition weight loss program, with 11 men completing the intervention. The 11 patients then underwent a self-managed home-based program comprising 150 minutes of aerobic and resistance training each week while maintaining a healthy balanced diet. Measurements included whole-body and regional fat mass (FM) and lean mass (LM) assessed by dual x-ray absorptiometry, muscle strength (1RM), cardiorespiratory fitness by 400m walk, and quality of life by self-report questionnaires. The initial intervention resulted in a significant reduction in FM (-2.8 ± 2.6 kg) with LM preserved (-0.05 ± 1.6 kg), and improvements in muscle strength and VO_{2max}. Following the self-managed program, there was no increase in FM (0.2 ± 1.4 kg, p = 0.619) and no significant change in LM (-0.8 ± 1.6 kg, p = 0.146), muscle strength (-0.2 to 4.1%, p = 0.086 – 0.745), or estimated VO_{2max} (0.3 ± 2.1 $mL \cdot min^{-1} \cdot kg^{-1}$, p = 0.649). However, quality of life domains role-physical (-

7.1 ± 7.2, p = 0.008), mental health (-3.6 ± 4.6, p = 0.027), and physical component (-3.6 ± 5.2, p = 0.048) decreased. Obese prostate cancer patients undertaking ADT were able to maintain improvements in body composition, muscle strength, and cardiorespiratory fitness using a self-managed, home-based exercise and nutrition program following a supervised exercise and nutrition weight loss intervention. Nevertheless, quality of life declined during this period and requires further investigation of maintenance strategies.

DECLARATION

I certify that this thesis does not, to the best of my knowledge and belief:

i. Incorporate without acknowledgement any material previously submitted for a degree or diploma in any institution of higher education;

ii. Contain any material previously published or written by another person except where due reference is made in the text of this thesis; or

iii. Contain any defamatory material.

iv. I also grant permission for the Library at Edith Cowan University to make duplicate copies of my thesis as required.

Signed

Rebekah Wilson

Date: 31st August 2020

ACKNOWLEDGEMENTS

The soul of a lazy man desires and has nothing, but the soul of the diligent shall be made rich. Proverbs 13:1. I read this Bible verse out at Kimberley's funeral, whom this thesis is dedicated to, as she sadly lost her battle to cystic fibrosis while I was undertaking my PhD. She was one of my best friends and this verse completely summed her up as well as acted as a reminder to me throughout my PhD that when you put in the effort, you get the reward. She never let her medical condition get in the way of getting involved and she did amazing things during her life. She was a constant inspiration and one of the many reasons I chose to research the use of exercise as medicine as I saw how much sport helped her physical and mental well-being and I thank her for being a kind and encouraging friend.

To my primary supervisors Prof Daniel Galvão and Prof Rob Newton. Your mentorship has been inspiring, and I have learnt so much in my time here with you. I can't thank you enough for your dedication to my PhD and the opportunities you have given me along the away. To my other supervisors Prof Dennis Taaffe, Dr Nicolas Hart, and A/Prof Philippa Lyons-Wall. I also thank you for your dedication to my PhD. All your feedback and the many hours put into providing it has been greatly appreciated. Philippa, I want to thank you in particular for offering to be the consulting dietitian for my participants and the hours you put in to do so. I also wanted to thank you for providing five Master of Nutrition and Dietetic students to help me with the nutrition components of my study and giving me the opportunity to supervise them.

To the Master of Nutrition and Dietetic students Thomas Hosking, Sabina Ferri, Rebecca Newton, Sarah Forrest, and Marija Karanfilovska. Thank you all for taking an interest in my PhD and for your contributions which included working with the participants, entering and analysing data, and providing new angles for how to examine the data which all contributed to your individual projects.

To Dr Tom Shannon and Dr Emily Calton. Thank you for allowing me to work with your pre-surgery weight loss program data and subsequently adding it as an important component of my PhD.

To my fellow PhD and Masters students Mary Kennedy, David Luo, Oliver Schumacher, Brendan Crosby, Jin Soo Kim, Christelle Schofield, Emily Jeffery, Pedro Lopez Da Cruz, and

Lucia Gill Herrero. Thank you! Your voluntary contributions with helping with testing, working with the participants, reading my drafts, listening to practice presentations, providing feedback, and also being amazing friends outside of uni was all a huge help in putting this thesis together. In addition, I would like to thank the other ECU undergraduate and postgraduate students who also volunteered their time to help with testing.

To the EMRI staff, thank you all for your support during my PhD. In particular I would like to thank Cailyn Walker, Audrey Cox, and Jackie Gilbert who were the first people I met on my first day here and made me feel so welcome! You helped me so much over the last few years whether it was getting in touch with potential participants and medical staff or helping with equipment orders and room organisation, your efforts were greatly appreciated. I would also like to thank the EPs, Kyle Smith, Claire Mason, Olivia Pisconeri, Dan Bomford, and Charlotte Cummins. Thank you for teaching me to use all the testing equipment and allowing me to shadow your consultations prior to starting my own study. Finally, I would like to thank the EMRI and ECU staff Dr Favil Singh, Dr Pauline Zaenker, Michael Morici, Dr Carolyn Peddle-Mcintyre, Dr Lauren Fortington, and Dr Ciaran Fairman who all helped me in one way or another whether it was reading drafts, teaching how to conduct tests, providing advice on tests, or just providing advice in general, thank you!

To the participants. Without you this PhD does not exist. Your motivation and dedication to the exercise and nutrition sessions was inspiring and I am grateful for your willingness to participate in my study. I thoroughly enjoyed working with you all and wish each one of you all the best as your cancer journey continues.

To my family and friends in New Zealand, here in Perth, and all over the world. Your prayers, thoughts, support, kind words, listening ears for complaints, advice, feedback on drafts (thank you Janet and Poppa), and many more things, thank you for being in my life! Especially my Mum and Dad your support through everything cannot be put into word, so simply thank you.

Finally, to the most amazing partner, Brad. I can’t thank you enough for leaving your life back in New Zealand and moving to Perth with me. Your constant love and support are some of the biggest reasons I got through this PhD. You were there to give me a reality check when I was feeling sorry for myself, comforted me when things weren’t going right, and always celebrated in my achievements whether big or small. We have had the most amazing adventure here and I cannot wait for the next chapter of our lives together. I love you so much, thank you for everything.

RESEARCH SUPPORT

1. Recipient of the Higher Degree by Research Scholarship.
2. NHMRC Centre for Research Excellence funding supported this thesis in addition to allocated funds from Edith Cowan University.
3. Access to data from The Prostate Clinic and Trench Health and Fitness.
4. Access to the Mt Lawley ECU Sport and Fitness Centre.

PUBLICATIONS AND PRESENTATIONS FROM THIS THESIS

Journal publications

Wilson, R., Shannon, T., Calton, E., Galvão, D., Taaffe, D., Hart, N., Lyons-Wall, P., Newton, R. (2020). Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer. *Surgical Oncology*. https://doi.org/10.1016/j.suronc.2020.08.006

Wilson, R., Newton, R., Taaffe, D., Hart, N., Lyons-Wall, P., Galvão, D. (2020). Weight loss for obese prostate cancer patients on androgen deprivation therapy. *Medicine & Science in Sport & Exercise* (*in press*) accepted 27th August 2020.

Conference and symposium abstracts and presentations

- Accepted abstract for oral presentation for 'Exercise and Sport Science Australia Conference' (2020). **Title:** Exercise and nutrition induced fat loss in prostate cancer patients on long-term androgen deprivation therapy. **Award:** Nominated for the Young Investigator for Exercise Science.
- Accepted abstract for oral presentation for 'European College of Sport Science' (2020). **Title:** Maintenance of body composition and physical function after intentional weight loss for prostate cancer patients on androgen deprivation therapy.

- Oral presentation for ‘EMRI and Alberta University Symposium’ (2020). **Title:** Exercise and nutrition induced fat loss in prostate cancer patients on long-term androgen deprivation therapy.

Community engagement presentations

- Radio interview with 882 6PR to promote recruitment for my study and discuss the importance of exercise for prostate cancer patients while on androgen deprivation therapy.
- Presentation at Leederville Prostate Cancer support group to discuss the importance of exercise after a prostate cancer diagnosis.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

3d-WR	–	Three day weighed food record
ADT	–	Androgen deprivation therapy
AEP	–	Accredited exercise physiologist
AMPK	–	Adenosine monophosphate-activated protein kinase
APD	–	Accredited practising dietitian
ASM	–	Appendicular skeletal muscle
BF%	–	Body fat percentage
BIA	–	Bioimpedance analysis
BMC	–	Bone mineral content
BMD	–	Bone mineral density
BMI	–	Body mass index
CF	–	Correction factor
CPET	–	Cardiopulmonary exercise test
CRP	–	C-reactive protein
CT	–	Computed tomography
CVD	–	Cardiovascular disease
DRE	–	Digital rectal examination
DXA	–	Dual x-ray absorptiometry
EBRT	–	External beam radiation therapy
EDTA	–	Ethylenediaminetetraacetic acid
ECG	–	Electrocardiogram
EORTC QLQ-PR25	–	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module
FFA	–	Free fatty acids

FM	–	Fat mass
HbA1c	–	Haemoglobin A1c
HDL	–	High-density lipoprotein
HR_{max}	–	Heart rate maximum
IGF	–	Insulin-like-growth-factor
IGFBP	–	Insulin-like-growth-factor binding protein
IL-6	–	Interleukin 6
LDL	–	Low-density lipoprotein
LHRH	–	Luteinizing hormone-releasing hormone
LM	–	Lean mass
LPA	–	Light physical activity
MRI	–	Magnetic resonance imaging
MVPA	–	Moderate-to-vigorous physical activity
NA	–	Not applicable
NATA	–	National Association of Testing Authorities
PCa	–	Prostate cancer
PSA	–	Prostate specific antigen
QoL	–	Quality of life
RARP	–	Robot assisted radical prostatectomy
RCT	–	Randomised control trial
RM	–	Repetition maximum
RMR	–	Resting metabolic rate
RPE	–	Rate of perceived exertion
SB	–	Sedentary behaviour
SBP	–	Systolic blood pressure
SD	–	Standard deviation
SF-36	–	36-item short-form health survey
SST	–	Serum separation tubes
VO_{2max}	–	Oxygen consumption

CHAPTER ONE

General introduction

BACKGROUND INFORMATION

Advances in screening, detection, diagnosis, and treatment of prostate cancer have improved overall survival with 95% of men living a minimum of 5 years beyond diagnosis [1]. However, while the survival rate is impressive, many men with prostate cancer experience a significantly reduced quality of life with long-term complications becoming more apparent across the natural history of the disease [2, 3]. Obesity has emerged as a critical concern attributed with negative long-term patient outcomes. Although obesity does not appear to be associated with increased prostate cancer incidence [4, 5], the World Cancer Research Fund & American Institute for Cancer Research described a strong level of evidence associating obesity with aggressive prostate cancer at diagnosis [6]. Obesity has also been associated with faster time to castrate resistance, cancer recurrence, and prostate cancer-specific and all-cause mortality [6-9]. The exact mechanisms attributed to the obesity and prostate cancer relationship are unclear, however, altered insulin/insulin-like-growth-factor axis, sex hormone concentrations, and abnormal adipokine and cytokine signalling are commonly suggested [5]. In addition, obesity has a well-established relationship with the development of comorbidities such as cardiovascular disease and diabetes [10], and increased risk of acute prostate cancer treatment-related complications and side effects [11-16], particularly for patients undergoing a radical prostatectomy or androgen deprivation therapy (ADT) who are of interest in this thesis.

Radical prostatectomy is commonly offered to patients who are generally fit and healthy and have contained or locally advanced prostate cancer [17]. The aim of surgery is to render a patient cancer free by removing the disease affected prostate, surrounding tissue, seminal vesicles, and/or lymph nodes (lymphadenectomy) [17]. Overweight and obese patients present a challenge to urologists as they often have multiple comorbidities which add risk to the procedure such as high blood pressure [18-20]. The surgical procedure may also be complicated

by the increased distance from the skin surface to the prostate and excess periprostatic fat mass [14, 15]. With fat acting as a physical barrier, surgical techniques may have to be adjusted for an obese patient, such as altering the angles of equipment insertion, use of alternative equipment (e.g. longer probes), or converting to an open prostatectomy [15, 21]. With the added technical difficulty of conducting a radical prostatectomy, obese patients are at increased risk of surgical complications including capsular incision, longer operation time, higher blood loss, and central nervous system and head and neck complications due to excessive peak expiratory airway pressure while in the Trendelenburg position [14-16]. While most patients will experience acute and long-term surgery-related side effects, obese patients may experience worse urinary and sexual outcomes, increased risk of post-operative infection, lymphedema, and positive surgical margins [14, 15, 22].

Prostate cancer is an androgen sensitive disease, where ADT is commonly used to prevent the growth of prostate cancer by reducing testosterone to castrate levels or eliminating the ability of testosterone to attach to receptors [23]. The most common types of ADT include luteinizing hormone-releasing hormone (LHRH) agonists/antagonists and anti-androgens [24]. LHRH agonists/antagonists are given by implant or injection at intervals between 1 and 6 months to continuously supress the production of testosterone [25]. Anti-androgens are given as oral medication and block the binding of androgens to their receptors [24]. Both treatments may be given in isolation, a combination of the two, or as neoadjuvant or adjuvant therapies alongside other prostate cancer treatments such as radiation therapy, chemotherapy, or surgery [26]. ADT may be prescribed for a few months, or in some cases indefinitely, depending on disease stage and treatment purpose [26]. As with any treatment, ADT is accompanied by side effects, however, patients who are obese have been reported to experience poorer quality of life through greater fatigue and lower vitality, higher blood triglyceride levels, and increased risk of skeletal-related events [11-13]. In addition to the association between obesity and more

severe ADT-related side effects, ADT can cause obesity in previously non-obese patients, or exacerbate adiposity in currently obese patients. Testosterone plays a role in the activation of lipolysis, muscle mass development, and bone growth [27, 28]. With the removal of testosterone, it has been reported that men on ADT experience a 6.6 - 13.8% gain in fat mass, 2.0 – 3.6% loss in lean mass, and 2.0 – 8.0% loss in bone mass within the first year of treatment [29, 30].

As obese prostate cancer patients are at increased risk of long-term adverse events including cancer progression, recurrence, and prostate cancer-specific mortality, as well as at increased risk of exacerbated acute treatment-related side effects and complications, it is important to manage these risks from the time of diagnosis. Obesity status, as well as common comorbidities and abnormal metabolic outcomes associated with obesity, may be targeted using a number of interventions including behaviour modification, surgical intervention, and pharmaceuticals [31]; however, exercise and nutrition strategies are often considered initially given the low cost and low risk of consequences when prescribed appropriately. There have been major advancements in the exercise oncology field in the last decade with healthier lifestyle changes now viewed as important contributors to improved survivorship [32, 33, 29]. Current clinical practice guidelines for the management of overweight and obesity in Australia recommend 300 minutes of moderate intensity or 150 minutes of vigorous intensity exercise per week combined with an energy deficit diet to achieve weight loss [31]. There are currently no specific weight loss guidelines for prostate cancer patients. When weight loss is required, prostate cancer patients are referred to the weight loss guidelines for the general population [34]. Although following these guidelines is unlikely to be harmful for prostate cancer patients, their effectiveness and efficacy in this population has not been clarified.

Despite the awareness of a need for weight management to be a part of clinical practice for patients with prostate cancer who are obese [35, 36], targeted research that aims to reduce

fat mass in obese patients is limited. In a systematic review of diet, exercise, and combined interventions undertaken in prostate cancer patients, Mohamad et al. [37] concluded combined exercise and diet interventions to be the most beneficial for weight loss. This is reflected in the work by O'Neill et al. [38] and Freedland et al. [39] who showed fat mass can be significantly reduced in men on ADT, and Henning et al. [40] who demonstrated similar results in patients prior to radical prostatectomy. The aim of this thesis is to build on these findings by examining several research gaps in this field. First, cancer progression has been shown to increase linearly with obesity status [41], therefore, the experimental studies conducted for this thesis have included overweight and obese (Chapter 4), or obese (Chapters 5, 6, 7) only patients, as these cohorts are of highest risk, and underrepresented in the exercise and nutrition oncology literature. Second, fat mass is considered critical to the relationship between obesity and poor prostate cancer prognosis, so where possible this thesis has used body fat percentage as assessed by dual x-ray absorptiometry, instead of body mass index, as an inclusion criterion to ensure that patients with excess fat mass were targeted. Third, in addition to fat loss, the maintenance of lean mass is also important and in previous studies has either been measured using inferior techniques such as skinfolds [38], or substantially reduced more than that of a usual care control group [39]. Finally, it is anticipated that the examination of clinical data and prescription of exercise and nutrition will provide external validity to the results by highlighting the importance of using exercise and nutrition as an adjuvant therapy within a clinical environment.

PURPOSE OF THE RESEARCH

The purpose of this thesis was to examine the efficacy and effectiveness of exercise and nutrition-based weight loss programs in reducing fat mass, while maintaining lean mass, in patients with prostate cancer who are overweight or obese. The first experimental study

presented in Chapter 4 of this thesis examines overweight and obese men who were scheduled to undergo a radical prostatectomy. This population was of interest due to the significant impact obesity can have on the surgical procedure and increased risk of experiencing complications and side effects. Patients with prostate cancer who are obese and receiving long-term ADT were also of interest and the studies and outcomes are reported in Chapters 5, 6, and 7. Fat mass gain is a common side effect of ADT, which can lead to reduced physical function, quality of life, and poor prostate cancer prognosis. Specifically, the chapters within this thesis are investigations of the following:

Chapter 2: This review is an exploration of the relationship between obesity and prostate cancer. It is an evaluation of the current evidence surrounding proposed mechanisms for the observed association between obesity and prostate cancer, how common prostate cancer treatments cause or are affected by obesity, and the potential for weight loss strategies to improve outcomes for patients with prostate cancer.

Chapter 3: Building on the previous chapter, this review is a critical appraisal of the effect exercise and combined exercise and nutrition interventions have on fat mass and lean mass in ADT-treated patients by providing a comprehensive discussion of the literature. In addition, Chapters 2 and 3 are a platform for the methodology undertaken in the experimental studies.

Chapter 4: This retrospective study is an examination of data previously collected within a clinical environment where overweight and obese patients with prostate cancer were requested and supported to lose weight prior to undergoing a robot assisted radical prostatectomy (RARP). The aim was to analyse the effect of a weight loss program on body composition in prostate cancer patients prior to surgery.

Chapter 5: This prospective study is an investigation of the efficacy of a 12-week exercise and nutrition weight loss intervention in obese prostate cancer patients on ADT to reduce fat mass,

maintain lean mass, and improve physical function and blood biomarkers associated with cancer progression and obesity.

Chapter 6: This study is a short clinical communication of the exercise and nutrition weight loss intervention described in Chapter 5 and focuses on quality of life.

Chapter 7: This study is an extension of the results reported in Chapters 5 and 6, by examining the efficacy of a 12-week self-managed home-based exercise and nutrition program to maintain body composition, quality of life, and physical function, while remaining on ADT.

SIGNIFICANCE OF THE RESEARCH

Obese patients with prostate cancer are a population in critical need for novel clinical interventions, however, they have not been commonly targeted in exercise oncology research studies. With the improved survival rate in men with prostate cancer, and an increase in the prevalence of obesity in both the cancer and general populations, it is becoming an important research area to understand how obese patients could benefit from combined exercise and nutrition interventions. Obese men with prostate cancer are at increased risk of advanced stage disease, experiencing a greater number and more severe treatment-related side effects, developing obesity-related comorbidities, disease recurrence, and all-cause and prostate cancer-specific mortality [6-8, 10]. It is anticipated that findings from the experimental studies presented in this thesis will improve the current understanding of how patients with prostate cancer who are obese respond to exercise and nutrition weight loss programs either prior to a RARP or while receiving ADT. This thesis will also provide further insights into the importance of including such programs within clinical practice.

RESEARCH QUESTIONS

Chapter 4

Title: Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer.

1. Can an exercise and nutrition weight loss program reduce fat mass in overweight and obese prostate cancer patients prior to undergoing a RARP?
2. Is lean mass maintained during an exercise and nutrition weight loss program prior to RARP?
3. Is blood pressure affected by a pre-surgery exercise and nutrition weight loss program?
4. Are changes in body composition associated with the number of surgery-related adverse effects?

Chapter 5

Title: Weight loss for obese prostate cancer patients on androgen deprivation therapy.

1. Can an exercise and nutrition weight loss program reduce fat mass in obese prostate cancer patients undergoing ADT?
2. Is lean mass maintained in obese prostate cancer patients on ADT during an exercise and nutrition weight loss program?
3. Can an exercise and nutrition weight loss program improve muscle strength and cardiorespiratory fitness in obese prostate cancer patients on ADT?
4. Does an exercise and nutrition weight loss program have an effect on blood serum biomarkers associated with prostate cancer progression and obesity?

Chapter 6

Title: Quality of life outcomes in obese men with prostate cancer on androgen deprivation therapy undergoing planned weight loss.

1. Can an exercise and nutrition weight loss program improve general health-related quality of life in obese prostate cancer patients undergoing ADT?
2. Can an exercise and nutrition weight loss program improve prostate cancer-specific quality of life in obese prostate cancer patients undergoing ADT?

Chapter 7

Title: A home-based exercise and nutrition program preserves body composition and physical function in obese prostate cancer patients on androgen deprivation therapy.

1. Can obese men with prostate cancer maintain fat mass previously lost during a supervised weight loss intervention by completing a self-managed home-based exercise and nutrition program while remaining on ADT.
2. Can obese men with prostate cancer maintain lean mass during a self-managed home-based exercise and nutrition program while remaining on ADT.
3. Does a self-managed home-based exercise and nutrition program maintain muscle strength, cardiorespiratory fitness, and quality of life in prostate cancer patients receiving ADT?

RESEARCH HYPOTHESES

Chapter 4

Title: Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer.

Comparing baseline and pre-surgery assessments, an exercise and nutrition weight loss program will:

1. Reduce total fat mass and regional trunk and visceral fat mass.
2. Maintain total lean mass and regional appendicular skeletal mass.
3. Reduce both systolic and diastolic blood pressures.

Examining the effects of the weight loss program on surgery-related adverse effects.

1. Those who lost the most amount of fat or had the lowest absolute amount of fat mass will experience less surgery-related adverse effects.

Chapter 5

Title: Weight loss for obese prostate cancer patients on androgen deprivation therapy.

A 12-week exercise and nutrition weight loss program will:

1. Reduce fat mass.
2. Maintain lean mass.
3. Improve upper and lower body muscle strength.
4. Improve cardiorespiratory fitness.
5. Improve blood serum biomarker concentrations associated with prostate cancer progression and obesity (lipid profile, insulin, HbA1c, CRP, IL-6, leptin, adiponectin, IGF-1, IGFBP-3).
6. Maintain testosterone and PSA concentrations.

Chapter 6

Title: Quality of life outcomes in obese men with prostate cancer on androgen deprivation therapy undergoing planned weight loss.

A 12-week exercise and nutrition weight loss program will:

1. Improve general health-related quality of life scores.
2. Improve prostate cancer-specific quality of life scores.

Chapter 7

Title: A home-based exercise and nutrition program preserves body composition and physical function in obese prostate cancer patients on androgen deprivation therapy.

Following a supervised 12-week exercise and nutrition weight loss program, a 12-week self-managed home-based exercise and nutrition program will:

1. Maintain fat and lean mass.
2. Maintain upper and lower body muscle strength.
3. Maintain cardiorespiratory fitness.
4. Maintain general health-related and prostate cancer-specific quality of life.

Overall, these positive effects of the respective interventions are hypothesised to improve, reverse, or prevent established and anticipated obesity-related complications and treatment-related adverse effects associated with a RARP or ADT. The resulting hypothesised changes will improve overall well-being of obese prostate cancer patients and improve their risk profile for comorbidity development and cancer progression.

REFERENCES

1. Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality (ACIM) books: Prostate cancer. Canberra: AIHW; 2017.

2. Chambers SK, Scuffham PA, Baade PD, Lowe AP, Dunn J, Galvao DA et al. Advancing prostate cancer survivorship research in Australia. Cancer Forum. 2015;39(3):204-9.

3. Narayan V, Harrison M, Cheng H, Kenfield S, Aggarwal R, Kwon D et al., editors. Improving research for prostate cancer survivorship: A statement from the Survivorship Research in Prostate Cancer (SuRECaP) working group. Urologic Oncology: Seminars and Original Investigations; 2019: Elsevier.

4. Golabek T, Bukowczan J, Chlosta P, Powroznik J, Dobruch J, Borowka A. Obesity and prostate cancer incidence and mortality: a systematic review of prospective cohort studies. Urol Int. 2014;92(1):7-14. doi:10.1159/000351325.

5. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol. 2013;63(5):800-9. doi:10.1016/j.eururo.2012.11.013.

6. World Cancer Research Fund, American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and prostate cancer 2018.

7. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2011;4(4):486-501. doi:10.1158/1940-6207.CAPR-10-0229.

8. Keto CJ, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL et al. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. BJU Int. 2012;110(4):492-8. doi:10.1111/j.1464-410X.2011.10754.x.

9. Troeschel AN, Hartman TJ, Jacobs EJ, Stevens VL, Gansler T, Flanders WD et al. Postdiagnosis body mass index, weight change, and mortality from prostate cancer, cardiovascular disease, and all causes among survivors of nonmetastatic prostate cancer. J Clin Oncol. 2020:JCO. 19.02185.

10. Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab. 2004;89(6):2583-9. doi:10.1210/jc.2004-0535.

11. Buttigliero C, Vana F, Bertaglia V, Vignani F, Fiori C, Osella G et al. The fat body mass increase after adjuvant androgen deprivation therapy is predictive of prostate cancer outcome. Endocrine. 2015;50(1):223-30. doi:10.1007/s12020-015-0525-x.

12. Newton RU, Jeffery E, Galvao DA, Peddle-McIntyre CJ, Spry N, Joseph D et al. Body composition, fatigue and exercise in patients with prostate cancer undergoing androgen-deprivation therapy. BJU Int. 2018;122(6):986-93. doi:10.1111/bju.14384.

13. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Acute versus chronic exposure to androgen suppression for prostate cancer: impact on the exercise response. J Urol. 2011;186(4):1291-7. doi:10.1016/j.juro.2011.05.055.

14. Wiltz AL, Shikanov S, Eggener SE, Katz MH, Thong AE, Steinberg GD et al. Robotic radical prostatectomy in overweight and obese patients: oncological and validated-functional outcomes. Urology. 2009;73(2):316-22. doi:10.1016/j.urology.2008.08.493.

15. Freedland SJ, Grubb KA, Yiu SK, Nielsen ME, Mangold LA, Isaacs WB et al. Obesity and capsular incision at the time of open retropubic radical prostatectomy. J Urol. 2005;174(5):1798-801; discussion 801. doi:10.1097/01.ju.0000177077.53037.72.

16. Ahlering TE, Eichel L, Edwards R, Skarecky DW. Impact of obesity on clinical outcomes in robotic prostatectomy. Urology. 2005;65(4):740-4. doi:10.1016/j.urology.2004.10.061.

17. Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v69-77. doi:10.1093/annonc/mdv222.

18. Hartle A, McCormack T, Carlisle J, Anderson S, Pichel A, Beckett N et al. The measurement of adult blood pressure and management of hypertension before elective surgery: Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British Hypertension Society. Anaesthesia. 2016;71(3):326-37. doi:10.1111/anae.13348.

19. Meng L, Yu W, Wang T, Zhang L, Heerdt PM, Gelb AW. Blood pressure targets in perioperative care. Hypertension. 2018;72(4):806-17. doi:10.1161/HYPERTENSIONAHA.118.11688.

20. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth. 2019;122(5):563-74. doi:10.1016/j.bja.2019.01.013.

21. Mikhail AA, Stockton BR, Orvieto MA, Chien GW, Gong EM, Zorn KC et al. Robotic-assisted laparoscopic prostatectomy in overweight and obese patients. Urology. 2006;67(4):774-9. doi:10.1016/j.urology.2005.10.049.

22. Knipper S, Mazzone E, Mistretta FA, Palumbo C, Tian Z, Briganti A et al. Impact of obesity on perioperative outcomes at robotic-assisted and open radical prostatectomy: results from the national inpatient sample. Urology. 2019;133:135-44.

23. Labrie F, Dupont A, Belanger A, St-Arnaud R, Giguere M, Lacourciere Y et al. Treatment of prostate cancer with gonadotropin-releasing hormone agonists. Endocr Rev. 1986;7(1):67-74. doi:10.1210/edrv-7-1-67.

24. National Cancer Institute. Hormone Therapy for Prostate Cancer. 2019. https://www.cancer.gov/types/prostate/prostate-hormone-therapy-fact-sheet. Accessed 20 May 2020.

25. Tolkach Y, Joniau S, Van Poppel H. Luteinizing hormone-releasing hormone (LHRH) receptor agonists vs antagonists: a matter of the receptors? BJU Int. 2013;111(7):1021-30. doi:10.1111/j.1464-410X.2013.11796.x.

26. Rhee H, Gunter JH, Heathcote P, Ho K, Stricker P, Corcoran NM et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. BJU Int. 2015;115 Suppl 5:3-13. doi:10.1111/bju.12964.

27. Mohamad NV, Soelaiman IN, Chin KY. A concise review of testosterone and bone health. Clin Interv Aging. 2016;11:1317-24. doi:10.2147/CIA.S115472.

28. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. Curr Opin Clin Nutr Metab Care. 2004;7(3):271-7. doi:10.1097/00075197-200405000-00006.

29. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Cardiovascular and metabolic complications during androgen deprivation: exercise as a potential countermeasure. Prostate Cancer Prostatic Dis. 2009;12(3):233-40. doi:10.1038/pcan.2009.12.

30. Mitsuzuka K, Arai Y. Metabolic changes in patients with prostate cancer during androgen deprivation therapy. Int J Urol. 2018;25(1):45-53. doi:10.1111/iju.13473.

31. Australian Government NH, Medical Research Council DoH, Ageing. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. Commonwealth of Australia Canberra, Australia; 2013.

32. Keogh JW, MacLeod RD. Body composition, physical fitness, functional performance, quality of life, and fatigue benefits of exercise for prostate cancer patients: a systematic review. J Pain Symptom Manage. 2012;43(1):96-110. doi:10.1016/j.jpainsymman.2011.03.006.

33. Patterson RE, Neuhouser ML, Hedderson MM, Schwartz SM, Standish LJ, Bowen DJ. Changes in diet, physical activity, and supplement use among adults diagnosed with cancer. J Am Diet Assoc. 2003;103(3):323-8. doi:10.1053/jada.2003.50045.

34. Skolarus TA, Wolf AM, Erb NL, Brooks DD, Rivers BM, Underwood W, 3rd et al. American Cancer Society prostate cancer survivorship care guidelines. CA Cancer J Clin. 2014;64(4):225-49. doi:10.3322/caac.21234.

35. Ligibel JA, Jones LW, Brewster AM, Clinton SK, Korde LA, Oeffinger KC et al. Oncologists' attitudes and practice of addressing diet, physical activity, and weight management with patients with cancer: findings of an ASCO survey of the Oncology Workforce. J Oncol Pract. 2019;15(6):e520-e8. doi:10.1200/JOP.19.00124.

36. Baker AM, Smith KC, Coa KI, Helzlsouer KJ, Caulfield LE, Peairs KS et al. Clinical care providers' perspectives on body size and weight management among long-term cancer survivors. Integr Cancer Ther. 2015;14(3):240-8. doi:10.1177/1534735415572882.

37. Mohamad H, McNeill G, Haseen F, N'Dow J, Craig LC, Heys SD. The effect of dietary and exercise interventions on body weight in prostate cancer patients: a systematic review. Nutr Cancer. 2015;67(1):43-60. doi:10.1080/01635581.2015.976313.

38. 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;9(3):431-40. doi:10.1007/s11764-014-0417-8.

39. Freedland SJ, Howard L, Allen J, Smith J, Stout J, Aronson W et al. A lifestyle intervention of weight loss via a low-carbohydrate diet plus walking to reduce metabolic disturbances caused by androgen deprivation therapy among prostate cancer patients: carbohydrate and prostate study 1 (CAPS1) randomized controlled trial. Prostate Cancer Prostatic Dis. 2019;22(3):428-37. doi:10.1038/s41391-019-0126-5.

40. Henning SM, Galet C, Gollapudi K, Byrd JB, Liang P, Li Z et al. Phase II prospective randomized trial of weight loss prior to radical prostatectomy. Prostate Cancer Prostatic Dis. 2018;21(2):212-20. doi:10.1038/s41391-017-0001-1.

41. Joshu CE, Mondul AM, Menke A, Meinhold C, Han M, Humphreys EB et al. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. Cancer Prev Res (Phila). 2011;4(4):544-51. doi:10.1158/1940-6207.CAPR-10-0257.

CHAPTER TWO

A review of the relationship between obesity and prostate cancer

Chapter Two of this thesis has been published by Elsevier in *Critical Reviews in Oncology/Hematology* at the below article:

Wilson, R. L., Taaffe, D. R., Newton, R. U., Hart, N. H., Lyons-Wall, P., & Galvão, D. A. (2022). Obesity and prostate cancer: A narrative review. *Critical Reviews in Oncology/Hematology, 169,* article 103543.

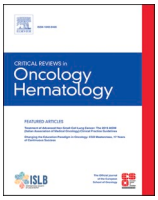
https://doi.org/10.1016/j.critrevonc.2021.103543

Critical Reviews in Oncology / Hematology 169 (2022) 103543

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc



Obesity and prostate cancer: A narrative review

Rebekah L. Wilson [a,b,*], Dennis R. Taaffe [c,d], Robert U. Newton [c,d], Nicolas H. Hart [c,d,e,f], Philippa Lyons-Wall [c,d], Daniel A. Galvão [c,d]

[a] Division of Population Sciences, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, 02215, United States
[b] Department of Medicine, Harvard Medical School, Boston, MA, 02215, United States
[c] Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, 6027, Australia
[d] School of Medical and Health Sciences, Edith Cowan University, Perth, WA, 6027, Australia
[e] Institute for Health Research, University of Notre Dame Australia, Perth, WA, 6160, Australia
[f] College of Nursing and Health Science, Flinders University, Adelaide, SA, 5042, Australia

ARTICLE INFO

Keywords:
Prostate cancer
Obesity
Weight management
Fat loss
Exercise
Nutrition

ABSTRACT

Overweight and obese men with prostate cancer are at an increased risk of disease recurrence, exacerbated treatment-related adverse effects, development of obesity-related comorbidities, earlier progression and development of metastatic disease, and higher all-cause and prostate cancer-specific mortality. The physiological mechanisms associating obesity with poor prostate cancer outcomes remain largely unknown; however, an increased inflammatory environment and metabolic irregularities associated with excess fat mass are commonly postulated. Although research is limited, fat loss strategies using exercise and nutrition programmes may slow down prostate cancer progression and improve a patient's prognosis. This review is an overview of: 1) the association between obesity and poor prostate cancer prognosis; 2) potential physiological mechanisms linking obesity and prostate cancer progression; 3) the effect of obesity on treatments for prostate cancer; and 4) the potential for weight loss strategies to improve outcomes in patients with prostate cancer.

1. Introduction

The prevalence of obesity is higher among people with cancer compared to the general population, with over 30 % of cancer-related deaths attributed to obesity (Balogh et al., 2018). Obesity is also a risk factor for the development of 13 different types of cancer and is likely to surpass tobacco as the leading preventable risk factor (Lauby-Secretan et al., 2016; Sung et al., 2019). With improvements in diagnosis and treatments, people with cancer are living longer, however, the acute and long-term side effects may significantly impair quality of life (Chambers et al., 2015). Consequently, obesity is becoming an increasingly important consideration throughout the cancer trajectory and is shown to impact the effectiveness of treatment, cancer progression, comorbidity development, and survival, particularly in people with colorectal, breast, and prostate cancer (Demark-Wahnefried et al., 2015, 2012; Ligibel et al., 2015; Jaspan et al., 2021).

For people with prostate cancer, obesity is associated with increased risk of recurrence following curative intent treatment, progression to advanced cancer, and prostate cancer-related mortality (Cao and Ma, 2011; Harrison et al., 2020; Hu et al., 2014; World Cancer Research Fund, 2021). While undergoing active treatment, obese men with prostate cancer are at increased risk of experiencing more severe, and a greater number of, acute and long-term adverse effects, and shorter time to develop castrate resistant prostate cancer relative to non-obese counterparts (Cao and Ma, 2011; Calle et al., 2003; Rhee et al., 2016). Obesity can also lead to the development of comorbidities such as cardiovascular disease (CVD) and diabetes mellitus (Bray, 2004), and impact mobility, social life, psychological status, and quality of life (Fontaine and Barofsky, 2001).

Following a prostate cancer diagnosis, non-obese men are vulnerable to becoming obese as a consequence of stress-related changes to eating habits due to heightened anxiety, decreased physical activity resulting from treatment side effects (Baker et al., 2015), and from androgen deprivation therapy (ADT), a common prostate cancer treatment which reduces androgen concentrations to suppress tumour growth (Labrie et al., 1986). Although clinicians treating overweight or obese men with prostate cancer often address weight loss, it is commonly discussed in relation to the patient's general health and well-being, rather than as a

* Corresponding author at: Dana Farber Cancer Institute, 375 Longwood Avenue, Boston, MA, 02215, United States.
E-mail address: rebekahl_wilson@dfci.harvard.edu (R.L. Wilson).

https://doi.org/10.1016/j.critrevonc.2021.103543
Received 17 September 2021; Received in revised form 25 October 2021; Accepted 26 October 2021
Available online 20 November 2021

potential adjuvant therapy (Baker et al., 2015; Ligibel et al., 2019). The advice given is often generic, encouraging patients to increase physical activity and eat a healthy balanced diet (Sutton et al., 2017). While prescribed exercise and nutrition interventions have been demonstrated to be safe for men with prostate cancer (Hayes et al., 2019; Moyad et al., 2016), their impact on weight loss and prostate cancer-related outcomes, is largely unknown, particularly as it pertains to obese patients.

The aim of this review is to examine how obese men with prostate cancer may be managed while on treatment by discussing: 1) association between obesity and poor prostate cancer prognosis; 2) potential physiological mechanisms linking obesity and prostate cancer progression; 3) effect of obesity on prostate cancer treatments; and 4) potential for weight loss strategies to improve outcomes in men with prostate cancer.

MEDLINE, Scopus, and PubMed databases were searched with published studies included until August 2021. Search terms included various combinations of: prostate cancer; obesity; radical prostatectomy; radiation therapy; androgen deprivation therapy; exercise; nutrition; body composition; fat mass; lean mass. Secondary searches involved reference lists of eligible articles. The key criterion was to identify studies that included prostate cancer patients with obesity or weight loss as a primary component of interest.

2. Obesity and prostate cancer prognosis

While there is strong evidence indicating an association between obesity and advanced or lethal prostate cancer, the association with prostate cancer incidence is complex and not well defined (Joshu et al., 2011; Pernar et al., 2018). A systematic review and meta-analysis conducted by the World Cancer Research Fund & American Institute for Cancer Research (World Cancer Research Fund, 2021) assessed a cohort of over 9 million men including 191,000 men with prostate cancer. They concluded there was a strong level of evidence indicating an 8–11 % increased risk of advanced prostate cancer and prostate cancer-specific mortality in obese men. Other meta-analyses have established similar conclusions (Cao and Ma, 2011; Harrison et al., 2020; Hu et al., 2014; Troeschel et al., 2020; Rivera-Izquierdo et al., 2021). In over 1 million initially cancer-free men, Cao and Ma (2011) reported a 15 % higher risk of prostate cancer mortality associated with every 5 kg/m^2 increase in body mass index (BMI); and in a subgroup of 15,000 men with prostate cancer, a 5 kg/m^2 increase in BMI was associated with a 21 % increased risk of biochemical recurrence. Hu et al. (2014) in a dose-response analysis of over 36,000 prostate cancer patients, found a 16 % increased risk of biochemical recurrence with every 5 kg/m^2 increase in BMI. Also completing dose-response analyses, Harrison et al. (2020), in over 1 million men with prostate cancer, reported a 6 % increased risk of advanced disease per 5 kg/m^2 increase in BMI, and Rivera-Izquierdo et al. (2021), in over 280,000 prostate cancer patients, reported a 9 % increased risk of prostate cancer-specific mortality with every 5 kg/m^2 increase in BMI. The risk increases associated with every 5 kg/m^2 change in these meta-analyses indicate that a substantial weight gain is required for a male to significantly increase their prostate cancer-related risks. For instance, a male weighing 85 kg and 1.8 m tall would need to gain ~13 kg to increase their BMI by 5 kg/m^2. However, Troeschel et al. (2020) in a prospective cohort study of nearly 7000 non-metastatic prostate cancer patients indicated those who self-reported a weight gain of >5 % between 2- and 4-years post-diagnosis were at increased risk of prostate cancer-specific (HR 1.65, 95 % CI 1.21–2.25) and all-cause mortality (HR 1.27, 95 % CI 1.12–1.45) compared to men who maintained their post-diagnosis weight. These analyses in a large number of patients report a positive relationship between obesity and advanced stage disease, recurrence, and prostate cancer-specific and all-cause mortality, with increased risk apparent in obese patients regardless of physical activity status and clinical factors such as tumour characteristics (Fig. 1) (Harrison et al., 2020; Joshu et al., 2011; Troeschel et al., 2020; Peisch et al., 2017).

In contrast to the literature identifying a relationship between obesity and prostate cancer progression, some studies have identified obesity to have a protective effect for prostate cancer patients. For example, Vidal et al. (2014) reported obese men to have a significantly lower risk of low-grade disease (OR 0.79, 95 % CI 0.65–0.94), however, this analysis also agreed with the previously described meta-analyses associating obesity with a higher risk of high-grade disease (OR 1.28, 95 % CI 1.01–1.63). In another analysis, Vidal et al. (2018) reported that men with non-metastatic castrate resistant prostate cancer with a higher BMI had a reduced risk of all-cause mortality (HR 0.98, 95 % CI 0.97–0.99), albeit very minor. This was further reflected in an analysis by Martini et al. (2021) who found a similar association but with metastatic castrate resistant prostate cancer patients where obesity was

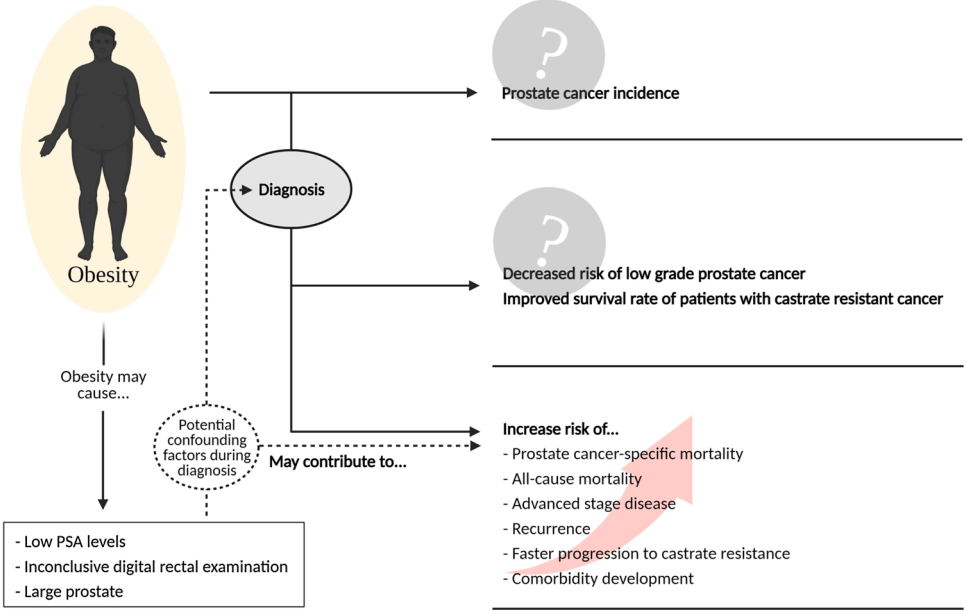


Fig. 1. Obese men with prostate cancer are at increased risk of poor prognosis and general health. Confounding factors at the time of prostate cancer diagnosis could contribute to this relationship. There is inconclusive evidence for obesity to increase risk of incidence, decrease risk of low-grade prostate cancer, and improve survival for patients with castrate resistant prostate cancer.

associated with reduced cancer-specific mortality (SHR 0.94, 95 % CI 0.91−0.98). Coined the obesity paradox, the protective nature of obesity compared to normal weight individuals requires further investigation across the entire scope of the prostate cancer population as it is unclear if the same relationships are also found among non-castrate resistant cancers. Additionally, much of the literature describing a relationship between obesity and prostate cancer outcomes utilise BMI as the clinical indicator for obesity. While BMI is useful for defining weight categories, it does not provide information on the metabolic health and proportions of fat and lean mass, which may be of greater importance for the development and progression of prostate cancer and further explain the various identified relationships between obese patients and their prognosis. In a study of 172 prostate cancer patients, Dickerman et al. (2019) examined the influence of fat mass distribution on prostate cancer aggressiveness measuring fat area of the abdomen (visceral and subcutaneous) and thigh (intermuscular and subcutaneous) through computed tomography, along with total body fat mass by bioimpedance analysis. In agreement with previous meta-analyses, BMI increases were associated with increased risk of advanced and fatal prostate cancer; however, these authors also demonstrated that greater visceral fat and thigh subcutaneous fat were associated with advanced and fatal prostate cancer, respectively. In another study, Salji et al. (2018) assessed peri-prostatic fat using magnetic resonance imaging, demonstrating those with greater fat around the prostate developed castrate resistant prostate cancer faster than those who had less fat. Notably, both studies reported that total body fat was not associated with any prostate cancer-related outcomes, suggesting that the type of fat and its distribution may be of importance (Dickerman et al., 2019; Salji et al., 2018). This concept is further reflected, although with contrasting results, in a recent meta-analysis by Lopez et al. (2021) who reported prostate cancer patients with higher subcutaneous fat mass to have ~32 % survival advantage. Although there was no association noted between total and visceral fat mass with survival, sarcopenia (low muscle mass) was associated with mortality risk.

While meta-analyses have established an association between obesity and poor prostate cancer outcomes (Harrison et al., 2020; Joshu et al., 2011; Troeschel et al., 2020; Peisch et al., 2017), research from clinical data presents several confounding factors at diagnosis that could explain why this relationship is evident (Fig. 1). Prostate cancer is more difficult to detect in obese men, potentially leading to a delayed diagnosis (Allott et al., 2013). In a recent meta-analysis, obese men (BMI $\geq$ 30 kg/m^2) had a 12.9 % lower serum prostate specific antigen (PSA) level, a marker for prostate cancer, compared to men with a normal BMI ($<$ 25 kg/m^2) (Harrison et al., 2020). Obese men have greater plasma volumes, which could lead to hemodilution resulting in lower PSA concentrations (Buschemeyer and Freedland, 2007; Freedland et al., 2020). The inverse relationships between BMI and blood volume with PSA is further highlighted using retrospective data of over 86,000 men screened for prostate cancer (Lin et al., 2021). A digital rectal examination can also be inconclusive or result in under-staging in obese men as they often have larger prostates, which mask the presence of abnormalities (Freedland et al., 2008). In addition, accurate biopsy testing is more difficult with an enlarged prostate (Buschemeyer and Freedland, 2007). Irrespective of these confounding factors at diagnosis potentially impacting the association between obesity and poor prostate cancer prognosis, a relationship still appears to exist. Vidal et al. (2014) completed routine prostate biopsies independent of PSA levels and other clinical covariates, which in obese patients could mask the presence of prostate cancer, and still reported a significant association between obesity and increased risk of diagnosis at the advanced stage of prostate cancer.

3. Potential mechanisms linking obesity and prostate cancer

Excess fat mass is characterised by low-level chronic inflammation resulting in abnormal secretion of adipokines leading to disrupted immune responses and other metabolic irregularities (Deng et al., 2016). This state leads to decreased cancer cell apoptosis, and increased cancer cell growth, dysregulated angiogenesis, and the development of metastases and chemoresistance (Deng et al., 2016; Adesunloye, 2021). The mechanisms for the association between fat mass and prostate cancer progression are not well understood, and it is likely that multiple factors work together to create a favourable tumour micro-environment for cancer growth (Deng et al., 2016). In this regard, proposed factors include alterations to the insulin and insulin-like-growth-factor (IGF) axis, sex hormone concentrations, and adipokine signalling (Fig. 2) (Allott et al., 2013; Adesunloye, 2021).

3.1. Insulin and IGF-axis

Insulin resistance is a common side effect of obesity, resulting in excess concentrations of insulin, relative to glucose, circulating in the blood (Ahmadi and Daneshmand, 2013). Insulin is a growth promoting hormone, which could enhance cellular proliferation and differentiation, and reduce apoptosis in cancer cells (Nandeesha, 2009). Prostate cancer cells contain insulin receptors, although it is unclear how insulin and cancer cells interact (Nandeesha, 2009; Di Sebastiano et al., 2017). The IGF-axis, a complex system of cell surface receptors, ligands, high- and low-affinity binding proteins, and proteases (Adesunloye, 2021), has been identified as a possible stimulator where increased levels of IGF-1 may enhance cellular proliferation (Barnard et al., 2003; Párrizas et al., 1997). However, IGF-binding proteins 1 and 3 (IGFBP-1 and IGFBP-3) may inhibit cancer cell proliferation and survival through IGF-independent actions or by regulating the availability of free IGF-1 (Fig. 2) (Adesunloye, 2021; Barnard et al., 2003; Sharma et al., 2014; Rajah et al., 1997). Barnard et al. (2003) compared serum samples from non-cancer male participants across three groups: exercise, diet plus exercise, and a control group of sedentary men who maintained their current exercise and dietary habits. The exercise and diet plus exercise groups had significantly lower IGF-1 and significantly higher IGFBP-1 concentrations, as well as lower BMI compared to the controls. Further, when the *in vivo* collected serum was combined *in vitro* with LNCaP prostate cancer cells, the higher levels of IGF-1 in serum collected from the control group increased cell growth, and the higher levels of IGFBP-1 in the exercise and diet plus exercise groups induced apoptosis (Barnard et al., 2003). Similarly, IGFBP-3 has induced apoptosis in a PC-3 cell line *in vitro* (Rajah et al., 1997), and Wright et al. (2013) found increased concentrations of IGFBP-3 in men with prostate cancer who undertook a weight loss program, compared to usual care controls. The results from Barnard et al. (2003) and Wright et al. (2013) indicate that exercise and nutrition interventions leading to lower BMI and weight loss may be beneficial in improving IGFBP concentrations, leading to reduced bioavailable IGF-1, and decreased risk of prostate cancer progression. Additionally, improved insulin resistance also decreases a patient's risk of developing other comorbidities, particularly type 2 diabetes and CVD (Ormazabal et al., 2018).

3.2. Sex hormone concentrations

Sex hormone concentrations do not appear to be associated with increased risk of prostate cancer incidence (Boyle et al., 2016); however, prostate cancer regresses in response to castration, hence ADT is a common treatment modality as it reduces testosterone availability to cells (Allott et al., 2013; Taplin and Ho, 2001). However, continued exposure to castrate levels of testosterone from ADT creates an environment in which prostate cancer cells will eventually adapt and mutate to an androgen independent disease (Taplin and Ho, 2001). This prostate cancer evolution has been reported to occur more rapidly in obese than non-obese men (Salji et al., 2018), although a genetic predisposition may also exist (Tong, 2021). Further, increased aromatase activity in obese individuals converts testosterone to estradiol resulting in increased concentrations (Calle et al., 2003), which promotes prostate cancer growth (Allott et al., 2013; Tahergorabi

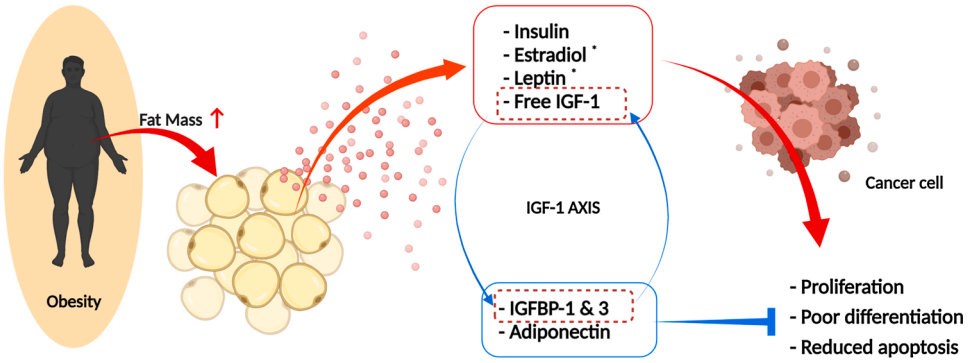


Fig. 2. Proposed mechanisms for the association between fat mass and prostate cancer progression. *Estradiol only appears to effect androgen-dependant cancer growth, and leptin androgen-independent growth.

et al., 2016). Massillo et al. (2019) examined the effect of estradiol on prostate cancer within two contexts. The first component was *in vitro*, where varying estradiol concentrations were applied to androgen-dependent and androgen-independent human prostate cancer cell lines. The second component was *in vivo*, that used a murine model comparing a control diet to a high fat diet designed to emulate the presence of metabolic syndrome, of which obesity is a key component (Massillo et al., 2019). This study showed increases in estradiol concentration led to increases in cell viability of the androgen-dependent prostate cancer cell line LNCaP, but not androgen-independent prostate cancer cell line PC-3. This was further examined in the murine model where mice on a high fat diet had a significantly higher concentration of estradiol and was associated with increased prostate cancer cell proliferation (Fig. 2). Although preclinical studies support the association between estradiol and prostate cancer progression (Bonkhoff and Berges, 2009), this relationship is yet to be confirmed in epidemiological and clinical studies (Yao et al., 2011).

3.3. Adipokine signalling

Adipokines are cell signalling proteins produced by adipose tissue (Galic et al., 2010). Leptin and adiponectin, in particular, have been proposed to promote prostate cancer progression and have anti-tumour properties, respectively (Adesunloye, 2021). Leptin inhibits hunger but also has pro-inflammatory and pro-angiogenic effects (Tahergorabi et al., 2016). High concentrations of leptin have been found to have a pro-tumour effect in androgen independent DU145 and PC-3 prostate cancer cell lines but not in androgen-dependent LNCaP-FGC cell lines (Onuma et al., 2003). However, a recent meta-analysis only identified a weak inverse relationship between leptin and prostate cancer risk using pooled effect estimates of prospective studies (3 % decreased risk per 2.5 ng/mL increase in leptin) (Burton et al., 2021). Conversely, high concentrations of adiponectin have anti-tumour properties inhibiting androgen-dependent and androgen-independent prostate cancer cell growth (Fig. 2) (Tahergorabi et al., 2016; Bub et al., 2006). Adiponectin concentrations are inversely associated with fat mass, and in high concentrations may have a protective effect against prostate cancer by inhibiting inflammation; activating adenosine monophosphate-activated protein kinase (AMPK) which has anti-tumour effects (Champ et al., 2016); stimulating fatty acid oxidation; and improving insulin sensitivity and glucose metabolism (Tahergorabi et al., 2016; Li et al., 2010). Men with prostate cancer on ADT have increased adiponectin concentrations despite a treatment-induced increase in fat mass (Smith et al., 2008). Although the relationship is inverse, the increased adiponectin concentration within this context does not appear to have an inhibitory effect on ADT-related adverse effects such as hyperinsulinemia (Smith et al., 2008). The relationship between these adipokines and prostate cancer incidence and progression is still unclear and further research is required to elucidate the role of leptin and adiponectin in prostate cancer (Burton et al., 2021).

4. Obesity and implications for prostate cancer treatments

Obese men with prostate cancer have an increased likelihood of developing treatment-related side effects of greater severity (Henning et al., 2018; Galvao et al., 2011; Newton et al., 2018; Knipper et al., 2019; Thomas et al., 2013). Men with prostate cancer are also at increased risk of developing obesity after initiating treatment with ADT, which causes fat gain, and as a consequence of reduced physical activity or adversely altered stress-related eating behaviours (Baker et al., 2015; Galvao et al., 2008). The impact of obesity is discussed below (Sections 4.1–4.3) for the most common treatments experienced by men with prostate cancer (Fig. 3).

4.1. Surgery

Obesity increases the difficulty of radical prostatectomy because of excess fat mass surrounding the prostate, and an increased distance from the skin surface to the prostate (Mikhail et al., 2006; Freedland et al., 2005; Wiltz et al., 2009). Therefore, alternative instruments, measurements, and adapted surgical techniques are required (Mikhail et al., 2006; Freedland et al., 2005; Wiltz et al., 2009). During surgery, obese men with prostate cancer have been reported to experience a higher number of surgery-related adverse effects, have a longer surgery duration, higher blood loss, increased risk of capsular incision, and conversion to an open prostatectomy, or an aborted surgery due to excessive peak expiratory airway pressure while in the Trendelenburg position, with complications such as pneumoperitoneum (Freedland et al., 2005; Wiltz et al., 2009; Wilson et al., 2020; Siddiqui et al., 2006; Ahlering et al., 2005; Neuenschwander et al., 2018). In addition, post-surgical complications are more apparent in obese compared to non-obese individuals and include increased risk of positive surgical margins, infection, lymphedema, and greater severity in urinary and sexual-related side effects (Knipper et al., 2019; Freedland et al., 2005; Wiltz et al., 2009; Wilson et al., 2020; Ferro et al., 2021). However, irrespective of the potential increased risk of a higher number or more severe complications for obese patients, the risks associated with surgical techniques can be reduced with greater surgeon experience (Wiltz et al., 2009).

4.2. Radiation therapy

External beam radiation therapy (EBRT) is the most common form of radiation (NML, 2014). Following EBRT obese prostate cancer patients are at increased risk of biochemical recurrence compared to non-obese patients (Hu et al., 2014). This is likely due to the technical difficulty of setting up the EBRT to accurately target the region of concern, due to increased day-to-day movement of the prostate in overweight and obese men, and larger levels of impedance between the radiation beam and the prostate (Cao and Ma, 2011; Stroup et al., 2007). Moreover, Wang, *et al.*

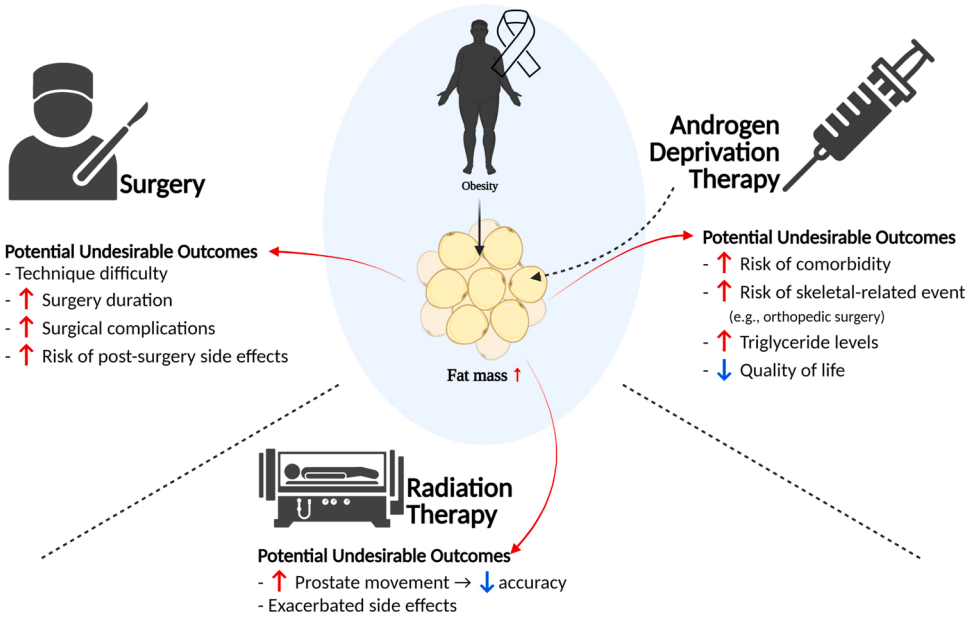


Fig. 3. Obese patients undertaking the prostate cancer treatments surgery, radiation therapy, or ADT are at increased risk of several undesirable outcomes (listed) compared to non-obese patients. Additionally, ADT can cause an increase in fat mass.

(Wang et al., 2015) showed that obese prostate cancer patients treated with image-guided radiation therapy, where the target area is imaged every session to allow for more precise radiation, still had increased risk of biochemical recurrence, higher propensity for distant metastases, and higher cancer-specific and overall mortality rates. Obesity has also been linked to the exacerbation of EBRT-related side effects including vitality, hormone function, skin irritation, rectal bleeding, and nocturia (Baker et al., 2015; Thomas et al., 2013; Sanda et al., 2008).

Brachytherapy is another common radiotherapy technique involving the surgical implantation of radioactive seeds into the prostate (Parker et al., 2015). When comparing obese and non-obese men with prostate cancer receiving surgical implantation of radioactive seeds, no differences in surgery-related outcomes have been reported (Mitsuyama et al., 2006). Merrick et al. (2002) reported that obesity does not appear to impact quality of life parameters such as bowel and sexual function while undertaking brachytherapy. Moreover, although Merrick, et al. (Merrick et al., 2002) did not directly compare an obese cohort (BMI > 35 kg/m^2) with non-obese patients, they did note that patient outcomes (e.g., urinary function, bowel function) in their obese patients were comparable to previous reports of the general brachytherapy population. Obese men with prostate cancer treated with radical prostatectomy or EBRT are at increased risk of biochemical recurrence, however, no such relationship has been established for obese patients receiving brachytherapy (Cao and Ma, 2011; Hu et al., 2014; van Roermund et al., 2010). This may be due to the dose escalation delivery of the implanted seeds in the prostate, whereby brachytherapy, more than other prostate cancer treatments, may effectively overcome biological factors, patient selection bias, radiation dose distributions, and physical barriers associated with accessing the prostate through more invasive means such as radical prostatectomy (Hu et al., 2014; Stroup et al., 2007). Although the current literature describes obese and non-obese patients of having similar risks when receiving brachytherapy, this is a largely understudied area and requires further examination.

4.3. Androgen deprivation therapy

Unlike other treatments, ADT can cause an increase in fat mass that will lead to obesity if unmanaged or will exacerbate obesity in those already overweight. This appears to occur regardless of whether ADT is given intermittent or continuously, although intermittent has been shown to have a reduced impact on metabolic complications (Rezaei et al., 2016). The purpose of ADT is to deprive the body of androgens by reducing testosterone to castrate levels and blocking the androgen receptors, as prostate cancer is initially an androgen sensitive disease (Labrie et al., 1986). This suppression of androgen access for all cells of the body results in significant adverse changes in body composition, as testosterone acts to promote the activation of lipolysis, and enhance muscle mass and bone growth (Mohamad et al., 2016; Herbst and Bhasin, 2004). Weight gain has been reported to occur in most (70 %) men with prostate cancer receiving ADT, with an average increase of 4.2 kg in the first 12 months of exposure (Kim et al., 2011). Specifically, prostate cancer patients receiving ADT experience a 6.6–13.8 % increase in fat mass, 2.0–3.6 % decrease in lean mass, and 2.0–8.0 % decrease in bone mass (depending on skeletal site) within the first year on treatment (Galvao et al., 2008, 2009). Accordingly, these men on ADT present with increased body fat, and thus are at an increased risk of high blood triglyceride levels, skeletal-related events e.g. orthopaedic surgery, and poor quality of life (Galvao et al., 2011; Newton et al., 2018; Buttigliero et al., 2015). In addition to treatment-induced changes in body composition, men on ADT are also at increased risk of developing CVD and type 2 diabetes (Keating et al., 2010). Although these comorbidities are often associated with obesity, it is unclear whether the greater likelihood of comorbidity development in men on ADT is related to the treatment itself or treatment-induced obesity.

5. Weight management for prostate cancer

Given the relationship between obesity and prostate cancer prognosis and negative impact on the incidence and severity of treatment toxicities, weight management strategies are needed to improve the risk profile and health outcomes of obese prostate cancer patients (Joshu et al., 2011). Exercise and nutrition interventions are first-line strategies to promote weight loss as they are low cost and, when prescribed appropriately, have low risk of adverse consequences (Heymsfield and Wadden, 2017). Exercise and nutrition also improve other cancer and treatment-induced side effects, including enhanced physical function and improved psychosocial outcomes (Moyad et al., 2016; Galvao et al., 2009; Cormie et al., 2015; Baguley et al., 2021). Current weight loss guidelines for men with prostate cancer are no different than those given to the general population and include high volume exercise and an

energy deficit diet (Fig. 4) (Skolarus et al., 2014). While there is no prostate cancer specific weight loss advice, Mohamad et al. (2015) systematically reviewed 20 randomised controlled trials examining exercise, nutrition, and combined exercise plus nutrition interventions in men with prostate cancer, and concluded nutrition or combined exercise plus nutrition programmes were the most effective in reducing weight for prostate cancer patients, particularly interventions using low-fat or energy restricted diets. The effectiveness of combined exercise plus nutrition interventions has continued to be confirmed as the best option, with recent studies by us (Wilson et al., 2020, 2021a) and others (Freedland et al., 2019) demonstrating significant fat loss for obese prostate cancer patients undertaking such interventions, that is able to be sustained when self-managed after a period of supervision (Wilson et al., 2021b).

Irrespective of weight loss, exercise and nutrition programmes may also influence cancer progression with a review by Peisch et al. (2017) describing a strong level of evidence for physical activity, which includes prescribed exercise, and also some evidence for specific nutritional intake of tomatoes, lycopene, fish, vegetable fat, and cruciferous vegetables, to decrease risk of prostate cancer progression. Moreover, Kenfield et al. (2011) reported that those who completed $\geq$ 3 h per week of vigorous exercise, compared to $<$ 1 h per week, had a 61 % lower risk of prostate cancer-specific mortality; and in a follow-up study by the same researchers those completing $\geq$ 3 h a week of vigorous exercise had a 57 % lower risk of prostate cancer progression (Richman et al., 2011). In support of observational studies, Rundqvist et al. (2013) demonstrated that serum from exercising non-cancer participants resulted in a significant 31 % inhibition of LNCaP cell growth *in vitro,* and more recently, we have demonstrated significant suppression of LNCaP cell growth *in vitro* with serum collected at rest from obese men with prostate cancer following a 12-week weight loss intervention (Kim et al., 2021).

Thomas et al. (2014) examined polyphenol-rich foods, given their anti-neoplastic properties, in prostate cancer patients on active surveillance or watchful waiting and showed that those who consumed an oral capsule 3 times per day containing a blend of pomegranate, green tea, broccoli, and turmeric for 6 months had a median PSA rise of only 14.7 % versus 78.5 % in the placebo group. Similarly, Freedland et al. (2020), in prostate cancer patients with biochemical recurrence, showed that a carbohydrate restricted diet compared to control diet resulted in a significantly longer PSA doubling time of 28 months versus 13 months, after adjusting for covariates including hemoconcentration, due to significant weight loss in the intervention group. It needs to be noted that their study was an exploratory hypothesis generating analysis and needs to be confirmed with larger studies. Evidence for an association for specific nutrients and prostate cancer progression is varied (Hackshaw-McGeagh et al., 2015). In observational studies there is a difference in prostate cancer incidence rates between countries worldwide, with a lower incidence in Asian countries comparatively to Westernised countries, although the Asian populace living within Westernised countries have an equal risk of prostate cancer to that of the Westernised populace. While discrepancies in screening programmes may account for some of these disparities, dietary patterns and the cultural environment should be explored further to identify exercise and dietary differences associated with prostate cancer incidence and progression (Hackshaw-McGeagh et al., 2015; Erdrich et al., 2015; Holly et al., 2020).

Interestingly, preliminary studies have shown that weight loss may increase prostate cancer proliferation. For example, Demark-Wahnefried et al. (2017) completed a weight loss intervention prior to radical prostatectomy in prostate cancer patients and found that the rapid weight loss group had an increased production of Ki67, a nuclear protein indicative of cancer proliferation. However, a follow-up analysis of this study (Frugé et al., 2020) demonstrated that a loss in lean mass was strongly and inversely correlated with Ki67, suggesting that catabolic environments support tumour growth via the degradation of lean mass into free amino acids via mitochondrial pathways (Frugé et al., 2020). The relationship between rapid weight loss and the increase of prostate cancer proliferation requires further examination, however, the authors suggested that an emphasis on resistance exercise when undergoing weight loss could be important if rapid weight loss is required (Frugé et al., 2020). Griffin et al. (2019) assessed prostate cancer patients receiving ADT after radical prostatectomy and found those who lost

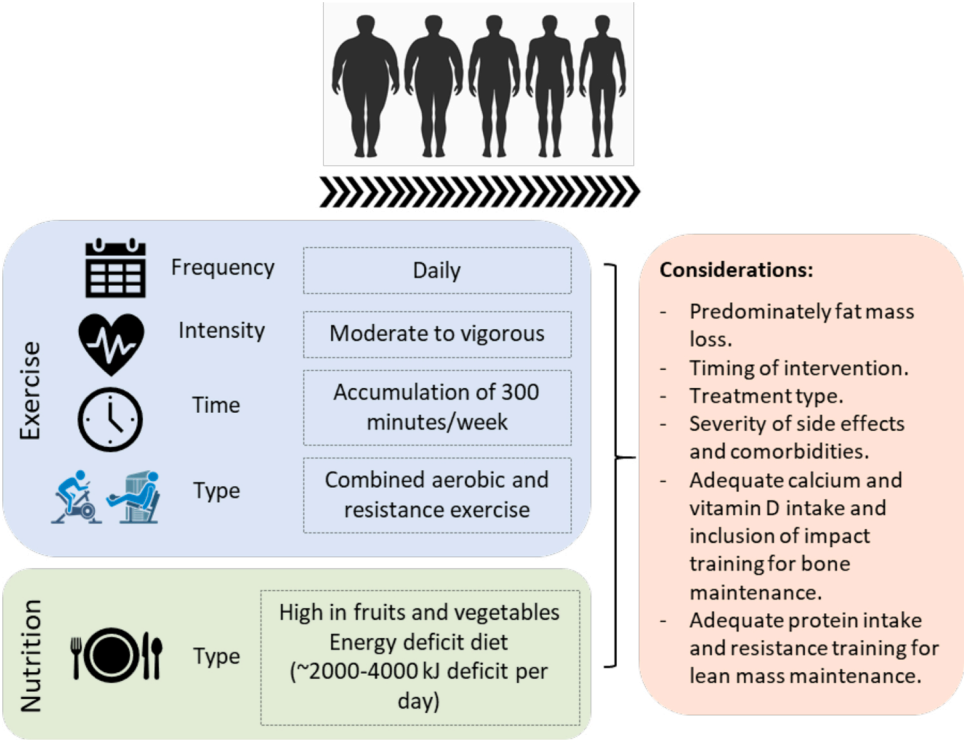


Fig. 4. Current exercise and nutrition weight loss recommendations for prostate cancer patients and the associated considerations for prescription.

weight throughout their ADT treatment were at increased risk of prostate cancer progression. However, those who lost weight had a significantly higher BMI pre-ADT (29.3 kg/m^2) than those who maintained (0–2.2 kg gain) or gained weight ($\geq$ 2.3 kg) (27.4−27.3 kg/m^2). Fat and lean mass were not identified so it is unclear how body composition was altered with weight loss or gain. Further, this was not an intervention-based study, and the reasons for weight change were not identified, therefore, it is unclear whether it was purposeful weight loss (e.g. the weight loss group had a higher BMI to start with so may have been encouraged to lose weight by their healthcare professional) or due to physiological changes because of the cancer or general poor health.

In contrast, other studies have found that weight loss had no impact, or produced improved outcomes associated with prostate cancer prognosis. For example, Henning et al. (2018) conducted an energy restricted weight loss study in men prior to radical prostatectomy and found no change in malignant epithelium apoptosis or proliferation levels of the tumour; but there was a significant decrease in fasting plasma insulin concentrations in the weight loss group compared to controls. Wright et al. (2013) also examined diet induced weight loss prior to radical prostatectomy and found similar effects, with significant improvements in IGFBP-3 concentrations in the weight loss group compared to controls. The method of weight loss (e.g. rapid versus progressive), inclusion of exercise, and the associated changes in fat and lean mass may influence the effect weight loss has as a stimulator of proliferative factors, or if it has a positive response by improving the inflammatory environment associated with an obese state. With the known positive impact of weight loss on comorbidities such as diabetes and CVD (Alamuddin et al., 2016), and the evidence linking obesity with prostate cancer progression, weight loss could be beneficial for prostate cancer patients. Patients undergoing weight loss should also be monitored by their attending clinician with further research required to clarify discrepancies between studies examining weight loss and prostate cancer progression.

Based on the current evidence that clinician monitored weight management is likely beneficial for obese prostate cancer patients, several considerations need to be deliberated before a weight loss intervention is prescribed (Fig. 4). A 5 % reduction in total body mass is considered a clinically significant change, however, this should predominately consist of a loss in fat mass with lean mass maintenance or increase (Skolarus et al., 2014). Cancer diagnosis is often described as a teachable moment and considered an optimal time to introduce healthy lifestyles and active therapies such as exercise as patients are more susceptible to change (Jain and Denlinger, 2017), although the type of treatment may dictate weight loss feasibility at diagnosis. For example, the time between diagnosis and surgery can be limited depending on availability and aggressiveness of the cancer and may not be sufficient to induce a clinically relevant change. However, we have previously demonstrated that a low-calorie diet and aerobic exercise can induce ~16 % reduction in fat mass, mostly attributed to trunk fat loss, within a median 6-week period (Wilson et al., 2020). Weight loss may not be desired for patients receiving EBRT as substantial weight loss may result in movement of the prostate leading to reduced accuracy of EBRT if image guiding is not used (Stroup et al., 2007). However, exercise during radiation therapy has been deemed safe and feasible (Segal et al., 2009). Moreover, it has been proposed that exercise immediately prior to radiation therapy may enhance tumour perfusion and reduce intratumoral hypoxia, thereby improving radiation therapy treatment outcomes (Schumacher et al., 2021). The hormonal changes experienced by men on ADT may also influence the effectiveness of a weight loss intervention with those on acute ADT (<6 months) shown to have a blunted response to exercise and nutrition interventions (Galvao et al., 2011; Ndjavera et al., 2020), although this may be overcome by prescribing a larger energy deficit diet as demonstrated by Freedland et al. (2019). Reducing meal portions is the simplest form of creating an energy deficit, however, the nutrient intake should not be dismissed. Bone and lean mass loss are common side effects of ADT (Galvao et al., 2008), as such, ensuring adequate intake of calcium, vitamin D, and protein, in addition to the inclusion of impact and resistance training, can assist in preventing treatment-induced, as well as age-induced, declines in bone and lean mass (Wilson et al., 2021a; Newton et al., 2019; Tsang and Alibhai, 2014).

6. Conclusion

Epidemiological and clinical evidence consistently associates obesity with expedited prostate cancer progression and increased mortality. However, the physiological mechanisms linking obesity and poor prostate cancer prognosis remain unclear. Pre-clinical and clinical studies provide evidence for altered insulin and IGF-axis, sex hormone concentrations, and adipokine signalling to enhance cancer cell proliferation in an obese environment. Men with prostate cancer who are obese or develop obesity as a result of androgen suppression, reduced physical activity, or stress-related eating, are at increased risk of enhanced severity of treatment-related side effects. Although caution is warranted due to limited research, weight loss strategies using exercise and nutrition interventions could be of substantial benefit to obese prostate cancer patients. On present knowledge, dietary strategies should include overall energy restriction, while maintaining adequate protein and calcium intake, with a focus on increased fruit and vegetable consumption. Any energy restriction should be accompanied by resistance and impact training to prevent or reduce loss of muscle and bone, combined with aerobic exercise to further increase energy expenditure. As research develops and understanding of the potential mechanisms involved in obesity and prostate cancer increases, clinical studies can assist in establishing prostate cancer specific weight loss guidelines by assessing the impact of weight loss on quality of life, markers of disease progression, treatment effectiveness, treatment-related side effects, and comorbidities.

Data availability

No data was used for the research described in the article.

Funding sources

RLW was supported by an Australian Government Research Training Programme postgraduate scholarship; RUN was supported by a Vice-Chancellor Professorial Research Fellowship; and NHH was supported by a Cancer Council Western Australia Postdoctoral Research Fellowship.

Author contribution statement

RLW conceptualised the narrative review, conducted the search, screened potentially eligible studies for discussion, interpreted results, and drafted the manuscript. DRT, RUN, NHH, PL-W, DAG contributed to the conception and design of the work, interpreted results, and provided manuscript feedback as well as approval of the final version.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

The authors would like to thank Jin-Soo Kim for drafting the figures used within this manuscript.

References

Adesunloye, B.A., 2021. Mechanistic insights into the link between obesity and prostate cancer. Int. J. Mol. Sci. 22 https://doi.org/10.3390/ijms22083935.

Ahlering, T.E., Eichel, L., Edwards, R., Skarecky, D.W., 2005. Impact of obesity on clinical outcomes in robotic prostatectomy. Urology 65, 740–744. https://doi.org/10.1016/j.urology.2004.10.061.

Ahmadi, H., Daneshmand, S., 2013. Androgen deprivation therapy: evidence-based management of side effects. BJU Int. 111, 543–548. https://doi.org/10.1111/j.1464-410X.2012.11774.x.

Alamuddin, N., Bakizada, Z., Wadden, T.A., 2016. Management of obesity. J. Clin. Oncol. 34, 4295–4305. https://doi.org/10.1200/JCO.2016.66.8806.

Allott, E.H., Masko, E.M., Freedland, S.J., 2013. Obesity and prostate cancer: weighing the evidence. Eur. Urol. 63, 800–809. https://doi.org/10.1016/j.eururo.2012.11.013.

Baguley, B.J., Skinner, T.L., Jenkins, D.G., Wright, O.R.L., 2021. Mediterranean-style dietary pattern improves cancer-related fatigue and quality of life in men with prostate cancer treated with androgen deprivation therapy: a pilot randomised control trial. Clin. Nutr. 40, 245–254. https://doi.org/10.1016/j.clnu.2020.05.016.

Baker, A.M., Smith, K.C., Coa, K.I., Helzlsouer, K.J., Caulfield, L.E., Peairs, K.S., Shockney, L.D., Klassen, A.C., 2015. Clinical care providers' perspectives on body size and weight management among long-term cancer survivors. Integr. Cancer Ther. 14, 240–248. https://doi.org/10.1177/1534735415572882.

Balogh, E., Patlak, M., Nass, S.J., 2018. Incorporating Weight Management and Physical Activity Throughout the Cancer Care Continuum: Proceedings of a Workshop. National Academies Press.

Barnard, R.J., Ngo, T.H., Leung, P.S., Aronson, W.J., Golding, L.A., 2003. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. Prostate 56, 201–206.

Bonkhoff, H., Berges, R., 2009. The evolving role of oestrogens and their receptors in the development and progression of prostate cancer. Eur. Urol. 55, 533–542. https://doi.org/10.1016/j.eururo.2008.10.035.

Boyle, P., Koechlin, A., Bota, M., d'Onofrio, A., Zaridze, D.G., Perrin, P., Fitzpatrick, J., Burnett, A.L., Boniol, M., 2016. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis. BJU Int. 118, 731–741. https://doi.org/10.1111/bju.13417.

Bray, G.A., 2004. Medical consequences of obesity. J. Clin. Endocrinol. Metab. 89, 2583–2589. https://doi.org/10.1210/jc.2004-0535.

Bub, J.D., Miyazaki, T., Iwamoto, Y., 2006. Adiponectin as a growth inhibitor in prostate cancer cells. Biochem. Biophys. Res. Commun. 340, 1158–1166. https://doi.org/10.1016/j.bbrc.2005.12.103.

Burton, A.J., Gilbert, R., Tilling, K., Langdon, R., Donovan, J.L., Holly, J.M.P., Martin, R.M., 2021. Circulating adiponectin and leptin and risk of overall and aggressive prostate cancer: a systematic review and meta-analysis. Sci. Rep. 11, 320. https://doi.org/10.1038/s41598-020-79345-4.

Buschemeyer III, W.C., Freedland, S.J., 2007. Obesity and prostate cancer: epidemiology and clinical implications. Eur. Urol. 52, 331–343.

Buttigliero, C., Vana, F., Bertaglia, V., Vignani, F., Fiori, C., Osella, G., Porpiglia, F., Tucci, M., Scagliotti, G.V., Berruti, A., 2015. The fat body mass increase after adjuvant androgen deprivation therapy is predictive of prostate cancer outcome. Endocrine 50, 223–230. https://doi.org/10.1007/s12020-015-0525-x.

Calle, E.E., Rodriguez, C., Walker-Thurmond, K., Thun, M.J., 2003. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N. Engl. J. Med. 348, 1625–1638. https://doi.org/10.1056/NEJMoa021423.

Cao, Y., Ma, J., 2011. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev. Res. (Phila) 4, 486–501. https://doi.org/10.1158/1940-6207.CAPR-10-0229.

Chambers, S.K., Scuffham, P.A., Baade, P.D., Lowe, A.P., Dunn, J., Galvao, D.A., Gordon, L., Smith, D.P., Sandoe, D.F., Wootten, A.C., Spry, N.A., Gardiner, R.A., Davis, I.D., Newton, R.U., 2015. Advancing prostate cancer survivorship research in Australia. Cancer Forum 39, 204–209.

Champ, C.E., Francis, L., Klement, R.J., Dickerman, R., Smith, R.P., 2016. Fortifying the treatment of prostate cancer with physical activity. Prostate Cancer 2016, 9462975. https://doi.org/10.1155/2016/9462975.

Cormie, P., Galvao, D.A., Spry, N., Joseph, D., Chee, R., Taaffe, D.R., Chambers, S.K., Newton, R.U., 2015. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU Int. 115, 256–266. https://doi.org/10.1111/bju.12646.

Demark-Wahnefried, W., Platz, E.A., Ligibel, J.A., Blair, C.K., Courneya, K.S., Meyerhardt, J.A., Ganz, P.A., Rock, C.L., Schmitz, K.H., Wadden, T., Philip, E.J., Wolfe, B., Gapstur, S.M., Ballard-Barbash, R., McTiernan, A., Minasian, L., Nebeling, L., Goodwin, P.J., 2012. The role of obesity in cancer survival and recurrence. Cancer Epidemiol. Biomarkers Prev. 21, 1244–1259. https://doi.org/10.1158/1055-9965.EPI-12-0485.

Demark-Wahnefried, W., Rogers, L.Q., Alfano, C.M., Thomson, C.A., Courneya, K.S., Meyerhardt, J.A., Stout, N.L., Kvale, E., Ganzer, H., Ligibel, J.A., 2015. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. CA Cancer J. Clin. 65, 167–189. https://doi.org/10.3322/caac.21265.

Demark-Wahnefried, W., Rais-Bahrami, S., Desmond, R.A., Gordetsky, J.B., Hunter, G.R., Yang, E.S., Azrad, M., Fruge, A.D., Tsuruta, Y., Norian, L.A., Segal, R., Grizzle, W.E., 2017. Presurgical weight loss affects tumour traits and circulating biomarkers in men with prostate cancer. Br. J. Cancer 117, 1303–1313. https://doi.org/10.1038/bjc.2017.303.

Deng, T., Lyon, C.J., Bergin, S., Caligiuri, M.A., Hsueh, W.A., 2016. Obesity, inflammation, and cancer. Annu. Rev. Pathol. 11, 421–449. https://doi.org/10.1146/annurev-pathol-012615-044359.

Di Sebastiano, K.M., Pinthus, J.H., Duivenvoorden, W.C., Patterson, L., Dubin, J.A., Mourtzakis, M., 2017. Elevated c-peptides, abdominal obesity, and abnormal adipokine profile are associated with higher gleason scores in prostate cancer. Prostate 77, 211–221. https://doi.org/10.1002/pros.23262.

Dickerman, B.A., Torfadottir, J.E., Valdimarsdottir, U.A., Giovannucci, E., Wilson, K.M., Aspelund, T., Tryggvadottir, L., Sigurdardottir, L.G., Harris, T.B., Launer, L.J., Gudnason, V., Markt, S.C., Mucci, L.A., 2019. Body fat distribution on computed tomography imaging and prostate cancer risk and mortality in the AGES-Reykjavik study. Cancer-Am. Cancer Soc. 125, 2877–2885. https://doi.org/10.1002/cncr.32167.

Erdrich, S., Bishop, K.S., Karunasinghe, N., Han, D.Y., Ferguson, L.R., 2015. A pilot study to investigate if New Zealand men with prostate cancer benefit from a Mediterranean-style diet. Peerj 3, e1080. https://doi.org/10.7717/peerj.1080.

Ferro, M., Terracciano, D., Musi, G., de Cobelli, O., Vartolomei, M.D., Damiano, R., Cantiello, F., Buonerba, C., Morelli, M., Mistretta, F.A., Luzzago, S., Perdonà, S., Del Prete, P., Del Giudice, F., Busetto, G.M., Porreca, A., Autorino, R., Manfredi, M., Porpiglia, F., Muto, M., Loizzo, D., Ditonno, P., Battaglia, M., Lucarelli, G., 2021. Increased body mass index is a risk factor for poor clinical outcomes after radical prostatectomy in men with International Society of Urological Pathology grade group 1 prostate cancer diagnosed with systematic biopsies. Urol. Int. 1–8. https://doi.org/10.1159/000516680.

Fontaine, K.R., Barofsky, I., 2001. Obesity and health-related quality of life. Obes. Rev. 2, 173–182. https://doi.org/10.1046/j.1467-789x.2001.00032.x.

Freedland, S.J., Grubb, K.A., Yiu, S.K., Nielsen, M.E., Mangold, L.A., Isaacs, W.B., Epstein, J.I., Partin, A.W., 2005. Obesity and capsular incision at the time of open retropubic radical prostatectomy. J. Urol. 174, 1798–1801. https://doi.org/10.1097/01.ju.0000177077.53037.72 discussion 1801.

Freedland, S.J., Sun, L., Kane, C.J., Presti Jr., J.C., Terris, M.K., Amling, C.L., Moul, J.W., Aronson, W.J., 2008. Obesity and oncological outcome after radical prostatectomy: impact of prostate-specific antigen-based prostate cancer screening: results from the Shared Equal Access Regional Cancer Hospital and Duke Prostate Center databases. BJU Int. 102, 969–974. https://doi.org/10.1111/j.1464-410X.2008.07934.x.

Freedland, S.J., Howard, L., Allen, J., Smith, J., Stout, J., Aronson, W., Inman, B.A., Armstrong, A.J., George, D., Westman, E., Lin, P.H., 2019. A lifestyle intervention of weight loss via a low-carbohydrate diet plus walking to reduce metabolic disturbances caused by androgen deprivation therapy among prostate cancer patients: carbohydrate and prostate study 1 (CAPS1) randomized controlled trial. Prostate Cancer P D 22, 428–437. https://doi.org/10.1038/s41391-019-0126-5.

Freedland, S.J., Allen, J., Jarman, A., Oyekunle, T., Armstrong, A.J., Moul, J.W., Sandler, H.M., Posadas, E., Levin, D., Wiggins, E., Howard, L.E., Wu, Y., Lin, P.H.A., 2020. Randomized controlled trial of a 6-month low-carbohydrate intervention on disease progression in men with recurrent prostate cancer: carbohydrate and prostate study 2 (CAPS2). Clin. Cancer Res. 26, 3035–3043. https://doi.org/10.1158/1078-0432.CCR-19-3873.

Frugé, A.D., Smith, K.S., Bail, J.R., Rais-Bahrami, S., Demark-Wahnefried, W., 2020. Biomarkers associated with tumor Ki67 and Cathepsin L Gene expression in prostate cancer patients participating in a presurgical weight loss trial. Front. Oncol. 10 https://doi.org/10.3389/fonc.2020.544201.

Galic, S., Oakhill, J.S., Steinberg, G.R., 2010. Adipose tissue as an endocrine organ. Mol. Cell. Endocrinol. 316, 129–139. https://doi.org/10.1016/j.mce.2009.08.018.

Galvao, D.A., Spry, N.A., Taaffe, D.R., Newton, R.U., Stanley, J., Shannon, T., Rowling, C., Prince, R., 2008. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 102, 44–47. https://doi.org/10.1111/j.1464-410X.2008.07539.x.

Galvao, D.A., Taaffe, D.R., Spry, N., Joseph, D., Newton, R.U., 2009. Cardiovascular and metabolic complications during androgen deprivation: exercise as a potential countermeasure. Prostate Cancer P D 12, 233–240. https://doi.org/10.1038/pcan.2009.12.

Galvao, D.A., Taaffe, D.R., Spry, N., Joseph, D., Newton, R.U., 2011. Acute versus chronic exposure to androgen suppression for prostate cancer: impact on the exercise response. J. Urol. 186, 1291–1297. https://doi.org/10.1016/j.juro.2011.05.055.

Griffin, K., Csizmadi, I., Howard, L.E., Pomann, G.M., Aronson, W.J., Kane, C.J., Amling, C.L., Cooperberg, M.R., Terris, M.K., Beebe-Dimmer, J., Freedland, S.J., 2019. First-year weight loss with androgen-deprivation therapy increases risks of prostate cancer progression and prostate cancer-specific mortality: results from SEARCH. Cancer Causes Control 30, 259–269. https://doi.org/10.1007/s10552-019-1133-5.

Hackshaw-McGeagh, L.E., Perry, R.E., Leach, V.A., Qandil, S., Jeffreys, M., Martin, R.M., Lane, J.A., 2015. A systematic review of dietary, nutritional, and physical activity interventions for the prevention of prostate cancer progression and mortality. Cancer Causes Control 26, 1521–1550. https://doi.org/10.1007/s10552-015-0659-4.

Harrison, S., Tilling, K., Turner, E.L., Martin, R.M., Lennon, R., Lane, J.A., Donovan, J.L., Hamdy, F.C., Neal, D.E., Bosch, J., Jones, H.E., 2020. Systematic review and meta-analysis of the associations between body mass index, prostate cancer, advanced prostate cancer, and prostate-specific antigen. Cancer Causes Control 31, 431–449. https://doi.org/10.1007/s10552-020-01291-3.

Hayes, S.C., Newton, R.U., Spence, R.R., Galvao, D.A., 2019. The Exercise and Sports Science Australia position statement: exercise medicine in cancer management. J. Sci. Med. Sport 22, 1175–1199. https://doi.org/10.1016/j.jsams.2019.05.003.

Henning, S.M., Galet, C., Gollapudi, K., Byrd, J.B., Liang, P., Li, Z., Grogan, T., Elashoff, D., Magyar, C.E., Said, J., Cohen, P., Aronson, W.J., 2018. Phase II prospective randomized trial of weight loss prior to radical prostatectomy. Prostate Cancer P D 21, 212–220. https://doi.org/10.1038/s41391-017-0001-1.

Herbst, K.L., Bhasin, S., 2004. Testosterone action on skeletal muscle. Curr. Opin. Clin. Nutr. Metab. Care 7, 271–277. https://doi.org/10.1097/00075197-200405000-00006.

Heymsfield, S.B., Wadden, T.A., 2017. Mechanisms, pathophysiology, and management of obesity. N. Engl. J. Med. 376, 254–266. https://doi.org/10.1056/NEJMra1514009.

Holly, J.M.P., Biernacka, K., Perks, C.M., 2020. The role of insulin-like growth factors in the development of prostate cancer. Expert Rev. Endocrinol. Metab. 15, 237–250. https://doi.org/10.1080/17446651.2020.1764844.

Hu, M.B., Xu, H., Bai, P.D., Jiang, H.W., Ding, Q., 2014. Obesity has multifaceted impact on biochemical recurrence of prostate cancer: a dose-response meta-analysis of 36,927 patients. Med. Oncol. 31, 829. https://doi.org/10.1007/s12032-013-0829-8.

Jain, R., Denlinger, C.S., 2017. Incorporating weight management into clinical care for cancer survivors: challenges, opportunities, and future directions. Obesity (Silver Spring) 25 (Suppl. 2), S27–S29. https://doi.org/10.1002/oby.22016.

Jaspan, V., Lin, K., Popov, V., 2021. The impact of anthropometric parameters on colorectal cancer prognosis: a systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. 159, 103232 https://doi.org/10.1016/j.critrevonc.2021.103232.

Joshu, C.E., Mondul, A.M., Menke, A., Meinhold, C., Han, M., Humphreys, E.B., Freedland, S.J., Walsh, P.C., Platz, E.A., 2011. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. Cancer Prev. Res. (Phila) 4, 544–551. https://doi.org/10.1158/1940-6207.CAPR-10-0257.

Keating, N.L., O'Malley, A.J., Freedland, S.J., Smith, M.R., 2010. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J. Natl. Cancer Inst. 102, 39–46. https://doi.org/10.1093/jnci/djp404.

Kenfield, S.A., Stampfer, M.J., Giovannucci, E., Chan, J.M., 2011. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J. Clin. Oncol. 29, 726–732. https://doi.org/10.1200/JCO.2010.31.5226.

Kim, H.S., Moreira, D.M., Smith, M.R., Presti Jr., J.C., Aronson, W.J., Terris, M.K., Kane, C.J., Amling, C.L., Freedland, S.J., 2011. A natural history of weight change in men with prostate cancer on androgen-deprivation therapy (ADT): results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. BJU Int. 107, 924–928. https://doi.org/10.1111/j.1464-410X.2010.09679.x.

Kim, J., Wilson, R.L., Taaffe, D.R., Galvão, D.A., Gray, E., Newton, R.U., 2021. Myokine expression and tumor-suppressive effect of serum following 12 weeks of exercise in prostate cancer patients on ADT. Med. Sci. Sports Exerc. https://doi.org/10.1249/MSS.0000000000002783. Epub ahead of print. PMID: 34559721.

Knipper, S., Mazzone, E., Mistretta, F.A., Palumbo, C., Tian, Z., Briganti, A., Saad, F., Tilki, D., Graefen, M., Karakiewicz, P.I., 2019. Impact of obesity on perioperative outcomes at robotic-assisted and open radical prostatectomy: results from the national inpatient sample. Urology 133, 135–144.

Labrie, F., Dupont, A., Belanger, A., St-Arnaud, R., Giguere, M., Lacourciere, Y., Emond, J., Monfette, G., 1986. Treatment of prostate cancer with gonadotropin-releasing hormone agonists. Endocr. Rev. 7, 67–74. https://doi.org/10.1210/edrv-7-1-67.

Lauby-Secretan, B., Scoccianti, C., Loomis, D., Grosse, Y., Bianchini, F., Straif, K., 2016. International Agency for Research on Cancer Handbook Working, G. Body fatness and cancer - viewpoint of the IARC Working Group. N. Engl. J. Med. 375, 794–798. https://doi.org/10.1056/NEJMsr1606602.

Li, H., Stampfer, M.J., Mucci, L., Rifai, N., Qiu, W., Kurth, T., Ma, J., 2010. A 25-year prospective study of plasma adiponectin and leptin concentrations and prostate cancer risk and survival. Clin. Chem. 56, 34–43. https://doi.org/10.1373/clinchem.2009.133272.

Ligibel, J.A., Alfano, C.M., Hershman, D., Ballard, R.M., Bruinooge, S.S., Courneya, K.S., Daniels, E.C., Demark-Wahnefried, W., Frank, E.S., Goodwin, P.J., Irwin, M.L., Levit, L.A., McCaskill-Stevens, W., Minasian, L.M., O'Rourke, M.A., Pierce, J.P., Stein, K.D., Thomson, C.A., Hudis, C.A., 2015. Recommendations for obesity clinical trials in cancer survivors: American Society of Clinical Oncology Statement. J. Clin. Oncol. 33, 3961–3967. https://doi.org/10.1200/JCO.2015.63.1440.

Ligibel, J.A., Jones, L.W., Brewster, A.M., Clinton, S.K., Korde, L.A., Oeffinger, K.C., Bender, C.M., Tan, W., Merrill, J.K., Katta, S., Alfano, C.M., 2019. Oncologists' attitudes and practice of addressing diet, physical activity, and weight management with patients with cancer: findings of an ASCO survey of the Oncology Workforce. J. Oncol. Pract. 15, e520–e528. https://doi.org/10.1200/JOP.19.00124.

Lin, D., Liu, T., Chen, L., Chen, Z., 2021. Body mass index in relation to prostate-specific antigen-related parameters. BMC Urol. 21, 130. https://doi.org/10.1186/s12894-020-00746-8.

Lopez, P., Newton, R.U., Taaffe, D.R., Singh, F., Buffart, L.M., Spry, N., Tang, C., Saad, F., Galvão, D.A., 2021. Associations of fat and muscle mass with overall survival in men with prostate cancer: a systematic review with meta-analysis. Prostate Cancer P D. https://doi.org/10.1038/s41391-021-00442-0.

Martini, A., Shah, Q.N., Waingankar, N., Sfakianos, J.P., Tsao, C.K., Necchi, A., Montorsi, F., Gallagher, E.J., Galsky, M.D., 2021. The obesity paradox in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. https://doi.org/10.1038/s41391-021-00418-0. Epub ahead of print. PMID: 34226662.

Massillo, C., Dalton, G.N., Porretti, J., Scalise, G.D., Farre, P.L., Piccioni, F., Secchiari, F., Pascuali, N., Clyne, C., Gardner, K., De Luca, P., De Siervi, A., 2019. CTBP1/CYP19A1/estradiol axis together with adipose tissue impacts over prostate cancer growth associated to metabolic syndrome. Int. J. Cancer 144, 1115–1127. https://doi.org/10.1002/ijc.31773.

Merrick, G.S., Butler, W.M., Wallner, K., Galbreath, R.W., Anderson, R.L., Kurko, B.S., Lief, J.H., 2002. Permanent prostate brachytherapy-induced morbidity in patients with grade II and III obesity. Urology 60, 104–108. https://doi.org/10.1016/s0090-4295(02)01638-2.

Mikhail, A.A., Stockton, B.R., Orvieto, M.A., Chien, G.W., Gong, E.M., Zorn, K.C., Brendler, C.B., Zagaja, G.P., Shalhav, A.L., 2006. Robotic-assisted laparoscopic prostatectomy in overweight and obese patients. Urology 67, 774–779. https://doi.org/10.1016/j.urology.2005.10.049.

Mitsuyama, H., Wallner, K.E., Merrick, G.S., 2006. Treatment of prostate cancer in obese patients. Oncology (Williston Park) 20, 1191–1197 discussion 1198, 1206, 1208.

Mohamad, H., McNeill, G., Haseen, F., N'Dow, J., Craig, L.C., Heys, S.D., 2015. The effect of dietary and exercise interventions on body weight in prostate cancer patients: a systematic review. Nutr. Cancer 67, 43–60. https://doi.org/10.1080/01635581.2015.976313.

Mohamad, N.V., Soelaiman, I.N., Chin, K.Y., 2016. A concise review of testosterone and bone health. Clin. Interv. Aging 11, 1317–1324. https://doi.org/10.2147/CIA.S115472.

Moyad, M.A., Newton, R.U., Tunn, U.W., Gruca, D., 2016. Integrating diet and exercise into care of prostate cancer patients on androgen deprivation therapy. Res. Rep. Urol. 8, 133–143. https://doi.org/10.2147/RRU.S107852.

Nandeesha, H., 2009. Insulin: a novel agent in the pathogenesis of prostate cancer. Int. Urol. Nephrol. 41, 267–272. https://doi.org/10.1007/s11255-008-9440-x.

National Collaborating Centre for Cancer (UK). Prostate Cancer: Diagnosis and Treatment. Cardiff (UK): National Collaborating Centre for Cancer (UK); 2014 Jan. (NICE Clinical Guidelines, No. 175.) Methodology.

Ndjavera, W., Orange, S.T., O'Doherty, A.F., Leicht, A.S., Rochester, M., Mills, R., Saxton, J.M., 2020. Exercise-induced attenuation of treatment side-effects in patients with newly diagnosed prostate cancer beginning androgen-deprivation therapy: a randomised controlled trial. BJU Int. 125, 28–37. https://doi.org/10.1111/bju.14922.

Neuenschwander, J., Burkhardt, O., Hess, L., Randazzo, M., Horton, K., Padevit, C., John, H., 2018. Obese patients undergoing robotic radical prostatectomy have no impaired operative outcome. Eur. Urol. Suppl. 17, e986.

Newton, R.U., Jeffery, E., Galvao, D.A., Peddle-McIntyre, C.J., Spry, N., Joseph, D., Denham, J.W., Taaffe, D.R., 2018. Body composition, fatigue and exercise in patients with prostate cancer undergoing androgen-deprivation therapy. BJU Int. 122, 986–993. https://doi.org/10.1111/bju.14384.

Newton, R.U., Galvão, D.A., Spry, N., Joseph, D., Chambers, S.K., Gardiner, R.A., Wall, B. A., Bolam, K.A., Taaffe, D.R., 2019. Exercise Mode Specificity for Preserving Spine and Hip Bone Mineral Density in Prostate Cancer Patients. Med Sci Sports Exerc. 51 (4), 607–614. https://doi.org/10.1249/MSS.0000000000001831.

Onuma, M., Bub, J.D., Rummel, T.L., Iwamoto, Y., 2003. Prostate cancer cell-adipocyte interaction: leptin mediates androgen-independent prostate cancer cell proliferation through c-Jun NH2-terminal kinase. J. Biol. Chem. 278, 42660–42667. https://doi.org/10.1074/jbc.M304984200.

Ormazabal, V., Nair, S., Elfeky, O., Aguayo, C., Salomon, C., Zuniga, F.A., 2018. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc. Diabetol. 17, 122. https://doi.org/10.1186/s12933-018-0762-4.

Parker, C., Gillessen, S., Heidenreich, A., Horwich, A., Committee, E.G., 2015. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 26 (Suppl. 5), v69–77. https://doi.org/10.1093/annonc/mdv222.

Párrizas, M., Saltiel, A.R., LeRoith, D., 1997. Insulin-like growth factor 1 inhibits apoptosis using the phosphatidylinositol 3′-kinase and mitogen-activated protein kinase pathways. J. Biol. Chem. 272, 154–161.

Peisch, S.F., Van Blarigan, E.L., Chan, J.M., Stampfer, M.J., Kenfield, S.A., 2017. Prostate cancer progression and mortality: a review of diet and lifestyle factors. World J. Urol. 35, 867–874. https://doi.org/10.1007/s00345-016-1914-3.

Pernar, C.H., Ebot, E.M., Wilson, K.M., Mucci, L.A., 2018. The epidemiology of prostate cancer. Cold Spring Harb. Perspect. Med. 8 https://doi.org/10.1101/cshperspect.a030361.

Rajah, R., Valentinis, B., Cohen, P., 1997. Insulin-like growth factor (IGF)-binding protein-3 induces apoptosis and mediates the effects of transforming growth factor-β1 on programmed cell death through a p53-and IGF-independent mechanism. J. Biol. Chem. 272, 12181–12188.

Rezaei, M.M., Rezaei, M.M., Ghoreifi, A., Kerigh, B.F., 2016. Metabolic syndrome in patients with prostate cancer undergoing intermittent androgen-deprivation therapy. Can. Urol. Assoc. J. 10, E300–e305. https://doi.org/10.5489/cuaj.3655.

Rhee, H., Vela, I., Chung, E., 2016. Metabolic syndrome and prostate cancer: a review of complex interplay amongst various endocrine factors in the pathophysiology and progression of prostate cancer. Horm. Cancer-US 7, 75–83. https://doi.org/10.1007/s12672-015-0238-x.

Richman, E.L., Kenfield, S.A., Stampfer, M.J., Paciorek, A., Carroll, P.R., Chan, J.M., 2011. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. Cancer Res. 71, 3889–3895. https://doi.org/10.1158/0008-5472.CAN-10-3932.

Rivera-Izquierdo, M., Pérez de Rojas, J., Martínez-Ruiz, V., Pérez-Gómez, B., Sánchez, M. J., Khan, K.S., Jiménez-Moleón, J.J., 2021. Obesity as a risk factor for prostate cancer mortality: a systematic review and dose-response meta-analysis of 280,199 patients. Cancers (Basel) 13. https://doi.org/10.3390/cancers13164169.

Rundqvist, H., Augsten, M., Stromberg, A., Rullman, E., Mijwel, S., Kharaziha, P., Panaretakis, T., Gustafsson, T., Ostman, A., 2013. Effect of acute exercise on prostate cancer cell growth. PLoS One 8, e67579. https://doi.org/10.1371/journal.pone.0067579.

Salji, M., Hendry, J., Patel, A., Ahmad, I., Nixon, C., Leung, H.Y., 2018. Peri-prostatic fat volume measurement as a predictive tool for castration resistance in advanced prostate cancer. Eur. Urol. Focus 4, 858–866. https://doi.org/10.1016/j.euf.2017.01.019.

Sanda, M.G., Dunn, R.L., Michalski, J., Sandler, H.M., Northouse, L., Hembroff, L., Lin, X., Greenfield, T.K., Litwin, M.S., Saigal, C.S., 2008. Quality of life and satisfaction with outcome among prostate-cancer survivors. New Engl. J. Med. 358, 1250–1261.

Schumacher, O., Galvão, D.A., Taaffe, D.R., Chee, R., Spry, N., Newton, R.U., 2021. Exercise modulation of tumour perfusion and hypoxia to improve radiotherapy response in prostate cancer. Prostate Cancer P D 24, 1–14. https://doi.org/10.1038/s41391-020-0245-z.

Segal, R.J., Reid, R.D., Courneya, K.S., Sigal, R.J., Kenny, G.P., Prud'Homme, D.G., Malone, S.C., Wells, G.A., Scott, C.G., Slovinec D'Angelo, M.E., 2009. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J. Clin. Oncol. 27, 344–351. https://doi.org/10.1200/jco.2007.15.4963.

Sharma, J., Gray, K.P., Evan, C., Nakabayashi, M., Fichorova, R., Rider, J., Mucci, L., Kantoff, P.W., Sweeney, C.J., 2014. Elevated insulin-like growth factor binding protein-1 (IGFBP-1) in men with metastatic prostate cancer starting androgen deprivation therapy (ADT) is associated with shorter time to castration resistance and overall survival. Prostate 74, 225–234. https://doi.org/10.1002/pros.22744.

Siddiqui, S.A., Inman, B.A., Sengupta, S., Slezak, J.M., Bergstralh, E.J., Leibovich, B.C., Zincke, H., Blute, M.L., 2006. Obesity and survival after radical prostatectomy: a 10-year prospective cohort study. Cancer-Am. Cancer Soc. 107, 521–529. https://doi.org/10.1002/cncr.22030.

Skolarus, T.A., Wolf, A.M., Erb, N.L., Brooks, D.D., Rivers, B.M., Underwood 3rd, W., Salner, A.L., Zelefsky, M.J., Aragon-Ching, J.B., Slovin, S.F., Wittmann, D.A., Hoyt, M.A., Sinibaldi, V.J., Chodak, G., Pratt-Chapman, M.L., Cowens-Alvarado, R. L., 2014. American Cancer Society prostate cancer survivorship care guidelines. CA Cancer J. Clin. 64, 225–249. https://doi.org/10.3322/caac.21234.

Smith, M.R., Lee, H., Fallon, M.A., Nathan, D.M., 2008. Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. Urology 71, 318–322. https://doi.org/10.1016/j.urology.2007.08.035.

Stroup, S.P., Cullen, J., Auge, B.K., L'Esperance, J.O., Kang, S.K., 2007. Effect of obesity on prostate-specific antigen recurrence after radiation therapy for localized prostate cancer as measured by the 2006 Radiation Therapy Oncology Group-American Society for Therapeutic Radiation and Oncology (RTOG-ASTRO) Phoenix consensus definition. Cancer-Am. Cancer Soc. 110, 1003–1009. https://doi.org/10.1002/cncr.22873.

Sung, H., Siegel, R.L., Rosenberg, P.S., Jemal, A., 2019. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. Lancet Public Health 4, e137–e147. https://doi.org/10.1016/s2468-2667(18)30267-6.

Sutton, E., Hackshaw-McGeagh, L.E., Aning, J., Bahl, A., Koupparis, A., Persad, R., Martin, R.M., Lane, J.A., 2017. The provision of dietary and physical activity advice for men diagnosed with prostate cancer: a qualitative study of the experiences and views of health care professionals, patients and partners. Cancer Causes Control 28, 319–329. https://doi.org/10.1007/s10552-017-0861-7.

Tahergorabi, Z., Khazaei, M., Moodi, M., Chamani, E., 2016. From obesity to cancer: a review on proposed mechanisms. Cell Biochem. Funct. 34, 533–545. https://doi.org/10.1002/cbf.3229.

Taplin, M.E., Ho, S.M., 2001. Clinical review 134: The endocrinology of prostate cancer. J. Clin. Endocrinol. Metab. 86, 3467–3477. https://doi.org/10.1210/jcem.86.8.7782.

Thomas, R.J., Holm, M., Williams, M., Bowman, E., Bellamy, P., Andreyev, J., Maher, J., 2013. Lifestyle factors correlate with the risk of late pelvic symptoms after prostatic radiotherapy. Clin. Oncol. (R. Coll. Radiol.) 25, 246–251. https://doi.org/10.1016/j.clon.2012.11.007.

Thomas, R., Williams, M., Sharma, H., Chaudry, A., Bellamy, P., 2014. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer–the U.K. NCRN Pomi-T study. Prostate Cancer P D 17, 180–186. https://doi.org/10.1038/pcan.2014.6.

Tong, D., 2021. Unravelling the molecular mechanisms of prostate cancer evolution from genotype to phenotype. Crit. Rev. Oncol. Hematol. 163, 103370 https://doi.org/10.1016/j.critrevonc.2021.103370.

Troeschel, A.N., Hartman, T.J., Jacobs, E.J., Stevens, V.L., Gansler, T., Flanders, W.D., McCullough, L.E., Wang, Y., 2020. Postdiagnosis body mass index, weight change, and mortality from prostate cancer, cardiovascular disease, and all causes among survivors of nonmetastatic prostate cancer. J. Clin. Oncol. 38, 2018–2027. https://doi.org/10.1200/JCO.19.02185.

Tsang, D.S., Alibhai, S.M., 2014. Bone health care for patients with prostate cancer receiving androgen deprivation therapy. Hosp. Pract. (1995) 42, 89–102. https://doi.org/10.3810/hp.2014.04.1107.

van Roermund, J.G., Hinnen, K.A., Battermann, J.J., Witjes, J.A., Bosch, J.L., Kiemeney, L.A., van Vulpen, M., 2010. Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy. BJU Int. 105, 42–48. https://doi.org/10.1111/j.1464-410X.2009.08687.x.

Vidal, A.C., Howard, L.E., Moreira, D.M., Castro-Santamaria, R., Andriole Jr., G.L., Freedland, S.J., 2014. Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. Cancer Epidemiol. Biomarkers Prev. 23, 2936–2942. https://doi.org/10.1158/1055-9965.EPI-14-0795.

Vidal, A.C., Howard, L.E., de Hoedt, A., Kane, C.J., Terris, M.K., Aronson, W.J., Cooperberg, M.R., Amling, C.L., Freedland, S.J., 2018. Obese patients with castration-resistant prostate cancer may be at a lower risk of all-cause mortality: results from the shared Equal Access Regional Cancer hospital (SEARCH) database. BJU Int. 122, 76–82. https://doi.org/10.1111/bju.14193.

Wang, L.S., Murphy, C.T., Ruth, K., Zaorsky, N.G., Smaldone, M.C., Sobczak, M.L., Kutikov, A., Viterbo, R., Horwitz, E.M., 2015. Impact of obesity on outcomes after definitive dose-escalated intensity-modulated radiotherapy for localized prostate cancer. Cancer-Am. Cancer Soc. 121, 3010–3017. https://doi.org/10.1002/cncr.29472.

Wilson, R.L., Shannon, T., Calton, E., Galvao, D.A., Taaffe, D.R., Hart, N.H., Lyons-Wall, P., Newton, R.U., 2020. Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer. Surg. Oncol. 35, 182–188. https://doi.org/10.1016/j.suronc.2020.08.006.

Wilson, R.L., Newton, R.U., Taaffe, D.R., Hart, N.H., Lyons-Wall, P., Galvao, D.A., 2021a. Weight loss for obese prostate cancer patients on androgen deprivation therapy. Med. Sci. Sports Exerc. 53, 470–478. https://doi.org/10.1249/MSS.0000000000002509.

Wilson, R.L., Taaffe, D.R., Newton, R.U., Hart, N.H., Lyons-Wall, P., Galvão, D.A., 2021b. Maintaining weight loss in obese men with prostate cancer following a supervised exercise and nutrition program-a pilot study. Cancers (Basel) 13. https://doi.org/10.3390/cancers13143411.

Wiltz, A.L., Shikanov, S., Eggener, S.E., Katz, M.H., Thong, A.E., Steinberg, G.D., Shalhav, A.L., Zagaja, G.P., Zorn, K.C., 2009. Robotic radical prostatectomy in overweight and obese patients: oncological and validated-functional outcomes. Urology 73, 316–322. https://doi.org/10.1016/j.urology.2008.08.493.

World Cancer Research Fund; American Institute for Cancer Research. Continuous Update Project Expert Report 2018: Body fatness and weight gain and the risk of cancer. Available online: https://www.wcrf.org/wp-content/uploads/2021/01/Body-fatness-and-weight-gain_0.pdf (Accessed on 11 May 2021).

Wright, J.L., Plymate, S., D'Oria-Cameron, A., Bain, C., Haugk, K., Xiao, L., Lin, D.W., Stanford, J.L., McTiernan, A., 2013. A study of caloric restriction versus standard diet in overweight men with newly diagnosed prostate cancer: a randomized controlled trial. Prostate 73, 1345–1351. https://doi.org/10.1002/pros.22682.

Yao, S., Till, C., Kristal, A.R., Goodman, P.J., Hsing, A.W., Tangen, C.M., Platz, E.A., Stanczyk, F.Z., Reichardt, J.K., Tang, L., Neuhouser, M.L., Santella, R.M., Figg, W.D., Price, D.K., Parnes, H.L., Lippman, S.M., Thompson, I.M., Ambrosone, C.B., Hoque, A., 2011. Serum estrogen levels and prostate cancer risk in the prostate cancer prevention trial: a nested case-control study. Cancer Causes Control 22, 1121–1131. https://doi.org/10.1007/s10552-011-9787-7.

Rebekah L. Wilson, PhD, is a postdoctoral fellow at Dana-Farber Cancer Institute and Harvard Medical School. She has a research interest in the application of exercise into clinical care for cancer patients.

Dennis R. Taaffe, PhD, DSc, MPH, is a Professor in the Exercise Medicine Research Institute at Edith Cowan University with research interests in exercise oncology and exercise gerontology.

Robert U. Newton, PhD, DSc, AEP, CSCS*D, FACSM, ESSAF, FNSCA, is a Professional Research Fellow in the Exercise Medicine Research Institute at Edith Cowan University.

Nicolas H. Hart, PhD, AES, CSCS, ESSAM, is Deputy Lead of the Cancer Survivorship Program and Senior Research Fellow at the Caring Futures Institute of Flinders University. His research specifically focuses on improving cancer care and cancer outcomes for people with advanced or metastatic cancers with an emphasis on exercise as medicine.

Philippa Lyons-Wall, PhD, is an Associate Professor in the School of Medical and Health Sciences at Edith Cowan University and member of the Exercise Medicine Research Institute. She is an Accredited Practising Dietitian and Discipline Lead for the Master of Nutrition and Dietetics program.

Daniel A. Galvão, PhD, is a Professor and Director of the Exercise Medicine Research Institute at Edith Cowan University.

CHAPTER THREE

Using exercise and nutrition to induce fat loss while preserving lean mass in prostate cancer patients receiving androgen deprivation therapy: a narrative review

Chapter Three of this thesis has been published by MDPI in *Nutrients*, as the below article:

Wilson, R. L., Taaffe, D. R., Newton, R. U., Hart, N. H., Lyons-Wall, P., & Galvão, D. A. (2021). Using exercise and nutrition to alter fat and lean mass in men with prostate cancer receiving androgen deprivation therapy: A narrative review. *Nutrients, 13*(15), article 1664.

https://doi.org/10.3390/nu13051664

nutrients

MDPI

Review

Using Exercise and Nutrition to Alter Fat and Lean Mass in Men with Prostate Cancer Receiving Androgen Deprivation Therapy: A Narrative Review

Rebekah L. Wilson [1,2,3,*], Dennis R. Taaffe [2,3], Robert U. Newton [2,3,4], Nicolas H. Hart [2,3,5,6], Philippa Lyons-Wall [3] and Daniel A. Galvão [2,3]

1 Division of Population Sciences, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
2 Exercise Medicine Research Institute, Edith Cowan University, Perth 6027, WA, Australia; d.taaffe@ecu.edu.au (D.R.T.); r.newton@ecu.edu.au (R.U.N.); nicolas.hart@qut.edu.au (N.H.H.); d.galvao@ecu.edu.au (D.A.G.)
3 School of Medical and Health Sciences, Edith Cowan University, Perth 6027, WA, Australia; p.lyons-wall@ecu.edu.au
4 School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane 4072, QLD, Australia
5 Institute for Health Research, University of Notre Dame Australia, Perth 6160, WA, Australia
6 Cancer and Palliative Care Outcomes Centre, Queensland University of Technology, Brisbane 4000, QLD, Australia
* Correspondence: rebekahl_wilson@dfci.harvard.edu; Tel.: +1-617-582-7174; Fax: +1-857-215-5653

Citation: Wilson, R.L.; Taaffe, D.R.; Newton, R.U.; Hart, N.H.; Lyons-Wall, P.; Galvão, D.A. Using Exercise and Nutrition to Alter Fat and Lean Mass in Men with Prostate Cancer Receiving Androgen Deprivation Therapy: A Narrative Review. *Nutrients* **2021**, *13*, 1664. https://doi.org/10.3390/nu13051664

Academic Editor: Line Merethe Oldervoll

Received: 12 March 2021
Accepted: 6 May 2021
Published: 14 May 2021

Abstract: Fat mass (FM) gain and lean mass (LM) loss are common side effects for patients with prostate cancer receiving androgen deprivation therapy (ADT). Excess FM has been associated with an increased risk of developing obesity-related comorbidities, exacerbating prostate cancer progression, and all-cause and cancer-specific mortality. LM is the predominant contributor to resting metabolic rate, with any loss impacting long-term weight management as well as physical function. Therefore, reducing FM and preserving LM may improve patient-reported outcomes, risk of disease progression, and ameliorate comorbidity development. In ADT-treated patients, exercise and nutrition programs can lead to improvements in quality of life and physical function; however, effects on body composition have been variable. The aim of this review was to provide a descriptive overview and critical appraisal of exercise and nutrition-based interventions in prostate cancer patients on ADT and their effect on FM and LM. Our findings are that FM gain and LM loss are side effects of ADT that could be reduced, prevented, or even reversed with the implementation of a combined exercise and nutrition program. However, the most effective combination of specific exercise and nutrition prescriptions are yet to be determined, and thus should be a focus for future studies.

Keywords: androgen deprivation therapy; prostate cancer; exercise; nutrition; fat mass; lean mass

1. Introduction

Androgen deprivation therapy (ADT) is a mainstay treatment for prostate cancer (PCa), where more than half of patients will receive ADT at some point during their cancer journey [1]. ADT is a pharmaceutical or surgical strategy that deprives the body of androgens, thereby slowing cancer growth [2]. This may be achieved by either reducing testosterone concentrations to castrate levels defined as <50 ng/dL (<1.7 nmol/L) using luteinizing hormone-releasing hormone agonists, antagonists or an orchiectomy procedure, or by blocking the androgen receptors to eliminate testosterone binding using anti-androgens [2]. Given that testosterone plays roles in the activation of lipolysis and hypertrophy of lean mass (LM) [3,4], substantial body composition changes, as well as loss of muscle strength and physical function, can occur [5,6]. Within the first 9 months of treatment initiation, patients have been reported to experience a 13.8% increase in fat

mass (FM) and a 2.4% decrease in LM [5]. This change in body composition places patients with PCa at increased risk of obesity-related comorbidities, treatment-related side effects, development of a more aggressive cancer, and PCa-specific mortality [7–10].

Excess FM upregulates pro-inflammatory cytokines, leading to a state of low-grade chronic inflammation, which is associated with decreased cancer cell apoptosis, increased cancer cell growth, angiogenesis, and metastases, and increased risk of developing cardiovascular disease and type 2 diabetes (Figure 1) [7,11,12]. Post-diagnosis obese prostate cancer patients with non-metastatic disease are more likely to experience cardiovascular disease-related mortality than non-obese patients (hazard ratio of 1.24) [13]. In addition, PCa patients on ADT with greater FM may experience higher fatigue, lower vitality, and higher blood triglyceride concentrations [14,15]. A loss of LM also contributes to poorer patient outcomes [14]. The development of sarcopenic obesity, a progressive loss of LM and gain in FM, has been associated with multiple physical disabilities (Figure 1) [16,17]. Lean mass is also the predominant contributor to resting metabolic rate. Therefore, preserving or increasing LM is important for long-term weight loss maintenance [18]. Promoting LM gain can also increase glucose storage, facilitate glucose clearance from circulation, and reduce the amount of insulin required to maintain normal glucose tolerance [19], which is important as insulin resistance may exacerbate cancer progression [20]. Owing to the association between FM gain or LM loss and worse patient outcomes, strategies to prevent or reverse this process are important to include as adjuvant therapies while on ADT, particularly for those who are obese [9].

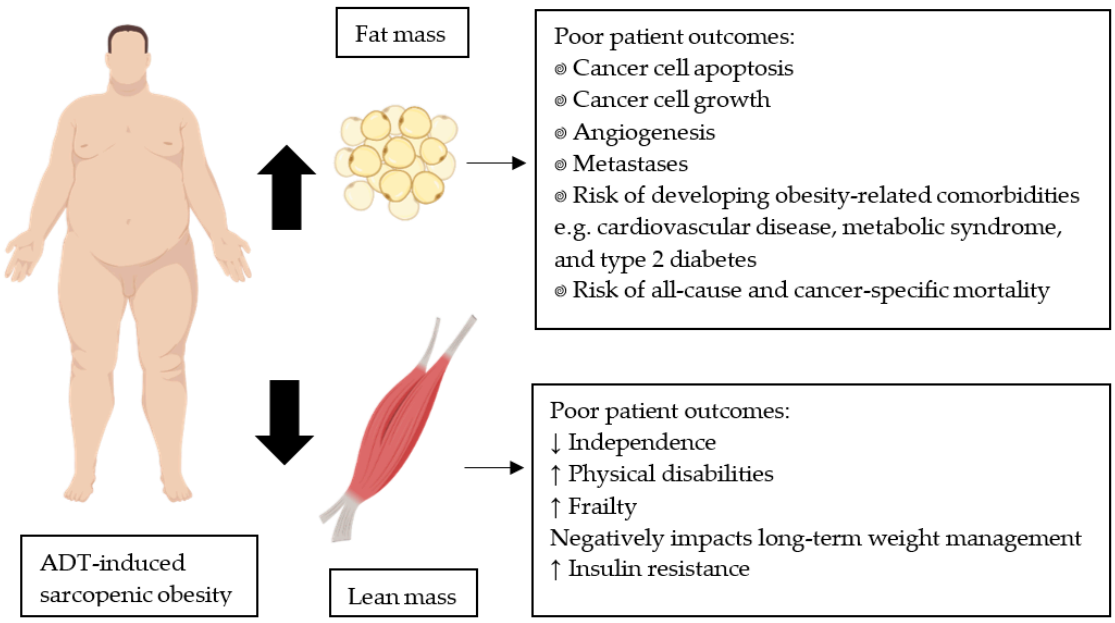


Figure 1. Prostate cancer patients receiving ADT can develop sarcopenic obesity due to a treatment-induced increase in fat mass and decrease in lean mass. These respective body composition changes can lead to poor patient outcomes. Images created with BioRender.com (accessed on 20 November 2020).

Exercise and nutrition interventions are effective strategies to reduce FM and increase LM in non-cancer populations [21]. Researchers conducting clinical studies in the PCa population have reported that exercise interventions result in improved quality of life and reduced ADT-related side effects such as cancer-related fatigue and poorer physical function [22]. Nutrition interventions have been demonstrated to induce weight loss, improve bone health, and in some instances slow PCa progression, although evidence is limited [23–25]. Despite these beneficial outcomes, the variety of intervention designs, aims, cohorts, and outcomes, presents variable evidence as to whether exercise and nutrition interventions have a desirable effect on FM and LM for patients undergoing ADT. When

examining body composition in ADT-treated patients, exercise has been the preferential intervention utilised. As such, there is a lack of clarity concerning the feasibility and efficacy of combined exercise and nutrition programs and the effect on FM loss, while simultaneously seeking to preserve or enhance LM. Therefore, this review is a descriptive overview and critical appraisal of exercise and nutrition-based interventions in ADT-treated PCa patients and the effect on FM and LM, and to propose possible avenues for further research.

MEDLINE and Scopus databases were searched with published studies included until November 2020. Search terms included various combinations of: prostate cancer; androgen deprivation therapy; exercise; nutrition; body composition; fat mass; lean mass. Secondary searches involved reference lists of eligible articles as well as systematic reviews and meta-analyses assessing interventions given to patients on ADT. The key criterion was to identify studies that included PCa patients receiving ADT at time of intervention, utilising an exercise, nutrition or combined intervention, while including a measure of FM and/or LM.

2. Using Exercise to Decrease Fat Mass and Preserve or Gain Lean Mass

2.1. Aerobic Exercise

Aerobic exercise is an ideal intervention for FM loss as it is familiar to non-exercisers, e.g., walking, easy to implement at home with little to no equipment, promotes higher utilisation of lipids, and includes modes allowing reduced impact on joints, e.g., swimming [26,27]. The aerobic exercise guidelines for prostate cancer patients recommended within clinical practice suggest an accumulation of 150 min/week of moderate-to-vigorous intensity or 300 min/week if weight loss is intended (Table 1) [28]. In this section, we evaluate six studies examining aerobic-based interventions and the effect on FM and LM.

Table 1. Current prostate cancer-specific exercise and nutrition guidelines, including weight loss guidelines.

	Current Exercise and Nutrition Guidelines	Current Weight Loss Guidelines
 Aerobic training	150 min/week of moderate intensity exercise or 75 min/week of vigorous intensity exercise	300 min/week of moderate intensity exercise or 150 min/week of vigorous intensity exercise
 Resistance training	Minimum two strength training sessions/week	
 Nutritional intake	Healthy balanced diet with high fruit and vegetables, low saturated fats, and adequate calcium (<1200 mg/d) and vitamin D (>600 IU)	2100–4200 kJ daily energy deficit

Images created with BioRender.com (accessed on 5 April 2021).

Hvid et al. [29] compared healthy aged-matched controls with normal testosterone concentrations (10–28 nmol/L), and ADT-treated PCa patients with castrate levels of testosterone (<1.7 nmol/L) completing the same 12 week aerobic-based cycling intervention utilising high-intensity interval training (Table 2). Both groups significantly lost whole-body, trunk, visceral, and subcutaneous FM, while preserving LM, with no between-group

differences. The castrate levels of testosterone in ADT-treated patients, therefore, does not appear to inhibit FM loss via high-intensity aerobic exercise. However, the healthy controls exhibited a superior loss of intermuscular FM (−8.5% vs. 0%). The presence of substantial intermuscular FM could interfere with muscle fibre quality and contribute to insulin resistance, reduction in muscle strength, and increased fatigue [27,30,31], although there was no between-group difference for insulin sensitivity; muscle strength and fatigue were not measured. However, this study contained a small sample size and did not include a PCa control group. Therefore, it is unclear whether the intervention prevented further ADT-induced increases in intermuscular FM and if this in turn affects muscle fibre quality. Furthermore, the groups had baseline cardiorespiratory fitness levels of 27.2 mL/kg/min and 25.2 mL/kg/min, respectively, and prostate cancer patients staged T1 a/b to T3 a/b. Therefore, the use of high-intensity aerobic-based exercise is uncertain for patients with poor cardiorespiratory fitness or more advanced disease.

Table 2. Exercise-only interventions assessing fat and lean mass in prostate cancer patients receiving ADT.

Study	Study Design	Primary Outcome	Intervention	Body Composition Assessment	Groups (*N*)	Outcome Variable	Mean Pre-Intervention Values (kg)	Mean Post-Intervention Values (kg)
Aerobic-based interventions								
Alberga et al. [32]	RCT	Body composition and fitness	24 weeks 3 ×/week Supervised aerobic exercise at 50–75% HRmax or Supervised resistance exercise at 60–70% 1 RM	DXA	Aerobic (*N* = 40)			
					ADT	BF%	31.2%	33.3% *
						Lean mass	65.0	63.0 *
					No ADT	BF%	29.9%	30.5%
						Lean mass	66.2	65.7
					Resistance (*N* = 40)			
					ADT	BF%	32.6%	33.0% §UC
						Lean mass	63.7	63.4 §UC
					No ADT	BF%	29.7%	29.2%
						Lean mass	66.7	67.3
					Usual care (*N* = 41)			
					ADT	BF%	32.0%	35.2% §R *
						Lean mass	64.2	61.1 §R *
					No ADT	BF%	31.2	30.6
						Lean mass	65.0	65.6
Hvid et al. [29]	Prospective cohort	Insulin sensitivity and body composition	12 weeks 3 ×/week 135 min/week Aerobic interval exercise 50–100% VO2max	DXA and MRI	Prostate cancer exercise (*N* = 9)	Fat mass	24.4	23.1 #
						Trunk fat	14.5	13.4 #
						Lean mass	52.3	52.3
						BF%	31.1%	29.8% #
						Visceral [a]	−8.4% #	
						Subcutaneous [a]	−4.9% #	
						Intermuscular [a]	0% § #	
					Non-cancer exercise (*N* = 10)	Fat mass	20.5	19.6 #
						Trunk fat	12.4	11.8 #
						Lean mass	56.3	56.2
						BF%	25.7%	25.0% #
						Visceral [a]	−5.8% #	
						Subcutaneous [a]	−2.5% #	
						Intermuscular [a]	−8.5% #	
Santa Mina et al. [33]	RCT	Quality of life	6 months 3–5 ×/week 90–300 min/week Home-based resistance band/ball/body weight exercise 12–15 RPE Or Home-based aerobic exercise at 60–80% HRmax	Skinfolds	Aerobic (*N* = 22)	Chest skinfold	35.6 mm	33.5 mm *3
						BF%	28.5%	27.3% *3
					Resistance (*N* = 34)	Chest skinfold	35.3 mm	33.7 mm
						BF%	28.0%	27.3%
Santa Mina et al. [34]	RCT	Blood biomarkers	See Santa Mina et al. [33]	Skinfolds	Aerobic (*N* = 13)	BF%	28.4%	26.4%
					Resistance (*N* = 13)	BF%	26.5%	25.3%
Uth et al. [35]	RCT	Lean mass	12 weeks 2 ×/week (1–8 weeks) 3 ×/week (9–12 weeks) 90–180 min/week Supervised football training	DXA	Football (*N*= 29)	Fat mass	27.6	26.3
						Lean mass	53.1	54.0 § *
						BF%	32.6%	31.7%
					Usual care (*N* = 28)	Fat mass	30.0	29.7
						Lean mass	56.7	56.8
						BF%	32.9%	32.9%

Table 2. *Cont.*

Study	Study Design	Primary Outcome	Intervention	Body Composition Assessment	Groups (*N*)	Outcome Variable	Mean Pre-Intervention Values (kg)	Mean Post-Intervention Values (kg)
Newton et al. [36]	RCT	Bone mineral density	12 months 2 ×/week Supervised impact exercise at ground reaction force of 3–5 × body weight Resistance exercise 6–12 RM, 2–4 sets 2 ×/week Home-based impact exercise Or 6 months 2 ×/week 150 min/week Supervised aerobic at 65–85% HRmax Resistance exercise 6–12 RM, 2–4 sets Home-based aerobic exercise 6 months Home-based aerobic Resistance (body weight/band) exercise Or 6 months waiting period 6 months 2 ×/week 80 min/week Aerobic exercise at 70% HRmax	DXA	Resistance/impact (*N* = 57)	Fat mass Lean mass ASM	24.0 57.9 25.0	25.1 59.3 25.9 §6DEL
					Aerobic/resistance (*N* = 50)	Fat mass Lean mass ASM	22.8 58.1 25.2	23.7 58.7 25.6
					Delay/aerobic (*N* = 47)	Fat mass Lean mass ASM	27.1 59.3 25.3	28.3 60.4 25.9
Resistance-based interventions								
Galvão et al. [37]	Prospective cohort	Muscle function	20 weeks 2 ×/week 120 min/week Supervised resistance exercise 6–12 RM, 2–4 sets	DXA	Resistance (*N* = 10)	Fat mass Lean mass BF% Quadriceps thickness Hamstring thickness Biceps thickness Triceps thickness	25.7 52.2 30.7% 2.15 cm 4.52 cm 2.69 cm 1.94 cm	24.9 52.0 30.6% 2.46 cm * 1.53 cm 2.91 cm 2.33 cm
Alberga et al. [32]	Details in aerobic section							
Santa Mina et al. [33]	Details in aerobic section							
Santa Mina et al. [34]	Details in aerobic section							
Hanson et al. [38]	Prospective cohort	Muscle size and function	12 weeks 3 ×/week 180 min/week Supervised high-intensity resistance exercise 15 repetitions, first 5 at 5 RM	DXA and CT	Resistance (*N* = 17)	Fat mass Subcutaneous Intermuscular Lean mass BF%	31.2 118 cm^2 7.9 cm^2 62.4 31.4%	31.1 118 cm^2 7.6 cm^2 64.1 * 30.7% *
Nilsen et al. [39]	RCT	Lean mass	16 weeks 3 ×/week Supervised resistance exercise 6–10 RM, 1–3 sets	DXA	Resistance (*N* = 28)	Fat mass Trunk fat Lean mass ASM BF%	26.5 14.7 59.8 25.2 29.5%	26.4 14.6 60.3 25.7 § 29.3%
					Control (*N* = 30)	Fat mass Trunk fat Lean mass ASM BF%	26.4 14.6 57.9 24.8 30.0%	26.7 14.7 57.9 24.7 30.2%

Table 2. *Cont.*

Study	Study Design	Primary Outcome	Intervention	Body Composition Assessment	Groups (*N*)	Outcome Variable	Mean Pre-Intervention Values (kg)	Mean Post-Intervention Values (kg)
Multi-modal interventions								
Galvão et al. [40]	RCT	Lean mass	12 weeks 2 ×/week Supervised aerobic at 65–80% HRmax Resistance exercise 6–12 RM, 2–4 sets	DXA	Exercise (*N* = 29)	Fat mass Trunk fat Lean mass ASM BF%	22.5 12.2 56.1 23.5 27.5%	22.3 11.9 56.8 § 24.0 § 27.2%
					Usual care (*N* = 28)	Fat mass Trunk fat Lean mass ASM BF%	23.2 12.4 57.8 24.6 27.3%	23.5 12.2 57.8 24.4 27.5%
Galvão et al. [15]	RCT	Various ADT side effects	See Galvão et al. [40]	DXA	Acute ADT (*N* = 16)	Fat mass Trunk fat Lean mass ASM BF%	22.7 12.2 58.5 24.7 26.8%	23.3 § * 12.4 59.1 25.2 27.2% §
					Chronic ADT (*N* = 34) [b]	Fat mass Trunk fat Lean mass ASM BF%	23.4 12.1 56.5 23.8 28.1%	23.0 * 11.8 * 57.4 * 24.4 * 27.4% *
Cormie et al. [41]	RCT	Lean mass	12 weeks 2 ×/week 150 min/week Supervised aerobic at 70–85% HRmax Resistance exercise at 60–85% 1 RM Home-based exercise of choice	DXA	Exercise (*N* = 32)	Fat mass Trunk fat Visceral fat Lean mass ASM BF%	26.9 14.8 913 g 56.6 23.7 30.6%	26.3 § 14.3 § 874 g * 56.0 23.5 § 30.5% §
					Usual care (*N* = 31)	Fat mass Trunk fat Visceral fat Lean mass ASM BF%	26.9 15.2 926 g 58.7 24.9 30.3%	27.8 * 15.5 922 g 57.3 * 24.3 * 31.4% *
Winters-Stone et al. [42]	RCT	Body composition	12 months 2 ×/week 165 min/week Supervised resistance at 60–80% 1 RM Impact exercise 1 ×/week Home-based exercise of choice	DXA	Exercise (*N* = 29)	Fat mass Trunk fat Lean mass BF%	24.3 13.5 59.2 28.7%	23.9 § 13.1 59.2 28.4%
					Flexibility (*N* = 22)	Fat mass Trunk fat Lean mass BF%	28.4 15.0 57.5 31.6%	29.9 15.4 57.2 32.4%
Wall et al. [43]	RCT	Cardiorespiratory fitness	6 months 2 ×/week 150 min/week Supervised aerobic at 70–90% HRmax Resistance exercise 6–12 RM, 1–4 sets 1 ×/week Home-based aerobic exercise	DXA	Exercise (*N* = 50)	Fat mass Trunk fat Lean mass BF%	24.1 13.2 59.4 27.2%	24.5 § 13.0 § 60.1 § 27.2% §
					Usual care (*N* = 47)	Fat mass Trunk fat Lean mass BF%	25.7 14.2 58.7 28.2%	27.2 14.9 58.6 30.3%
Newton et al. [36]	Details in aerobic section							
Ndjavera et al. [44]	RCT	Fat mass	12 weeks 2 ×/week Supervised aerobic at 55–85% HRmax Resistance exercise 10 RM, 2–4 sets Home-based aerobic exercise	BIA	Exercise (*N* = 24)	Fat mass Fat-free mass	24.3 58.2	21.7 58.9
					Usual care (*N* = 26)	Fat mass Fat-free mass	23.3 59.1	22.7 58.2

* = Significant within group change; § = significant between-group change; §UC = significant between-group change with usual care control group; §R = significant between-group change with resistance training group; # = effect of time in the two groups pooled together; §6DEL = significantly different to delayed/aerobic group at 6 months only, not 12 months which is the value reported in the table; *3 = significant loss at 3 months only, but not 6 months which is the value reported in the table. [a] Only reported mean change; [b] Acute ADT < 6 months, chronic ADT ≥ 6 months. RCT = randomised controlled trial; ×/week = times per week; HRmax = maximum heart rate; RM = repetition maximum; DXA = dual x-ray absorptiometry; ADT = androgen deprivation therapy; BF% = body fat percent; VO2max = oxygen consumption; MRI = magnetic resonance imaging; RPE = rate of perceived exertion; CT = computed tomography; ASM = appendicular skeletal muscle; BIA = bioimpedance analysis.

Uth et al. [35] utilised an unstructured form of interval-based aerobic training, in the form of football (soccer) game play and skill development (Table 2). Unlike Hvid et al. [29], they recruited patients with bone metastases (19.3%), but similarly assessed an apparently healthy prostate cancer cohort with only 5.3% of patients self-reporting a sedentary lifestyle, with baseline cardiorespiratory fitness of 27.2 and 26.4 mL/kg/min, and mean body mass index of 26.7 and 27.6 kg/m^2, respectively. They reported a mean 0.5 kg significant increase in LM and a mean 0.6 kg loss of FM that approached within-group significance. With the improvement in LM and a trend for an effect on FM, sport-orientated activities may be an effective alternative to clinic-based interventions in ameliorating treatment-related body composition changes. Several adverse events were reported in the football group including fracture, tendon tear, and sprain. While no injury was related to bone metastases and most participants recovered and continued with the study, there is uncertainty whether such an intervention would be feasible for high-risk patients, e.g., obese patients with multiple comorbidities. Injury risk is higher within a team sport environment, compared to individual sport or exercise, due to the unpredictable nature of opponents, teammates, and ball. The authors suggested a lead-in period may be required to improve strength, balance, and ball handling to reduce injury risks [35].

In contrast to the previous studies using interval training [29,35], Newton et al. [36] and Alberga et al. [32] utilised clinic-based continuous aerobic exercise (Table 2). Examining a cohort that excluded patients with bone metastases, Newton et al. [36] used a three-arm study design over 12 months comparing impact and resistance exercise, aerobic and resistance exercise, and delayed aerobic exercise after 6 months of usual care. When compared to the aerobic-only exercise group during the 6–12 month period, no differences in FM or LM were noted between groups. Alberga et al. [32] also utilised a three-arm study design comparing aerobic exercise, resistance exercise, and usual care across a 24-week period, in ADT and non-ADT groups, although the two treatment types were not compared. The ADT aerobic group exhibited an undesirable significant increase in body fat percentage (BF%) and 2 kg reduction in LM, although not statistically different to the other ADT groups. The researchers did not report FM, so it is unclear whether a change in FM, in addition to the LM loss, contributed to the modification in BF%. The decline in LM is substantial and concerning, suggesting the prescribed aerobic exercise was insufficient to prevent ADT-related declines in LM, in contrast to a non-significant 0.5 kg loss in LM in the non-ADT aerobic group.

The previously described studies were supervised interventions [29,32,35,36]. However, ongoing supervision is not always viable. Santa Mina et al. [33,34] compared home-based aerobic and resistance exercise over 6 months examining patients with non-metastatic disease. Santa Mina et al. [34] used a smaller non-randomised group of the same cohort to report on blood biomarkers (Table 2). There were significant within-group declines in chest skinfold thickness and BF% at 3 months, but not 6 months [33] and weight change was positively associated with changes in leptin and the leptin:adiponectin ratio, and negatively associated with IGF-1:IGFBP-3 ratio [34], which are proposed markers associated with PCa progression [45]. Although the use of anthropometric measures suggest weight loss may improve risk of cancer progression, the researchers could not confirm if these changes were subject to alterations in FM or LM. Nonetheless, both studies provide valuable insight into the potential of home-based programs, although there is still uncertainty if those with metastatic disease would benefit from a similar program.

2.2. Resistance Exercise

Weight loss can occur through loss of both fat and muscle tissue [46]; however, substantial loss of LM may exacerbate sarcopenia, reduce physical function, and increase risk of falls [47]. Resistance exercise is commonly prescribed for muscle hypertrophy [48]. Within clinical practice prostate cancer patients are recommended to complete resistance training on a minimum of two days each week (Table 1) [28]. This section is an evaluation of six studies examining resistance exercise and the effect on FM and LM.

Galvão et al. [37] and Hanson et al. [38] conducted single-group studies and both excluded patients with metastatic disease (Table 2). Galvão et al. [37] prescribed a traditional periodised resistance training program over 20 weeks and found no change in FM or LM except for a significant increase in quadriceps thickness. In contrast, Hanson et al. [38] utilised drop sets and repetitions to failure over a 12-week program. The exercise set began at five repetition maximum and once volitional fatigue was reached the resistance was reduced until 15 repetitions were achieved. A significant decrease in BF% and increase in LM were reported. The differing results may be explained by the period between the two studies and cohort examined. At the time of the Galvão et al. [37] study, the use of resistance training for PCa patients was somewhat revolutionary and a conservative exercise prescription was implemented with only 10 patients recruited. The Hanson et al. [38] study was completed over a decade later in a cohort of 17 patients of African American ethnicity with higher intensity and sophistication of resistance training design. While these studies demonstrate the feasibility of resistance training in promoting changes to LM, both studies utilised small or non-diverse cohorts, so the generalisability of these results is unclear.

Nilsen et al. [39] examined a 16-week clinic-based high-load periodised resistance training program in which the intervention group significantly improved appendicular skeletal muscle (ASM). However, no changes were found for whole-body LM or FM or for any body composition measure when compared to the usual care controls (Table 2). High-risk patients with medical conditions that could complicate participation were excluded from this study, although cancer stage of included patients was not reported. Nevertheless, three patients withdrew from the intervention group due to pain. Further research is required into the appropriateness of high-load resistance training for high-risk patients and may require a gradual increase in intensity. Furthermore, while the recruitment goal was met in this study, the authors reported to be uncertain whether the effect size selected to calculate sample size was appropriate to detect a change in LM.

Resistance and aerobic exercise are both recommended in the PCa survivorship guidelines [28]. Therefore, it is important to understand how patients respond to each exercise mode. Alberga et al. [32] and Santa Mina et al. [33,34] compared aerobic and resistance exercise (Table 2). Alberga et al. [32] utilised clinic-based periodised resistance training conducted over 24 weeks and reported preservation of BF% and LM, which was significantly different to usual care controls who gained BF% and lost LM. The 2 kg LM loss in the aerobic group although not statistically different to the 0.3 kg loss in the resistance group, is of clinical relevance and highlights the importance of resistance training in preserving LM. Santa Mina et al. [33,34] examined home-based resistance exercise utilising bands, balls, and body weight exercises, and reported no training effect [33,34]. From this work, it appears that resistance training alone is insufficient to induce FM loss. However, it may prevent further ADT-induced body composition changes and specifically alleviate loss of LM.

2.3. Multi-Modal Interventions

The inclusion of multiple exercise modes is important when the intention is to alter both FM and LM. In this section, we evaluate seven studies utilising multi-modal interventions and the effect on FM and LM.

Several authors examined similar cohorts without bone metastases and compared combined aerobic and resistance exercise interventions to usual care controls (Table 2). Galvão et al. [40] reported significant between-group differences in whole-body LM and ASM, but no change in FM over 12 weeks. Cormie et al. [41] found significant between-group differences for whole-body and trunk FM, BF%, and ASM over the 12-week intervention. The intervention group demonstrated a significant within-group loss of visceral FM, while the control group significantly lost LM, ASM, and gained whole-body FM and BF%. Wall et al. [43] reported significant between-group differences for whole-body FM and LM, trunk FM, and BF% but conducted a longer intervention of six months. Ndjavera et al. [44] reported no body composition changes over their 12-week intervention. Cormie et al. [41],

Wall et al. [43], and Ndjavera et al. [44] reported greater adjusted group mean differences for FM (−1.4, −1.1, and −1.9 kg, respectively) than Galvão et al. [40] (−0.01 kg), which could be explained by the larger volume of aerobic exercise prescribed in these studies.

Galvão et al. [15] was a secondary analysis of the previously described Galvão et al. [40] study and they compared different durations of ADT: chronic ≥ 6 months, and acute < 6 months, completing the same intervention (Table 2). The authors reported a significant between-group difference in FM with those on chronic ADT experiencing a 0.4 kg loss compared to a 0.6 kg gain in the acute ADT group over 12 weeks. Furthermore, triglyceride concentrations were significantly different between groups, which was associated with the observed changes in FM. Despite these significant findings it resulted in an uneven distribution between acute (n = 16) and chronic (n = 34) ADT-treated patients due to the use of a delayed exercise control group. The smaller number in the acute group may have limited the ability to observe differences between groups. Regardless, it is important to note that body composition declines are greater during the initial 3–6 months of ADT commencement and appear more difficult to ameliorate with exercise therapy.

Aerobic and resistance-based exercise are the most commonly prescribed modes; however, both Newton et al. [36] and Winters-Stone et al. [42] examined the combined effect of impact training, e.g., bounding movements, and resistance training (Table 2). Newton et al. [36] reported that the combined impact/resistance group significantly improved ASM compared to the usual care controls at 6 months. However, no effect on ASM was noted after the same resistance training was undertaken by the aerobic/resistance group. The authors described a potential interference effect when combining aerobic and resistance training within the same session, which may have compromised muscle hypertrophy [49]. Winters-Stone et al. [42] reported that FM was significantly decreased in the impact/resistance group compared to a flexibility control group who continued to gain FM. Additionally, in line with the Santa Mina et al. [34] findings, Winters-Stone et al. [42] reported that the changes in FM mediated differences in insulin, suggesting FM loss induced an insulin-lowering effect.

3. Using Nutrition to Decrease Fat Mass and Preserve or Gain Lean Mass

3.1. Healthy Eating Guidelines and/or Energy Deficit

Healthy eating guidelines are recommended portions of each food group to be consumed daily [50]. Weight loss in its simplest form is achieved through greater energy expenditure over intake creating a daily energy deficit (Figure 2) [51]. Clinical practice guidelines recommend prostate cancer patients to consume a healthy balanced diet high in fruit and vegetables, low in saturated fat, and consume adequate amounts of vitamin D (>600 IU) and calcium (<1200 mg/d), with an energy deficit if weight loss is required (Table 1) [28]. In this section, we review six studies in which healthy eating guidelines and/or an energy deficit were implemented and the effect on FM and LM evaluated.

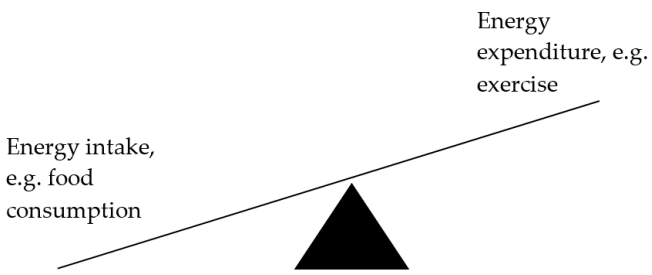


Figure 2. Weight loss occurs when energy expenditure is greater than energy intake.

Gilbert et al. [52] and Focht et al. [53] prescribed combined aerobic and resistance-based exercise and conducted small group healthy eating seminars over a 12-week period (Table 3). Gilbert et al. [52] reported a significant difference in LM but no change in FM compared to usual care controls. However, the intervention group reduced their mean

FM from 34.5 to 31.6 kg compared to 30.4 to 29.0 kg in the control group. Although the 2.9 kg FM loss for the intervention group is potentially clinically meaningful, no within-group changes were reported. Focht et al. [53] additionally included group-mediated behaviour modification seminars based on social cognitive theory. Compared to usual care controls, the intervention group significantly lost FM and BF%, with no change in LM. Although the exercise and nutrition sessions were well adhered to, only a small subset of the patients provided 3 day weighed food records and, therefore, overall nutritional intake and compliance to nutrition advice were not confirmed. Further, 80% of patients in the intervention group were overweight or obese and prescribed an energy deficit diet. Therefore, the contribution of healthy eating guidelines versus an energy deficit diet to promote FM and LM changes is unclear.

Table 3. Studies incorporating a nutrition component and assessed fat and lean mass in prostate cancer patients receiving ADT.

Study	Study Design	Primary Outcome	Intervention	Body Composition Assessment	Groups (*N*)	Outcome Variable	Mean Pre-Intervention Values (kg)	Mean Post-Intervention Values (kg)
Healthy eating guidelines and/or energy deficit								
O'Neill et al. [54]	RCT	Fat mass	6 months ≥5 ×/week 150 min/week Home-based brisk walking UK healthy eating guidelines + energy deficit diet if overweight.	Skinfolds	Intervention (*N* = 47)	Fat mass Lean mass BF%	28.8 58.3 32.6%	26.9 § 59.8 30.8% §
					Control (*N* = 47)	Fat mass Lean mass BF%	29.5 59.8 32.4%	30.1 59.1 32.8%
Gilbert et al. [52]	RCT	Brachial artery flow mediated dilatation	12 weeks 180 min/week 2 ×/week (1–6 weeks) 1 ×/week (7–12 weeks) Supervised aerobic at 55–75% HRmax + resistance exercise at 60% 1 RM 1 ×/week (1–6 weeks) 2 ×/week (7–12 weeks) Home-based exercise of choice Fortnightly healthy eating seminars	BIA	Intervention (*N* = 25)	Fat mass Skeletal muscle mass	34.5 31.9	31.6 32.9 §
					Usual care (*N* = 25)	Fat mass Skeletal muscle mass	30.4 31.2	29.6 32.3
Focht et al. [53]	RCT	Mobility	12 weeks 150 min/week 2 ×/week (1–6 weeks) 1 ×/week (7–8 weeks) Supervised aerobic 3–4 RPE (1–10 scale) + resistance 8–12 RM, 3 sets 1 ×/week (7–8 weeks) 2 ×/week (9–12 weeks) Unsupervised aerobic + resistance Home-based exercise of choice Nutrition counselling sessions—8 as a group and 2 individual phone calls + energy deficit diet if overweight.	Bod Pod	Intervention (*N* = 16)	Fat mass [b] Fat-free mass [b] BF% [b]	−1.8 § −0.06 −1.05% §	
					Usual care (*N* = 16)	Fat mass [b] Fat-free mass [b] BF% [b]	0.9 −0.5 0.82%	
Freedland et al. [55]	RCT	Insulin resistance	6 months ≥5 d/week 150 min/week Home-based walking Carbohydrate intake ≤ 20 g/day	DXA	Intervention (*N* = 11)	Fat mass Lean mass BF%	32.3 61.0 28.3%	24.0 § 58.9 § 26.6% §
					Control (*N* = 18)	Fat mass Lean mass BF%	25.3 55.9 30.5%	28.3 55.4 32.3%
Baguley et al. [56]	RCT	Cancer-related fatigue and quality of life	12 weeks Individualised consultation with dietician every 2 weeks Mediterranean-style diet	DXA	Intervention (*N* = 12)	Fat mass Lean mass	29.5 53.2	27.8 * 52.0
					Usual care (*N* = 11)	Fat mass Lean mass	29.8 53.4	29.3 53.4

Table 3. *Cont.*

Study	Study Design	Primary Outcome	Intervention	Body Composition Assessment	Groups (*N*)	Outcome Variable	Mean Pre-Intervention Values (kg)	Mean Post-Intervention Values (kg)
Wilson et al. [57]	Prospective cohort	Fat mass	12 weeks 3 ×/week 300 min/week Supervised resistance exercise at 6–12 RM, 2–4 sets Daily home-based aerobic exercise, RPE 3–8 (1–10 scale) 3 nutrition counselling sessions Calorie deficit diet 40 g protein powder after each supervised exercise session	DXA	Intervention (*N* = 14)	Fat mass	39.8	37.0 *
						Trunk fat	20.1	18.3 *
						Visceral fat	954 g	866 g *
						Lean mass	55.9	55.9
						ASM	23.3	23.3
						BF%	40.0%	38.3% *
Protein intake								
Dawson et al. [58]	RCT	Lean mass	12 weeks 3 ×/week 150 min/week Supervised resistance exercise at 60–83% 1 RM 2 × 25 g protein powder per day	DXA	Exercise (*N* = 8) + Exercise/protein (*N* = 8)	Fat mass	30.3	31.2
						Lean mass	48.5	53.2 §
						Fat-free mass	54.6	56.4 §
						ASM	23.5	24.8 §
						BF%	36.8%	35.9% §
					Protein (*N* = 10) + Flexibility control (*N* = 11) [a]	Fat mass	25.6	26.2
						Lean mass	51.5	48.6
						Fat-free mass	51.4	51.5
						ASM	21.5	21.6
						BF%	33.9%	34.5%

* = Significant within group change; § = significant between-group change. [a] Patients were randomised to 4 groups: exercise, protein and exercise, protein, usual care control; however, for the analysis the two exercising groups and two non-exercising groups were combined as protein had no effect; [b] only reported mean change. RCT = randomised controlled trial; ×/week = times per week; RM = repetition maximum; DXA = dual x-ray absorptiometry; RPE = rate of perceived exertion; BF% = body fat percent; HRmax = maximum heart rate; BIA = bioimpedance analysis; UK = United Kingdom.

O'Neill et al. [54] prescribed a 6-month home-based walking program, with a dietary booklet encouraging healthy eating habits to patients of all cancer stages (T1–4), although metastatic status was not reported (Table 3). The authors reported a significant reduction in FM and BF%, with no change in LM when compared to usual care controls. While they showed that a home-based intervention can reduce FM, body composition was measured using the less precise technique of skinfold measurement. Similarly, to Focht et al. [53], O'Neill et al. [54] encouraged an energy deficit diet only for patients who were overweight or obese.

Freedland et al. [55] and Wilson et al. [57] targeted overweight or obese patients who did not have symptomatic or bone metastases, respectively (Table 3). Freedland et al. [55] prescribed home-based walking and a low carbohydrate diet over 6 months. Compared to an 11% increase in FM for the usual care controls, the intervention group significantly lost 16.2%. This substantial loss in FM has not been previously achieved in PCa patients on ADT. However, the intervention group also had a significant decline in LM compared to controls. A loss in LM is not uncommon while undergoing weight loss [46], with similar patterns also noted by Baguley et al. [56] in their 12-week nutrition-only intervention (Table 3). Wilson et al. [57] also demonstrated a significant reduction in FM but in contrast, achieved LM preservation. Wilson et al. [57] included supervised resistance training and protein supplementation, which are both considered important for LM preservation [59]. While the intervention designs are different, these studies provide preliminary evidence on the potential for effective FM and LM management for obese ADT-treated PCa patients through diet and exercise, which includes resistance training.

3.2. Protein Intake

The optimisation of protein intake is often incorporated into weight loss nutrition plans to assist the body to mobilise fat and preserve muscle tissue by supporting the upregulation of muscle protein synthesis [59]. Next, we describe a study examining protein supplementation and resistance exercise.

Dawson et al. [58] examined four groups of patients with PCa, including those with metastatic disease (54.3%), over a 12-week period: exercise-only, exercise and protein supplement, protein supplement-only, and usual care control (Table 3). No additional effect was found for protein supplementation and as the study was not powered to detect changes using a four-armed design, results were reported for exercise versus non-exercise groups. In the exercise groups there was a significant increase in LM, ASM, and fat-free mass, a significant reduction in BF%, with no changes in FM. The lack of a synergistic effect of protein supplementation could be attributed to the low adherence of the protein-only group who consumed 1.0 g/kg/day compared to 1.1–1.4 g/kg/dayin the other three groups. Further, the protein supplements were given as 2 × 25 g daily doses. This may not have been sufficient to stimulate muscle protein synthesis as each dose was equivalent to ~0.3 g protein/kg body weight/day, compared to the ~0.4 g protein/kg body weight/daywhich has been shown to be effective in increasing muscle protein synthesis when combined with an acute bout of resistance exercise in ADT-treated PCa patients [59].

4. Discussion

The field of exercise oncology has rapidly developed over the last two decades and we have presented 22 exercise and nutrition interventions conducted in ADT-treated PCa patients between 2006 and 2020. Despite this growth in awareness of the benefits that can be derived from undertaking these practices, most of the studies report only modest changes in FM and LM. In this discussion, we summarise the key conclusions from these studies and propose future research directions to progress the field.

The American Cancer Society weight loss guidelines for PCa patients are no different to that of the general population (Table 1) [28]. Notably, Wilson et al. [57] was the only study to incorporate these guidelines, which are recommended in clinical practice but have not been verified in the ADT-treated population. Although these guidelines have the potential to provide successful body composition changes, the metabolic changes induced by ADT likely require different strategies to induce change compared to the non-ADT population, as alluded to by the results of Alberga et al. [32], although the ADT and non-ADT cohorts were not compared. In this regard, we provide an important initial platform to help identify how these guidelines may be tailored to suit hypogonadal men. Potential questions that would lead to further understanding of how to tailor these weight loss guidelines for ADT-treated patients to maximise FM and LM changes are presented in Table 4.

With body composition changes occurring early in the treatment process [60], it would be preferable to implement an exercise and nutrition intervention at initiation of ADT. However, the magnitude of intervention-induced body composition changes could depend on length of time on ADT, as demonstrated by Galvão et al. [15], where those initiating ADT may experience small or no intervention-induced changes compared to those on chronic ADT. Similarly, Hvid et al. [29] highlighted a patient on ADT for <6 months who did not respond to the exercise intervention and gained 2.6 kg of FM accompanied by a loss in LM of 5.0 kg. Ndjavera et al. [44] also reported no training effect on body composition within the first 3 months of ADT. However, each of these studies were exercise only and it has been established that manipulation of nutrition substantially decreases FM more than exercise alone [61]. Therefore, those initiating ADT may only experience substantial FM loss when nutrition is also addressed, as was demonstrated by Freedland et al. [55]. Regardless of the influence of length of time on ADT on body composition changes, exercise and nutrition should still be recommended from therapy onset as there will be additional health benefits and likely prevention of substantial FM and LM changes, as demonstrated by Cormie et al. [41].

Table 4. Potential questions for future research relating to the prescription of exercise and nutrition for prostate cancer patients receiving ADT aiming to lose fat mass and gain lean mass.

	Unanswered Questions for Prostate Cancer Patients on ADT Aiming to Induce Fat Loss and Muscle Gain.
 Aerobic training	1. Will a low-intensity lead-in period designed to build baseline fitness reduce injury risk and improve adherence, particularly for high-risk patients? 2. Is there a minimum intensity/volume for lipolysis and muscle protein synthesis stimulation?
 Resistance training	1. Will a low-intensity familiarisation period designed to build baseline strength reduce injury risk and improve adherence, particularly for high-risk patients? 2. Is there a minimum intensity/volume for muscle protein synthesis stimulation?
 Nutritional intake	1. Who is an energy deficit or healthy eating guideline diet most appropriate for? 2. What is the optimum protein intake to enhance muscle protein synthesis leading to muscle gain?
Other questions inclusive of all elements	1. Are the benefits gained from a combined exercise and nutrition intervention influenced by length of time on ADT? 2. What is a clinically significant change in fat and lean mass for prostate cancer patients on ADT?

Images created with BioRender.com (accessed on 5 April 2021).

Studies utilising a multi-modal intervention compared to a single-exercise mode showed more consistent beneficial responses in both FM and LM. However, the majority of the multi-modal studies were conducted by the same research group [15,36,40,41,43,57] and, therefore, may not represent the wider PCa population. Capitalising on the unique benefits gained from utilising multiple exercise modes can induce concurrent desired adaptations of FM and LM. However, there is uncertainty of best practice regarding exercise prescription to induce concurrent FM loss and LM preservation or gain. While high-intensity [29,35,38] and high-volume [54,55,57] exercise resulted in the greatest changes in FM or LM, they may not initially be suitable for obese patients who have multiple comorbidities without undergoing a lead-in phase to improve baseline fitness. Moreover, the impact of such interventions on patients with metastatic disease is unclear with only two studies actively recruiting patients of this disease stage [35,58]. Further research is required into the benefits of high-intensity or interval-based interventions, such as high-intensity interval training or team/individual sports, for ADT-treated PCa patients. There may also be a minimum-intensity threshold that stimulates lipolysis and muscle protein synthesis, as demonstrated by Alberga et al. [32], where patients undertaking aerobic exercise continued to gain BF% and lose LM. Furthermore, the use of multiple modes within the same session, as noted by Newton et al. [36], may have an interference effect where physiological pathways involved in manipulating body composition are not stimulated compared to when a single-exercise mode is undertaken.

While bone measurements are not reported in the current review, it is important to highlight that in addition to FM gain and LM loss patients receiving ADT may also experience a loss of bone mass placing them at increased risk of osteopenia or osteoporosis [5]. Newton et al. [36] assessed bone health as their primary outcome and reported preliminary efficacy for the inclusion of impact training in a multi-modal intervention to prevent ADT-induced bone loss. Patients at increased risk of bone loss may also benefit

from increased calcium and vitamin D intake, which are included as part of the exercise and nutrition guidelines for prostate cancer patients [28].

The number of interventions measuring body composition that encompassed a nutrition component were less common than those investigating exercise. The employment of an energy deficit was effective at reducing FM as shown in both the O'Neill et al. [54] and Freedland et al. [55] studies. However, preventing LM loss when the body enters a catabolic state requires further clarity. Protein optimisation and the inclusion of resistance training may be important components to promote LM preservation or gain when undergoing weight loss as suggested by Wilson et al. [57] and Dawson et al. [58]. However, as protein supplementation is currently understudied in this population, it is not included in the PCa weight loss guidelines and needs further evaluation. Continued research into optimal diet and exercise prescriptions for prostate cancer patients may further improve the benefits of weight loss and the potential impact on a patient's prognosis with particular interest in diet and exercise modes that influence microbiome activity. Differences in composition of the gut microbiome have been reported in men with prostate cancer compared to men with benign prostatic conditions and could contribute to prostate cancer pathogenesis and progression [62].

As noted by Nilsen et al. [39], the definition of a clinically significant change in FM and LM needs to be established. A 5% loss of body weight, which should be predominantly FM loss [63], has been shown in the non-cancer population to improve blood pressure, cholesterol, and insulin resistance [64]. While this percentage is also used for cancer patients, the significance is unknown. For example, increases in trunk, visceral, and intermuscular FM are associated with increased insulin resistance, a potential mechanism for the observed association between FM and PCa progression [65,66]. Therefore, a loss of FM in these regional areas, independent of whole-body FM loss, may be more beneficial for PCa patients on ADT than a 5% loss in total body mass [29,63]. Further, it is unknown whether a loss in FM will improve a PCa patient's risk of disease progression, treatment-related side effects, or comorbidity development. Both Santa Mina et al. [34] and Winters-Stone et al. [42] demonstrated that weight or FM loss was associated with improvements in biomarkers related to cancer progression, which has also been demonstrated in non-ADT PCa patients [67]. Moreover, Galvão et al. [15] reported that a decrease in FM was associated with decreased serum triglyceride levels. These studies provide preliminary evidence that FM loss could improve patient outcomes.

5. Conclusions

Fat mass gain and LM loss are side effects of ADT that might be prevented or reversed with the implementation of an exercise and nutrition intervention. Patients on ADT, particularly those who are obese, require effective strategies to improve their body composition, which in turn may improve general health and cancer-free survival. The implementation of such strategies will be most successful through the effective communication of a multi-disciplinary team including, but not limited to, oncologists, urologists, dietitians, and exercise physiologists. The inclusion of a multi-modal exercise program is needed to stimulate both lipolysis and muscle protein synthesis to ensure FM loss and LM preservation. While exercise should be tailored to the preferences and fitness level of the patient, when FM loss is the objective, energy expenditure should be maximised, which is best achieved through higher volume and intensity with the inclusion of an energy deficit diet. The optimal macronutrient composition of a diet for PCa patients on ADT is unclear but should ultimately follow healthy eating guidelines and optimise protein intake.

Author Contributions: R.L.W. was responsible for designing the narrative review protocol, conducting the search, screening potentially eligible studies for discussion, interpreting results, and writing the manuscript. D.R.T., R.U.N., N.H.H., P.L.-W. and D.A.G. contributed to the conception and design of the work and provided study selection and manuscript feedback as well as approval of the final version. All authors have read and agreed to the published version of the manuscript.

Funding: The APC was funded by Edith Cowan University.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: R.L.W. is supported by a scholarship from Edith Cowan University.

Conflicts of Interest: The authors declare that they have no conflict of interest.

References

1. Rhee, H.; Gunter, J.H.; Heathcote, P.; Ho, K.; Stricker, P.; Corcoran, N.M.; Nelson, C.C. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. *BJU Int.* **2014**, *115*, 3–13. [CrossRef]
2. Labrie, F.; Dupont, A.; Bélanger, A.; St-Arnaud, R.; Giguère, M.; Lacourcière, Y.; Emond, J.; Monfette, G. Treatment of prostate cancer with gonadotropin-releasing hormone agonists. *Endocr. Rev.* **1986**, *7*, 67–74. [CrossRef]
3. Herbst, K.L.; Bhasin, S. Testosterone action on skeletal muscle. *Curr. Opin. Clin. Nutr. Metab. Care* **2004**, *7*, 271–277. [CrossRef]
4. Saad, F.; Aversa, A.; Isidori, A.M.; Gooren, L.J. Testosterone as potential effective therapy in treatment of obesity in men with testosterone deficiency: A review. *Curr. Diabetes Rev.* **2012**, *8*, 131–143. [CrossRef] [PubMed]
5. Galvão, D.A.; Spry, N.A.; Taaffe, D.R.; Newton, R.U.; Stanley, J.; A Shannon, T.; Rowling, C.; Prince, R.L. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int.* **2008**, *102*, 44–47. [CrossRef] [PubMed]
6. Galvao, D.; Taaffe, D.; Spry, N.; Joseph, D.; Turner, D.; Newton, R. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: A comprehensive cross-sectional investigation. *Prostate Cancer Prostatic Dis.* **2008**, *12*, 198–203. [CrossRef]
7. Keating, N.L.; O'Malley, A.J.; Freedland, S.J.; Smith, M.R. Diabetes and cardiovascular disease during androgen deprivation therapy: Observational study of veterans with prostate cancer. *J. Natl. Cancer Inst.* **2009**, *102*, 39–46. [CrossRef]
8. Cao, Y.; Ma, J. Body Mass Index, Prostate Cancer–Specific Mortality, and Biochemical Recurrence: A Systematic Review and Meta-analysis. *Cancer Prev. Res.* **2011**, *4*, 486–501. [CrossRef]
9. Joshu, C.E.; Mondul, A.M.; Menke, A.; Meinhold, C.; Han, M.; Humphreys, E.B.; Freedland, S.J.; Walsh, P.C.; Platz, E.A. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the psa era. *Cancer Prev. Res.* **2011**, *4*, 544–551. [CrossRef] [PubMed]
10. World Cancer Research Fund. American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, Nutrition, Physical Activity and Prostate Cancer. Available online: https://www.wcrf.org/dietandcancer/prostate-cancer (accessed on 20 May 2020).
11. Rhee, H.; Vela, I.; Chung, E. Metabolic syndrome and prostate cancer: A review of complex interplay amongst various endocrine factors in the pathophysiology and progression of prostate cancer. *Horm. Cancer* **2015**, *7*, 75–83. [CrossRef]
12. Deng, T.; Lyon, C.J.; Bergin, S.; Caligiuri, M.A.; Hsueh, W.A. Obesity, inflammation, and cancer. *Annu. Rev. Pathol. Mech. Dis.* **2016**, *11*, 421–449. [CrossRef] [PubMed]
13. Troeschel, A.N.; Hartman, T.J.; Jacobs, E.J.; Stevens, V.L.; Gansler, T.; Flanders, W.D.; McCullough, L.E.; Wang, Y. Postdiagnosis body mass index, weight change, and mortality from prostate cancer, cardiovascular disease, and all causes among survivors of nonmetastatic prostate cancer. *J. Clin. Oncol.* **2020**, *38*, 2018–2027. [CrossRef]
14. Newton, R.U.; Jeffery, E.; Galvão, D.A.; Peddle-McIntyre, C.J.; Spry, N.; Joseph, D.; Denham, J.W.; Taaffe, D.R.; Denham, J. Body composition, fatigue and exercise in patients with prostate cancer undergoing androgen-deprivation therapy. *BJU Int.* **2018**, *122*, 986–993. [CrossRef]
15. Galvão, D.A.; Taaffe, D.R.; Spry, N.; Joseph, D.; Newton, R.U. Acute versus chronic exposure to androgen suppression for prostate cancer: Impact on the exercise response. *J. Urol.* **2011**, *186*, 1291–1297. [CrossRef] [PubMed]
16. Baumgartner, R.N. Body composition in healthy aging. *Ann. N. Y. Acad. Sci.* **2006**, *904*, 437–448. [CrossRef]
17. Cruz-Jentoft, A.J.; Baeyens, J.P.; Bauer, J.M.; Boirie, Y.; Cederholm, T.; Landi, F.; Martin, F.C.; Michel, J.-P.; Rolland, Y.; Schneider, S.M.; et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European working group on sarcopenia in older people. *Age Ageing* **2010**, *39*, 412–423. [CrossRef]
18. Hills, A.P.; Emokhtar, N.; Byrne, N.M. Assessment of physical activity and energy expenditure: An overview of objective measures. *Front. Nutr.* **2014**, *1*, 5. [CrossRef]
19. Dieli-Conwright, C.M.; Courneya, K.S.; Demark-Wahnefried, W.; Sami, N.; Lee, K.; Buchanan, T.A.; Spicer, D.V.; Tripathy, D.; Bernstein, L.; Mortimer, J.E. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: A randomized controlled trial. *J. Clin. Oncol.* **2018**, *36*, 875–883. [CrossRef]
20. Barnard, R.J.; Ngo, T.H.; Leung, P.-S.; Aronson, W.J.; Golding, L.A. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. *Prostate* **2003**, *56*, 201–206. [CrossRef] [PubMed]

21. Christiansen, T.; Paulsen, S.K.; Bruun, J.M.; Pedersen, S.B.; Richelsen, B. Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: A 12-week randomized intervention study. *Am. J. Physiol. Metab.* **2010**, *298*, E824–E831. [CrossRef]
22. Bourke, L.; Smith, D.; Steed, L.; Hooper, R.; Carter, A.; Catto, J.; Albertsen, P.C.; Tombal, B.; Payne, H.A.; Rosario, D.J. Exercise for men with prostate cancer: A systematic review and meta-analysis. *Eur. Urol.* **2016**, *69*, 693–703. [CrossRef]
23. Tsang, D.S.; Alibhai, S.M.H. Bone health care for patients with prostate cancer receiving androgen deprivation therapy. *Hosp. Pract.* **2014**, *42*, 89–102. [CrossRef]
24. Hackshaw-McGeagh, L.E.; Perry, R.E.; Leach, V.A.; Qandil, S.; Jeffreys, M.; Martin, R.M.; Lane, J.A. A systematic review of dietary, nutritional, and physical activity interventions for the prevention of prostate cancer progression and mortality. *Cancer Causes Control.* **2015**, *26*, 1521–1550. [CrossRef]
25. Barnes, K.A.; Ball, L.E.; Galvao, D.A.; Newton, R.U.; Chambers, S.K. Nutrition care guidelines for men with prostate cancer undergoing androgen deprivation therapy: Do we have enough evidence? *Prostate Cancer Prostatic Dis.* **2019**, *22*, 221–234. [CrossRef]
26. Falcone, P.H.; Tai, C.-Y.; Carson, L.R.; Joy, J.M.; Mosman, M.M.; McCann, T.R.; Crona, K.P.; Kim, M.P.; Moon, J.R. Caloric expenditure of aerobic, resistance, or combined high-intensity interval training using a hydraulic resistance system in healthy men. *J. Strength Cond. Res.* **2015**, *29*, 779–785. [CrossRef] [PubMed]
27. Collins, K.H.; Herzog, W.; Macdonald, G.Z.; Reimer, R.A.; Rios, J.L.; Smith, I.C.; Zernicke, R.F.; Hart, D.A. Obesity, metabolic syndrome, and musculoskeletal disease: Common inflammatory pathways suggest a central role for loss of muscle integrity. *Front. Physiol.* **2018**, *9*, 112. [CrossRef]
28. Skolarus, T.A.; Wolf, A.M.; Erb, N.L.; Brooks, D.D.; Rivers, B.M.; Underwood, W.; Salner, A.L.; Zelefsky, M.J.; Aragon-Ching, J.B.; Slovin, S.F.; et al. American Cancer Society prostate cancer survivorship care guidelines. *CA Cancer J. Clin.* **2014**, *64*, 225–249. [CrossRef]
29. Hvid, T.; Winding, K.; Rinnov, A.; Dejgaard, T.; Thomsen, C.; Iversen, P.; Brasso, K.; Mikines, K.J.; Van Hall, G.; Lindegaard, B.; et al. Endurance training improves insulin sensitivity and body composition in prostate cancer patients treated with androgen deprivation therapy. *Endocr. Relat. Cancer* **2013**, *20*, 621–632. [CrossRef] [PubMed]
30. Cheung, A.S.; Hoermann, R.; Dupuis, P.; Joon, D.L.; Zajac, J.D.; Grossmann, M. Relationships between insulin resistance and frailty with body composition and testosterone in men undergoing androgen deprivation therapy for prostate cancer. *Eur. J. Endocrinol.* **2016**, *175*, 229–237. [CrossRef]
31. Chang, D.; Joseph, D.J.; Ebert, M.A.; Galvão, D.A.; Taaffe, D.R.; Denham, J.W.; Newton, R.U.; Spry, N.A. Effect of androgen deprivation therapy on muscle attenuation in men with prostate cancer. *J. Med. Imaging Radiat. Oncol.* **2013**, *58*, 223–228. [CrossRef]
32. Alberga, A.S.; Segal, R.J.; Reid, R.D.; Scott, C.G.; Sigal, R.J.; Khandwala, F.; Jaffey, J.; Wells, G.A.; Kenny, G.P. Age and androgen-deprivation therapy on exercise outcomes in men with prostate cancer. *Support. Care Cancer* **2012**, *20*, 971–981. [CrossRef] [PubMed]
33. Mina, D.S.; Alibhai, S.M.; Matthew, A.G.; Guglietti, C.L.; Pirbaglou, M.; Trachtenberg, J.; Ritvo, P.; Alibhai, S.M. A randomized trial of aerobic versus resistance exercise in prostate cancer survivors. *J. Aging Phys. Act.* **2013**, *21*, 455–478. [CrossRef] [PubMed]
34. Mina, D.S.; Connor, M.K.; Alibhai, S.M.; Toren, P.; Guglietti, C.; Matthew, A.G.; Trachtenberg, J.; Ritvo, P. Exercise effects on adipokines and the IGF axis in men with prostate cancer treated with androgen deprivation: A randomized study. *Can. Urol. Assoc. J.* **2013**, *7*, 692–698. [CrossRef] [PubMed]
35. Uth, J.; Hornstrup, T.; Schmidt, J.F.; Christensen, J.F.; Frandsen, C.; Christensen, K.B.; Helge, E.W.; Brasso, K.; Rørth, M.; Midtgaard, J.; et al. Football training improves lean body mass in men with prostate cancer undergoing androgen deprivation therapy. *Scand. J. Med. Sci. Sports* **2014**, *24* (Suppl. S1), 105–112. [CrossRef]
36. Newton, R.U.; Galvão, D.A.; Spry, N.; Joseph, D.; Chambers, S.K.; Gardiner, R.A.; Wall, B.A.; Bolam, K.A.; Taaffe, D.R. Exercise mode specificity for preserving spine and hip BMD in prostate cancer patients. *Med. Sci. Sports Exerc.* **2018**, *51*, 607–614. [CrossRef]
37. Galvão, D.A.; Nosaka, K.; Taaffe, D.R.; Spry, N.; Kristjanson, L.J.; Mcguigan, M.R.; Suzuki, K.; Yamaya, K.; Newton, R.U. Resistance training and reduction of treatment side effects in prostate cancer patients. *Med. Sci. Sports Exerc.* **2006**, *38*, 2045–2052. [CrossRef]
38. Hanson, E.D.; Sheaff, A.K.; Sood, S.; Ma, L.; Francis, J.D.; Goldberg, A.P.; Hurley, B.F. Strength training induces muscle hypertrophy and functional gains in black prostate cancer patients despite androgen deprivation therapy. *J. Gerontol. Ser. A Boil. Sci. Med. Sci.* **2012**, *68*, 490–498. [CrossRef]
39. Nilsen, T.S.; Raastad, T.; Skovlund, E.; Courneya, K.S.; Langberg, C.W.; Lilleby, W.; Fosså, S.D.; Thorsen, L. Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. *Acta Oncol.* **2015**, *54*, 1805–1813. [CrossRef]
40. Galvão, D.A.; Taaffe, D.R.; Spry, N.; Joseph, D.; Newton, R.U. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: A randomized controlled trial. *J. Clin. Oncol.* **2010**, *28*, 340–347. [CrossRef]

41. Cormie, P.; Galvão, D.A.; Spry, N.; Joseph, D.; Chee, R.; Taaffe, D.R.; Chambers, S.K.; Newton, R.U. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: A randomised controlled trial. *BJU Int.* **2015**, *115*, 256–266. [CrossRef]
42. Winters-Stone, K.M.; Dieckmann, N.F.; Maddalozzo, G.F.; Bennett, J.A.; Ryan, C.W.; Beer, T.M. Resistance exercise reduces body fat and insulin during androgen-deprivation therapy for prostate cancer. *Oncol. Nurs. Forum* **2015**, *42*, 348–356. [CrossRef] [PubMed]
43. Wall, B.; Galvao, D.; Fatehee, N.; Taaffe, D.; Spry, N.; Joseph, D.; Hebert, J.; Newton, R. Exercise improves VO2max and body composition in ADT-treated prostate cancer patients. *Med. Sci. Sports Exerc.* **2017**, *49*, 333–334. [CrossRef]
44. Ndjavera, W.; Orange, S.T.; O'Doherty, A.F.; Leicht, A.S.; Rochester, M.; Mills, R.; Saxton, J.M. Exercise-induced attenuation of treatment side-effects in patients with newly diagnosed prostate cancer beginning androgen-deprivation therapy: A randomised controlled trial. *BJU Int.* **2020**, *125*, 28–37. [CrossRef]
45. Allott, E.H.; Masko, E.M.; Freedland, S.J. Obesity and prostate cancer: Weighing the evidence. *Eur. Urol.* **2013**, *63*, 800–809. [CrossRef]
46. Weinheimer, E.M.; Sands, L.P.; Campbell, W.W. A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: Implications for sarcopenic obesity. *Nutr. Rev.* **2010**, *68*, 375–388. [CrossRef]
47. Batsis, J.A.; Gill, L.E.; Bs, R.K.M.; Adachi-Mejia, A.M.; Blunt, H.B.; Bagley, P.J.; Lopez-Jimenez, F.; Bartels, S.J. Weight loss interventions in older adults with obesity: A systematic review of randomized controlled trials since 2005. *J. Am. Geriatr. Soc.* **2017**, *65*, 257–268. [CrossRef]
48. Lam, T.; Birzniece, V.; McLean, M.; Gurney, H.; Hayden, A.; Cheema, B.S. The adverse effects of androgen deprivation therapy in prostate cancer and the benefits and potential anti-oncogenic mechanisms of progressive resistance training. *Sports Med. Open* **2020**, *6*, 13–14. [CrossRef] [PubMed]
49. Wilson, J.M.; Marin, P.J.; Rhea, M.R.; Wilson, S.M.; Loenneke, J.P.; Anderson, J.C. Concurrent training. *J. Strength Cond. Res.* **2012**, *26*, 2293–2307. [CrossRef]
50. National Health Medical Research Council. *Australian Dietary Guidelines*; National Health and Medical Research Council: Canberra, Australia, 2013.
51. Gibson, A.L.; Wagner, D.; Heyward, V. *Advanced Fitness Assessment and Exercise Prescription*, 8th ed.; Human Kinetics: Champaign, IL, USA, 2018.
52. Gilbert, S.E.; Tew, G.A.; Fairhurst, C.; Bourke, L.; Saxton, J.M.; Winter, E.M.; Rosario, D.J. Effects of a lifestyle intervention on endothelial function in men on long-term androgen deprivation therapy for prostate cancer. *Br. J. Cancer* **2016**, *114*, 401–408. [CrossRef]
53. Focht, B.C.; Lucas, A.R.; Grainger, E.; Simpson, C.; Fairman, C.M.; Thomas-Ahner, J.M.; Buell, J.; Monk, J.P.; Mortazavi, A.; Clinton, S.K. Effects of a group-mediated exercise and dietary intervention in the treatment of prostate cancer patients undergoing androgen deprivation therapy: Results from the IDEA-P trial. *Ann. Behav. Med.* **2018**, *52*, 412–428. [CrossRef]
54. O'Neill, R.F.; Haseen, F.; Murray, L.J.; O'Sullivan, J.M.; Cantwell, M.M. 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**, *9*, 431–440. [CrossRef] [PubMed]
55. Freedland, S.J.; Howard, L.; Allen, J.; Smith, J.; Stout, J.; Aronson, W.; Inman, B.A.; Armstrong, A.J.; George, D.; Westman, E.; et al. A lifestyle intervention of weight loss via a low-carbohydrate diet plus walking to reduce metabolic disturbances caused by androgen deprivation therapy among prostate cancer patients: Carbohydrate and prostate study 1 (CAPS1) randomized controlled trial. *Prostate Cancer Prostatic Dis.* **2019**, *22*, 428–437. [CrossRef] [PubMed]
56. Baguley, B.J.; Skinner, T.L.; Jenkins, D.G.; Wright, O.R. Mediterranean-style dietary pattern improves cancer-related fatigue and quality of life in men with prostate cancer treated with androgen deprivation therapy: A pilot randomised control trial. *Clin. Nutr.* **2021**, *40*, 245–254. [CrossRef] [PubMed]
57. Wilson, R.L.; Newton, R.U.; Taaffe, D.R.; Hart, N.H.; Lyons-Wall, P.; Galvão, D.A. Weight loss for obese prostate cancer patients on androgen deprivation therapy. *Med. Sci. Sports Exerc.* **2020**, *53*, 470–478. [CrossRef] [PubMed]
58. Dawson, J.K.; Dorff, T.B.; Schroeder, E.T.; Lane, C.J.; Gross, M.E.; Dieli-Conwright, C.M. Impact of resistance training on body composition and metabolic syndrome variables during androgen deprivation therapy for prostate cancer: A pilot randomized controlled trial. *BMC Cancer* **2018**, *18*, 368. [CrossRef] [PubMed]
59. Hanson, E.D.; Nelson, A.R.; West, D.W.D.; Violet, J.A.; O'Keefe, L.; Phillips, S.M.; Hayes, A. Attenuation of resting but not load-mediated protein synthesis in prostate cancer patients on androgen deprivation. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 1076–1083. [CrossRef]
60. Smith, J.C.; Bennett, S.; Evans, L.M.; Kynaston, H.G.; Parmar, M.; Mason, M.D.; Cockcroft, J.R.; Scanlon, M.F.; Davies, J.S. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 4261–4267. [CrossRef]
61. Mohamad, H.; McNeill, G.; Haseen, F.; N'Dow, J.; Craig, L.C.A.; Heys, S.D. The effect of dietary and exercise interventions on body weight in prostate cancer patients: A systematic review. *Nutr. Cancer* **2015**, *67*, 43–60. [CrossRef]

62. Golombos, D.M.; Ayangbesan, A.; O'Malley, P.; Lewicki, P.; Barlow, L.; Barbieri, C.E.; Chan, C.; DuLong, C.; Abu-Ali, G.; Huttenhower, C.; et al. The role of gut microbiome in the pathogenesis of prostate cancer: A prospective, pilot study. *Urology* **2018**, *111*, 122–128. [CrossRef]
63. Verheggen, R.J.H.M.; Maessen, M.F.H.; Green, D.J.; Hermus, A.R.M.M.; Hopman, M.T.E.; Thijssen, D.H.T. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: Distinct effects on body weight and visceral adipose tissue. *Obes. Rev.* **2016**, *17*, 664–690. [CrossRef]
64. Alamuddin, N.; Bakizada, Z.; Wadden, T.A. Management of obesity. *J. Clin. Oncol.* **2016**, *34*, 4295–4305. [CrossRef] [PubMed]
65. Ferro, M.; Terracciano, D.; Buonerba, C.; Lucarelli, G.; Bottero, D.; Perdonà, S.; Autorino, R.; Serino, A.; Cantiello, F.; Damiano, R.; et al. The emerging role of obesity, diet and lipid metabolism in prostate cancer. *Futur. Oncol.* **2017**, *13*, 285–293. [CrossRef] [PubMed]
66. Foulkes, S.J.; Daly, R.M.; Fraser, S.F. The clinical importance of quantifying body fat distribution during androgen deprivation therapy for prostate cancer. *Endocr. Relat. Cancer* **2017**, *24*, R35–R48. [CrossRef]
67. Henning, S.M.; Galet, C.; Gollapudi, K.; Byrd, J.B.; Liang, P.; Li, Z.; Grogan, T.; Elashoff, D.; Magyar, C.E.; Said, J.; et al. Phase II prospective randomized trial of weight loss prior to radical prostatectomy. *Prostate Cancer Prostatic Dis.* **2017**, *21*, 212–220. [CrossRef] [PubMed]

CHAPTER FOUR

Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer

This chapter has been published as:
Wilson, R. L., Shannon, T., Calton, E., Galvão, D. A., Taaffe, D. R., Hart, N. H., ... & Newton, R. U. (2020). Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer. *Surgical Oncology, 35*, 182 - 188. *https://doi.org/10.1016/j.suronc.2020.08.006.*

Chapter 4 of this thesis has been published by Elsevier as the below article:

Wilson, R. L., Shannon, T., Calton, E., Galvão, D. A., Taaffe, D. R., Hart, N. H., . . . Newton, R. U. (2020). Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer. *Surgical Oncology, 35*, 182-188.

https://doi.org/10.1016/j.suronc.2020.08.006

Surgical Oncology 35 (2020) 182–188

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: http://www.elsevier.com/locate/suronc

Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer

Rebekah L. Wilson [a,b], Tom Shannon [c,d], Emily Calton [e], Daniel A. Galvão [a,b], Dennis R. Taaffe [a,b,f], Nicolas H. Hart [a,b,g], Philippa Lyons-Wall [b], Robert U. Newton [a,b,f,*]

[a] Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia
[b] School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia
[c] The Prostate Clinic, Perth, WA, Australia
[d] Hollywood Private Hospital, Perth, WA, Australia
[e] School of Public Health, Curtin University, Perth, WA, Australia
[f] School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia
[g] Institute for Health Research, University of Notre Dame Australia, Perth, WA, Australia

ARTICLE INFO

Keywords:
Radical prostatectomy
Prostate cancer
Weight loss

ABSTRACT

Background: Obesity in prostate cancer patients is associated with poor prostate-cancer specific outcomes. Exercise and nutrition can reduce fat mass; however, few studies have explored this as a combined pre-surgical intervention in clinical practice.

Purpose: This study examined the efficacy of a weight loss program for altering body composition in prostate cancer patients prior to robot assisted radical prostatectomy (RARP).

Methods: A retrospective analysis of 43 overweight and obese prostate cancer patients, aged 47–80 years, who completed a very low-calorie diet (~3000–4000 kJ) combined with moderate-intensity exercise (90 min/day) prior to RARP. Whole body and regional fat mass (FM) and lean mass (LM) were assessed by dual-energy x-ray absorptiometry pre- and post-program. Body weight, waist circumference, and blood pressure were assessed weekly, with surgery-related adverse effects recorded at time of surgery and follow-up appointments.

Results: With a median of 29 days (IQR: 24–35days) on the program, patients significantly ($p < 0.001$) reduced weight (−7.3 ± 2.9 kg), FM (−5.0 ± 2.6 kg), percent body fat (−3.1 ± 2.5%), trunk FM (−3.4 ± 1.8 kg), LM (−2.4 ± 1.8 kg), and appendicular LM (−1.2 ± 1.0 kg). Lower weight, FM, percent FM, trunk FM, and visceral FM were associated with less surgery-related adverse effects ($r_s = 0.335$ to 0.468, $p < 0.010$). Systolic and diastolic blood pressure were reduced ($p < 0.001$) by 15 ± 22 and 8 ± 10 mmHg, respectively over the weight loss intervention.

Conclusion: Undertaking a combined low-calorie diet and exercise program for weight loss in preparation for RARP resulted in substantial reductions in FM, with improvements in blood pressure, that may benefit surgical outcomes.

1. Introduction

Reducing obesity is of critical interest when considering prostate cancer patients' tolerance and response to treatment as well as their long-term health outcomes [1]. Radical prostatectomy is a common surgical treatment for prostate cancer, however, obesity status places a patient at increased risk of poor surgical and prostate-cancer specific outcomes [2,3]. During surgery, obese patients are at increased risk of longer operation time and higher blood loss, as well as central nervous system and head and neck complications due to excessive peak expiratory airway pressure while in the Trendelenburg position, with complications such as pneumoperitoneum [2,4,5]. The surgical technique may also be impacted, with obese patients reported to be at increased odds of capsular incision (inferior surgical technique), and a higher risk of converting to an open prostatectomy [6]. Post-surgery, obese patients may experience inferior urinary and sexual outcomes, increased risk of post-operative infection, lymphedema, and positive surgical margins [2,6,7]. Furthermore, there is a strong level of evidence for the association

* Corresponding author. Exercise Medicine Research Institute, 270 Joondalup Drive, JOONDALUP Perth, W.A., 6027, Australia.
E-mail address: r.newton@ecu.edu.au (R.L. Wilson).

https://doi.org/10.1016/j.suronc.2020.08.006
Received 27 March 2020; Received in revised form 3 July 2020; Accepted 2 August 2020
Available online 7 August 2020

of obesity and increased risk of aggressive prostate cancer [8], as well as an increased risk of biochemical recurrence, reduced time to the development of castrate resistance, development of other comorbidities such as cardiovascular disease (CVD), and earlier prostate cancer-specific death [1,9–14].

Lifestyle medicine is the inclusion of non-surgical and non-pharmaceutical therapies, such as exercise and nutrition, within a patient's treatment plan to prevent the development, or worsening, of side effects and chronic medical conditions such as obesity [15,16]. While one third of prostate cancer patients are likely to make lifestyle changes upon receiving a cancer diagnosis [17], the substantial amount of clinician contact at diagnosis represents an opportune time to implement a clinically delivered lifestyle medicine weight loss intervention. This ensures patients can be monitored collaboratively by medical and allied health (exercise and nutrition) professionals to provide a tailored prescription to achieve the desired outcome of healthy intentional weight loss [18], a reduction in fat mass (FM) and maintenance of lean mass (LM). The majority of previous pre-surgical studies in men with prostate cancer have assessed physiotherapy-led programs focusing on a particular disease-specific outcome, such as urinary incontinence [19–22], or utilised exercise or nutrition strategies in isolation [23–25]. Only two randomized controlled trials have examined weight loss using a combined exercise and nutrition intervention prior to radical prostatectomy but results were inconsistent. Demark-Wahnefried et al. [26] demonstrated no significant change in FM or LM compared to a usual care control group, however, the intervention group did experience a substantial reduction in FM (3.1 kg), although within group significance was not reported. Henning et al. [27] reported a significant reduction in total and gynoid fat with no change in trunk FM compared to a usual care control. Both studies were controlled research trials, rather than the evaluation of weight loss achieved in clinical practice pragmatically recommended by a clinician as part of their pre-surgery standard of care.

Clinically, it is important to quantify both FM and LM alterations with weight loss induced by combined exercise and nutrition interventions, as substantial loss in LM may negatively impact physical function, patient independence, and long-term weight maintenance [28]. Except for monitoring bone health, assessment of body composition by dual-energy x-ray absorptiometry (DXA) in a clinical setting is not often performed, 'nor considered a part of standard practice when weight loss is advised. The use of total body weight, body mass index, and waist/hip circumference are considered satisfactory indicators of positive FM change; however, these do not accurately identify changes in body composition [29] 'nor differentiate between subcutaneous and visceral fat reductions. Here we report a retrospective analysis of the effect of a weight loss program in prostate cancer patients prior to robotic assisted radical prostatectomy (RARP) surgery using DXA to assess change in body composition.

2. Methods

2.1. Patients

Between 2016 and 2018, 78 men with prostate cancer attending a single urology clinic in Perth, Western Australia, were referred by a single urologist, prior to RARP, to an external allied health clinic specialising in exercise and nutrition programs for persons with chronic conditions including cancer. Patients undertook a weight loss program supervised by certified allied health professionals (Accredited Practising Dietitian (APD) or Accredited Exercise Physiologist (AEP)) prior to receiving a RARP. The urologist referred patients who were overweight or obese, as defined by a waist circumference $\geq$94 cm [30] at the initial consultation following a confirmed prostate cancer diagnosis. Of the 78 patients referred to the weight loss program, a pre or post DXA scan was not available for 32 patients (declined scan, insufficient time before surgery) and 3 patients did not undertake a RARP. As a result, 43 patients were included in the analysis. The study was approved by the Human Research Ethics Committee at Edith Cowan University (ID: 18832).

2.2. Measurements

Body composition was assessed by DXA at the initial and final nutrition consultations prior to RARP. Body weight, waist circumference, and systolic and diastolic blood pressure were monitored at weekly scheduled appointments with an APD or AEP.

2.2.1. Body composition

Whole body fat mass (FM, kg), lean mass (LM, kg), and body fat percent (%), and regional trunk FM (kg), visceral FM (g), and appendicular skeletal muscle (ASM, kg) were assessed by DXA (Horizon W, Hologic Inc., Waltham, MA, USA). ASM was calculated as the sum of upper and lower limb LM [31]. Visceral FM estimated from DXA scanning has been shown to be strongly associated with that derived from computed tomography [32].

2.2.2. Anthropometric and blood pressure measures

Body weight was measured using a calibrated electronic weight scale (Model #22089, SECA, Germany) and height using a wall-mounted stadiometer (Livingstone International Healthcare Pty Ltd, Australia), with body mass index (BMI) calculated from weight divided by height in meters squared (kg/m^2). Waist circumference was measured following standard procedures [33]. Systolic and diastolic blood pressure were measured using a sphygmomanometer (Model #HEM-907, Omron, Japan) with the patient in a seated position after a minimum of 15 min of conversing with an APD.

2.2.3. Surgical outcomes

Written medical notes from the patient's urologist were reviewed to determine the number and type of adverse side effects recorded during and up to 1-month post RARP (identified by the urologist as undesirable events during and post-surgery). Erectile dysfunction was not considered a side effect if it was evident pre-surgery. Incontinence was defined as an ongoing concern up to 1-month post-surgery with patients continuing to use at least one continence pad daily [34].

2.3. Data collection process

Data used in the analysis were obtained from the urology clinic and allied health clinic. At the initial consultation with the urologist, patients provided consent for their information to be used in future research projects. A secondary consent form was also completed at the initial consultation at the allied health clinic. Patient age (years), cancer stage (TNM), smoking status (yes/no), alcohol intake (number of standard drinks/day), medications, comorbidities, information related to the surgical procedure and side effects were obtained from the urology clinic, while DXA scans were obtained from the allied health clinic. Records from nutrition consultations were also reviewed, providing information on weekly measurements of weight, waist circumference, and blood pressure.

2.4. Weight loss program

The weight loss program was a collaborative initiative between the urology clinic and allied health clinic to ensure safe practice of rapid weight loss required for surgery. Patients were referred by their urologist to the external allied health clinic where they attended weekly appointments. The program was part of the urology clinic's standard of care for overweight and obese patients prior to RARP and designed to induce rapid weight loss by reducing FM, yet maintaining LM, while meeting exercise and micro- and macronutrient requirements. Patients participated in the program for up to 12 weeks, although this was dictated by surgery date, client willingness to continue with the

program, or target weight being reached. The standard clinic protocol required patients to begin losing weight before a surgery date was scheduled, however, prostate cancers that showed aggressive signs requiring immediate attention were scheduled for surgery without evidence of weight loss. Nevertheless, these patients were still required to initiate the program prior to surgery. Compliance to exercise and diet were monitored through attendance of nutrition consultations with APD, where a weekly weigh-in was completed to ensure patients were consistently losing weight. Barriers to completing exercise and diet and continued encouragement to comply with program guidelines were also addressed during weekly sessions using behaviour change techniques such as motivational interviewing and cognitive behavioural therapy. In addition to implementing exercise and nutrition changes, the clinic protocol required patients who smoked to cease.

Patients were prescribed 90 min of moderate intensity aerobic exercise to complete daily at 60–80% of their age-predicted maximum heart rate (using the formula: 220 - age), if patient owned a wearable heart rate monitor, or at an intensity where they could still hold a conversation. Intensity was not recorded. Moderate intensity aerobic exercise was chosen to minimise injury risk, optimise compliance, and maximise caloric expenditure over the pre-operative period. Resistance training was not required, although it was permitted if a patient had been undertaking this exercise mode prior to referral to the clinic. The exercise prescription was personalised to patient preference for aerobic exercise mode and target duration (example one: three, 30-min bouts of walking per day; example two: 90 min of cycling per day; example 3: 30 min of swimming and 60 min of walking per day). Patients were provided access to fitness facilities under the supervision of an AEP while undertaking the program, or if they preferred, patients could perform exercise at home, outdoors, or their own local recreational facility.

An APD prescribed a very low-calorie diet of ~3360–4200 kJ consumed per day consisting of the following recommendations: 1) 3 very low-calorie diet meal replacement products consisting of shakes, bars, or soups (KicStart; Optifast; Dr MaCleod's) consumed throughout the day according to the preferred eating pattern of the patient (example one: 1 product for breakfast, 1 for lunch, 1 for dinner; example two: 1 product for breakfast, ½ product mid-morning, ½ product lunch, ½ product dinner, ½ product after dinner); 2) at least 2 cups of low starch vegetables (defined as < 4g carbohydrate per 100g) or salad per day; 3) optimisation of fluid intake calculated based on body weight [35]; and 4) optimisation of daily protein (1.0–1.07 g/kg body weight/d according to age related recommendations) (from late 2017 only) [35]. Additional permitted food and drink items included miso soup or low starch vegetable soups (excluding soups with cream), sauces in small amounts, herbs and spices, sugar free lollies and gum, diet jelly, artificial sweeteners, lemon and lime juice, tea/coffee with no sugar and minimal milk, diet soft drink, and diet cordial. Patients were instructed to refrain from consuming all other foods and drinks with emphasised restriction on fruit juice, alcohol, and sugar-sweetened drinks. Patients continued with this nutrition program until their scheduled surgical appointment at which time nutrition advice was provided by the urologist for how to prepare for surgery.

2.5. Statistical analysis

Statistical analyses were conducted using IBM SPSS version 25 (SPSS Inc., IBM Corp, Armonk, NY, USA). Normality of the distributions were assessed using the Kolmogorov-Smirnov test. To examine differences pre-to post-intervention Student's paired t-tests were used or the Wilcoxon signed-rank test, as appropriate. Associations between variables were assessed using Pearson's correlation or Spearman's rank correlation, as appropriate. Data are presented as mean ± standard deviation (SD), median and interquartile range [IQR], or number (percentage). Tests were two-tailed and statistical significance was set at $p < 0.05$.

3. Results

Forty-three men aged 47–80 years were included in the analysis and their clinical characteristics are presented in Table 1. The majority of men had a Gleason score of 7 (76.7%), had their cancer contained within the prostate (86.0%), and a BMI range of 23.9–37.9 kg/m^2; no patients were current smokers. Patients spent a median [IQR] of 29 [24–35] days undertaking the weight loss program as indicated by number of days between DXA scans. This included a median [IQR] of 5 [4–6] nutrition consultations with 81.4% of patients attending all scheduled weekly appointments. The most common reasons for missing an appointment were holiday or work.

There were significant ($p < 0.001$) declines in FM (−5.0 ± 2.6 kg), percent body fat (−3.1 ± 2.5%), trunk FM (−3.4 ± 1.8 kg), visceral fat (−297 [375 – 245] g), LM (−2.4 ± 1.8 kg), and ASM (−1.2 ± 1.0 kg) from pre to post DXA scans (Table 2). Of the loss in FM, 68.5% of the reduction was the result of trunk FM loss. Individual responses to the program are shown in Fig. 1. All patients lost total FM and trunk FM with only 5 patients (11.6%) showing an increase in LM or ASM. Patients with a higher body weight at program initiation experienced a greater loss in weight, ASM, and LM ($r = -0.563$ to -0.727, $p < 0.001$), however, there was no association with loss in total FM ($r = -0.136$, $p = 0.386$) or trunk FM ($r = -0.035$, $p = 0.824$). Further, age was not significantly associated with any baseline body composition measure ($p = 0.098$–0.530) or change in body composition ($p = 0.112$–0.920). Based on BMI at baseline, 4 patients were considered 'normal weight', however, they attained a similar magnitude of loss in FM (−4.9 ± 2.7 kg) but less change in LM (−0.6 ± 1.3 kg) when compared to the values for all patients.

Total body weight (−7.3 ± 2.9 kg), BMI (−2.4 ± 0.9 kg/m^2), waist circumference (−8.3 ± 3.4 cm), systolic (15 ± 22 mmHg) and diastolic (−8 ± 10 mmHg) blood pressure all decreased significantly ($p \leq 0.001$) over the course of the diet and exercise program (Table 2). Those patients on the program for longer and who attended a greater number of consultations with the APD experienced a greater loss of body weight ($r_s = 0.669$; $p < 0.001$; $r_s = 0.436$; $p = 0.003$, respectively).

The most common adverse effects of surgery were urinary

Table 1
Patient characteristics.

Variable	Patients (N = 43)
Age (years), mean ± SD	66 ± 7
Height (m), mean ± SD	1.78 ± 0.07
Total body weight (kg) mean ± SD	91.7 ± 12.5
Daily alcohol intake (number of standard drinks/day), median [IQR]	2 [0–2]
Number of medications, median [IQR]	3 [1–4]
Number of comorbidities [a], median [IQR]	2 [0–3]
Number of nutrition consultations, median [IQR]	5 [4–6]
Days between pre/post DXA scan, median [IQR]	29 [24–35]
Days between post DXA and surgery, median [IQR]	7 [2–21]
Gleason score, N (%)	
Gleason 7	33 (76.7)
Gleason 8	2 (4.7)
Gleason 9	8 (18.6)
T stage 2, N (%)	21 (48.8)
T stage 3, N (%)	16 (37.2)
Positive lymph involvement, N (%)	6 (14.0)
Radical prostatectomy [b], N (%)	26 (60.5)
Radical prostatectomy + lymph node resection [b], N (%)	17 (39.5)
Adjuvant radiation and androgen deprivation therapy, N (%)	1 (2.3)
Positive surgical margins (n = 39) [c], N (%)	2 (5.1)

[a] Type of comorbidities: Arthritis, chronic obstructive pulmonary disease, CVD, depression/anxiety, diabetes, dyslipidaemia, gastroesophageal reflux disease, glaucoma, other cancer, Peyronie's disease, peripheral neuropathy, sleep apnoea, thyroid condition.[b] A total of 23 (53.5%) surgeries involved full or partial nerve sparring, with a further 1 (2.3%) including an umbilical hernia repair.[c] Four patients did not have surgical margin data recorded, rendering n = 39 patients' data available for inclusion.

Table 2
Body composition, anthropometric, and blood pressure measures of prostate cancer patients undergoing weight loss pre-RARP.

	Pre-intervention	Post-intervention	Mean change	P-value
DXA derived measures				
Total body weight (kg)	91.7 ± 12.5	84.4 ± 11.1	−7.3 ± 2.9	<0.001
Total fat mass (kg)	30.7 ± 6.7	25.7 ± 6.5	−5.0 ± 2.6	<0.001
Body fat percent (%)	33.2 ± 3.6	30.1 ± 4.4	−3.1 ± 2.5	<0.001
Trunk fat (kg)	18.0 ± 4.2	14.6 ± 4.2	−3.4 ± 1.8	<0.001
Visceral fat (g)	1216 [1014–1505]	877 [758–1150]	–	<0.001
Total lean mass (kg)	57.9 ± 6.7	55.5 ± 5.7	−2.4 ± 1.8	<0.001
ASM (kg)	25.0 ± 3.3	23.8 ± 2.9	−1.2 ± 1.0	<0.001
Anthropometric and blood pressure measures				
Body mass index (kg/m^2)	29.4 ± 3.4	27.0 ± 2.8	−2.4 ± 0.9	<0.001
Waist circumference (cm) (N = 39) [a]	108.3 ± 8.2	100.0 ± 7.3	−8.3 ± 3.4	<0.001
Systolic blood pressure (mmHg) (N = 28) [b]	138 ± 17	123 ± 16	15 ± 22	0.001
Diastolic blood pressure (mmHg) (N = 28) [b]	79 ± 9	70 ± 11	−8 ± 10	<0.001

[a] Four patients did not have waist circumference recorded at their initial and/or final nutrition consultation, rendering n = 39 patients' data available for inclusion.
[b] Similarly, fifteen patients did not have brachial blood pressure recorded at their initial and/or finial nutrition consultation, rendering n = 28 patients' data available for inclusion.

incontinence (67.4%) and erectile dysfunction (32.6%), followed by lymphedema (11.6%) (Table 3). Patients who experienced a higher number of surgery-related adverse effects also had higher body weight, FM, body fat percent, trunk FM, and visceral FM (r_s = 0.335 to 0.468, p < 0.010) post-intervention, prior to RARP. Change in FM and LM, and age were not associated with surgery-related adverse effects. There were no major adverse events recorded as a result of the dietary or exercise intervention. Minor adverse effects associated with the diet included hunger, headache, change in bowel habits, and light-headedness.

4. Discussion

To our knowledge, this is the first evaluation of a weight loss program conducted as part of standard care procedures for overweight and obese patients prior to RARP within clinical practice. There were four important findings: 1) total body and regional FM were significantly

Table 3
RARP related adverse effects experienced during surgery and up to 1-month post-surgery in men who had completed a pre-RARP weight loss program.

Adverse effect (N = 43)	Number (%)
Incontinence	31 (72.1)
Erectile dysfunction	15 (34.9)
Lymphedema	5 (11.6)
Pain	3 (7.0)
Surgery difficulty [a]	2 (4.7)
Constipation	2 (4.7)
Poor wound healing	1 (2.3)
Cardiac concerns	1 (2.3)
Neuropraxia	1 (2.3)
Herpetic neuralgia	1 (2.3)
Urinary tract infection	1 (2.3)

[a] Unexpected difficulty during surgery.

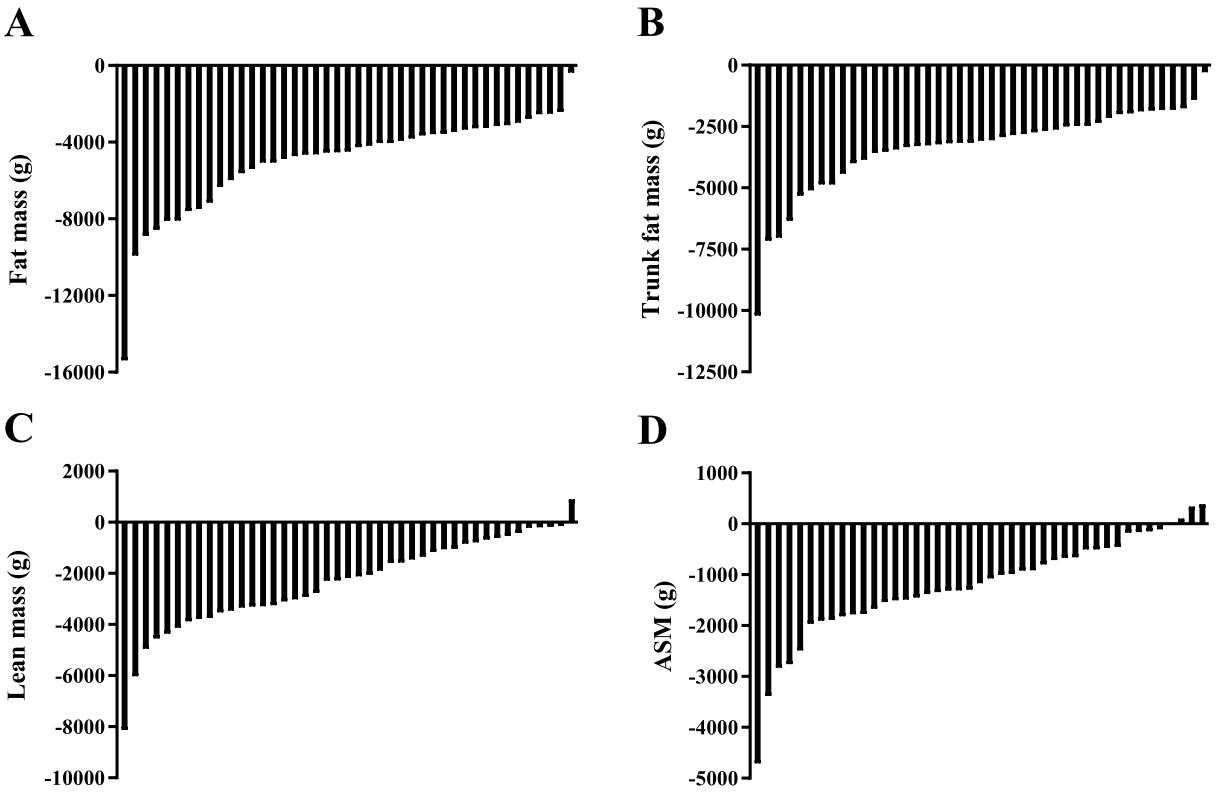


Fig. 1. Waterfall plots of individual participant changes in ascending order for A) whole body fat mass, B) trunk fat mass, C) whole body lean mass, and D) appendicular skeletal muscle mass, after a pre-RARP weight loss program.

decreased, 2) lower absolute FM was associated with reduced number of surgery-related adverse effects, 3) decrease in FM was accompanied by a reduction in LM, and 4) improvements in blood pressure were observed.

Significant reductions in FM around the surgical region is of clinical significance as it provides a promising setting for a less complicated surgery [2,6,36]. We found a significant 16.3% reduction in total FM with an average loss of 5.0 ± 2.6 kg. The majority of this fat was lost in the abdominal region where nearly 80% was attributable to trunk and visceral fat with a resulting 8.3 ± 3.4 cm reduction in waist circumference. Henning et al. [27] completed a similar weight loss program in men prior to prostatectomy that consisted of an energy restricted diet (consuming 5000–6000 kJ/day) and 60 min of exercise per day, and found a significant reduction in total FM of 2.1 kg and gynoid fat by 1.4%, compared to a usual care control group. The more than 2-fold greater loss in FM achieved in our cohort and in a shorter period (29 vs. 51 days) was likely due to the more severe caloric restriction (~3000–4000 kJ/day) and greater amount of exercise (90 min/day) prescribed. However, in one pre-radical prostatectomy weight loss program [26], an increase in Ki67, a marker of tumour cell proliferation, in the intervention group compared to usual care was noted. Although the intervention group did reduce their FM by −3.1 ± 2.2 kg and LM by −1.2 ± 1.0 kg, this was not significantly different to the usual care control group, and no within group significances were reported. Consequently, the implications of this finding regarding tumour cell proliferation in response to rapid weight loss requires further examination.

With the substantial reduction in FM, it appears that those patients with lower central and subcutaneous FM at the time of surgery experienced less surgery-related adverse effects during and following the procedure. This relationship must be carefully interpreted as although statistically significant, it was not the primary aim of this analysis and could not be compared to a BMI-matched, non-weight loss control group. As such, this finding should be considered as hypothesis generating where further research should assess the benefits of weight loss on both acute and long-term surgery-related adverse effects inclusive of the effect weight loss has on cancer progression. However, in support of our findings Knipper et al. [7] in a study evaluating clinical outcomes of obese (BMI ≥ 30 kg/m^2) versus non-obese prostate cancer patients undergoing RARP or open-radical prostatectomy, also reported that obese patients had more complications peri-operatively for both surgical techniques. Additionally, older men receiving surgery are also at a higher risk of surgical complications [37]. Despite the broad age range (47–80 years) in the present study, age was not associated with number of surgery-related adverse events.

While the loss in FM in the current study was substantial, patients also lost a significant amount of LM (−2.4 ± 1.8 kg; 32% of total weight lost), despite the inclusion of an exercise requirement, albeit without emphasis on resistance training, and increased dietary protein intake. This is a concern given that patients post-surgery have been observed to lose LM as well. For instance, Singh et al. [25] reported that patients had a mean loss of 2.7 kg in LM 6-weeks post-prostatectomy. The loss in LM has been associated with poor long term weight management, longer hospital stays, increased risk of infection, and surgical complications [28,38,39]. The lack of monitored exercise via a written log, heart rate, or pedometer, or a supervised exercise component that included resistance exercise for all patients, are possible explanations for the significant loss in LM found in the current study compared to no loss in other pre-radical prostatectomy weight loss studies [26,27]. Nevertheless, excess weight can act as a barrier to exercise for many individuals [40]. Therefore, despite the significant loss in LM, the act of rapidly losing weight may act as a facilitator and provide patients with increased confidence and self-motivation to continue or start an exercise program post-surgery, and contribute to increasing LM and maintaining a healthy weight [18,41]. Consequently, the benefits of losing an average of 5 kg in FM may outweigh the negatives of the absolute loss in LM. Long-term survivorship goals for prostate cancer patients who have undergone weight loss prior to RARP should therefore focus on increasing LM and transitioning to a sustainable diet and exercise regimen after recovery from surgery.

Weight loss is commonly accompanied with a reduction in blood pressure, another risk factor associated with CVD development [42]. Clinically significant reductions were evident in both systolic and diastolic blood pressure, similar to reductions obtained by medication [43]. A minimum 10 mmHg reduction in systolic blood pressure has been shown to reduce the occurrence of a cardiovascular event by 20% [44]. Although the baseline mean brachial systolic blood pressure was not considered hypertensive, patients were commonly taking prescribed blood pressure medication. Blood pressure control is also necessary for safe surgery. Sudden or prolonged hypo- or hypertension pre-, during- or post-surgery can place a patient at increased risk for longer hospitalisation, myocardial injury, and all-cause mortality [45–47]. For elective surgeries, a pre-surgery systolic blood pressure >180 mmHg, and/or consistent systolic blood pressure ≥160 mmHg in the primary care setting may result in postponement of surgery, although this is controversial [45,48]. No participant had a systolic blood pressure ≥160 mmHg after the weight loss program, compared to 4 patients prior. Clinician communication was that many patients were able to cease antihypertensive medication, under the care of their general practitioner. This was not managed by the treating urologist and was, therefore, not recorded in this study. However, the cost savings from cessation of medication could offset the cost of a weight loss program conducted in the clinical setting and would be an interesting avenue for further research. Nevertheless, given the significant reduction in blood pressure observed, it is important that a patient's blood pressure management plan is monitored by their general practitioner during rapid, pre-surgery weight loss as medications may need to be altered. This further highlights the importance of a multidisciplinary team when undertaking weight loss.

Our analysis has several strengths. The utilisation of DXA scans demonstrated clinically relevant changes in FM and its distribution that can occur between diagnosis and surgery. This multidisciplinary, clinically run program resulted in a high level of patient engagement and adherence with over 80% of patients attending all scheduled appointments and all patients losing FM. However, there are several limitations which must be acknowledged. The absence of a control group prevented the ability to make comparisons to a non-weight loss group (current standard care). Patients were given the choice to complete a self-directed exercise and nutrition regime post-surgery, which did not include follow-up body composition measures, or continue with a supervised programme. All but one patient selected self-directed lifestyle management post-surgery, as such, follow-up body composition data were not available. Not all patients completed the final DXA close to their surgery date, therefore, the post-program DXA scans may not reflect body composition at time of surgery. It should also be noted that DXA may not be readily accessible to clinicians and patients due to the cost involved of the equipment and for some patients, such as the morbidly obese, DXA scanning may not be physically possible. All data were collated from clinical notes designed to satisfy information on health status for the attending practitioner. As such, the patients' compliance to exercise and nutrition requirements, as well as their physical function and quality of life, were not assessed by questionnaire but in conversation during the weekly nutrition consultation where weigh-ins showed consistent weight loss suggesting patients made significant lifestyle changes. Future studies should collect compliance data to better establish pre-surgery weight loss guidelines. Further, the intervention emphasis was on creating a large energy deficit with fat loss as the primary goal, however, this compromised LM which is a negative outcome. Whether, LM can be maintained or enhanced through targeted resistance training incorporated into the intervention needs to be determined.

5. Conclusion

In summary, this study completed within clinical practice demonstrated the efficacy of a significant reduction in FM, with additional improvements in blood pressure, while undertaking a weight loss program prior to RARP. Obese patients are at high risk of poor surgical outcomes as well as comorbidity development and weight lost prior to RARP may be a viable strategy to improve patient outcomes and comorbidity risk profile. Future interventions should address this through incorporating supervised resistance training and optimisation of protein intake to help minimise the loss of muscle and increase protein metabolism. Future research should consider the translation of this clinically undertaken weight loss program as it could be impactful in other obese populations with chronic diseases, especially those who are morbidly obese. Consideration should also be given to exploring the effect that improving obesity status pre-surgery has on radical prostatectomy side effects and recovery, long-term health benefits and diet and exercise behaviours, and cancer progression and recurrence.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-for-profit sectors.

Ethical approval

Ethical approval was gained from Human Research Ethics Committee at Edith Cowan University (ID: 18832). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Two informed consent forms were obtained from all individual participants included in the study after attending the urology clinic and allied health clinic, respectively.

CRediT authorship contribution statement

Rebekah L. Wilson: Data curation, Formal analysis, Conceptualization, Methodology, data collection, data analysis, Writing - original draft, preparation, Writing - review & editing. **Tom Shannon:** Data curation, Formal analysis, Conceptualization, Methodology, data collection, data analysis, Writing - review & editing. **Emily Calton:** Data curation, Formal analysis, Methodology, data collection, data analysis, Writing - original draft, preparation. **Daniel A. Galvão:** Data curation, Formal analysis, Conceptualization, Methodology, data collection, data analysis, Writing - original draft, preparation, Writing - review & editing. **Dennis R. Taaffe:** Data curation, Formal analysis, Conceptualization, Methodology, data collection, data analysis, Writing - original draft, preparation, Writing - review & editing. **Nicolas H. Hart:** Data curation, Formal analysis, Conceptualization, Methodology, data collection, data analysis, Writing - original draft, preparation, Writing - review & editing. **Philippa Lyons-Wall:** Data curation, Formal analysis, Conceptualization, Methodology, data collection, data analysis, Writing - original draft, preparation, Writing - review & editing. **Robert U. Newton:** Data curation, Formal analysis, Conceptualization, Methodology, data collection, data analysis, Writing - original draft, preparation, Writing - review & editing.

Declaration of competing interest

None.

References

[1] J.A. Ligibel, C.M. Alfano, K.S. Courneya, W. Demark-Wahnefried, R.A. Burger, R. T. Chlebowski, et al., American Society of Clinical Oncology position statement on obesity and cancer, J. Clin. Oncol. 32 (31) (2014) 3568–3574, https://doi.org/10.1200/JCO.2014.58.4680.

[2] A.L. Wiltz, S. Shikanov, S.E. Eggener, M.H. Katz, A.E. Thong, G.D. Steinberg, et al., Robotic radical prostatectomy in overweight and obese patients: oncological and validated-functional outcomes, Urology 73 (2) (2009) 316–322, https://doi.org/10.1016/j.urology.2008.08.493.

[3] E. Ballon-Landa, J.K. Parsons, Nutrition, physical activity, and lifestyle factors in prostate cancer prevention, Curr. Opin. Urol. 28 (1) (2018) 55–61, https://doi.org/10.1097/MOU.0000000000000460.

[4] T.E. Ahlering, L. Eichel, R. Edwards, D.W. Skarecky, Impact of obesity on clinical outcomes in robotic prostatectomy, Urology 65 (4) (2005) 740–744, https://doi.org/10.1016/j.urology.2004.10.061.

[5] J. Neuenschwander, O. Burkhardt, L. Hess, M. Randazzo, K. Horton, C. Padevit, et al., Obese patients undergoing robotic radical prostatectomy have no impaired operative outcome, Eur. Urol. Suppl. 17 (2) (2018) e986.

[6] S.J. Freedland, K.A. Grubb, S.K. Yiu, M.E. Nielsen, L.A. Mangold, W.B. Isaacs, et al., Obesity and capsular incision at the time of open retropubic radical prostatectomy, J. Urol. 174 (5) (2005) 1798–1801, https://doi.org/10.1097/01.ju.0000177077.53037.72.

[7] S. Knipper, E. Mazzone, F.A. Mistretta, C. Palumbo, Z. Tian, A. Briganti, et al., Impact of obesity on perioperative outcomes at robotic-assisted and open radical prostatectomy: results from the national inpatient sample, Urology 133 (2019) 135–144.

[8] S.E. Bonn, A. Sjolander, A. Tillander, F. Wiklund, H. Gronberg, K. Balter, Body mass index in relation to serum prostate-specific antigen levels and prostate cancer risk, Int. J. Canc. 139 (1) (2016) 50–57, https://doi.org/10.1002/ijc.30052.

[9] S.F. Peisch, E.L. Van Blarigan, J.M. Chan, M.J. Stampfer, S.A. Kenfield, Prostate cancer progression and mortality: a review of diet and lifestyle factors, World J. Urol. 35 (6) (2017) 867–874, https://doi.org/10.1007/s00345-016-1914-3.

[10] C.E. Joshu, A.M. Mondul, A. Menke, C. Meinhold, M. Han, E.B. Humphreys, et al., Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era, Canc. Prev. Res. 4 (4) (2011) 544–551, https://doi.org/10.1158/1940-6207.CAPR-10-0257.

[11] H. Rhee, I. Vela, E. Chung, Metabolic syndrome and prostate cancer: a review of complex interplay amongst various endocrine factors in the pathophysiology and progression of prostate cancer, Horm Cancer 7 (2) (2016) 75–83, https://doi.org/10.1007/s12672-015-0238-x.

[12] Y. Cao, J. Ma, Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis, Canc. Prev. Res. 4 (4) (2011) 486–501, https://doi.org/10.1158/1940-6207.CAPR-10-0229.

[13] W.C. Buschemeyer III, S.J. Freedland, Obesity and prostate cancer: epidemiology and clinical implications, Eur. Urol. 52 (2) (2007) 331–343.

[14] J. Sharma, K.P. Gray, L.C. Harshman, C. Evan, M. Nakabayashi, R. Fichorova, et al., Elevated IL-8, TNF-α, and MCP-1 in men with metastatic prostate cancer starting androgen-deprivation therapy (ADT) are associated with shorter time to castration-resistance and overall survival, Prostate 74 (8) (2014) 820–828.

[15] B.I. Bodai, T.E. Nakata, W.T. Wong, D.R. Clark, S. Lawenda, C. Tsou, et al., Lifestyle medicine: a brief review of its dramatic impact on health and survival, Perm. J. 22 (2018) 17–25, https://doi.org/10.7812/TPP/17-025.

[16] S.B. Heymsfield, T.A. Wadden, Mechanisms, pathophysiology, and management of obesity, N. Engl. J. Med. 376 (3) (2017) 254–266.

[17] E. Sutton, L.E. Hackshaw-McGeagh, J. Aning, A. Bahl, A. Koupparis, R. Persad, et al., The provision of dietary and physical activity advice for men diagnosed with prostate cancer: a qualitative study of the experiences and views of health care professionals, patients and partners, Cancer Causes Control 28 (4) (2017) 319–329, https://doi.org/10.1007/s10552-017-0861-7.

[18] A.M. Baker, K.C. Smith, K.I. Coa, K.J. Helzlsouer, L.E. Caulfield, K.S. Peairs, et al., Clinical care providers' perspectives on body size and weight management among long-term cancer survivors, Integr. Canc. Ther. 14 (3) (2015) 240–248, https://doi.org/10.1177/1534735415572882.

[19] C. Sueppel, K. Kreder, W. See, Improved continence outcomes with preoperative pelvic floor muscle strengthening exercises, Urol. Nurs. 21 (3) (2001) 201–210.

[20] K.L. Burgio, P.S. Goode, D.A. Urban, M.G. Umlauf, J.L. Locher, A. Bueschen, et al., Preoperative biofeedback assisted behavioral training to decrease post-prostatectomy incontinence: a randomized, controlled trial, J. Urol. 175 (1) (2006) 196–201, https://doi.org/10.1016/S0022-5347(05)00047-9, discussion.

[21] A. Centemero, L. Rigatti, D. Giraudo, M. Lazzeri, G. Lughezzani, D. Zugna, et al., Preoperative pelvic floor muscle exercise for early continence after radical prostatectomy: a randomised controlled study, Eur. Urol. 57 (6) (2010) 1039–1043, https://doi.org/10.1016/j.eururo.2010.02.028.

[22] G.T. Bales, G.S. Gerber, T.X. Minor, D.A. Mhoon, J.M. McFarland, H.L. Kim, et al., Effect of preoperative biofeedback/pelvic floor training on continence in men undergoing radical prostatectomy, Urology 56 (4) (2000) 627–630, https://doi.org/10.1016/s0090-4295(00)00687-7.

[23] D. Santa Mina, W.J. Hilton, A.G. Matthew, R. Awasthi, G. Bousquet-Dion, S.M. H. Alibhai, et al., Prehabilitation for radical prostatectomy: a multicentre randomized controlled trial, Surg Oncol 27 (2) (2018) 289–298, https://doi.org/10.1016/j.suronc.2018.05.010.

[24] J.L. Wright, S. Plymate, A. D'Oria-Cameron, C. Bain, K. Haugk, L. Xiao, et al., A study of caloric restriction versus standard diet in overweight men with newly diagnosed prostate cancer: a randomized controlled trial, Prostate 73 (12) (2013) 1345–1351, https://doi.org/10.1002/pros.22682.

[25] F. Singh, R.U. Newton, M.K. Baker, N.A. Spry, D.R. Taaffe, J. Thavaseelan, et al., Feasibility of presurgical exercise in men with prostate cancer undergoing prostatectomy, Integr. Canc. Ther. 16 (3) (2017) 290–299, https://doi.org/10.1177/1534735416666373.
[26] W. Demark-Wahnefried, S. Rais-Bahrami, R.A. Desmond, J.B. Gordetsky, G. R. Hunter, E.S. Yang, et al., Presurgical weight loss affects tumour traits and circulating biomarkers in men with prostate cancer, Br. J. Canc. 117 (9) (2017) 1303–1313, https://doi.org/10.1038/bjc.2017.303.
[27] S.M. Henning, C. Galet, K. Gollapudi, J.B. Byrd, P. Liang, Z. Li, et al., Phase II prospective randomized trial of weight loss prior to radical prostatectomy, Prostate Cancer Prostatic Dis. 21 (2) (2018) 212–220, https://doi.org/10.1038/s41391-017-0001-1.
[28] P. Stiegler, A. Cunliffe, The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss, Sports Med. 36 (3) (2006) 239–262, https://doi.org/10.2165/00007256-200636030-00005.
[29] J.A. Pasco, K.L. Holloway, A.G. Dobbins, M.A. Kotowicz, L.J. Williams, S. L. Brennan, Body mass index and measures of body fat for defining obesity and underweight: a cross-sectional, population-based study, BMC Obes 1 (1) (2014) 9, https://doi.org/10.1186/2052-9538-1-9.
[30] M.E. Lean, T.S. Han, C.E. Morrison, Waist circumference as a measure for indicating need for weight management, BMJ 311 (6998) (1995) 158–161, https://doi.org/10.1136/bmj.311.6998.158.
[31] S.B. Heymsfield, R. Smith, M. Aulet, B. Bensen, S. Lichtman, J. Wang, et al., Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry, Am. J. Clin. Nutr. 52 (2) (1990) 214–218, https://doi.org/10.1093/ajcn/52.2.214.
[32] S. Kaul, M.P. Rothney, D.M. Peters, W.K. Wacker, C.E. Davis, M.D. Shapiro, et al., Dual-energy X-ray absorptiometry for quantification of visceral fat, Obesity 20 (6) (2012) 1313–1318, https://doi.org/10.1038/oby.2011.393.
[33] American College of Sports Medicine, ACSM's Guidelines for Exercise Testing and Prescription, Lippincott Williams & Wilkins, 2013.
[34] M.A. Liss, K. Osann, N. Canvasser, W. Chu, A. Chang, J. Gan, et al., Continence definition after radical prostatectomy using urinary quality of life: evaluation of patient reported validated questionnaires, J. Urol. 183 (4) (2010) 1464–1468, https://doi.org/10.1016/j.juro.2009.12.009.
[35] National Collaborating Centre for Acute Care, Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition, 2006.
[36] A.A. Mikhail, B.R. Stockton, M.A. Orvieto, G.W. Chien, E.M. Gong, K.C. Zorn, et al., Robotic-assisted laparoscopic prostatectomy in overweight and obese patients, Urology 67 (4) (2006) 774–779, https://doi.org/10.1016/j.urology.2005.10.049.
[37] S.M. Alibhai, M. Leach, G. Tomlinson, M.D. Krahn, N. Fleshner, E. Holowaty, et al., 30-day mortality and major complications after radical prostatectomy: influence of age and comorbidity, J. Natl. Cancer Inst. 97 (20) (2005) 1525–1532, https://doi.org/10.1093/jnci/dji313.
[38] E.M. Cespedes Feliciano, C.H. Kroenke, B.J. Caan, The obesity paradox in cancer: how important is muscle? Annu. Rev. Nutr. 38 (2018) 357–379.
[39] C.M. Prado, S.A. Purcell, C. Alish, S.L. Pereira, N.E. Deutz, D.K. Heyland, et al., Implications of low muscle mass across the continuum of care: a narrative review, Ann. Med. 50 (8) (2018) 675–693, https://doi.org/10.1080/07853890.2018.1511918.
[40] K. Ball, D. Crawford, N. Owen, Too fat to exercise? Obesity as a barrier to physical activity, Aust. N. Z. J. Publ. Health 24 (3) (2000) 331–333, https://doi.org/10.1111/j.1467-842x.2000.tb01579.x.
[41] J. Bidgood, J. Buckroyd, An exploration of obese adults' experience of attempting to lose weight and to maintain a reduced weight, Counsell. Psychother. Res. J. 5 (3) (2005) 221–229, https://doi.org/10.1080/17441690500310395.
[42] V.J. Stevens, E. Obarzanek, N.R. Cook, I.M. Lee, L.J. Appel, D. Smith West, et al., Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II, Ann. Intern. Med. 134 (1) (2001) 1–11, https://doi.org/10.7326/0003-4819-134-1-200101020-00007.
[43] J. Wu, A.T. Kraja, A. Oberman, C.E. Lewis, R.C. Ellison, D.K. Arnett, et al., A summary of the effects of antihypertensive medications on measured blood pressure, Am. J. Hypertens. 18 (7) (2005) 935–942, https://doi.org/10.1016/j.amjhyper.2005.01.011.
[44] D. Ettehad, C.A. Emdin, A. Kiran, S.G. Anderson, T. Callender, J. Emberson, et al., Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis, Lancet 387 (10022) (2016) 957–967, https://doi.org/10.1016/S0140-6736(15)01225-8.
[45] A. Hartle, T. McCormack, J. Carlisle, S. Anderson, A. Pichel, N. Beckett, et al., The measurement of adult blood pressure and management of hypertension before elective surgery: joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British Hypertension Society, Anaesthesia 71 (3) (2016) 326–337, https://doi.org/10.1111/anae.13348.
[46] L. Meng, W. Yu, T. Wang, L. Zhang, P.M. Heerdt, A.W. Gelb, Blood pressure targets in perioperative care, Hypertension 72 (4) (2018) 806–817, https://doi.org/10.1161/HYPERTENSIONAHA.118.11688.
[47] D.I. Sessler, J.A. Bloomstone, S. Aronson, C. Berry, T.J. Gan, J.A. Kellum, et al., Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery, Br. J. Anaesth. 122 (5) (2019) 563–574, https://doi.org/10.1016/j.bja.2019.01.013.
[48] R.D. Sanders, F. Hughes, A. Shaw, A. Thompson, A. Bader, A. Hoeft, et al., Perioperative Quality Initiative consensus statement on preoperative blood pressure, risk and outcomes for elective surgery, Br. J. Anaesth. 122 (5) (2019) 552–562, https://doi.org/10.1016/j.bja.2019.01.018.

CHAPTER FIVE

Weight loss for obese prostate cancer patients on androgen deprivation therapy

This chapter has been published as:
Wilson, R. L., Newton, R. U., Taaffe, D. R., Hart, N. H., Lyons-Wall, P., & Galvão, D. A. (2020). Weight loss for obese prostate cancer patients on androgen deprivation therapy. *Medicine and science in sports and exercise*, 53(3), 470. https://doi.org/10.1249/MSS.0000000000002509

Chapter 5 of this thesis has been published as the below article:

Wilson, R. L., Newton, R. U., Taaffe, D. R., Hart, N. H., Lyons-Wall, P., & Galvão, D. A. (2021). Weight loss for obese prostate cancer patients on androgen deprivation therapy. *Medicine & Science in Sports & Exercise, 53*(3), 470-478.

https://doi.org/10.1249/MSS.0000000000002509

OPEN

Weight Loss for Obese Prostate Cancer Patients on Androgen Deprivation Therapy

REBEKAH L. WILSON[1,2], ROBERT U. NEWTON[1,2,3], DENNIS R. TAAFFE[1,2], NICOLAS H. HART[1,2,4,5], PHILIPPA LYONS-WALL[2], and DANIEL A. GALVÃO[1,2]

[1]Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, AUSTRALIA; [2]School of Medical and Health Sciences, Edith Cowan University, Perth, WA, AUSTRALIA; [3]School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, QLD, AUSTRALIA; [4]Institute for Health Research, University of Notre Dame Australia, Perth, WA, AUSTRALIA; and [5]Cancer and Palliative Care Outcomes Centre, Queensland University of Technology, Brisbane, QLD, AUSTRALIA

ABSTRACT

WILSON, R. L., R. U. NEWTON, D. R. TAAFFE, N. H. HART, P. LYONS-WALL, and D. A. GALVÃO. Weight Loss for Obese Prostate Cancer Patients on Androgen Deprivation Therapy. *Med. Sci. Sports Exerc.*, Vol. 53, No. 3, pp. 470–478, 2021. **Purpose:** Excess fat mass (FM) contributes to poor prostate cancer (PCa) prognosis and comorbidity. However, FM gain is a common side effect of androgen deprivation therapy (ADT). We examined the efficacy of a 12-wk weight loss intervention to reduce FM and maintain lean mass (LM) in ADT-treated obese PCa patients. **Methods:** Fourteen ADT-treated obese PCa patients (72 ± 9 yr, 39.7% ± 5.4% body fat) were recruited for a self-controlled prospective study, with 11 completing the 6-wk control period, followed by a 12-wk intervention comprising 300 min·wk^{-1} of exercise including supervised resistance training and home-based aerobic exercise, and dietitian consultations advising a daily energy deficit (2100–4200 kJ) and protein supplementation. Body composition was assessed by dual x-ray absorptiometry. Secondary outcomes included muscle strength (one-repetition maximum), cardiorespiratory fitness (maximal oxygen consumption), and blood biomarkers. **Results:** There were no significant changes during the control period. Patients attended 89% of supervised exercise sessions and 100% of dietitian consultations. No changes in physical activity or energy intake were observed. During the intervention, patients experienced significant reductions in weight (−2.8 ± 3.2 kg, $P = 0.016$), FM (−2.8 ± 2.6 kg, $P < 0.001$), and trunk FM (−1.8 ± 1.4 kg, $P < 0.001$), with LM preserved (−0.05 ± 1.6 kg, $P = 0.805$). Muscle strength (4.6%–24.7%, $P < 0.010$) and maximal oxygen consumption (3.5 ± 4.7 mL·min^{-1}·kg^{-1}, $P = 0.041$) significantly improved. Leptin significantly decreased (−2.2 (−2.7 to 0.5) ng·mL^{-1}, $P = 0.016$) with no other changes in blood biomarkers such as testosterone and lipids ($P = 0.051$–0.765); however, C-reactive protein ($r_s = -0.670$, $P = 0.024$) and triglycerides ($r = -0.667$, $P = 0.025$) were associated with individual changes in LM. **Conclusions:** This study shows preliminary efficacy for an exercise and nutrition weight loss intervention to reduce FM, maintain LM, and improve muscle strength and cardiorespiratory fitness in ADT-treated obese PCa patients. The change in body composition may affect blood biomarkers associated with obesity and PCa progression; however, further research is required. **Key Words:** NUTRITION, DIET, AEROBIC EXERCISE, RESISTANCE EXERCISE, FAT MASS, LEAN MASS

Overweight and obese men with prostate cancer are at increased risk of recurrence, progression to castrate resistance, advanced-stage disease, and prostate cancer-specific mortality (1–3). Obesity is also associated with the development of comorbidities such as cardiovascular disease (CVD) and diabetes (4). Although much of the evidence on obesity and poor prostate cancer outcomes relies on body mass index (BMI) as a measure of obesity (2), it is the altered metabolic environment created by excess fat mass (FM) that is critical (1,5). Accumulation of fat has been associated with increased risk of advanced and fatal prostate cancer (1,5). Although the exact mechanisms are unclear, altered insulin/insulin-like-growth-factor axis and sex hormone concentrations, and abnormal adipokine and cytokine signaling are commonly suggested (6).

Obese prostate cancer patients initiating androgen deprivation therapy (ADT) may be at a higher risk of faster cancer progression than those of normal weight on the same treatment (7). ADT reduces testosterone to castrate levels resulting in significant changes in body composition (8). Prostate cancer patients treated with ADT have been reported to gain 13.8% in FM and lose 2.4% in both lean and bone mass within the first year of treatment (9). Greater FM has also been associated with exacerbating other ADT-related side effects, including

Address for correspondence: Rebekah Wilson, M.Phys.Ed., Exercise Medicine Research Institute, 270 Joondalup Drive, Joondalup, Perth, WA 6027, Australia; E-mail: rebekah.wilson719@gmail.com.

Submitted for publication June 2020.
Accepted for publication August 2020.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.acsm-msse.org).

0195-9131/21/5303-0470/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000002509

increased serum triglycerides and reduced quality of life, specifically higher fatigue and lower vitality levels (10,11). ADT may be prescribed from 3 months to several years, or indefinitely in some cases, with most patients receiving ADT at some stage after diagnosis (8). Therefore, it is fundamental to establish management strategies that can ameliorate or prevent further ADT-induced changes to improve prostate cancer patients' quality of life and physical well-being.

Lifestyle changes involving exercise and nutrition are often strategies implemented for weight loss. Exercise can be safely performed by ADT-treated prostate cancer patients to improve physical function, quality of life, fatigue levels, and lean mass (LM) (12). Appropriate nutrition may also mitigate ADT-related side effects by inducing weight loss, supporting bone health by optimizing calcium and vitamin D intake, and potentially reducing prostate cancer progression with the consumption of specific foods or eating patterns (13,14). However, evidence for appropriate nutrition prescription is variable (14,15). To date, three combined exercise and nutrition studies have reported weight loss. Freedland et al. (16) and O'Neill et al. (17) both targeted weight loss, and Focht et al. (18) aimed to improve mobility; however, all demonstrated significant fat loss to be feasible in prostate cancer patients on ADT showing declines of 1.8–8.2 kg. Although all studies included obese patients, only Freedland et al. (16) specifically targeted patients who were overweight or obese. Cancer progression has been suggested to increase linearly with obesity status (3), and development of multiple comorbidities is also more likely for obese individuals (4). Therefore, obese patients with prostate cancer, compared with those who are considered of normal weight or overweight, are a high-risk population, and it is important to clarify how they respond to exercise and nutrition interventions, especially those expected to receive long-term ADT (7). In addition, Freedland et al. (16) reported a significant 2.1-kg loss in LM with their weight loss program, although both O'Neill et al. (17) and Focht et al. (18) found no change in LM. It is important for an intervention to stimulate both lipolysis and muscle protein synthesis, as the preservation of LM plays a key role in the maintenance of weight loss and improvement in insulin resistance and physical function (19).

Currently, men with prostate cancer are recommended to maintain a healthy weight and stay physically active during their treatment to prevent or reduce treatment-related side effects (20). If weight loss is required, patients are recommended to undertake high-volume exercise and consume a healthy balanced diet with an energy deficit, which is the same advice for the general population (20). Although these recommendations are likely beneficial for prostate cancer patients, their efficacy within this population has not been confirmed, especially for obese patients who are at increased risk. Therefore, this study aimed to examine the preliminary efficacy of a 12-wk exercise and nutrition weight loss intervention in obese prostate cancer patients on ADT to reduce FM, maintain LM, and improve physical function and blood biomarkers associated with cancer progression and obesity. We hypothesized that the weight loss program would reduce FM while preserving LM.

METHODS

Participants

Fifty-four men with prostate cancer were screened from February 2018 to June 2019 in Perth, Western Australia. Potential participants were identified through clinician referral, advertisements in local newspapers, and presentations at cancer support groups and cancer-related events. Patients were screened for eligibility over the phone (n = 54) with a recruitment package mailed to interested and eligible patients (n = 27). Inclusion criteria were as follows: receiving ADT for a minimum of 6 months, anticipated to remain on ADT for the entire study period, and being obese, defined as a body fat percentage ≥25% (21) assessed by dual x-ray absorptiometry (DXA; Horizon A, Hologic, Waltham, MA) at their first visit. Exclusion criteria were as follows: presence of bone metastases, a secondary cancer diagnosis, a musculoskeletal or uncontrolled comorbidity preventing participation in moderate-to-vigorous intensity exercise, or did not speak English. Fourteen patients were recruited to the study after written informed consent, with further medical clearance gained from their general practitioner before baseline testing. The study was approved by the Edith Cowan University Human Research Ethics Committee (ID: 18832).

Study Design

This was a single-group, self-controlled 18-wk prospective study comprising a 6-wk control period during which patients undertook their usual activities and were not provided with any exercise or nutrition information, followed by a 12-wk exercise and nutrition weight loss intervention. The use of a self-controlled study design was deemed ethically appropriate for this population given the plethora of evidence highlighting exercise to be beneficial for prostate cancer patients on ADT. As such, the 6-wk control period was included in lieu of a randomized control trial design to inform whether the changes observed during the 12-wk intervention period were due to the intervention compared with activities of normal day-to-day living and usual care. Testing was conducted in the Exercise Medicine Research Institute (Edith Cowan University), over 2 to 3 nonconsecutive days at baseline (week 0), preintervention (week 6), and postintervention (week 18). Supervised exercise was conducted at exercise clinics in Joondalup or Mt Lawley (Edith Cowan University) nearest to each patient.

Exercise and Nutrition Intervention

Patients undertook combined aerobic and resistance training to accumulate 300 min of exercise per week for 12 wk. Patients attended three supervised resistance training sessions each week targeting the major muscle groups of the upper and lower body, with exercise variations provided every 3 wk. A periodized and progressive resistance training program was provided, with intensity ranging from 6 to 12 repetition maximum over 1–4 sets per exercise, with the load increased by 5%–10% based on a subjective assessment of the patient's

ability to complete the prescribed volume with the correct technique. Each session was designed to span 60 min in duration, including a 5- to 10-min aerobic-based warm-up and cool down. Patients also completed self-directed moderate-to-vigorous intensity aerobic exercise daily, defined as an RPE of 3–8 on the Borg 1–10 scale according to the Exercise and Sport Science Australia's exercise intensity guidelines (22), using modalities of their own choice. Patients were provided with an education booklet containing information on goal setting and exercise and nutrition advice to assist with construction of a self-directed home-based routine.

Patients attended three consultations with an Accredited Practising Dietitian including an initial session to complete a diet history at preintervention (week 6) and 2 nutrition counseling sessions during the first and third weeks of the 12-wk intervention. Individual nutrition goals were developed with each patient. The advice was designed to 1) establish an estimated energy deficit of 2100–4200 kJ (500–1000 kcal), 2) reduce consumption of discretionary items including alcoholic drinks and foods containing refined sugars, and 3) maintain protein intake. Patients were also provided with a 40-g whey protein supplement (Whey Protein Concentrate; Bulk Nutrients, Tasmania, Australia) three times per week immediately after each supervised resistance exercise session to support muscle protein synthesis.

Measurements

Body composition and anthropometry. The primary outcome FM (in kilograms), in addition to secondary outcomes total body mass (in kilograms), bone-mineral free LM (in kilograms), body fat percent, trunk FM (in kilograms), visceral FM (in grams), appendicular skeletal mass (ASM; in kilograms), and bone mineral content (BMC; in grams), was assessed by DXA. ASM was calculated as the sum of upper limb and lower limb LM (23). Waist and hip circumference (in centimeters) were measured with a constant-tension tape measure, and BMI was calculated as body mass in kilograms divided by height in meters squared ($kg \cdot m^{-2}$).

Muscle strength and cardiorespiratory fitness. Upper and lower body muscle strength was assessed using the one-repetition maximum (24) for the chest press, leg press, and seated row at baseline, preintervention, and postintervention, with a familiarization session provided before baseline. Cardiorespiratory fitness was assessed using a cardiopulmonary exercise test (CPET) at preintervention and postintervention only. Patients completed a standardized progressive maximal walking test (Modified Bruce Protocol) on a motorized treadmill (25) with expired gas collected via a face mask (Hans Rudolph Inc., Shawnee, KS) to obtain maximal oxygen consumption ($\dot{V}O_{2max}$; analyzed by TrueOne 2400; Parvo Medics, Salt Lake City, UT). The protocol included monitoring of heart rhythm and rate using a 12-lead ECG (CardioDirect 12S; SpaceLabs HealthCare, Snoqualmie, WA) supervised by a medical doctor. Patients completed a 3- to 5-min warm-up at a self-selected walking pace at 0% gradient that continued into stage 1 of the test (2.7 $km \cdot h^{-1}$, 0% gradient). Speed and/or gradient was increased every 3 min until the patient reached volitional fatigue, defined as an RPE of 9 or 10 on the 10-item Borg scale. A secondary criterion for attainment of $\dot{V}O_{2max}$ was a respiratory exchange ratio greater than 1.1. The test was concluded if the patient voluntarily stopped, or if signs of chest pain, dizziness, faintness, ischemic ECG changes, abnormal blood pressure, or significant symptoms of concern were evident. Total time of test (in seconds), absolute $\dot{V}O_{2max}$ (in liters per minute), and relative $\dot{V}O_{2max}$ (in milliliters per minute per kilogram) were recorded.

Blood biomarkers. Blood serum biomarkers were assessed at preintervention and postintervention. Patients attended a National Association of Testing Authorities–accredited phlebotomy clinic (Australian Clinical Laboratories, Perth, WA, Australia) where two serum separation tubes and one ethylenediaminetetraacetic acid tube were obtained in the morning after a minimum of 10-h overnight fast. Lipid profile including total cholesterol, HDL, LDL, triglycerides, C-reactive protein (CRP), insulin, hemoglobin A1c (HbA1c), testosterone, and prostate-specific antigen (PSA) were commercially analyzed (Australian Clinical Laboratories). Serum from one serum separation tube was stored in a −80°C alarm-controlled freezer at the Exercise Medicine Research Institute until analyzed for adiponectin, leptin, insulin-like growth factor-1 (IGF-1), IGF-binding protein-3 (IGFBP-3), and interleukin 6 (IL-6) in duplicate or triplicate, depending on agent volume available, using human serum enzyme-linked immunosorbent assays (Abcam, Cambridge, United Kingdom).

Monitoring intervention adherence. Adherence was assessed using a customized adherence questionnaire (Table, Supplemental Digital Content 1, adherence questionnaire, http://links.lww.com/MSS/C134) completed weekly during the 12-wk intervention. This questionnaire was adapted from Erdrich et al. (26) and Martínez-González et al. (27), and designed to provide an estimated frequency of consumption and number of serves of foods of interest over the previous week, based on the nutrition advice given, and whether patients completed at least 30 $min \cdot d^{-1}$ of purposeful exercise. Food items of interest included fruit, vegetables and nuts, high-protein foods, dairy, grains and cereals, beverages and alcoholic drinks, and discretionary and take-away items. It also addressed barriers and facilitators to meeting exercise and nutrition goals, which were discussed during supervised exercise sessions. Patients were asked 25 yes/no questions, where a score of 1 was given if the patient met a predetermined desired outcome or 0 if not. A higher total score indicated greater compliance, with a maximum score of 25. Adherence to the supervised resistance sessions was also recorded based on attendance and exercise volume completed each session compared with what was prescribed.

Physical activity monitoring. Physical activity and sedentary behavior were assessed using the ActiGraph wGT3X-BT (ActiGraph LLC, Pensacola, FL) at baseline, preintervention, midintervention, and postintervention. Patients wore the accelerometer on their hip for 3 consecutive days (1 weekend day and 2 weekdays) excluding water-based activities. ActiLife

software (ActiLife 6; ActiGraph LLC) was used to analyze the ActiGraph data. Only wake wear time was used with a minimal data collection period set for inclusion in analysis of 1 d of at least 600 min. Nonwear time was excluded from the analysis, defined as ≥90 min of consecutive zeros with a 2-min spike tolerance (28). Commonly used cutoff points among cancer patients were used to classify sedentary time (<100 counts per minute), light physical activity (100–1951 counts per minute), and moderate-to-vigorous physical activity (≥1952 counts per minute) (29–31).

Nutrition monitoring. Patients completed a 3-d weighed food record (3d-WR) over 3 consecutive days (1 weekend day and 2 weekdays) at baseline, preintervention, midintervention, and postintervention. This information provided an estimate of total energy intake (in kilojoules per day) and macronutrients and micronutrients consumed. The 3d-WR data were analyzed using FoodWorks (FoodWorks 10 Professional; Xyris Software Pty Ltd, Brisbane, QLD, Australia).

Statistical Analysis

Sample size was determined using data from three trials completed within the Exercise Medicine Research Institute (24,32,33). Based on a total sample of 78 prostate cancer patients undertaking ADT who had completed an exercise program of 12 or 24 wk in duration, the calculated SD of change for our primary outcome FM was 2.1 kg. The goal was to achieve a ≥2-kg reduction in FM over the 12-wk intervention period, which would be considered clinically significant (≥5% reduction) (34). For a single-group study design, 12 patients were required to achieve power of 90% at an α of 0.05 (two-tailed). To account for a potential dropout of ~15%, our goal was to recruit 14 patients. Data were analyzed using IBM SPSS version 25 (SPSS Inc., IBM Corp, Armonk, NY). Normality of the distribution was assessed using the Shapiro–Wilk test. Analysis included one-way repeated-measures ANOVA followed by a Bonferroni *post hoc* test to account for multiple comparisons, or Friedman's ANOVA for nonnormally distributed data followed by a Bonferroni-adjusted Wilcoxon signed rank test to locate significant differences, as appropriate. Associations between variables were assessed using Pearson correlation or Spearman rank correlation, as appropriate. Data are presented as mean ± SD, median and interquartile range (IQR), or number (percentage). All tests were two-tailed with statistical significance set at $P < 0.05$.

RESULTS

Fourteen men with prostate cancer age 48 to 84 yr were included in the study (Table 1). Most patients had a Gleason score of 9 (57.1%), with 42.9% diagnosed with metastatic prostate cancer in lymph nodes or organs at study entry. All patients were on ADT for a minimum of 6 months (range, 6–55 months), and 13 men had additional therapy, mainly radiation (92.9%). Two patients withdrew after baseline testing (loss to follow-up, time commitment), and a third withdrew at preintervention testing (family commitments). Eleven patients (age 63–82 yr) completed the 12-wk intervention. There was a significant increase in the weekly adherence questionnaire score from 14.6 ± 2.2 at week 1 of the intervention to 17.6 ± 2.3 at week 12 ($P = 0.001$). Changes for physical activity and nutrition over the control period and intervention are provided in the supplementary materials (Tables; Supplemental Digital Content 2, physical activity and sedentary data, http://links.lww.com/MSS/C135; Supplemental Digital Content 3, nutritional intake, http://links.lww.com/MSS/C136). No significant differences were observed during the 6-wk control period. Patients attended 89% of the 36 supervised resistance training sessions (range, 25–36 sessions), with a 100% compliance in consuming the whey protein supplement after every attended session. Number of sessions missed, modified, or completed as prescribed is provided in the supplemental figure (Figure, Supplemental Digital Content 4, adherence to supervised resistance exercise sessions, http://links.lww.com/MSS/C137). No significant changes in physical activity occurred during the intervention, with a nonsignificant decrease from preintervention to postintervention in sedentary behavior (68.4% ± 9.5% vs 64.9% ± 5.3%, $P = 0.110$) and an increase in light-intensity physical activity (31.1% ± 9.3% vs 34.5% ± 5.3%, $P = 0.083$). Patients attended 100% of the nutrition consultations. During the 12-wk intervention, there was a modest nonsignificant reduction in mean energy intake from 7728 ± 1131 kJ at preintervention to 7268 ± 2209 kJ at postintervention. There was a significant difference across the four time points for percent protein intake (baseline: 19.3% ± 1.6%, preintervention: 17.9% ± 2.4%, midintervention: 21.8% ± 2.9%, postintervention: 20.8% ± 4.0%, $P = 0.016$); however, the *post hoc* test was unable to locate the source of the difference. No other significant differences were found.

Body composition. No significant changes in body composition were observed during the 6-wk control period (Table 2). From preintervention to postintervention, there were significant reductions

TABLE 1. Baseline patient characteristics of men with prostate cancer.

Variable	Patients (n = 14)
Age, mean ± SD, yr	72 ± 9
BMI, mean ± SD, kg·m^{-2}	34.4 ± 6.4
Postsecondary education, *n* (%)	8 (57.1)
Married, *n* (%)	14 (100)
Employed, *n* (%)	4 (28.6)
No. medications/supplements, mean ± SD	4.2 ± 2.7
No. comorbidities, mean ± SD[a]	3.0 ± 1.7
Years since prostate cancer diagnosis, median (IQR), yr	1.8 (1.2–5.6)
Gleason score, *n* (%)	
Gleason 7	4 (28.6)
Gleason 8	1 (7.1)
Gleason 9	8 (57.1)
Gleason 10	1 (7.1)
Contained within prostate, *n* (%)	8 (57.1)
Lymph node metastases, *n* (%)	4 (28.6)
Organ metastases, *n* (%)[b]	2 (14.3)
ADT, *n* (%)	
Gonadotropin-releasing hormone agonist + antiandrogen	8 (57.1)
Gonadotropin-releasing hormone agonist only	5 (35.7)
Antiandrogen only	1 (7.1)
Months on ADT, median (IQR)	13.5 (6.7–23.3)
Other prostate cancer–related treatment, *n* (%)	
Surgery	4 (28.6)
Radiation therapy	13 (92.9)
Chemotherapy	2 (14.3)

[a]Arthritis, atrial fibrillation, CVD, carpel tunnel syndrome, colitis, dyslipidemia, hypertension, sleep apnea, thyroid disease, emphysema, type 2 diabetes, peripheral neuropathy, anxiety disorder.
[b]Lung.

TABLE 2. Body composition and anthropometry at baseline, preintervention, and postintervention.

Variable	Baseline	Preintervention	Postintervention	*P*	Comparison
Total body mass, kg	98.6 ± 15.1	98.3 ± 14.7	95.5 ± 14.1	0.016	3 < 2
Total FM, kg	40.4 ± 10.2	39.8 ± 10.3	37.0 ± 9.5	<0.001	3 < 2, 1
% body fat	40.5 ± 4.7	40.0 ± 4.9	38.3 ± 4.6	<0.001	3 < 2, 1
Trunk fat, kg	20.6 ± 6.3	20.1 ± 5.9	18.3 ± 5.4	<0.001	3 < 2, 1
Visceral fat, g	922 ± 293	954 ± 372	866 ± 333	0.023	3 < 2
Total LM, kg	55.6 ± 6.6	55.9 ± 6.5	55.9 ± 6.2	0.805	—
ASM, kg	23.2 ± 3.3	23.3 ± 3.3	23.3 ± 3.1	0.695	—
BMC, g	2610 ± 283	2567 ± 278	2576 ± 291	0.082	—
Waist circumference, cm	109.2 ± 11.5	108.7 ± 10.8	103.9 ± 8.9	0.002	3 < 1, 2
Hip circumference, cm	113.8 ± 8.4	113.5 ± 7.6	109.7 ± 8.1	0.008	3 < 1, 2

Values are the mean ± SD or median (IQR).
1, baseline; 2, preintervention; 3, postintervention.

in total body mass (−2.8 ± 3.2 kg), FM (−2.8 ± 2.6 kg), trunk FM (−1.8 ± 1.4 kg), and visceral FM (−88 ± 87 g; all, $P < 0.05$), whereas LM (−0.05 ± 1.6 kg), ASM (0.06 ± 0.82 kg), and BMC (8 ± 58 g) were preserved. The mean reduction in total FM was 6.8%, and for trunk FM it was 8.8%. FM was primarily lost from the trunk (84.8%), accompanied by a significant decrease in waist (−4.8 ± 3.5 cm) and hip circumferences (−3.8 ± 4.1 cm). Individual changes in body composition are presented in Figure 1. All but one patient lost FM, whereas the results were mixed for LM, with about half of the patients gaining and half experiencing a reduction.

Muscle strength and cardiorespiratory fitness. Muscle strength did not significantly change during the 6-wk control period (Table 3). After training, there was a significant increase in leg press (24.7% ± 24.5%) and chest press (19.8% ± 16.5%) strength compared with baseline and preintervention (Table 3). There was also a significant change for seated row strength ($P = 0.006$); however, *post hoc* analysis was not able to locate the source of the difference. Patients improved their cardiorespiratory fitness with a significant increase in CPET time of 83 ± 78 s from preintervention to postintervention, and a significant increase in $\dot{V}O_{2max}$ of a 3.5 ± 4.7 mL·min^{-1}·kg^{-1} ($P = 0.041$).

Blood biomarkers. Mean preintervention and postintervention concentrations of blood biomarkers (lipid profile, CRP, insulin, and HbA1c) were within the recommended reference ranges, except for LDL, which was higher (reference range, <2.5 nmol·L^{-1}; preintervention, 2.8 ± 1.4 nmol·L^{-1}; postintervention, 2.6 ± 1.2 nmol·L^{-1}; Table 4). There was no change in

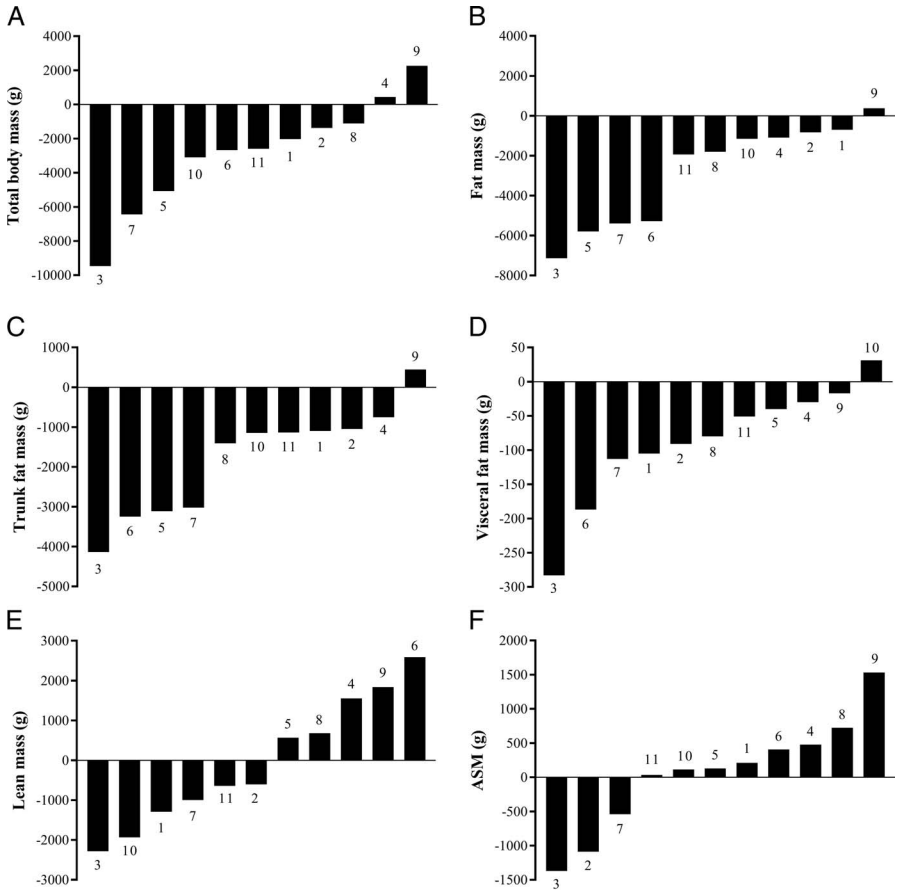


FIGURE 1—Waterfall plots of individual patients in ascending order showing change in total body mass (A), total FM (B), trunk FM (C), visceral FM (D), total LM (E), and ASM (F) over a 12-wk weight loss intervention. Individual patient numbers are identified in association with the *bars*.

TABLE 3. Muscle strength and cardiorespiratory fitness at baseline, preintervention, and postintervention.

Variable	Baseline	Preintervention	Postintervention	*P*	Comparison
Muscle strength					
Leg press, kg	90.0 (69.8–108.0)	87.8 (72.0–120.0)	101.3 (87.8–145.0)	<0.001	3 > 1, 2
Chest press, kg[a]	41.3 ± 10.1	44.5 ± 12.7	52.4 ± 12.7	<0.001	3 > 1, 2
Seated row, kg	62.6 ± 7.0	64.8 ± 7.3	67.7 ± 7.7	0.006	—
Cardiorespiratory fitness					
CPET time[a], s	—	660 ± 173	743 ± 163	0.008	—
Relative $\dot{V}O_{2max}$[a], mL·min^{-1}·kg^{-1}	—	16.5 ± 4.8	20.0 ± 5.0	0.041	—
Absolute $\dot{V}O_{2max}$[a], L·min^{-1}	—	1.6 ± 0.5	1.9 ± 0.5	0.071	—

Values are the mean ± SD or median (IQR).
[a]Only n = 10 patients completed both chest press and CPET at all time points.
1, baseline; 2, preintervention; 3, postintervention.

any of the biomarkers over the 12-wk intervention, except for a decrease in leptin concentration (P = 0.016; Table 4). Significant inverse associations were evident between the change in LM and change in CRP (r_s = −0.670, P = 0.024) and triglycerides (r = −0.667, P = 0.025).

Adverse events. No adverse events occurred during the supervised exercise sessions. One patient was referred to their general practitioner as a precaution because of an abnormal ECG result after completing the CPET but was cleared of any cardiac concerns. During home-based exercise, two patients described back pain while walking. This was addressed by reducing the volume of supervised exercise and removal of exercises involving the back until pain was reduced. One patient experienced an infected leg wound caused by resistance band exercises completed at home. Resistance band exercises were ceased, and all exercises putting pressure on the wound were removed until healed.

DISCUSSION

This study evaluated an exercise and nutrition weight loss program in obese prostate cancer patients undertaking ADT to induce fat loss while preserving LM. There were three important findings: 1) total and regional FM significantly decreased, whereas LM was preserved; 2) muscle strength and cardiorespiratory fitness significantly improved; and 3) serum leptin concentrations significantly decreased, with changes in serum CRP and triglycerides inversely associated with the individual changes in LM.

Body mass is associated with prostate cancer recurrence after prostatectomy, where weight gain of more than 2.2 kg increases the risk twofold, whereas weight loss potentially reduces risk (3). We found a significant 2.8-kg mean decrease in total body mass, which was attributed to a loss of FM. Notably, the majority of fat loss occurred in the abdominal region from a loss in trunk FM. FM loss ranged from −0.7 to −7.1 kg and was observed in 10 (90.9%) patients. O'Neill et al. (17) and Focht et al. (18) also examined combined exercise and nutrition interventions in prostate cancer patients on ADT and reported significant fat losses of 1.8 and 1.9 kg, respectively. In contrast to the individualized nutrition advice prescribed in the present study aiming to induce an energy deficit, reduce discretionary items, and optimize protein intake, both O'Neill et al. (17) and Focht et al. (18) followed healthy eating guidelines. O'Neill et al. (17) also provided tailored nutrition advice; however, only participants who were overweight were prescribed an energy deficit, whereas the Focht et al. (18) study mostly utilized group nutrition sessions. Although the nutrition and physical activity changes were modest in the present study, the individualized nutrition advice as well as the greater exercise volume (300 vs 150 min·wk^{-1}) prescribed likely contributed to the greater FM loss. In another weight loss study conducted in overweight and obese men with prostate cancer, Freedland et al. (16) reported an FM loss of 8.2 kg. The greater fat loss was due to the carbohydrate-restricted diet utilized resulting in a significant energy deficit, in contrast to the lack of significant energy deficit in the present study. However, Freedland et al. (16) only included walking in their exercise

TABLE 4. Serum blood biomarkers associated with obesity and prostate cancer progression.

Variable	Preintervention	Postintervention	*P*	Reference Range[a]
Insulin, mmol·L^{-1}	9.0 (8.0–23.0)	9.0 (6.0–23.0)	0.262	2–12
CRP, mg·L^{-1}	1.3 (0.7–4.0)	2.8 (0.7–5.8)	0.612	<3.0
Total cholesterol, mmol·L^{-1}	4.7 ± 1.5	4.5 ± 1.4	0.438	<5.6
LDL cholesterol, mmol·L^{-1}	2.8 ± 1.4	2.6 ± 1.2	0.387	<2.5
HDL cholesterol, mmol·L^{-1}	1.3 ± 0.5	1.3 ± 0.4	0.255	>1.0
Triglycerides, mmol·L^{-1}	1.2 ± 0.5	1.3 ± 0.6	0.295	<2.0
HbA1c, mmol·mol^{-1}	41.0 (38.0–48.0)	42.0 (39.0–48.0)	0.765	<48
Testosterone, nmol·L^{-1}	0.1 (0.1–0.4)	0.1 (0.1–0.3)	0.257	NA
PSA, µg·L^{-1}	0.30 (0.02–2.27)	0.39 (0.01–2.21)	0.213	NA
Leptin, ng·mL^{-1}	6.3 (4.7–14.3)	6.1 (3.3–11.7)	0.016	—
Adiponectin, µg·mL^{-1}	65.5 ± 34.6	58.5 ± 24.4	0.215	—
IGFBP-3, ng·mL^{-1}	139.2 ± 55.8	135.3 ± 46.7	0.529	—
IGF-1 (n = 9), ng·mL^{-1}	9.3 (1.6–294.8)	10.8 (2.0–348.4)	0.051	—
IL-6 (n = 8), pg·mL^{-1}	4.7 (3.0–37.9)	5.5 (1.7–51.1)	0.327	—

Values are the mean ± SD or median (IQR).
[a]Reference ranges were obtained from Australian Clinical Laboratory pathology reports for the standard of care blood biomarkers.
NA, not applicable.

program, which was not sufficient to stimulate muscle protein synthesis as the FM loss was accompanied by a significant 2.1-kg LM loss. We also provided data on trunk and estimated-visceral fat loss, which, to our knowledge, has not been measured in any combined exercise and nutrition study in men on ADT. Visceral fat is more metabolically active compared with subcutaneous fat and has been associated with increased risk of progression to advanced prostate cancer (5), as well as the development of comorbidities such as diabetes (35). Therefore, the observed reduction in visceral fat may be of greater clinical importance than the reduction in total FM.

Contrary to previous weight loss studies in ADT-treated prostate cancer patients reporting significant losses of LM or utilizing less accurate measuring techniques such as skinfolds to estimate LM (16,17), our study showed that LM can be preserved concurrent to significant FM loss. Despite the overall preservation of LM, five (45.5%) patients experienced a gain in total LM. Responders (LM gain) and nonresponders (LM loss) to exercise have been previously demonstrated in the prostate cancer population on ADT (36). The reasons for the difference in response in our cohort, that is, some gained LM and others lost LM, are unclear. Considerations include absolute weight at preintervention, amount of FM lost, intensity and volume of resistance and aerobic exercise, and protein intake. However, no relationships were found between these variables and change in LM. During the intervention, patients consumed a mean daily intake of 1.0 $g \cdot kg^{-1}$ body weight (BW) of protein, inclusive of the protein supplement consumed 3 $d \cdot wk^{-1}$, which is slightly lower than the 1.07 $g \cdot kg^{-1}$ BW daily recommendation for men older than 70 yr (37). It is possible this was too low to adequately support muscle protein synthesis, although daily average protein intake increased to 1.2 $g \cdot kg^{-1}$ BW on the day of resistance training when the protein supplement was provided, where similar protein intakes, in conjunction with resistance training, have been previously shown in prostate cancer patients on ADT to acutely increase muscle protein synthesis (38). However, anabolic suppression (i.e., a blunted training response) to resistance training while in an energy deficit state has been previously demonstrated even in the presence of protein supplementation and adequate daily protein intake of 1.2 $g \cdot kg^{-1}$ BW, and may have been a contributing factor to the observed LM changes in our study (39). Dawson et al. (40) conducted a resistance training intervention in prostate cancer patients on ADT using four groups, exercise, exercise and protein supplement, protein supplement, and control, providing a daily protein supplement of 50 g, which is higher than the protein supplement of 40 g provided 3 $d \cdot wk^{-1}$ in the current study. They found a significant increase in LM with exercise but no additional effect from the protein supplement. However, this study was not powered to assess the effect of protein intake across the four study arms. The optimal protein intake to effect body composition changes in prostate cancer patients requires further examination.

Although the desired loss of FM and preservation of LM are likely attributable to the intervention, the accelerometry and 3d-WR did not indicate a change in incidental physical activity or nutritional intake during the intervention, with the exception of percent of daily intake contributed to by protein. Several patients ($n = 5$) reported undertaking home-based cycling, and all patients attended resistance training sessions, both modes of which are not accurately captured with the ActiGraph technology used in this study and may explain the lack of change in accelerometry-measured physical activity (31). In addition, the use of individual nutrition goals may further explain the lack of a significant energy deficit. Individual goals were selected with the intention that patients would be more compliant to nutrition changes if goals were tailored to their lifestyle. Although all patients were advised to reduce meal portion sizes, specific goals such as reduction in alcohol or cake/biscuit intake, or increase amount of fruit per day, were better adhered to as indicated in discussions during supervised exercise sessions when completing the weekly adherence questionnaire. Irrespective of the lack of observable change in accelerometry and 3d-WR data, there was a high adherence to the resistance training sessions, protein supplement, and dietitian consultations demonstrating a change in exercise and nutritional habits.

LM can be substantially lost with energy-restricted diets (41). Therefore, it is important to ensure physical function is maintained, as a loss in either muscle strength or cardiorespiratory fitness is associated with clinical morbidity (42,43). Accompanying the significant loss in FM and preservation of LM, our study showed a significant increase in upper and lower body muscle strength. We also found a significant increase in the length of time patients could sustain the CPET (83 ± 78 s) and an increase in relative $\dot{V}O_{2max}$ of 3.5 ± 4.7 $mL \cdot min^{-1} \cdot kg^{-1}$ indicating increased cardiorespiratory fitness. These findings of increased muscle strength and cardiorespiratory fitness while undergoing weight loss are consistent with other combined exercise and nutrition interventions in ADT-treated prostate cancer patients (16–18). In addition, the current study provides more comprehensive and valid results by reporting directly measured $\dot{V}O_{2max}$ using a maximal CPET, rather than the submaximal tests used by other combined intervention studies.

Weight loss is recommended as a viable strategy to decrease an obese patient's increased risk of prostate cancer progression by improving insulin/IGF axis and sex hormone concentrations, and the signaling of adipokines and cytokines (3,6). In our study, a significant decline in leptin was found, where eight (72.7%) patients showed a decrease in serum concentration. Although the change in leptin was not associated with change in body mass or FM in the current study, Santa Mina et al. (44) in a larger sample size of 44 prostate cancer patients on ADT showed a significant positive association between a reduction in leptin and reductions in BMI, waist circumference, and body mass after the completion of a home-based exercise program. Serum leptin has been associated with prostate cancer progression, mostly in androgen-independent prostate cancers; however, the evidence is inconsistent (45,46). Nevertheless, there is preliminary evidence indicating that weight loss may slow down prostate cancer progression by increasing PSA doubling time (47). Further research is required to examine whether a reduction in FM can affect prostate cancer progression, as our study found

no change in IGF-1, IGFBP-3, IL-6, or adiponectin, which are potentially more strongly associated with prostate cancer progression than leptin (6). Our study also found that those who had a higher increase in CRP lost greater LM. CRP is an inflammatory biomarker with high levels associated with increased risk of CVD (48). An increase in triglycerides, which is a known risk factor for CVD (49), was also associated with a loss in LM. These associations highlight the importance of targeting both FM and LM when undertaking a weight loss program.

Strengths and limitations. This study has several strengths. The use of DXA permitted the evaluation of not only whole body but also regional changes in FM, that is, trunk FM and visceral FM. The weight loss intervention had a high adherence rate, with patients attending 100% of nutrition consultations and 89% of supervised resistance training sessions. The intervention also has external validity. Patients adopted exercise and nutrition-based lifestyle changes, which are growing in awareness as important adjuvant therapies to improve treatment-related outcomes such as body composition and physical function. Study limitations include a small sample size, although recruitment was powered for our primary outcome, and the lack of a separate control group, which prevented comparison of our results to usual care. Although this study had a small sample, the minimal recruitment goals were met. Furthermore, the study was designed to include an initial 6-wk period with no intervention, where each patient acted as their own control. As no changes were observed in any variable during the 6-wk control period, it is assumed the changes observed during the 12-wk intervention resulted from the exercise and nutrition weight loss program. Lastly, as stated previously, the ActiGraph technology used in this trial may not have been the most appropriate to assess resistance training and cycling activities.

CONCLUSIONS

This study shows preliminary efficacy for an exercise and nutrition weight loss program to induce FM loss and preserve LM in obese prostate cancer patients undergoing ADT. Muscle strength and cardiorespiratory fitness were also significantly improved. Because FM is associated with obesity-related comorbidities and prostate cancer progression, it is important to monitor body composition, particularly in patients where the treatment is likely to substantially alter FM and LM. To extend the findings of this study, larger-scale studies are required to examine the metabolic significance of purposeful FM loss in obese prostate cancer patients, as it is unclear if reductions in FM will reduce cancer progression and improve survivorship. Furthermore, the translation of this intervention to other populations such as non–ADT-treated prostate cancer, breast cancer, and colorectal cancer patients, where obesity is a contributor to poor patient outcomes, should also be of interest.

The authors would like to acknowledge the valuable contribution of the participants, who donated their time and effort to complete the research study, and five Master of Nutrition and Dietetic students at Edith Cowan University—Thomas Hosking, Sabina Ferri, Rebecca Newton, Sarah Forrest, and Marija Karanfilovska—for their expertise and analysis of nutrition-related questionnaires.

R. L. W. is supported by an Australian Government Research Training Program Scholarship. R. U. N. is supported by a Vice-Chancellor Professorial Research Fellowship. N. H. H. is supported by a Cancer Council of Western Australia Postdoctoral Research Fellowship. NHMRC Centre for Research Excellence funding supported this project in addition to allocated funds from Edith Cowan University.

The authors declare they have no conflict of interest.

The results of the present study do not constitute endorsement by the American College of Sports Medicine. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Ethical approval was gained from Human Research Ethics Committee at Edith Cowan University (ID: 18832). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consent was obtained from participating patients after reading an information letter outlining study procedures, risks, and benefits.

The contributions of each author are as follows: R. L. W., significant manuscript writer, concept and design, data acquisition, and data analysis and interpretation; R. U. N., significant manuscript reviewer/revisor and concept and design; D. R. T., significant manuscript reviewer/revisor, concept and design, and statistical expertise; N. H. H., significant manuscript reviewer/revisor and concept and design; P. L.- W., significant manuscript reviewer/revisor, concept and design, and data acquisition; D. A. G., significant manuscript reviewer/revisor and concept and design.

REFERENCES

1. Salji M, Hendry J, Patel A, Ahmad I, Nixon C, Leung HY. Peri-prostatic fat volume measurement as a predictive tool for castration resistance in advanced prostate cancer. *Eur Urol Focus*. 2018;4(6):858–66.
2. World Cancer Research Fund, American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and prostate cancer. 2018. Available from: https://www.wcrf.org/dietandcancer/prostate-cancer. Accessed May 20, 2020.
3. Joshu CE, Mondul AM, Menke A, et al. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. *Cancer Prev Res (Phila)*. 2011;4(4):544–51.
4. Bray GA. Medical consequences of obesity. *J Clin Endocrinol Metab*. 2004;89(6):2583–9.
5. Dickerman BA, Torfadottir JE, Valdimarsdottir UA, et al. Body fat distribution on computed tomography imaging and prostate cancer risk and mortality in the AGES-Reykjavik study. *Cancer*. 2019;125(16):2877–85.
6. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol*. 2013;63(5):800–9.
7. Keto CJ, Aronson WJ, Terris MK, et al. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. *BJU Int*. 2012;110(4):492–8.
8. Rhee H, Gunter JH, Heathcote P, et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. *BJU Int*. 2015;115(5 Suppl):3–13.
9. Galvao DA, Spry NA, Taaffe DR, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int*. 2008;102(1):44–7.
10. Newton RU, Jeffery E, Galvao DA, et al. Body composition, fatigue and exercise in patients with prostate cancer undergoing androgen-deprivation therapy. *BJU Int*. 2018;122(6):986–93.
11. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Acute versus chronic exposure to androgen suppression for prostate cancer: impact on the exercise response. *J Urol*. 2011;186(4):1291–7.
12. Bourke L, Smith D, Steed L, et al. Exercise for men with prostate cancer: a systematic review and meta-analysis. *Eur Urol*. 2016;69(4):693–703.

13. Lin PH, Aronson W, Freedland SJ. Nutrition, dietary interventions and prostate cancer: the latest evidence. *BMC Med*. 2015;13(1):3.
14. Hackshaw-McGeagh LE, Perry RE, Leach VA, et al. A systematic review of dietary, nutritional, and physical activity interventions for the prevention of prostate cancer progression and mortality. *Cancer Causes Control*. 2015;26(11):1521–50.
15. Barnes KA, Ball LE, Galvao DA, Newton RU, Chambers SK. Nutrition care guidelines for men with prostate cancer undergoing androgen deprivation therapy: do we have enough evidence? *Prostate Cancer Prostatic Dis*. 2019;22(2):221–34.
16. Freedland SJ, Howard L, Allen J, et al. A lifestyle intervention of weight loss via a low-carbohydrate diet plus walking to reduce metabolic disturbances caused by androgen deprivation therapy among prostate cancer patients: Carbohydrate and Prostate Study 1 (CAPS1) randomized controlled trial. *Prostate Cancer Prostatic Dis*. 2019;22(3):428–37.
17. 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;9(3):431–40.
18. Focht BC, Lucas AR, Grainger E, et al. Effects of a group-mediated exercise and dietary intervention in the treatment of prostate cancer patients undergoing androgen deprivation therapy: results from the IDEA-P trial. *Ann Behav Med*. 2018;52(5):412–28.
19. Soenen S, Martens EA, Hochstenbach-Waelen A, Lemmens SG, Westerterp-Plantenga MS. Normal protein intake is required for body weight loss and weight maintenance, and elevated protein intake for additional preservation of resting energy expenditure and fat free mass. *J Nutr*. 2013;143(5):591–6.
20. Skolarus TA, Wolf AM, Erb NL, et al. American Cancer Society prostate cancer survivorship care guidelines. *CA Cancer J Clin*. 2014;64(4):225–49.
21. Okorodudu DO, Jumean MF, Montori VM, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. *Int J Obes (Lond)*. 2010;34(5):791–9.
22. Exercise and Sport Science Australia. Exercise intensity guidelines. 2011 [cited 2018]. Available from: https://www.essa.org.au/wp-content/uploads/2014/06/Exercise-Intensity-Guildines.pdf.
23. Heymsfield SB, Smith R, Aulet M, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr*. 1990;52(2):214–8.
24. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*. 2010;28(2):340–7.
25. Lerman J, Bruce RA, Sivarajan E, Pettet GE, Trimble S. Low-level dynamic exercises for earlier cardiac rehabilitation: aerobic and hemodynamic responses. *Arch Phys Med Rehabil*. 1976;57(8):355–60.
26. Erdrich S, Bishop KS, Karunasinghe N, Han DY, Ferguson LR. A pilot study to investigate if New Zealand men with prostate cancer benefit from a Mediterranean-style diet. *PeerJ*. 2015;3:e1080.
27. Martínez-González MA, García-Arellano A, Toledo E, et al, PREDIMED Study Investigators. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. *PLoS One*. 2012;7(8):e43134.
28. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. *Med Sci Sports Exerc*. 2011;43(2):357–64.
29. Matthews CE, Chen KY, Freedson PS, et al. Amount of time spent in sedentary behaviors in the United States, 2003–2004. *Am J Epidemiol*. 2008;167(7):875–81.
30. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. *Med Sci Sports Exerc*. 1998;30(5):777–81.
31. Peddle-McIntyre CJ, Cavalheri V, Boyle T, et al. A review of accelerometer-based activity monitoring in cancer survivorship research. *Med Sci Sports Exerc*. 2018;50(9):1790–801.
32. Taaffe DR, Newton RU, Spry N, et al. Effects of different exercise modalities on fatigue in prostate cancer patients undergoing androgen deprivation therapy: a year-long randomised controlled trial. *Eur Urol*. 2017;72(2):293–9.
33. Cormie P, Galvao DA, Spry N, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU Int*. 2015;115(2):256–66.
34. Jensen MD, Ryan DH, Donato KA, et al. Executive summary: guidelines (2013) for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society published by the Obesity Society and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Based on a systematic review from The Obesity Expert Panel, 2013. *Obesity*. 2014;22(S2):S5–39.
35. Bray GA, Jablonski KA, Fujimoto WY, et al. Relation of central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. *Am J Clin Nutr*. 2008;87(5):1212–8.
36. Taaffe DR, Newton RU, Spry N, Joseph DJ, Galvao DA. Responsiveness to resistance-based multimodal exercise among men with prostate cancer receiving androgen deprivation therapy. *J Natl Compr Canc Netw*. 2019;17(10):1211–20.
37. Capra S, Members of the Working Party. *Nutrient Reference Values for Australia and New Zealand: Including Recommended Dietary Intakes*. Canberra, Australia: Commonwealth of Australia; 2006.
38. Hanson ED, Nelson AR, West DW, et al. Attenuation of resting but not load-mediated protein synthesis in prostate cancer patients on androgen deprivation. *J Clin Endocrinol Metab*. 2017;102(3):1076–83.
39. Murphy C, Koehler K. Caloric restriction induces anabolic resistance to resistance exercise. *Eur J Appl Physiol*. 2020;120(5):1155–64.
40. Dawson JK, Dorff TB, Todd Schroeder E, Lane CJ, Gross ME, Dieli-Conwright CM. Impact of resistance training on body composition and metabolic syndrome variables during androgen deprivation therapy for prostate cancer: a pilot randomized controlled trial. *BMC Cancer*. 2018;18(1):368.
41. Weinheimer EM, Sands LP, Campbell WW. A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. *Nutr Rev*. 2010;68(7):375–88.
42. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *BMJ*. 2008;337(7661):a439.
43. Davidson T, Vainshelboim B, Kokkinos P, Myers J, Ross R. Cardiorespiratory fitness versus physical activity as predictors of all-cause mortality in men. *Am Heart J*. 2018;196:156–62.
44. Santa Mina D, Connor MK, Alibhai SM, et al. Exercise effects on adipokines and the IGF axis in men with prostate cancer treated with androgen deprivation: a randomized study. *Can Urol Assoc J*. 2013;7(11–12):E692–8.
45. Li H, Stampfer MJ, Mucci L, et al. A 25-year prospective study of plasma adiponectin and leptin concentrations and prostate cancer risk and survival. *Clin Chem*. 2010;56(1):34–43.
46. Di Sebastiano KM, Pinthus JH, Duivenvoorden WC, Patterson L, Dubin JA, Mourtzakis M. Elevated C-peptides, abdominal obesity, and abnormal adipokine profile are associated with higher Gleason scores in prostate cancer. *Prostate*. 2017;77(2):211–21.
47. Freedland SJ, Allen J, Jarman A, et al. A randomized controlled trial of a 6-month low-carbohydrate intervention on disease progression in men with recurrent prostate cancer: Carbohydrate And Prostate Study 2 (CAPS2). *Clin Cancer Res*. 2020;26(12):3035–43.
48. Ridker PM, Bassuk SS, Toth PP. C-reactive protein and risk of cardiovascular disease: evidence and clinical application. *Curr Atheroscler Rep*. 2003;5(5):341–9.
49. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;384(9943):626–35.

CHAPTER SIX

Quality of life outcomes in obese men with prostate cancer on androgen deprivation therapy undergoing planned weight loss

Rebekah L. Wilson; Dennis R. Taaffe; Robert U. Newton; Nicolas H. Hart; Philippa Lyons-Wall; Daniel A. Galvão.

This is a short clinical communication formated to a word count of 1500 and 10 reference limit for Psycho-Oncology.

INTRODUCTION

Androgen deprivation therapy (ADT) has a number of adverse effects that can reduce the quality of life (QoL) in men with prostate cancer [1]. Specifically, common ADT-related side effects, including fat gain and muscle loss, predisposes prostate cancer patients to obesity or sarcopenic obesity, which increases their risk of developing obesity-related comorbidities, frailty, disability, and prostate cancer progression, and may exacerbate declines in QoL [2]. ADT may be prescribed for several months, years, or indefinitely, and as such, patients may experience long-term treatment-related side effects that need to be monitored throughout the natural history of the cancer to ensure the best QoL is experienced [1].

In the prostate cancer population, exercise interventions have had a positive effect on QoL, independent of weight loss [3]. However, the effect of combined exercise and nutrition inducing weight loss, and their effect on QoL, are underrepresented in the prostate cancer literature [3]. Further, the generalisability of exercise and nutrition interventions is unclear, as many studies are conducted in relatively healthy prostate cancer populations, e.g. non-sedentary and non-obese [3]. It is critical to understand if various populations and intervention types invoke different responses so that treatments and interventions can be better tailored to the patient. Therefore, we report changes in QoL from a single-cohort, prospective weight loss intervention in obese prostate cancer patients undertaking ADT; a population at increased risk of poor patient outcomes. Our combined exercise and nutrition-based weight loss intervention reduced fat mass and preserved lean mass with a mean change of -2.8 kg and -0.05 kg, respectively, and led to improvements in muscle strength and cardiorespiratory fitness (Chapter 5). We hypothesised that a combined exercise and nutrition weight loss intervention would improve general health-related and prostate cancer-specific QoL.

METHODS

Fourteen obese prostate cancer patients on ADT were recruited and 11 patients completed a 6-week control period followed by a 12-week exercise and nutrition-based weight loss intervention (see Chapter 5). Assessments were conducted at baseline (Week-0), pre-intervention (Week-6), and post-intervention (Week-18). The exercise intervention was designed so that patients accumulated a total of 300 minutes each week of exercise, including 3 supervised resistance training sessions combined with daily home-based aerobic exercise. Patients attended 2 nutrition counselling sessions where individually tailored nutrition goals were provided to induce a daily energy deficit of 2100 – 4200 kJ and optimise protein intake, which included a 40g whey protein supplement after each supervised resistance exercise session. The study was approved by the Human Research Ethics Committee at Edith Cowan University (ID: 18832).

General health-related QoL was assessed via the 36-Item Short-Form Health Survey (SF-36; Version 2) (Appendix C2) [4]. The SF-36 comprises eight domains of perceived health status including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, where a higher score indicates an improved perceived status, with two summary scores derived, a physical component summary and mental component summary. Prostate cancer-specific QoL was assessed via the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Prostate Cancer Module (QLQ-PR25) (Appendix C3) [5]. The QLQ-PR25 comprises the domains of urinary, bowel, and hormonal treatment symptoms, and sexual activity, where higher scores reflect more symptoms (urinary, bowel, hormonal treatment) or higher levels of functioning (sexual).

Data were analysed using IBM SPSS version 25 (SPSS Inc., IBM Corp, Armonk, NY, USA). Normality of the distribution was assessed using the Shapiro-Wilk test. Analysis included one-way repeated measures ANOVA or Friedman's ANOVA for non-normally distributed data. Data are reported as mean ± standard deviation (SD) and median or interquartile range [IQR]. All tests were two-tailed with statistical significance set at $p < 0.05$.

RESULTS

This analysis included 11 obese prostate cancer patients aged 62 to 80 years. More than half of the patients had a Gleason score of 9 (54.5%), with 54.5% diagnosed with metastatic cancer in the lymph nodes or organs. Patients had received ADT for a median of 16 [9 – 27] months, and 90.9% received other prostate cancer-related treatment, mainly radiation therapy (90.9%). Patients had a mean of 3.4 ± 1.4 comorbidities with hypertension (63.6%), dyslipidaemia (63.6%), and arthritis (54.5%) being the most common.

There were no significant changes observed for general health-related or prostate cancer-specific QoL over the control period (Table 6.1 and 6.2). Over the 12-week weight loss intervention, general health-related QoL was maintained ($p = 0.142$ - 0.902) (Table 6.1). An improvement in hormone treatment symptoms was noted over the study period with a difference between time points approaching statistical significance ($p = 0.059$) (Table 6.2). All other prostate cancer-specific QoL domains were maintained ($p = 0.072$ – 0.913).

Table 6.1: *Norm-based scores for the general health-related QoL domains of the SF-36 questionnaire over the 6-week control period and 12-week weight loss intervention.*

Variable [§]	Baseline	Pre-intervention	Post-intervention	P-value
Physical functioning	46.1 ± 6.8	46.8 ± 6.4	48.1 ± 6.7	0.445
Role-physical	43.3 ± 9.2	45.1 ± 8.4	46.9 ± 5.9	0.364
Bodily pain	46.7 [42.2 – 62.0]	50.7 [46.7 – 62.0]	50.7 [38.2 – 55.6]	0.902
General health	49.9 ± 4.9	50.9 ± 5.6	50.0 ± 8.6	0.845
Vitality	50.4 ± 7.0	51.5 ± 5.2	53.1 ± 6.9	0.301
Social functioning	57.3 [57.3 – 57.3]	57.3 [57.3 – 57.3]	57.3 [47.3 – 57.3]	0.142
Role-emotional	52.7 [49.2 – 56.2]	49.2 [46.2 – 56.2]	56.2 [49.2 – 56.2]	0.279
Mental health	59.4 ± 2.9	57.8 ± 3.6	59.2 ± 4.2	0.458
Physical component	44.3 ± 6.1	45.3 ± 7.4	45.3 ± 6.6	0.757
Mental component	57.5 ± 4.1	57.6 ± 2.5	58.0 ± 4.7	0.922

§ All data are reported as norm-based scores. Higher score indicates an improved perceived status.

Table 6.2: *Prostate cancer-specific QoL as reported by the QLQ-PR25 questionnaire over the 6-week control period and 12-week weight loss intervention.*

Variable	Baseline	Pre-intervention	Post-intervention	P-value
Urinary symptoms [*]	22.0 ± 11.2	20.5 ± 15.2	20.8 ± 12.5	0.913
Bowel symptoms [*]	0.0 [0.0 – 8.3]	8.3 [0.0 – 8.3]	0.0 [0.0 – 0.0]	0.072
Hormone treatment symptoms [*]	31.3 ± 20.2	26.3 ± 17.0	20.2 ± 10.6	0.059
Sexual activity [#]	16.7 [16.7 – 33.3]	0.0 [0.0 – 33.3]	0.0 [0.0 – 16.7]	0.100

* Higher scores reflect more symptoms. # Higher score reflects increased level of functioning.

DISCUSSION

This short clinical communication is a report of the effects of a combined exercise and nutrition weight loss intervention on QoL in obese prostate cancer patients on ADT. Following the 12-week intervention, we found no change in general health-related or prostate cancer-specific QoL.

All domains for general health-related QoL were maintained. In previous work from our research group [6], the cohort in the current study reported a lower baseline physical health component score (44.3 versus 52.5 points), while the mental health component was slightly higher (57.5 versus 54.1 points). The discrepancies could be explained by differences in the cohorts examined. Patients in the present study had multiple comorbidities of which arthritis was prominent and self-reported by patients to negatively impact tasks of daily living, which likely contributed to the lower physical component score. Cormie et al. [6] included patients initiating ADT in contrast to the current study where patients had been on ADT for a minimum of 6 months. Patients commencing a new treatment, whether related to a recent prostate cancer diagnosis or relapse, will likely result in heightened health concerns, which may have contributed to a lower mental health component score in the earlier study [6].

Exercise and nutrition interventions play an important role in maintaining or improving QoL. In the non-cancer obese population, Villareal et al. [7] reported that QoL improved for obese older adults undertaking a year-long weight management intervention using either exercise, diet, or combined exercise and diet compared to a control group. The improvement in QoL was similar across the three intervention groups irrespective of weight being maintained (exercise group) or lost (diet and combined exercise and diet group). In the prostate cancer population, Bourke et al. [8] examined patients on ADT and demonstrated that QoL improved significantly after 12 weeks in the exercise and nutrition intervention group compared to usual

care; however, QoL decreased once supervision was ceased suggesting supervision may be important for QoL. In contrast O'Neill et al. [9] in a home-based exercise and nutrition intervention in prostate cancer patients on ADT reported that overall QoL was maintained, which is a similar finding to the present study as O'Neill et al. [9] also reported a significant reduction in fat mass. Despite the home-based setting, patients in the O'Neill et al. [9] study received phone calls every 2-3 weeks, which may have been sufficient contact with an allied health professional to maintain QoL compared to the diminished QoL noted by Bourke et al. [8] during a period of no supervision. While the previous prostate cancer studies [8, 9] provide support for the findings of the present study in showcasing that a weight loss intervention is feasible in maintaining general health-related QoL, their direct comparison is limited by the use of different questionnaires.

Prostate cancer-specific QoL was also maintained in our patient group. Notably, there was a trend towards a reduction in hormone treatment symptoms that approached statistical significance. Cormie et al. [6] also utilised the QLQ-PR25 and similar to above, the descrepancies in baseline measures are likely related to the cohort examined. The current study had higher hormone treatment symptoms (31.3 versus 5.2 points), however, at baseline the Cormie et al. [6] cohort were only initiating ADT. Cormie et al. [6] also reported an increase in hormone treatment symptoms across the 12-week study for both the intervention and control group. This is related to ADT side effects being more prominent in the first few months of treatment compared to stabilisation of ADT-related physiological changes after a longer period on ADT at which point side effects are more likely subject to improvement using lifestyle interventions [10]. Further, in the present study only 2 patients were sexually active and 1 utilised a urinary pad. Therefore, sexual functioning and incontinence aid domains were not included, so it is unclear how these outcomes would alter in obese men undergoing a weight loss intervention. Future research is required to clarify the impact of a combined exercise and

nutrition-based weight loss programme on prostate cancer-specific QoL, particularly sexual functioning, given ADT-induced deterioration was prevented when compared to usual care controls in previous reports [6].

Study Strengths and Limitations

Strengths of this short communication include the use of a combined exercise and nutrition weight loss intervention, which is underrepresented in the prostate cancer literature, and inclusion of obese patients on ADT. Study limitations include the use of a single group cohort that was powered for the study's primary outcome, fat mass. As such, the small sample size may have limited the ability to detect clinically meaningful and statistically significant changes in QoL given the large variation in results.

Clinical Implications

Obese prostate cancer patients receiving ADT are at increased risk of poor patient outcomes, leading to poorer QoL. Exercise and nutrition weight loss interventions may be a viable strategy in preventing further ADT-related declines in QoL and should be investigated further as adjuvant therapy.

CONCLUSION

This short communication provides preliminary findings that a combined exercise and nutrition weight loss intervention in obese prostate cancer patients on ADT might maintain general health-related and prostate cancer-specific QoL. Further research is required into the impact on sexual activity-related domains of QoL.

REFERENCES

1. Rhee H, Gunter JH, Heathcote P, Ho K, Stricker P, Corcoran NM et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. BJU Int. 2015;115 Suppl 5:3-13. doi:10.1111/bju.12964.

2. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol. 2013;63(5):800-9. doi:10.1016/j.eururo.2012.11.013.

3. Baguley BJ, Bolam KA, Wright ORL, Skinner TL. The effect of nutrition therapy and exercise on cancer-related fatigue and quality of life in men with prostate cancer: a systematic review. Nutrients. 2017;9(9). doi:10.3390/nu9091003.

4. Ware Jr JE, Gandek B. Overview of the SF-36 health survey and the international quality of life assessment (IQOLA) project. J Clin Epidemiol. 1998;51(11):903-12.

5. van Andel G, Bottomley A, Fossa SD, Efficace F, Coens C, Guerif S et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer. 2008;44(16):2418-24. doi:10.1016/j.ejca.2008.07.030.

6. Cormie P, Galvao DA, Spry N, Joseph D, Chee R, Taaffe DR et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU Int. 2015;115(2):256-66. doi:10.1111/bju.12646.

7. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med. 2011;364(13):1218-29. doi:10.1056/NEJMoa1008234.

8. Bourke L, Gilbert S, Hooper R, Steed LA, Joshi M, Catto JW et al. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation

therapy for advanced prostate cancer: a randomised controlled trial. Eur Urol. 2014;65(5):865-72. doi:10.1016/j.eururo.2013.09.040.

9. 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;9(3):431-40. doi:10.1007/s11764-014-0417-8.

10. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Acute versus chronic exposure to androgen suppression for prostate cancer: impact on the exercise response. J Urol. 2011;186(4):1291-7. doi:10.1016/j.juro.2011.05.055.

CHAPTER SEVEN

A home-based exercise and nutrition program preserves body composition and physical function in obese prostate cancer patients on androgen deprivation therapy

Rebekah L. Wilson; Dennis R. Taaffe; Robert U. Newton; Philippa Lyons-Wall; Nicolas H. Hart; Daniel A. Galvão.

Chapter Seven of this thesis has been published by MDPI in *Cancers*, as the below article:

Wilson, R. L., Taaffe, D. R., Newton, R. U., Hart, N. H., Lyons-Wall, P., & Galvão, D. A. (2021). Maintaining weight loss in obese men with prostate cancer following a supervised exercise and nutrition program - a pilot study. *Cancers, 13*(14), article 3411.

https://doi.org/10.3390/cancers13143411

cancers

MDPI

Article

Maintaining Weight Loss in Obese Men with Prostate Cancer Following a Supervised Exercise and Nutrition Program—A Pilot Study

Rebekah L. Wilson [1,2,3], Dennis R. Taaffe [2,3], Robert U. Newton [2,3], Nicolas H. Hart [2,3,4], Philippa Lyons-Wall [2,3] and Daniel A. Galvão [2,3,*]

1 Division of Population Sciences, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA; rebekahl_wilson@dfci.harvard.edu
2 Exercise Medicine Research Institute, Edith Cowan University, Perth, WA 6027, Australia; d.taaffe@ecu.edu.au (D.R.T.); r.newton@ecu.edu.au (R.U.N.); nicolas.hart@qut.edu.au (N.H.H.); p.lyons-wall@ecu.edu.au (P.L.-W.)
3 School of Medical and Health Sciences, Edith Cowan University, Perth, WA 6027, Australia
4 Cancer and Palliative Care Outcomes Centre, Queensland University of Technology, Brisbane, QLD 4000, Australia
* Correspondence: d.galvao@ecu.edu.au; Tel.: +61-8-6304-3444; Fax: +61-8-6304-2499

Simple Summary: More than 50% of prostate cancer patients will receive androgen deprivation therapy (ADT) and 70% will experience ADT-induced weight gain. Supervised exercise and nutrition interventions are viable strategies to mitigate or reverse ADT-induced body composition changes; however, the ability to preserve these benefits when supervision is no longer available is unclear. Our study examined the effects of a home-based weight maintenance program on body composition and physical function in obese men with prostate cancer on ADT who had previously completed a supervised weight loss intervention. We demonstrated that a home-based weight maintenance program can preserve body composition and physical function for at least 12 weeks following a supervised intervention. This study provides insight into the prospect of home-based programs to preserve benefits gained within a supervised environment for patients remaining on ADT when ongoing in-person services are no longer viable.

Abstract: Supervised exercise and nutrition programs can mitigate or reverse androgen deprivation therapy (ADT) induced fat mass (FM) gain, lean mass (LM) loss, and impaired physical function. It is unclear whether these benefits are retained following transition to self-management. This study examined the effect of a home-based weight maintenance program on body composition and physical function in obese men with prostate cancer (PCa) on ADT following a 12-week supervised weight loss intervention. Eleven obese PCa patients (74 ± 5 years, 40.0 ± 4.9% body fat) on ADT (>6 months) completed a 12-week self-managed home-based weight maintenance program consisting of 150 min/week of aerobic and resistance training while maintaining a healthy balanced diet. Body composition (DXA), muscle strength (1RM), and cardiorespiratory fitness (400 m walk) were assessed. Significant reductions in weight (−2.8 ± 3.2 kg) and FM (−2.8 ± 2.6 kg), preservation of LM (−0.05 ± 1.6 kg), and improvements in muscle strength and VO_{2max} were achieved across the supervised intervention. Across the home-based program, no significant changes were observed in weight (−0.6 ± 2.8 kg, $p = 0.508$), FM (0.2 ± 1.4 kg, $p = 0.619$), LM (−0.8 ± 1.6 kg, $p = 0.146$), muscle strength (−0.2 to 4.1%, $p = 0.086$–0.745), or estimated VO_{2max} (0.3 ± 2.1 mL/min/kg, $p = 0.649$). Self-managed, home-based exercise and nutrition programs are a viable strategy to promote maintenance of body composition and physical function following a supervised intervention in obese PCa patients on ADT.

Keywords: nutrition; exercise; body composition; physical function; androgen deprivation therapy; home-based

check for updates

Citation: Wilson, R.L.; Taaffe, D.R.; Newton, R.U.; Hart, N.H.; Lyons-Wall, P.; Galvão, D.A. Maintaining Weight Loss in Obese Men with Prostate Cancer Following a Supervised Exercise and Nutrition Program—A Pilot Study. *Cancers* **2021**, *13*, 3411. https://doi.org/10.3390/cancers13143411

Academic Editor: Richard Crevenna

Received: 3 June 2021
Accepted: 2 July 2021
Published: 7 July 2021

1. Introduction

Improvements in screening procedures and medical treatments have elevated prostate cancer to a chronic condition where ~90% of patients with localised disease survive more than 10 years beyond diagnosis [1,2]. While beneficial, increasing survival rates are accompanied by long-term treatment and cancer-related adverse effects that can negatively impact quality of life [3,4]. Androgen deprivation therapy (ADT) is a common neoadjuvant, adjuvant, and primary treatment for prostate cancer, prescribed for months or years, intermittently or indefinitely [5]. Adverse changes in body composition are a common side effect of ADT with previous reports indicating a 6.6 to 13.8% gain in fat mass (FM), 2.0 to 3.6% loss in lean mass (LM), and 2.0 to 8.0% loss in bone mass within the first year of treatment [6,7]. Fat mass gain is associated with faster development of castrate resistance, an increased risk of fatal prostate cancer, and development of obesity-related comorbidities [8–10]. Loss of LM and bone mass can reduce physical function and increase risk of falls and fractures, which may lead to increased morbidity [11]. More than half of men with prostate cancer are likely to receive ADT at some point during their cancer journey [5], so it is important to determine appropriate adjuvant therapies to prevent or regulate long-term ADT-induced side effects.

Exercise and nutrition programs are often provided as adjuvant therapies for men with prostate cancer [12]. While supervised interventions are typically more effective due to face-to-face instruction and personal accountability resulting in high adherence [13], home-based unsupervised or minimally supervised programs are of interest to some clinicians and patients to reduce costs and allow increased access to people who cannot travel frequently to an exercise venue [14,15]. Two exercise and nutrition-based interventions by Bourke et al. [16,17] examined a self-managed period after progressively reducing supervision for men with prostate cancer on ADT compared to usual care controls. Both studies demonstrated an improvement in aerobic fitness and exercise and nutrition behaviour during the supervised intervention, which were maintained during the non-supervised follow-up period, with Bourke, et al. [16] also reporting improvements in muscle strength. While these studies provided preliminary feasibility for a self-managed period to preserve aerobic fitness, muscle strength, and exercise and nutrition behaviours, neither study targeted obese men with prostate cancer or reported an intervention effect on body composition-related measures during the supervised or non-supervised period. This needs to be further investigated, particularly as their programs only examined anthropometric measures.

Previously we have reported preliminary efficacy of a 12-week supervised exercise and nutrition weight loss intervention to significantly reduce FM and maintain LM in obese men with prostate cancer receiving ADT, with improvements in muscle strength and cardiorespiratory fitness also observed [18]. Weight regain is common after a weight loss intervention [19]. Additionally, this patient population may be at increased risk of weight regain due to ongoing ADT [6,7] and it is unclear if a self-managed home-based exercise and nutrition program is a viable approach to maintain previously established benefits in body composition and physical function after a period of effective supervision. Therefore, this pilot study examines the effect of a 12-week self-managed home-based exercise and nutrition program on body composition and physical function in obese men with prostate cancer on ADT, following completion of the supervised weight loss intervention. We hypothesized that a 12-week home-based exercise and nutrition program would preserve the body composition and physical function improvements achieved subsequent to the supervised exercise and nutrition program.

2. Materials and Methods

2.1. Study Design and Participants

This is a follow-up report to a self-controlled prospective study of a supervised exercise and nutrition weight loss intervention [18]. Eleven obese men with prostate cancer completed the 12-week supervised intervention and continued with the presently examined self-managed home-based program. Details of inclusion criteria, recruitment, and study

design for the self-controlled prospective study have been previously reported [18]. Briefly, patients completed a 6-week control period undertaking their normal activities followed by a 12-week supervised weight loss intervention that included combined aerobic and resistance training 3 times per week, and individualised nutrition advice to establish an energy deficit of 2100–4200 kJ per day (d). Men were also provided with a 40 g whey protein supplement after each supervised exercise session (Whey protein concentrate, Bulk Nutrients, TAS, Australia). The study was approved by the Edith Cowan University Human Research Ethics Committee (ID: 18832). All patients provided written informed consent.

2.2. Home-Based Program

Patients were advised to complete 150 min of combined aerobic and resistance training each week, while maintaining a healthy balanced diet based on the Australian Dietary Guidelines [20]. The lead researcher (RLW) facilitated the transition from a supervised weight loss intervention to a self-managed home-based weight maintenance program, by providing an information booklet and a single face-to-face training session of resistance exercises to be completed at home with use of a GYMSTICK^{TM} (Ratavartijankatu, Finland). Examples of aerobic and resistance exercises to be completed at moderate-to-vigorous intensity, and strategies to maintain a healthy balanced diet were included in the booklet. Patients attended a nutrition counselling session immediately following the supervised intervention where individual goals established at the start of the supervised weight loss intervention were reassessed and adapted based on the patient's weight loss progress, with weight maintenance being the general goal. As a protein supplement was not provided for the home-based program, advice was given to maintain an adequate protein intake (1.07 g/kg body weight/d [21]). Patients were contacted once by telephone at week 6 of the 12-week home-based program to address any questions or concerns about maintaining their exercise and nutrition regimen. All tests were conducted at post-supervised intervention (week 1 of home-based program) and after week 12 of the home-based program, unless otherwise stated.

2.3. Measurements

2.3.1. Body Composition

Total body mass (kg), FM (kg), bone-mineral free LM (kg), body fat percent (%), trunk FM (kg), visceral FM (g), appendicular skeletal muscle (ASM, kg), and bone mineral content (BMC, g) were assessed by dual-energy x-ray absorptiometry (DXA). ASM was calculated as the sum of upper limb and lower limb LM [22]. Waist and hip circumference (cm) were measured according to standardised procedures with a constant-tension tape measure [23].

2.3.2. Muscle Strength and Cardiorespiratory Fitness

Muscle strength was assessed by one-repetition maximum (1RM) for the chest press, leg press (seated or incline), and seated row exercises [24], and cardiorespiratory fitness (VO_{2max}) was estimated by the 400 m walk test [25]. Estimated VO_{2max} was calculated using the following equation and is highly correlated (r = 0.83) with directly measured peak VO_2 in men [25]:

$$VO_2 = 39.431 - (0.054 \times 400\text{ m time}) + (2.832 \times \text{long stride}) - (0.031 \times \text{end SBP}) - (0.064 \times \text{CF})$$

where 400 m time is in seconds, long stride is 1 for stride <1.2 steps/m or 0 for stride >1.2 steps/m, end SBP is measured in mmHg, and CF refers to the correction factor, which, if the time taken to perform the 400 m course is slower than 240 s, is 0, but if the time is faster than 240 s, then the CF is time in seconds to complete the 400 m minus 240.

2.3.3. Resting Metabolic Rate

Resting metabolic rate (RMR, kcal/d) was measured in the morning via indirect calorimetry using a canopy hood (Fitmate, COSMED, Rome, Italy) [26]. Prior to arrival, patients were instructed to complete a minimum 10-h overnight fast with allowance for

water and morning medications. On arrival, patients rested in a supine position in a darkened room for 10 min, after which the ventilated hood was placed over their head and secured to avoid leakage of gases. Exhaled breath was collected until sufficient data were collected for analysis or until 10 min, whichever occurred first.

2.3.4. Physical Activity Monitoring

Physical activity and sedentary behaviour were objectively assessed using the ActiGraph wGT3X-BT accelerometer (ActiGraph LLC, Pensacola, FL, USA). Patients were instructed to wear the accelerometer on their hip continuously for 24 h/d for 3 consecutive days (1 weekend day and 2 weekdays), excluding water-based activities, with ActiLife software used for analysis (ActiLife 6, ActiGraph LLC, Pensacola, FL, USA). Only wake wear time was used with a minimum data collection period required for inclusion in the analysis set at 1 day of at least 600 min. Non-wear time was excluded from analysis and defined as 90 min or more of consecutive zeros with a 2-min spike tolerance [27]. Commonly used cut-off points among cancer patients were used to classify sedentary time (<100 counts per min, cpm), light physical activity (100–1951 cpm), and moderate-to-vigorous physical activity (≥1952 cpm) [28–30]. The modified Godin Leisure-Time Exercise Questionnaire was also completed pre and post the home-based program to assess the average time spent undertaking resistance training during a typical week in the previous month [31].

2.3.5. Nutrition Monitoring

Patients completed a 3-day weighed food record (3d-WR) comprising 1 weekend day and 2 weekdays. This information was used to estimate the average daily intake of energy (kJ) and macronutrients. The 3d-WR was analysed using FoodWorks dietary analysis software (FoodWorks 10 Professional, Xyris Software Pty Ltd, Brisbane, QLD, Australia).

2.4. Statistical Analysis

Sample size was calculated based on the anticipated fat mass changes to occur during the supervised intervention and has been previously described [18]. Briefly, to achieve 90% power at an α level of 0.05 (two-tailed) in a single-group study and account for an attrition rate of up to 15%, 14 participants were required to detect a ≥2 kg reduction in fat mass. Data were analysed using IBM SPSS version 25 (SPSS Inc., IBM Corp, Armonk, NY, USA). The Shapiro–Wilk test was used to determine normality of the distribution. Paired *t*-tests were used to compare normally distributed variables between post-supervised intervention and post-home-based program, while the Wilcoxon signed rank test was used for non-normally distributed data. Pearson's correlation or Spearman's rank correlation were used to assess associations, as appropriate. Data are presented as mean ± standard deviation (SD), median and interquartile range [IQR], or number (percentage). All tests were two-tailed with statistical significance set at $p < 0.05$.

3. Results

Eleven patients aged 63 to 82 years completed the 12-week self-managed home-based program (Table 1). More than half of the men had a Gleason score of 9 (54.5%), with 54.5% of patients also diagnosed with metastatic cancer in the lymph nodes or visceral organs at study entry. During the home-based program, one patient developed nodal metastases resulting in an anti-androgen being prescribed, and a second patient developed metastases to their adrenal glands resulting in further radiation therapy.

Table 1. Patient characteristics at post-supervised intervention.

Variable	Patients (*n* = 11)
Age (years), mean ± SD	74 ± 5
Body mass index (kg/m^2), mean ± SD	33.1 ± 5.3
Post-secondary education, *n* (%)	8 (72.7)
Married, *n* (%)	11 (100)
Employed, *n* (%)	1 (9.1)
Current smoker, *n*	0
Number of medications/supplements, mean ± SD	4.5 ± 2.9
Number of comorbidities, mean ± SD [a]	3.4 ± 1.4
Years since prostate cancer diagnosis, median [IQR]	3.9 [1.5–9.7]
Gleason score, *n* (%)	
Gleason 7	3 (27.3)
Gleason 8	1 (9.1)
Gleason 9	6 (54.5)
Gleason 10	1 (9.1)
Contained within prostate, *n* (%)	5 (45.5)
Lymph node metastasis, *n* (%)	4 (36.4)
Organ metastasis, *n* (%) [b]	2 (18.2)
Androgen deprivation therapy, *n* (%)	
LHRH agonist + antiandrogen	7 (63.6)
LHRH agonist only	4 (36.4)
Months on ADT, median [IQR]	16 [9–27]
Other prostate cancer-related treatment, *n* (%)	
Surgery	4 (36.4)
Radiation therapy	10 (90.9)
Chemotherapy	2 (18.2)

[a] Types of comorbidities: Arthritis, atrial fibrillation, cardiovascular disease, carpel tunnel syndrome, colitis, dyslipidaemia, hypertension, sleep apnoea, thyroid disease, emphysema, type 2 diabetes, peripheral neuropathy. [b] Lung, adrenal gland. LHRH—luteinizing hormone-releasing hormone; ADT—androgen deprivation therapy.

3.1. Nutrition and Physical Activity

A significant increase in total energy intake was observed from post-supervised to post-home-based program with a median change from 6759 to 7972 kJ/d (p = 0.041) (Table 2). Carbohydrate intake (179.8 ± 68.0 vs 206.1 ± 67.1 g/d, p = 0.016) was also significantly increased across the home-based period. There were no significant changes in the percentage of energy derived from protein, total fat, carbohydrate, or alcohol, and intakes were within Acceptable Macronutrient Distribution Ranges [21]. There was a significant increase from post-supervised to post-home-based program in the percentage of wake time spent in sedentary behaviour (65.9 to 70.2%, p = 0.003) and a significant decrease in the average time and percentage of wake time spent in light physical activity (4.8 to 4.0 h/day, p = 0.011; 33.3 to 28.6%, p < 0.001, respectively) (Table 2). Additionally, self-reported resistance training duration decreased from 143 to 113 min/week but was not significantly different (p = 0.685).

Table 2. Nutrition intake as assessed by 3d-WR and physical activity as assessed by ActiGraph at post-supervised intervention and post-home-based program.

Variable	Post-Supervised Intervention	Post-Home-Based Program	Mean Change	*p*-Value
Nutrition intake				
Energy intake (kJ/d)	6759 [4994–8980]	7972 [6353–8535]	-	0.041
Protein (g/d)	85.9 ± 24.3	93.8 ± 21.1	8.0 ± 20.3	0.222
Protein (% total energy)	21.2 ± 4.0	20.1 ± 2.9	−1.1 ± 4.5	0.433
Fat (g/d)	60.7 ± 21.8	67.7 ± 20.9	7.0 ± 24.1	0.360
Fat (% total energy)	31.5 ± 4.8	31.0 ± 4.8	−0.5 ± 6.7	0.823
Carbohydrate (g/d)	179.8 ± 68.0	206.1 ± 67.1	26.2 ± 29.9	0.016
Carbohydrate (% total energy)	40.3 ± 4.3	40.7 ± 6.1	0.4 ± 5.9	0.848
Alcohol (% total energy)	0.0 [0.0–3.0]	2.1 [0.0–6.8]	-	0.310
Physical activity				
Average time in SB (h/d)	9.6 ± 1.9	9.5 ± 2.0	−0.1 ± 2.0	0.871
Time spent in SB (% wake hours)	65.9 ± 6.2	70.2 ± 8.8	4.3 ± 3.8	0.003
Average time in LPA (h/d)	4.8 ± 1.2	4.0 ± 1.6	−0.9 ± 0.9	0.011
Time spent in LPA (% wake hours)	33.3 ± 6.3	28.6 ± 8.1	−4.8 ± 3.1	<0.001
Average time in MVPA (min/d)	6.9 ± 5.4	10.7 ± 10.1	3.8 ± 11.2	0.286
Time spent in MVPA (% wake hours)	0.6 [0.3–1.1]	0.7 [0.3–2.2]	-	0.424

Values are the mean ± SD where a paired *t*-test was used or median [IQR] where a Wilcoxon signed rank test was used. SB—sedentary behaviour; LPA—light physical activity; MVPA—moderate to vigorous physical activity.

3.2. Body Composition

No significant changes were observed in body mass or any body composition measure except for a modest increase in body fat percent (0.6 ± 0.8%, $p = 0.034$) from post-supervised to post-home-based program (Table 3). Individual changes in body composition are presented in Figure 1. During home-based follow-up, four (36.4%) patients lost FM and five (45.5%) patients gained LM. Correlation analysis indicated resistance training duration (min/week) was significantly associated with change in LM ($r_s = 0.606$, $p = 0.048$). No significant associations were found for absolute values or change in energy intake ($r_s = -0.091$–0.173, $p = 0.612$–0.811), sedentary time, light physical activity, and protein intake per kg of body weight with change in FM or LM ($r = -0.316$–0.438, $p = 0.178$–0.928).

Table 3. Body composition and anthropometric changes over the 12-week home-based program.

Variable	Post-Supervised Intervention	Post-Home-Based Program	Mean Change	Percent Change (%)	*p*-Value
Total body mass (kg)	95.5 ± 14.1	94.9 ± 12.9	−0.6 ± 2.8	−0.4 ± 2.7	0.508
Total fat mass (kg)	37.0 ± 9.5	37.3 ± 8.7	0.2 ± 1.4	1.1 ± 4.0	0.619
Percent body fat (%)	38.3 ± 4.6	38.9 ± 4.5	0.6 ± 0.8	-	0.034
Trunk fat (kg)	18.3 ± 5.4	18.5 ± 5.2	0.3 ± 0.7	2.0 ± 4.5	0.271
Visceral fat (g)	866 ± 333	860 ± 277	−7 ± 156	−1.6 ± 17.0	0.888
Total lean mass (kg)	55.9 ± 6.2	55.1 ± 6.2	−0.8 ± 1.6	−1.3 ± 2.7	0.146
ASM (kg)	23.3 ± 3.1	22.7 ± 3.1	−0.6 ± 1.2	−2.5 ± 4.9	0.130
BMC (g)	2576 ± 291	2544 ± 261	−32 ± 56	−1.1 ± 2.0	0.087
Waist circumference (cm)	103.9 ± 8.9	103.5 ± 8.5	−0.4 ± 2.6	−0.3 ± 2.5	0.626
Hip circumference (cm)	109.7 ± 8.1	108.7 ± 7.9	−1.0 ± 2.2	−0.9 ± 1.9	0.141

Values are the mean ± SD. ASM—appendicular skeletal muscle; BMC—bone mineral content.

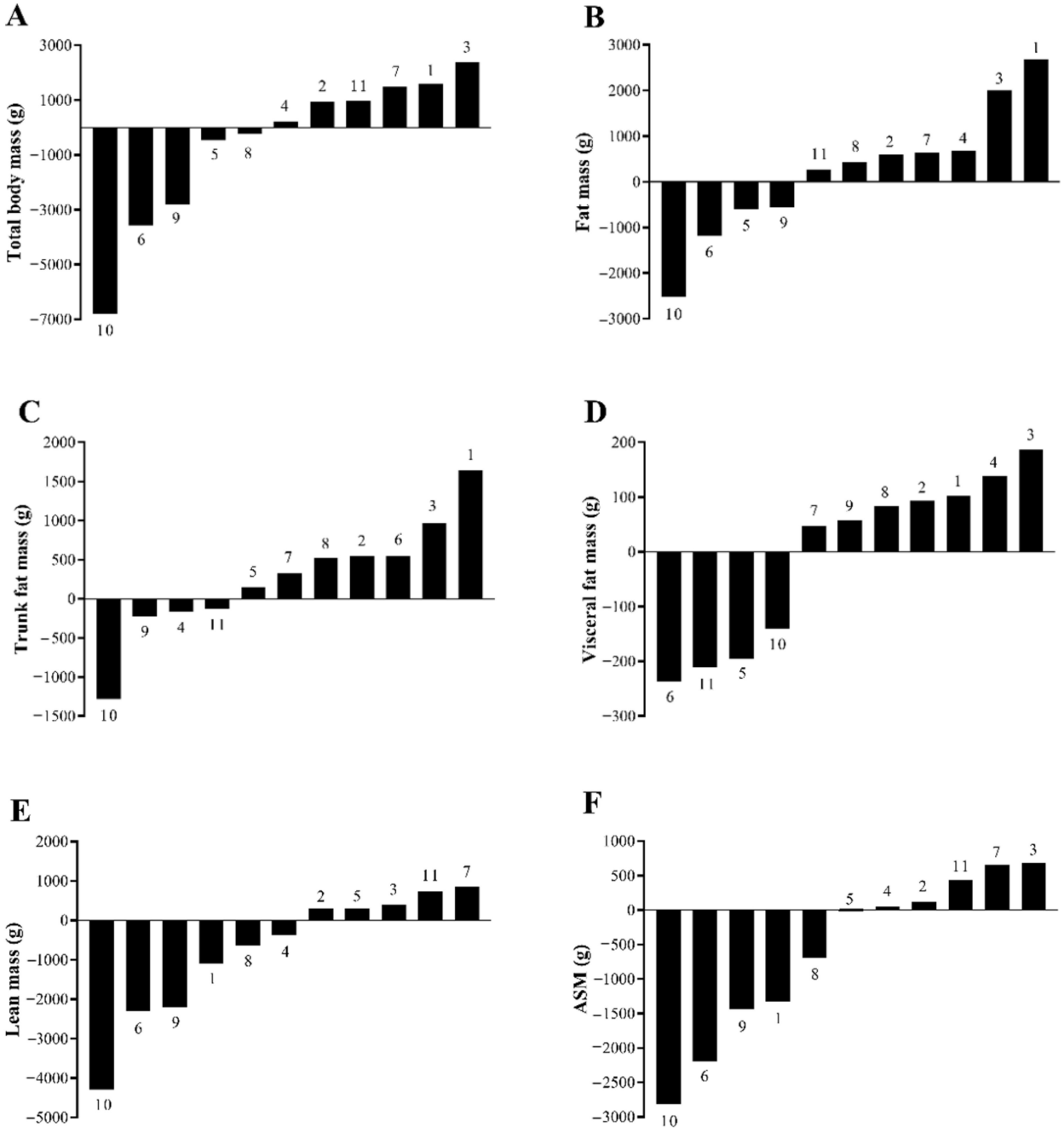


Figure 1. Waterfall plots of individual patient changes over a 12-week self-managed home-based program presented in ascending order for: (**A**) total body mass, (**B**) total fat mass, (**C**) trunk fat mass, (**D**) visceral fat mass, (**E**) total lean mass, and (**F**) appendicular skeletal muscle (ASM) mass. Individual patient numbers are identified in association with the bars.

3.3. Muscle Strength, Cardiorespiratory Fitness, and Resting Metabolic Rate

No significant changes in chest press strength (p = 0.745) or seated row strength (p = 0.744) were observed; however, leg press strength approached significance (p = 0.086) with a 6.1 kg increase reported across the home-based program (Table 4). No significant changes were observed for RMR (p = 0.450) or cardiorespiratory fitness as determined by estimated VO_{2max} (p = 0.640) (Table 4).

Table 4. Changes in muscle strength, cardiorespiratory fitness, and resting metabolic rate over the 12-week self-managed home-based program.

Variable	Post-Supervised Intervention	Post-Home-Based Program	Mean Change	*p*-Value
Leg press (kg) (n = 7)	126.3 ± 47.4	132.4 ± 53.7	6.1 ± 7.9	0.086
Chest press (kg) (n = 8)	51.8 ± 14.1	51.0 ± 13.0	−0.7 ± 6.0	0.745
Seated row (kg) (n = 10)	68.2 ± 7.9	68.8 ± 8.9	0.6 ± 5.4	0.744
Estimated VO_{2max} (mL/min/kg) (n = 9)	20.6 ± 3.6	20.3 ± 3.3	−0.3 ± 1.6	0.602
RMR (kcal/d) (n = 11)	1516 ± 207	1482 ± 186	−34 ± 143	0.450

Values are the mean ± SD. VO_{2max}—maximal oxygen consumption; RMR—resting metabolic rate.

3.4. Adverse Events

One patient experienced a muscle strain in their chest and gluteal muscles in the final week of the home-based program while completing the prescribed exercise. This precluded him from completing the chest and leg press strength 1RM at the post-test session. No other study-related adverse events were reported while undertaking study-related activities. However, four patients experienced adverse events associated with pre-existing comorbidities and musculoskeletal conditions. One patient was hospitalised with a septic wound on their foot and could not complete any physical function testing following the home-based program. Three patients experienced progressive pain in the knee, back, shoulder, or ankle that prevented the completion of the leg press 1RM at the post-home-based program testing session. Each patient received medical care and reduced their activity levels as per clinician recommendations.

4. Discussion

In this research, we examined the effect of a self-managed home-based weight maintenance program in obese men with prostate cancer on ADT following a self-controlled prospective study of a supervised weight loss intervention. There were two main findings: (1) total and regional FM and LM were preserved; and (2) muscle strength and cardiorespiratory fitness were preserved.

Weight regain in obese men is common after intentional weight loss [19] and is likely to be exacerbated by ADT. As ADT can be prescribed for years or indefinitely, it is important to examine exercise and nutrition intervention strategies that may help mitigate treatment-related side effects. This study showed that a self-managed home-based exercise and nutrition program can promote weight maintenance by preserving FM for at least 12 weeks after a supervised intervention in obese men with prostate cancer while on ADT who had previously benefited from a supervised weight loss intervention. This occurred irrespective of a reduction in physical activity and an increase in energy intake suggesting that the FM previously lost across a supervised intervention may be maintained with a lower workload. Freedland, et al. [32] also examined overweight and obese men with prostate cancer on ADT and compared a home-based intervention to usual care. While it was a home-based program, their intention was to induce weight loss, not preserve body weight as in our current study, thus changes across intervention groups are not directly comparable. However, the usual care control group in the Freedland, et al. [32] study demonstrated a 10.9% increase in FM, which was statistically different to the intervention group, compared to a non-significant 1.1% FM increase in the present study. Our study duration was 12 weeks and engaged men who had been on ADT for a minimum of 6 months, whereas the Freedland, et al. [32] study was 6 months in duration and engaged men initiating ADT. Patients initiating ADT experience substantial changes in body composition in the first few months that slowly plateaus within the first year and FM remains elevated if no intervention is implemented [33,34]. This may account for the larger changes in the usual care control group of the Freedland, et al. [32] study. Nonetheless, the

comparatively small changes observed in our study demonstrate potential for home-based exercise and nutrition programs to preserve FM in obese patients on ADT for at least 12 weeks following a period of supervised weight loss. However, the results of the present study may not be applicable to a population who has not undertaken a supervised exercise intervention as the participants examined here were likely more motivated to continue with the recommended lifestyle behaviours previously introduced in a supervised environment that resulted in observable benefits [18].

Lean mass is the predominant contributor to RMR [35,36]; therefore, the maintenance of LM is vital for long-term weight management. While there was no significant change in LM, suggesting overall continued preservation from the supervised intervention, there was a mean 0.8 kg decrease over the 12-week home-based program. Had the follow-up period been longer, LM could have continued to decline resulting in a different statistical outcome. This highlights the value of the inclusion of strength training as a potentially critical component for LM preservation in this patient population when completing home-based exercise. This was a small sample size, so correlation analysis has limited applicability; however, our preliminary analysis showed the duration of self-reported resistance exercise was positively correlated with LM change. No relationship between LM change and the changes in energy intake, sedentary behaviour, light physical activity, and protein intake were found. All patients were provided with a GYMSTICK^{TM} as well as actively encouraged to join a gym or fitness group to undertake resistance training. How patients distributed their resistance training practices, e.g., utilising resistance machines, free weights, and GYMSTICK^{TM}, is unknown due to a lack of returned activity logs. While it has been suggested that there are no superior strength gains when using conventional resistance equipment compared to elastic-based resistance equipment [37], their differing effects on LM is unclear. This may further explain the trend for a decline in LM as the use of a GYMSTICK^{TM} alone, in addition to the removal of the protein supplement provided during the supervised period, may not have satisfied the necessary threshold to stimulate muscle protein synthesis when transitioning from a clinic-based supervised weight loss intervention to a home-based weight maintenance program.

Several patients in our study experienced an injury or illness related to known pre-existing comorbidities and musculoskeletal conditions during the home-based program; consequently, we further explored the individual changes that occurred across the two intervention phases to better understand how these events may be addressed in future research. For example, patient #6 achieved a desirable FM loss (−5.3 kg) and LM gain (2.6 kg) during the supervised intervention [18]. However, due to progressive deterioration of a musculoskeletal condition, this patient reported avoidance of exercise during the home-based program. Although patient #6 lost further FM (−1.2 kg), they reversed their LM gain with a 2.3 kg loss over the 12-week home-based program. Similar patterns were noted for patients #4 and #9. In contrast, patient #3 had a desirable FM loss (−7.1 kg), but also lost LM (−2.3 kg) during the supervised intervention. During the last 4 weeks (12 sessions) of the supervised intervention, this patient missed six sessions due to illness and had to complete four sessions at a reduced intensity. However, with the implementation of exercise at home, this patient prevented further LM loss with a 0.4 kg gain over the 12-week period. These individual changes raise questions about the feasibility of LM maintenance in injured or ill patients who may not be able to undertake sufficient exercise to stimulate muscle protein synthesis, particularly resistance training. Such patients in a supervised environment have assistance readily available to them to adjust their exercise prescription as required, whereas those undertaking self-managed exercise do not. Other LM management strategies could include protein supplementation and regular video or telephone consultations via telehealth to monitor adherence and compliance and assist with exercise program modification to account for injury or illness if in-person supervision is not viable or desired.

Prolonged ADT significantly impacts the musculoskeletal system placing men with prostate cancer at increased risk of disability [38]. Additionally, patients typically reduce

their physical activity levels because of severe treatment-related side effects such as fatigue, reduced physical function, or urinary incontinence [39], which can lead to diminished cardiorespiratory fitness. For this reason, it is important to ensure muscular strength and cardiorespiratory fitness are maintained. In the current follow-up study, patients in a self-managed home-based program maintained upper- and lower-body muscle strength, walking endurance, and cardiorespiratory fitness irrespective of a decline in LM. Previous studies using home-based programs following supervised exercise and nutrition [16,17] or exercise-only [40] programs also reported maintenance of muscle strength and cardiorespiratory fitness, which is reflected in the results of our study. The present study extends these findings by demonstrating that obese patients on long-term ADT can also preserve their muscle strength and cardiorespiratory fitness using a home-based program following a supervised intervention.

This study has several strengths. First, DXA allowed the evaluation of whole-body and regional changes in FM and LM. Second, this study reports on a novel cohort, that is, obese men with prostate cancer on long-term ADT and their response to a self-managed home-based exercise and nutrition program following supervised exercise and dietary advice. Limitations include the use of a small single group cohort with no control group comparison, although a control period was undertaken prior to the supervised component and the study was powered for the primary outcome of FM [18]. Four patients were not able to complete all measures of physical function at the post-home-based program due to poor physical health. Implementing a self-managed home-based exercise and nutrition program in future studies could benefit from increased frequency of contact with patients to ensure exercise and nutrition modifications reflect any changes to their health status. Daily physical activity logbooks were poorly kept by patients and as such were not utilised. However, the comparison of self-reported resistance exercise from the modified Godin Leisure-Time Exercise Questionnaire, physical activity data collected using ActiGraph, and nutritional intake assessed using the 3d-WR at post-supervised and post-home-based program, provided important insight into the behaviour changes undertaken.

5. Conclusions

This pilot study provides preliminary evidence that obese men with prostate cancer receiving ADT, who previously benefited from a supervised weight loss exercise and nutrition intervention, can maintain their body composition and physical function improvements by undertaking a self-managed home-based exercise and nutrition program. However, maintenance of LM was dependent on the duration of weekly resistance exercise and should be an important consideration for future programs. As ADT may be prescribed for several months, years or even indefinitely, it is important to implement interventions such as exercise and nutrition programs that may prevent or regulate ADT side effects and improve patient outcomes. Home-based programs will likely play an important role in maintaining the positive effects gained from clinic-based programs once supervision is no longer available or feasible for the patient. However, further research is required to investigate the feasibility of self-managed programs for obese people with cancer who are likely to have multiple comorbidities placing them at increased risk of illness and injury. From this study, we provide the foundation for larger scale interventions to further examine long-term adherence and compliance, and whether obese people with cancer can continue to effectively manage ongoing treatment-related adverse effects, in particular FM gain and LM loss.

Author Contributions: R.L.W.: Significant manuscript writer, concept and design, data acquisition, data analysis and interpretation. D.R.T.: Significant manuscript reviewer/revisor, concept and design, statistical expertise. R.U.N.: Significant manuscript reviewer/revisor, concept, and design. N.H.H.: Significant manuscript reviewer/revisor, concept and design. P.L.-W.: Significant manuscript reviewer/revisor, concept and design, data acquisition. D.A.G.: Significant manuscript reviewer/revisor, concept and design. All authors have read and agreed to the published version of the manuscript.

Funding: R.L.W. is supported by an Australian Government Research Training Program Scholarship. R.U.N. is supported by a Vice-Chancellor Professorial Research Fellowship. N.H.H. was supported by a Cancer Council of Western Australia Postdoctoral Research Fellowship. D.A.G. and R.U.N. are funded by a National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Prostate Cancer Survivorship.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Edith Cowan University Human Research Ethics Committee (ID: 18832).

Informed Consent Statement: Written informed consent was obtained from participating patients after reading an information letter outlining study procedures, risks, and benefits.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments: The authors would like to acknowledge the valuable contribution of the patients who donated their time and effort to complete the research study and five Master of Nutrition and Dietetic students at Edith Cowan University: Thomas Hosking, Sabina Ferri, Rebecca Newton, Sarah Forrest, and Marija Karanfilovska, for their expertise and analysis of nutrition related questionnaires.

Conflicts of Interest: The authors declare they have no conflict of interest.

References

1. Moyad:, M.A.; Newton, R.U.; Tunn, U.W.; Gruca, D. Integrating diet and exercise into care of prostate cancer patients on androgen deprivation therapy. *Res. Rep. Urol.* **2016**, *8*, 133–143. [CrossRef]
2. Neal, D.E.; Metcalfe, C.; Donovan, J.L.; Lane, J.A.; Davis, M.; Young, G.J.; Dutton, S.J.; Walsh, E.I.; Martin, R.M.; Peters, T.J.; et al. Ten-year mortality, disease progression, and treatment-related side effects in men with localised prostate cancer from the ProtecT randomised controlled trial according to treatment received. *Eur. Urol.* **2020**, *77*, 320–330. [CrossRef]
3. Shahinian, V.B.; Kuo, Y.F.; Freeman, J.L.; Orihuela, E.; Goodwin, J.S. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer Am. Cancer Soc.* **2005**, *103*, 1615–1624. [CrossRef]
4. Narayan, V.; Harrison, M.; Cheng, H.; Kenfield, S.; Aggarwal, R.; Kwon, D.; McKay, R.; Hauger, R.; Hart, N.; Conzen, S.; et al. Improving research for prostate cancer survivorship: A statement from the Survivorship Research in Prostate Cancer (SuRECaP) working group. *Urol. Oncol.* **2020**, *38*, 83–93. [CrossRef] [PubMed]
5. Rhee, H.; Gunter, J.H.; Heathcote, P.; Ho, K.; Stricker, P.; Corcoran, N.M.; Nelson, C.C. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. *BJU Int.* **2015**, *115*, 3–13. [CrossRef] [PubMed]
6. Galvao, D.A.; Taaffe, D.R.; Spry, N.; Joseph, D.; Newton, R.U. Cardiovascular and metabolic complications during androgen deprivation: Exercise as a potential countermeasure. *Prostate Cancer Prostatic Dis* **2009**, *12*, 233–240. [CrossRef] [PubMed]
7. Mitsuzuka, K.; Arai, Y. Metabolic changes in patients with prostate cancer during androgen deprivation therapy. *Int. J. Urol.* **2018**, *25*, 45–53. [CrossRef]
8. Keto, C.J.; Aronson, W.J.; Terris, M.K.; Presti, J.C.; Kane, C.J.; Amling, C.L.; Freedland, S.J. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: esults from the SEARCH database. *BJU Int.* **2012**, *110*, 492–498. [CrossRef]
9. Dickerman, B.A.; Torfadottir, J.E.; Valdimarsdottir, U.A.; Giovannucci, E.; Wilson, K.M.; Aspelund, T.; Tryggvadottir, L.; Sigurdardottir, L.G.; Harris, T.B.; Launer, L.J.; et al. Body fat distribution on computed tomography imaging and prostate cancer risk and mortality in the AGES-Reykjavik study. *Cancer* **2019**, *125*, 2877–2885. [CrossRef]
10. Keating, N.L.; O'Malley, A.J.; Freedland, S.J.; Smith, M.R. Diabetes and cardiovascular disease during androgen deprivation therapy: Observational study of veterans with prostate cancer. *J. Natl. Cancer Inst.* **2010**, *102*, 39–46. [CrossRef]
11. Galvão, D.A.; Taaffe, D.R.; Spry, N.; Newton, R.U. Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. *Prostate Cancer Prostatic Dis.* **2007**, *10*, 340–346. [CrossRef]
12. Hayes, S.C.; Newton, R.U.; Spence, R.R.; Galvao, D.A. The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. *J. Sci. Med. Sport* **2019**, *22*, 1175–1199. [CrossRef] [PubMed]
13. Storer, T.W.; Miciek, R.; Travison, T.G. Muscle function, physical performance and body composition changes in men with prostate cancer undergoing androgen deprivation therapy. *Asian J. Androl.* **2012**, *14*, 204–221. [CrossRef] [PubMed]
14. Morey, M.C.; Snyder, D.C.; Sloane, R.; Cohen, H.J.; Peterson, B.; Hartman, T.J.; Miller, P.; Mitchell, D.C.; 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*, 1883–1891. [CrossRef] [PubMed]
15. Coughlin, S.S.; Caplan, L.; Stone, R.; Stewart, J. A review of home-based physical activity interventions for breast cancer survivors. *Curr. Cancer Rep.* **2019**, *1*, 6–12. [CrossRef] [PubMed]

16. Bourke, L.; Doll, H.; Crank, H.; Daley, A.; Rosario, D.; Saxton, J.M. Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: A feasibility study. *Cancer Epidemiol. Biomark. Prev.* **2011**, *20*, 647–657. [CrossRef] [PubMed]
17. Bourke, L.; Gilbert, S.; Hooper, R.; Steed, L.A.; Joshi, M.; Catto, J.W.; Saxton, J.M.; Rosario, D.J. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: A randomised controlled trial. *Eur. Urol.* **2014**, *65*, 865–872. [CrossRef] [PubMed]
18. Wilson, R.L.; Newton, R.U.; Taaffe, D.R.; Hart, N.H.; Lyons-Wall, P.; Galvão, D.A. Weight loss for obese prostate cancer patients on androgen deprivation therapy. *Med. Sci. Sports Exerc.* **2021**, *53*, 470–478. [CrossRef]
19. Alamuddin, N.; Bakizada, Z.; Wadden, T.A. Management of obesity. *J. Clin. Oncol.* **2016**, *34*, 4295–4305. [CrossRef]
20. National Health Medical Research Council (2013). Australian Dietary Guidelines. Available online: https://www.nhmrc.gov.au/adg (accessed on 20 April 2020).
21. National Health and Medical Research Council, Australian Government Department of Health and Ageing, New Zealand Ministry of Health. *Nutrient Reference Values for Australia and New Zealand*; National Health and Medical Research Council: Canberra, Australia, 2006.
22. Heymsfield, S.B.; Smith, R.; Aulet, M.; Bensen, B.; Lichtman, S.; Wang, J.; Pierson, R.N., Jr. Appendicular skeletal muscle mass: Measurement by dual-photon absorptiometry. *Am. J. Clin. Nutr.* **1990**, *52*, 214–218. [CrossRef]
23. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription—Ninth Edition*; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2013.
24. Taaffe, D.R.; Duret, C.; Wheeler, S.; Marcus, R. Once-weekly resistance exercise improves muscle strength and neuromuscular performance in older adults. *J. Am. Geriatr. Soc.* **1999**, *47*, 1208–1214. [CrossRef]
25. Simonsick, E.M.; Fan, E.; Fleg, J.L. Estimating cardiorespiratory fitness in well-functioning older adults: Treadmill validation of the long distance corridor walk. *J. Am. Geriatr. Soc.* **2006**, *54*, 127–132. [CrossRef]
26. Vandarakis, D.; Salacinski, A.J.; Broeder, C.E. A comparison of COSMED metabolic systems for the determination of resting metabolic rate. *Res. Sports Med.* **2013**, *21*, 187–194. [CrossRef]
27. Choi, L.; Liu, Z.; Matthews, C.E.; Buchowski, M.S. Validation of accelerometer wear and nonwear time classification algorithm. *Med. Sci. Sports Exerc.* **2011**, *43*, 357–364. [CrossRef]
28. Matthews, C.E.; Chen, K.Y.; Freedson, P.S.; Buchowski, M.S.; Beech, B.M.; Pate, R.R.; Troiano, R.P. Amount of time spent in sedentary behaviors in the United States, 2003-2004. *Am. J. Epidemiol.* **2008**, *167*, 875–881. [CrossRef]
29. Freedson, P.S.; Melanson, E.; Sirard, J. Calibration of the Computer Science and Applications, Inc. accelerometer. *Med. Sci. Sports Exerc.* **1998**, *30*, 777–781. [CrossRef] [PubMed]
30. Peddle-McIntyre, C.J.; Cavalheri, V.; Boyle, T.; McVeigh, J.A.; Jeffery, E.; Lynch, B.M.; Vallance, J.K. A review of accelerometer-based activity monitoring in cancer survivorship research. *Med. Sci. Sports Exerc.* **2018**, *50*, 1790–1801. [CrossRef] [PubMed]
31. Jacobs, D.R., Jr.; Ainsworth, B.E.; Hartman, T.J.; Leon, A.S. A simultaneous evaluation of 10 commonly used physical activity questionnaires. *Med. Sci. Sports Exerc.* **1993**, *25*, 81–91. [CrossRef] [PubMed]
32. Freedland, S.J.; Howard, L.; Allen, J.; Smith, J.; Stout, J.; Aronson, W.; Inman, B.A.; Armstrong, A.J.; George, D.; Westman, E.; et al. A lifestyle intervention of weight loss via a low-carbohydrate diet plus walking to reduce metabolic disturbances caused by androgen deprivation therapy among prostate cancer patients: Carbohydrate and prostate study 1 (CAPS1) randomized controlled trial. *Prostate Cancer Prostatic Dis.* **2019**, *22*, 428–437. [CrossRef]
33. Galvão, D.A.; Spry, N.A.; Taaffe, D.R.; Newton, R.U.; Stanley, J.; Shannon, T.; Rowling, C.; Prince, R. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int.* **2008**, *102*, 44–47. [CrossRef]
34. Ziaran, S.; Goncalves, F.M.; Sn, J.B. Complex metabolic and skeletal changes in men taking long-term androgen deprivation therapy. *Clin. Genitourin. Cancer* **2013**, *11*, 33–38. [CrossRef]
35. Pratley, R.; Nicklas, B.; Rubin, M.; Miller, J.; Smith, A.; Smith, M.; Hurley, B.; Goldberg, A. Strength training increases resting metabolic rate and norepinephrine levels in healthy 50- to 65-yr-old men. *J. Appl. Physiol. (1985)* **1994**, *76*, 133–137. [CrossRef] [PubMed]
36. Hills, A.P.; Mokhtar, N.; Byrne, N.M. Assessment of physical activity and energy expenditure: An overview of objective measures. *Front. Nutr.* **2014**, *1*, 5. [CrossRef] [PubMed]
37. Lopes, J.S.S.; Machado, A.F.; Micheletti, J.K.; de Almeida, A.C.; Cavina, A.P.; Pastre, C.M. Effects of training with elastic resistance versus conventional resistance on muscular strength: A systematic review and meta-analysis. *SAGE Open Med.* **2019**, *7*, 2050312119831116. [CrossRef]
38. Winters-Stone, K.M.; Dobek, J.C.; Bennett, J.A.; Dieckmann, N.F.; Maddalozzo, G.F.; Ryan, C.W.; Beer, T.M. Resistance training reduces disability in prostate cancer survivors on androgen deprivation therapy: Evidence from a randomized controlled trial. *Arch. Phys. Med. Rehabil.* **2015**, *96*, 7–14. [CrossRef] [PubMed]
39. Baker, A.M.; Smith, K.C.; Coa, K.I.; Helzlsouer, K.J.; Caulfield, L.E.; Peairs, K.S.; Shockney, L.D.; Klassen, A.C. Clinical care providers' perspectives on body size and weight management among long-term cancer survivors. *Integr. Cancer Ther.* **2015**, *14*, 240–248. [CrossRef]
40. Newton, R.U.; Galvão, D.A.; Spry, N.; Joseph, D.; Chambers, S.K.; Gardiner, R.A.; Wall, B.A.; Bolam, K.A.; Taaffe, D.R. Exercise mode specificity for preserving spine and hip BMD in prostate cancer patients. *Med. Sci. Sports Exerc.* **2019**, *51*, 607–614. [CrossRef]

CHAPTER EIGHT

General discussion

This thesis was an exploration of the efficacy of exercise and nutrition interventions to induce weight loss in overweight and obese patients with prostate cancer. In particular, patients scheduled for a radical prostatectomy and those prescribed long-term (≥ 6 months) androgen deprivation therapy (ADT) were identified as being at increased risk for obesity-related complications and were examined within this thesis. Although much of the literature associating obesity and poor prostate cancer prognosis was established using body mass index, it is the excess fat mass, its distribution, and the abnormal metabolic environment it creates that has been suggested to be of most importance [1, 2]. As such, the experimental studies presented in this thesis utilised body composition data assessed by dual x-ray absorptiometry to provide gold standard measures of whole body and regional measures of fat and lean mass, where fat mass was considered the primary outcome. With the accompanying information on treatment side effects, physical function, blood biomarkers, and quality of life, there is convincing evidence that exercise and nutrition interventions are beneficial for overweight and obese patients, which is an important finding given these patients have been underrepresented within the prostate cancer literature.

CHAPTER SUMMARIES

The literature review presented in Chapter 2 is an examination of the relationship between obesity and prostate cancer and why obese patients are important to target. This chapter highlights the evidence established by systematic reviews and meta-analyses, which conclude that obese patients are at increased risk of advanced cancer disease, recurrence, and prostate cancer-specific mortality, although the evidence is less conclusive for prostate cancer incidence [3-6]. Furthermore, clinical studies demonstrate excess fat mass is a key component to poor prostate cancer prognosis with potential mechanisms including altered insulin/insulin-like-growth-factor axis, sex hormone, and adipokine concentrations [7]. Not only is the cancer

biology affected by obesity, but obese prostate cancer patients have an increased likelihood of developing treatment-related side effects of greater severity [8-12]. Given these risks, the reduction of fat mass has the potential to improve the risk profile of obese prostate cancer patients. Exercise and nutrition induced weight loss may be a beneficial adjuvant therapy; however, further research is required to understand the efficacy of such programs.

The notion that exercise and nutrition interventions are viable strategies to induce weight loss is developed in Chapter 3, where a critical appraisal of the evidence is provided for interventions to induce fat mass loss, while preserving lean mass, in patients receiving ADT. This review highlights the paucity of studies examining combined exercise and nutrition interventions conducted in ADT-treated patients measuring fat mass and lean mass, with only 6 combined interventions, compared to 15 exercise only and no nutrition only studies. Furthermore, no study utilised the American Cancer Society prostate cancer weight loss guidelines as proposed in their survivorship document [13]. Although these guidelines are drawn from the general population where they have been deemed effective, they have not been validated in the prostate cancer population. As such, much can be learnt from the studies discussed in Chapter 3 in how exercise and nutrition advice may be tailored to induce weight loss and suit hypogonadal men with prostate cancer, who have high fat mass and low lean mass. For example, the use of protein supplementation is not included in the weight loss guidelines, however, has been highlighted as potentially important for men on ADT to prevent treatment-induced lean mass loss [14, 15]. Irrespective of a lack of interventions complying with the weight loss guidelines, combined exercise and nutrition interventions induced the greatest loss of fat mass, with those incorporating resistance training more likely to prevent lean mass loss than aerobic exercise alone. Furthermore, exercise-only interventions are effective in preventing ADT-related fat mass gain and lean mass loss if sufficient intensity and volume of exercise is prescribed and include both aerobic and resistance training [16].

The first experimental study (Chapter 4) presented in this thesis examines retrospective data, collected within a clinical environment at a Urology clinic. The effect of a weight loss program on body composition of overweight and obese prostate cancer patients scheduled for robot assisted radical prostatectomy (RARP) surgery is reported. This study established that the prescription of a very low-calorie diet (~3000-4000 kJ/d) combined with moderate intensity exercise (90 minutes/day) was effective in significantly reducing weight, total fat mass, trunk fat mass, visceral fat mass, and blood pressure. Additionally, patients who experienced a higher number of surgery-related adverse effects also had greater absolute weight and fat mass. However, contrary to our hypothesis lean mass declined significantly following the intervention. The exercise and nutrition prescribed was unlikely sufficient enough to stimulate or support muscle protein synthesis, particularly as resistance training and optimised protein intake was not advised for all patients. Diagnosis is considered an opportune time to implement exercise and nutrition interventions [17]. This study established that newly diagnosed overweight and obese men with prostate cancer can reduce their fat mass and blood pressure prior to RARP and was associated with improved surgical outcomes.

Chapter 5 is a report of a prospective study assessing the efficacy of a 12-week exercise and nutrition weight loss intervention in obese prostate cancer patients on ADT to reduce fat mass, maintain lean mass, and improve physical function and blood biomarkers associated with cancer progression and obesity. The results of self-reported outcomes such as general health-related and prostate cancer-specific quality of life results from the intervention are reported in Chapter 6. This intervention consisted of 300 minutes of exercise per week including supervised resistance training and home-based aerobic exercise, and dietitian consultations advising a daily energy deficit of 2100 – 4200 kJ and protein supplementation. The intervention resulted in reductions of body weight, fat mass, trunk fat mass, and visceral fat mass, while preserving lean mass. Improved upper and lower body muscular strength and cardiorespiratory

fitness was also observed. The exploratory analyses of blood biomarkers and quality of life predominantly found no changes, except for a significant decline in leptin and a trend for an improvement in the hormone treatment symptoms domain of prostate cancer-specific quality of life. ADT is known to result in fat mass gain, lean mass loss, and reduced physical function, and this research indicates that prostate cancer patients who are obese and receiving long-term ADT may reverse or prevent these changes using a weight loss exercise and nutrition intervention.

Chapter 7 was an investigation of how obese patients with prostate cancer on ADT transitioned to a 12-week self-managed home-based exercise and nutrition program and if they could maintain the benefits gained from the supervised weight loss intervention. This study demonstrated that obese patients, who continued to receive ADT, could maintain their body composition, upper and lower body strength, and cardiorespiratory fitness during a home-based program where they were recommended to complete 150 minutes of moderate-to-vigorous aerobic and resistance exercise per week, and maintain a healthy balanced diet. However, individual changes in lean mass were dependant on weekly resistance training duration, with those completing more sessions gaining or maintaining lean mass. Furthermore, contrary to our original hypothesis quality of life was not maintained during this follow-up period. The domains role-physical, mental health, and physical component significantly declined, with vitality showing a substantial, albeit not statistically significant, decline as well. Several patients experienced changes to their physical health during the 12-week home-based period and were among the patients who reported a substantial decline in quality of life. Patients subject to illness and injury require additional home-based strategies to prevent a deterioration in physical and mental health.

CLINICAL SIGNIFICANCE AND RESEARCH IMPACT

The findings of this thesis are of clinical significance and exhibit a meaningful treatment effect of exercise and nutrition and might have implications to reduce obesity-related and prostate cancer treatment-related adverse effects and enhance general health and well-being of overweight and obese patients with prostate cancer. Through clinically collected data, Chapter 4 revealed that patients were receptive to urologist recommended weight loss and that fat mass and blood pressure could be significantly reduced by completing an exercise and nutrition program when undertaken from the time of diagnosis to prior surgery. The importance of fat mass loss was further highlighted by those with less fat mass experiencing a lower number of surgery-related adverse effects. The evaluation of clinical data in the urology practice setting has a significant translational impact as it demonstrates the efficacy of weight loss outside the constraints of a tightly controlled laboratory trial. Furthermore, DXA is not considered a measure of standard care for prostate cancer patients unless bone health is of concern, as such, the novel presentation of whole body and regional fat mass and lean mass provides further insights into the impact of a clinic-based weight loss intervention. Consequently, this study highlighted lean mass was significantly lost and prompts further investigation into how this may be prevented in future interventions.

The findings of the prospective exercise and nutrition intervention presented in Chapters 5, 6, and 7 are of significant research impact and clinical significance as patients adopted exercise and nutrition-based interventions and long-term changes, which are being increasingly acknowledged as important adjuvant therapies to ameliorate ADT-related side effects. Additionally, the exploration of obese men on ADT is also of clinical importance as they are at increased risk of exacerbated treatment side effects, poor prostate cancer prognosis, and have been underrepresented in prostate cancer research. Accordingly, we have provided

novel findings reporting the efficacy of fat mass loss and the preservation of lean mass in this population during a supervised weight loss intervention and how these changes may be preserved during a home-based program. In addition, patients were able to improve and maintain their muscular strength and cardiorespiratory fitness, which further highlights the multitude of clinical benefits obtained from implementing exercise and nutrition changes for obese patients with prostate cancer. However, the finding of a decline in quality of life during the home-based program is a cause for concern. While quality of life was associated with individual changes in lean mass as well as a decline in physical health for some patients, it does demonstrate that home-based exercise and nutrition programs may not be appropriate for patients at increased risk of illness or injury, that is, obese patients with multiple comorbidities. This is of clinical significance and highlights the importance of tailored care as patients who are self-managing their exercise and nutrition regimes may not be able to appropriately adjust their practices to reflect changes in their health status. As a result, additional strategies are required to be tested in the future to address these concerns and provide better opportunities to patients with multiple comorbidities.

In addition to the clinical significance and research impact of the thesis in relation to the outcome measures, it is also important to highlight the perceived or subjective impact the intervention had on patients in the prospective clinic-based exercise trial and self-managed home-based program. A questionnaire (Appendix C6) was given to the patients at the end of the intervention to assess their perceived benefit, if any, in addition to the physical changes objectively measured throughout the study. This information provides further substance to the work undertaken as part of this thesis and highlights the perceived clinical impact such interventions can have for patients, which is not necessarily conveyed through quantifiable changes.

Table 8.1: *Written feedback of patients receiving ADT who participated in the prospective exercise and nutrition intervention (Chapters 5, 6, and 7).*

Question	Responses
What benefits did you notice by following the exercise and nutrition program?	- "I've lost a little bit of weight. I am a lot stronger and have more stamina. I've got used to eating less." - "My energy level improved and I was able to do a lot more strenuous work and exercising than previously." - "Don't feel depressed anymore; helped with everything; more confident; stronger." - "Fitter (until back injury), mentally felt better." - "Better overall fitness and 10kg weight loss, overall more energy." - "Weight loss -7 kg" - "Lost weight, big improvement in moving/walking, feeling good, muscle build up." - "Felt healthier and assisted mentally knowing I was doing something positive to assist with my condition." - "It is very hard for me to notice benefits because of the side effects of the drug Lucrin." - "Until my recent illness I feel much fitter." - "Able to move the body easier."

FUTURE RESEARCH DIRECTIONS

The summary of literature presented in the two reviews and the results reported in the experimental studies conveyed a number of important findings. However, just as equally, they have revealed several areas for further research.

All experimental studies were conducted using a single group study design. The first study (Chapter 4), utilised retrospective data where a non-weight loss group was not available.

The decision to utilise a single group design for the second, prospective study (Chapters 5, 6, and 7) was based on limited recruitment time, and the plethora of evidence highlighting exercise to be beneficial for prostate cancer patients, so it was deemed inappropriate to include a non-exercising control group. As such, a 6-week control period was incorporated into the design to ensure any changes observed across the intervention period were due to the prescribed program. A randomised controlled trial with a non-weight loss, delayed, or low-intensity exercise control group would further validate the findings of the present thesis.

This thesis demonstrates the efficacy of exercise and nutrition induced weight loss for overweight and obese prostate cancer patients scheduled for RARP or prescribed long-term ADT; however, the physiological benefits of the associated fat and lean mass changes are still unclear. As described in Chapter 2, there is no certainty which mechanistic pathways are responsible for the associations between obesity and poor prostate cancer prognosis. However, examining the proposed mechanistic pathways within an obese and weight loss state may provide further insight into the impact weight loss does or does not have on prostate cancer prognosis. The proposed blood biomarkers associated with obesity and prostate cancer progression were assessed, however, this was not a primary outcome of the study, as such, conclusions about the impact that weight loss has on prostate cancer progression is hypothesis generating and a potential guide for additional studies. Future studies would benefit from multifaceted designs that incorporate *in vivo* and/or *in vitro* methodologies in conjunction with combined exercise and nutrition-based interventions to examine the impact of weight loss on prostate cancer progression and tumour biology.

Two undesirable findings were reported that need to be addressed and examined further. First, within Chapter 4 a significant loss of lean mass was reported. Lean mass loss is not unexpected when undergoing weight loss [18], however, prostate cancer patients are already at

an increased risk of lean mass decline after a radical prostatectomy [19] and as a side effect of ADT [20]. While patients were encouraged to exercise, resistance training was not actively prescribed for all patients prior to RARP. In contrast to this, lean mass was maintained in conjunction with fat mass loss in the exercise trial reported in Chapter 5. While the two cohorts cannot be directly compared, the inclusion of supervised resistance training and protein supplementation in the intervention reported in Chapter 5 is likely to have attributed to the maintenance of lean mass. Further research is required into the benefit of incorporating resistance training and protein supplementation into a weight loss program prior to radical prostatectomy to prevent loss of lean mass. Second, general health-related quality of life significantly decreased during the home-based program reported in Chapter 7. The decrease in role-physical, mental health, vitality, and physical component domains of quality of life were associated with a loss of lean mass and change in physical health during the home-based period. A prostate cancer diagnosis and the side effects of the various treatments can negatively impact a patient's quality of life. While home-based programs are attractive given their low cost and increased access to rural communities and those who cannot travel, the lack of supervision may not be appropriate for all patients, particularly those at increased risk of illness and injury. Future studies should examine the feasibility and effectiveness of home-based programs for patients at increased risk of illness and injury. Consideration should be given for the use of regular video or phone consultations to assist those who may not be able to appropriately manage or adjust their self-managed exercise and nutrition practices in order to maintain their physical and mental health.

CONCLUSION

The experimental studies presented in this thesis provide preliminary efficacy that overweight and obese prostate cancer patients scheduled for a RARP or receiving long-term

ADT can significantly reduce fat mass while undertaking combined exercise and nutrition-based weight loss interventions. Furthermore, this fat loss may improve patient outcomes, however, only exploratory analyses to assess this relationship were conducted in this thesis and requires further clarification. ADT and weight loss induced lean mass loss can be prevented with the incorporation of resistance training and protein supplementation in a weight loss program, although further studies are required to assess the influential impact each had in isolation or synergistically. The findings established here create a foundation for future research in weight loss and the impact this may have on treatment-related side effects and prostate cancer prognosis. As research develops and exercise and nutrition programs become more accepted as adjuvant therapy within clinical practice in the care of patients with prostate cancer, it will be important for weight loss to be considered in their treatment plan, especially for patients who are obese, or at risk of developing obesity throughout the natural history of the cancer.

REFERENCES

1. Dickerman BA, Torfadottir JE, Valdimarsdottir UA, Giovannucci E, Wilson KM, Aspelund T et al. Body fat distribution on computed tomography imaging and prostate cancer risk and mortality in the AGES-Reykjavik study. Cancer. 2019;125(16):2877-85. doi:10.1002/cncr.32167.

2. Salji M, Hendry J, Patel A, Ahmad I, Nixon C, Leung HY. Peri-prostatic fat volume measurement as a predictive tool for castration resistance in advanced prostate cancer. Eur Urol Focus. 2018;4(6):858-66. doi:10.1016/j.euf.2017.01.019.

3. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2011;4(4):486-501. doi:10.1158/1940-6207.CAPR-10-0229.

4. Harrison S, Tilling K, Turner EL, Martin RM, Lennon R, Lane JA et al. Systematic review and meta-analysis of the associations between body mass index, prostate cancer, advanced prostate cancer, and prostate-specific antigen. Cancer Causes Control. 2020;31(5):431-49. doi:10.1007/s10552-020-01291-3.

5. 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. Med Oncol. 2014;31(2):829. doi:ARTN 829

10.1007/s12032-013-0829-8.

6. World Cancer Research Fund, American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and prostate cancer 2018.

7. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol. 2013;63(5):800-9. doi:10.1016/j.eururo.2012.11.013.

8. Henning SM, Galet C, Gollapudi K, Byrd JB, Liang P, Li Z et al. Phase II prospective randomized trial of weight loss prior to radical prostatectomy. Prostate Cancer Prostatic Dis. 2018;21(2):212-20. doi:10.1038/s41391-017-0001-1.

9. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Acute versus chronic exposure to androgen suppression for prostate cancer: impact on the exercise response. J Urol. 2011;186(4):1291-7. doi:10.1016/j.juro.2011.05.055.

10. Newton RU, Jeffery E, Galvao DA, Peddle-McIntyre CJ, Spry N, Joseph D et al. Body composition, fatigue and exercise in patients with prostate cancer undergoing androgen-deprivation therapy. BJU Int. 2018;122(6):986-93. doi:10.1111/bju.14384.

11. Knipper S, Mazzone E, Mistretta FA, Palumbo C, Tian Z, Briganti A et al. Impact of obesity on perioperative outcomes at robotic-assisted and open radical prostatectomy: results from the national inpatient sample. Urology. 2019;133:135-44.

12. Thomas RJ, Holm M, Williams M, Bowman E, Bellamy P, Andreyev J et al. Lifestyle factors correlate with the risk of late pelvic symptoms after prostatic radiotherapy. Clin Oncol (R Coll Radiol). 2013;25(4):246-51. doi:10.1016/j.clon.2012.11.007.

13. Skolarus TA, Wolf AM, Erb NL, Brooks DD, Rivers BM, Underwood W, 3rd et al. American Cancer Society prostate cancer survivorship care guidelines. CA Cancer J Clin. 2014;64(4):225-49. doi:10.3322/caac.21234.

14. Owen PJ, Daly RM, Livingston PM, Fraser SF. Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: an update. Prostate Cancer Prostatic Dis. 2017;20(2):137-45. doi:10.1038/pcan.2016.69.

15. Moyad MA, Newton RU, Tunn UW, Gruca D. Integrating diet and exercise into care of prostate cancer patients on androgen deprivation therapy. Res Rep Urol. 2016;8:133-43. doi:10.2147/RRU.S107852.

16. Cormie P, Galvao DA, Spry N, Joseph D, Chee R, Taaffe DR et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU Int. 2015;115(2):256-66. doi:10.1111/bju.12646.

17. Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. J Clin Oncol. 2005;23(24):5814-30. doi:10.1200/jco.2005.01.230.

18. Weinheimer EM, Sands LP, Campbell WW. A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. Nutr Rev. 2010;68(7):375-88. doi:10.1111/j.1753-4887.2010.00298.x.

19. Singh F, Newton RU, Baker MK, Spry NA, Taaffe DR, Thavaseelan J et al. Feasibility of presurgical exercise in men with prostate cancer undergoing prostatectomy. Integr Cancer Ther. 2017;16(3):290-9. doi:10.1177/1534735416666373.

20. Galvão DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008;102(1):44-7. doi:10.1111/j.1464-410X.2008.07539.x.

APPENDICES

A. PARTICIPANT RECRUITMENT INFORMATION

A1. Recruitment flyer

Exercise Medicine Research Institute

AUSTRALIA ECU EDITH COWAN UNIVERSITY

VARIO health clinic

WEIGHT LOSS PROGRAMME FOR PROSTATE CANCER PATIENTS

Exercise Medicine Research Institute at Edith Cowan University is a world leading research collaboration that specialises in understanding the role of exercise in managing chronic disease.

Take part in a research study designed to improve your body composition and well-being.

- Receive a FREE 3 month exercise intervention.
- Receive 3 FREE consultations with a dietician.
- The programme is supervised by qualified exercise scientists who specialise in prostate cancer.
- To be eligible you need to be on androgen deprivation therapy for localised prostate cancer and be overweight or obese. Also you should not have any medical conditions that could inhibit you from exercising.

FOR MORE INFORMATION PLEASE CONTACT:

Rebekah Wilson

Phone: [redacted]

Email: [redacted]

Web: www.exercisemedicine.org.au

Images not available in this version of the thesis

A2. Phone screening questionnaire

REBEKAH PHD - PHONE SCREENING ELIGIBILITY QUESTIONNAIRE

1. **Brief introduction about the study •**

- 12-week exercise and diet intervention (3 exercise sessions a week + 3 nutrition counselling sessions with a dietician over the 12-weeks).
- The entire study involves a 6-week delay period (control period), followed by the 12-week intervention, followed by a 12-week home-based programme.
- Study is assessing the effect of the exercise and diet on changes in body composition
- Everyone completes the exercise and diet intervention (no control group).
- Involves DXA, pQCT, physical testing, questionnaires, blood and urine samples.

2. **Get verbal permission to ask a few questions about themselves and their cancer •**

3. **Have you had a prostate cancer diagnosis?**
   Yes • No • (*ineligible*)

4. **Have you ever had another cancer diagnosis?**
   Yes • (*ineligible*) (*basal cell carcinoma accepted*) No •

5. **Are you <u>currently</u> receiving androgen deprivation therapy?**
   Yes • No • (*ineligible*)

6. **When did you start your course of ADT?**
   Start date (day/month/year): _____(*ineligible if within 6 months of start date*).
   NB: *If ineligible please hold on to participants information as we may contact them later on in their treatment process if they are otherwise eligible within the study recruitment period – January 2018-January 2019.*

7. **When is your expected last dose of ADT?**
   End date (day/month/year): _____(*ineligible if NOT receiving any more ADT. MUST be getting at least one more dose while completing the study*).

8. **Have you received or expecting to receive any other treatment for your prostate cancer?**
   Yes • No •
   Treatment type: _____
   Date completed:_____
   (*ineligible if receiving during study period).*

9. **Are you taking/receiving any experimental drugs or treatment for your prostate cancer?**
   Yes • (*ineligible*) No •

10. **Have you been told that you have <u>bone</u> metastases?**
    Yes • (*ineligible*) No •

11. **Do you have a body mass index (BMI) between 25 and 50 kg/m^2?** (If you don't know, what is your weight and height?)
    Yes • No •

12. **Would you describe yourself as having excess fat mass around your abdomen or a waist circumference > 102cm?**
    Yes • No •

13. **Do you perform two or more sessions of <u>supervised</u> aerobic or resistance training each week?** e.g. gym class, personal training session, sporting game (excluding golf), walking group.
    Yes • (*ineligible*) No •

14. **Do you feel comfortable walking 400m?**
    Yes • No • (*ineligible*)

15. **Are you currently seeking dietary advice from a dietician?**
    Yes • (*ineligible*) No •

16. **Have you ever been told you have a kidney condition?**
    Yes • (*ineligible*) No •

17. **Have you ever been told you have cardiovascular disease?**
    Yes • No •
    a) Are you under the care of a cardiologist?
    Yes • No •
    Name: _____ Hospital: _____

18. **Have you ever been told you have diabetes?**
    Yes • No •

19. **Have you ever been told you have a thyroid condition?**
    Yes • No •

20. **If yes to questions 15, 16, or 17 has your doctor stated the condition is well controlled?**
    Yes • Not well controlled • (*ineligible*)

21. **Do you have any other known conditions that may <u>prevent</u> you from completing <u>high-intensity</u> exercise?** E.g. serious cardiac event in the last 12 months, spinal cord problems, chest pain when exercising, severe bone pain, musculoskeletal injury/condition (severe arthritis, fracture).
    Yes • (*ineligible*) No •

22. **Will you be away for more than 2 consecutive weeks during the next 8 months?**
    Yes • (*ineligible*) No •

NB: *if away approximately at the time of the first 6 weeks or final 12 weeks of the study period still accept for further screening and we can try work with dates.*

23. Can you read and speak English?

Yes • No • (*ineligible*)

24. Are you willing to obtain medical consent/clearance from your GP?

Yes • No • (*ineligible*)

25. Are you willing to attend regular testing at Joondalup Campus, ECU and exercise training, and nutrition counselling sessions at Joondalup or Mt Lawley Campus, ECU?

Yes • No • (*ineligible*)

26. Are they willing to complete exercise and adhere to a nutrition programme outside of the clinic setting?

Yes • No • (*ineligible*)

NB: *If no, explain that they will be expected to attend 3 exercise sessions a week at the clinic and then complete 30 minutes of exercise at home on the days they do not attend a clinic session. The diet will be an individually tailored nutrition programme developed over 3 sessions with a dietician.*

Send recruitment pack?

Yes • No •

Postal address of patient:_____

_____

Home phone: _____ **Mobile phone:** _____

Email: _____

A3. Participant information package

PARTICIPANT INFORMATION LETTER

Project title:
Effects of a combined exercise and diet intervention in obese prostate cancer patients on androgen deprivation therapy: a prospective study.

Purpose:
Exercise has been established to be safe and result in improved physical function and quality of life for cancer patients. The purpose of this study is to assess the efficacy of a combined exercise and diet programme designed to induce a loss in fat mass while maintaining skeletal muscle mass in men with prostate cancer receiving ADT. We will also be investigating the effects of the diet and exercise intervention on blood and inflammatory biomarkers, cardiorespiratory fitness, resting metabolic rate, muscle strength, and quality of life. This study is being conducted as part of the requirement for a Doctor of Philosophy degree.

Who can participate?
We require men with prostate cancer who are currently receiving ADT and are overweight or obese. To be eligible, participants must:

1. Be receiving ADT as part of their prostate cancer treatment plan.
2. Have been on ADT for at least 6 months and anticipate remaining on ADT while participating in the study (that is, receiving at least one more dose of ADT).
3. Not have bone metastases or a secondary cancer diagnosis.
4. Have a body mass index (BMI) between 25-50 kg/m^2. However, after completing a body composition assessment at the Exercise Medicine Research Institute, only those with a body fat percentage ≥25% will be included in the study. *
5. Comfortably walk 400 m.
6. Not performing regular exercise as defined by undertaking structured aerobic or resistance training two or more times a week within the past 3 months.
7. Not receiving professional dietary advice as defined by seeking nutritional information from an Accredited Practising Dietician.
8. Not have any acute illness, musculoskeletal, cardiovascular, kidney, thyroid, or neurological disorder that could place the participant at risk of injury or illness resulting from the exercise or diet.
9. Your nominated GP must provide consent and clear you for participation in the study.
10. Be able to read and speak English.

- If you do not qualify for the study based on your body fat percentage, you will be provided with information of other opportunities internal and external to the Exercise Medicine Research Institute, including other studies undertaken at ECU (if appropriate), or an enhanced primary care (EPC) plan to receive Medicare rebate exercise physiology consultations.

If you qualify and choose to take part in the study all participants will complete the exercise and diet intervention.

What will I be asked to do?

Exercise programme
All participants will complete a 12-week exercise programme and then asked to maintain this level of activity for a further 12 weeks via a prescribed home-based programme (see study commitment timeline below, *Figure 1*). The exercise programme will consist of three supervised aerobic/resistance training sessions per

week for the 12-week intervention period and completion of daily self-monitored aerobic activity of your own choice. In total, the participant will be asked to complete 300 minutes of exercise a week (3 x 60-minute supervised training sessions (180 minutes) + 120 minutes of self-monitored aerobic exercise) aiming for approximately 45 minutes of exercise per day. Participants will be asked to maintain this level of exercise for a further 12 weeks after the supervised sessions have stopped. Further advice and exercise prescription will be provided by the lead researcher (Ms Rebekah Wilson) for the home-based programme.

The supervised training programme will be conducted in small groups of up to 10 participants exercising under direct supervision to ensure correct technique and to minimize the risk for injury. Sessions will take approximately 60 minutes (this includes the warm-up and cool down). Three times weekly training sessions will start with a 5-minute warm-up comprising of low-level aerobic activity such as walking and cycling. Resistance training will involve exercises that target all major muscle groups of the upper and lower body. Intensity will be manipulated from 6-12 repetition maximum (RM; i.e. the maximal weight that can be lifted 6 to 12 times which is equivalent to ~60-85% of 1RM or your maximal strength) of 1-4 sets per exercise (a set is a series of repetitions). The aerobic component will involve the participants completing ~30-45 minutes of aerobic training on those days where resistance training will not be completed. The participants may partake in an aerobic exercise of their own choice such as swimming, walking, jogging, or cycling. Participants will be asked to maintain a moderate-vigorous intensity of 50-90% of maximum heart rate (220-age) where participants will receive consultation during the supervised sessions on how to monitor and complete the aerobic exercise. The exercise prescription will be progressive and modified according to individual response.

Diet programme

All participants will be asked to attend three nutritional counselling sessions conducted by the lead researcher (Ms Rebekah Wilson) and Accredited Practising Dietician (A/Prof Philippa Lyons-Wall). These will be completed at weeks 7, 9, and 18 of the study period (see *Figure 1* for study timeline). Participants will not be asked to stick to a strict diet but simply be provided with individualised nutritional advice and goals that suit each participant's lifestyle and preferences. The nutritional counselling sessions will include the development of an individualised meal plan highlighting portion sizes and appropriate food choices that will assist in making the necessary changes to induce fat mass loss. We will be targeting a 2-4MJ (500-1000 kcal) energy deficit as recommended by the Australian Weight Loss Guidelines. The advice will also aim to reduce consumption of refined carbohydrates (e.g. white bread, cakes, biscuits), saturated fats (e.g. processed meats, butter, cream), and to optimise protein intake (e.g. fish, skinless chicken). We will be aiming for a daily protein intake of 1-1.2 g/kg/day which aligns with the daily intake recommended by the Australian Healthy Eating Guidelines and for cancer patients. We will also be providing each participant with a protein supplement (vanilla whey protein powder shake, supplied by Bulk Nutrients) after each supervised training session during the 12-week supervised period of the study.

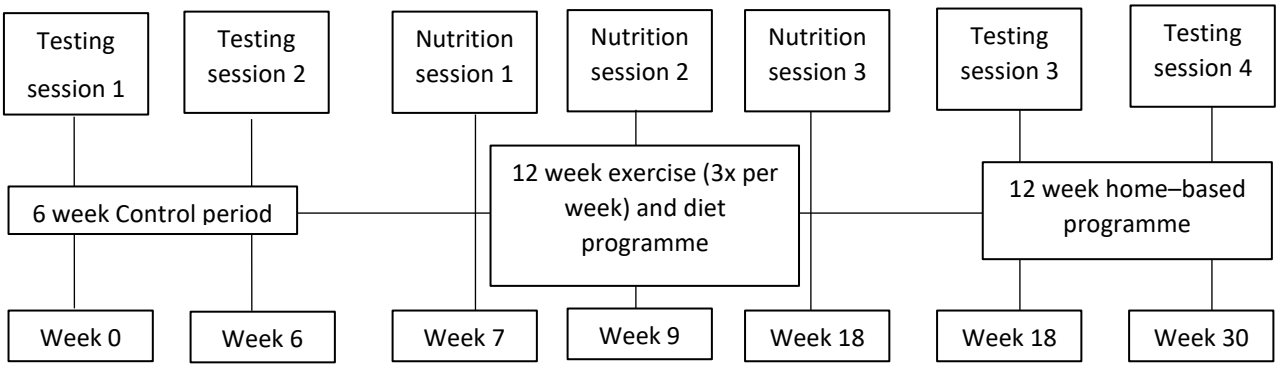


Figure 1: Participant timeline of commitment to study.

Assessments

As a participant in this research project you will be required to complete a series of assessments that will occur at 0 weeks, 6 weeks, 18 weeks, and 30 weeks (as shown in *Figure 1*). Participants will be thoroughly instructed on each of the assessments and supervised by qualified professionals at all times throughout these

sessions. The assessment appointments will take approximately 1-2 hours and will be conducted over 3 separate days during a ~1-week period (see *Table 1* below for assessment commitments).

Body composition

- Body mass index (BMI) will be calculated by measuring your weight and height.
- Waist and hip circumference will be measured using a constant tension measuring tape.
- Fat, muscle, and bone density will be measured with Dual Energy X-ray Absorptiometry (DXA). This assessment involves lying still for approximately 10-minutes and a scanning arm will move above your body. A low-dosage x-ray will pass underneath the table to the scanning arm.
- Bone and muscle size of the lower leg will be measured using the Peripheral Quantitative Computed Tomography (pQCT). The assessment involves you sitting in a chair with your leg extended and the circular scanning arm moving from your ankle to your knee.
- The total radiation dose for all scans undertaken during the study is very low, only a little more than normal background radiation from an airplane flight and much less than, for example, an international flight.

Blood and inflammatory markers

- We will be assessing lipid profile, C-reactive protein, insulin, HbA1c, PSA, testosterone, interleukin-6 (IL-6), and insulin-like-growth-factor-1 (IGF-1). These markers will be analysed from venous blood samples collected and analysed by an accredited Australian National Association of Testing Authorities laboratory (i.e. Australian Clinical Labs). Participants will be asked to attend this appointment in a fasted state (consumption of no food or beverages (other than water) 6 hours prior to appointment), preferably first thing in the morning having fasted overnight.

Resting metabolic rate

- This measure requires all participants to attend the **first testing day in a fasted state**. This requires the consumption of no food or beverages (water is fine) 6 hours prior to appointment (we recommend having dinner the night before and only water after 10pm until your appointment the following morning). Participants are also asked to abstain from smoking in the 6 hours leading up to the appointment and vigorous exercise during the previous 24 hours. Morning medications may be consumed prior to appointment but with water only. **Please bring your own breakfast,** tea and coffee will be provided. Resting metabolic rate assessment involves lying down for up to 25 minutes. For the final 10-15 minutes of the test, participants will have a see through plastic hood covering their head (like an astronaut helmet), this will collect and analyse the expired air.

Cardiorespiratory fitness

- Maximal aerobic capacity test: This will involve walking/jogging on a treadmill until volitional fatigue. The test will last ~8-12 minutes. This test will be supervised by a medical doctor as well as by Accredited Exercise Physiologists. During the test, participants will have a 12-lead electrocardiography (ECG) system attached to the body which will be assessing heart rhythm and rate. Participants will also have a blood pressure cuff around the arm and a mask over the nose and mouth that will be assessing their expired air. The speed and gradient of the treadmill will be gradually increased every 3 minutes until the participant says stop or we feel it is unsafe to proceed.
- 400 metre corridor walk: Participants will be asked to walk 20 metres in a corridor, turn and return to the starting position and repeat another 9 times.

Muscle strength

- One-repetition maximum test: Maximal muscle strength will be determined for three of the resistance exercises performed during the exercise training sessions using weight-training machines (leg press, chest press, seated row). The maximal strength is the most weight that can be lifted one time using correct technique.

Protein intake (urine assessment)

- As a participant, you may be required to provide a 24-hour urine sample while completing day two of the 3-day diet weighed food record described below. This will involve participants collecting their

urine in a provided container over a period of 24 hours. We will be analysing total urinary nitrogen which allows us to calculate protein intake.

Dietary monitoring

- 3-day diet weighed food record: Participants will be asked to weigh and record all food and beverages consumed over three consecutive days; two week days and one weekend day. Participants will be provided with scales as well as written and verbal instructions on how to accurately complete this.

Physical activity monitoring

- Participants will be asked to wear an activity monitor (triaxial accelerometer) for a 3-day period, including while sleeping (same 3 days as completing above described weighed food record). This will allow us to accurately measure the duration and intensity of any physical activity completed. The device is very small (4.6cm x 3.3cm x 1.5 cm), lightweight (19g), and will be worn on the waist. Participants will also be provided with a heart rate monitor to monitor exercise intensity completed outside of the supervised sessions. The participant will be required to record their exercise length and average/peak heart rate in a logbook.

Questionnaires

- Participants will be asked to complete standardised questionnaires used to record demographic and health history information as well as to assess quality of life (both general and prostate cancer specific including treatment side effects e.g. incontinence, sexual health, bowel dysfunction), usual leisure time exercise and sedentary habits, and eating patterns/habits. These questionnaires will be completed at home at your leisure. During the 12-week supervised programme participants will be asked to fill out a weekly questionnaire looking at their food intake and exercise over the previous 7 days. This questionnaire will also be undertaken via a phone call once at the mid-point of the home-based period. Participants thoughts on the programme will also be asked.

The assessments conducted during this study could reveal information that may be significant for your health. You have a choice to receive this information or not and, if you choose to receive it, you can also indicate how you would like it to be provided. Please note that the research team do not have the expertise to provide a medical diagnosis or advice on medical treatment. They will simply bring your attention to the abnormal result and recommend you seek further medical advice. The consent form allows you to provide your wishes, which will be respected by the research team.

Table 1: *Participants commitment for testing procedures to be repeated at each testing time point unless specified and will be conducted over the period of a week, subject to participant availability.*

	Procedures	Time
Testing day 1	・Body composition (DXA, pQCT) ・Resting metabolic rate (fasting) ・Questionnaires (completed at home)	1-2 hours
Off-site testing (completed at home/off campus)	・Blood test (fasting) (weeks 6 and 18 only) ・24 hr urine sample (weeks 6 and 18 only) ・3-day diet weighed food record (additional measurement at week 12) ・3-day physical activity monitoring (additional measurement at week 12)	3 days
Testing day 2	・Strength testing familiarisation session (week 0 only) ・Maximal aerobic capacity test (weeks 6 and 18 only)	1-2 hours
Testing day 3	・400m walk ・Strength testing ・Diet history (week 6 only)	1 hour

All testing will take place at Edith Cowan University, Joondalup Campus. However, exercise training sites will be available at both Joondalup and Mt Lawley Campuses. We are not able to offer re-imbursement of your travel costs to testing and exercise training sessions.

What risks are involved?
Any exercise may result in mild discomfort and muscle soreness. Furthermore, there is the possibility of muscle pulls or strains associated with the exercise, common to any type of physical activity. In order to minimize these risks participants will perform an adequate warm-up and cool-down before and after any exercise bout, be comprehensively instructed on the correct lifting technique, thoroughly familiarised with the movements involved in this investigation, and supervised at all times when completing exercise sessions within the clinic facilities by a qualified professional. Risk of falling may exist in the performance of some tasks, however, participants will be closely supervised and spotted to prevent a fall from occurring. Furthermore, during exercise it is possible to experience symptoms such as abnormal blood pressure, fainting, light-headedness, muscle cramps or strain, nausea, and in very rare cases heart rhythm disturbances or heart attack. These potential risks are common to any form of physical activity.

DXA scans are routine clinical tests but carry a small risk to the participant. DXA involves exposure to radiation. The level of radiation exposure is exceedingly small (10-30 microSieverts [µSv]) in comparison to the natural annual radiation dose in western communities (approximately 3000 µSv). A person would receive radiation exposure of approximately 80 µSv on an airline flight of 8-hours or 30-40 µSv during a typical chest x-ray. The number of scans proposed in this study is well within the guidelines provided by the manufacturer of DXA machines.

The discomforts associated with the blood drawing procedures are minimal. There is a risk that sometimes bruising and infection may occur and that the arm might become sore. Risk of bruising or infection from the blood draws will be minimised because all blood draws will be performed by a trained phlebotomist with extensive experience. The total amount of blood drawn during each session will not exceed 15 ml. No syringes, lancets, needles or other devices capable of transmitting infection from one person to another shall be reused. All of these items, which are disposable, will be destroyed after each use. As an additional safeguard in preventing contamination new disposable gloves will be required for all blood draws. All contaminated items will be disposed of promptly in sharps containers.

Participants will be required to consume a protein supplement after each supervised training session. It is possible a participant may have an allergic reaction to the contents of the powder e.g. lactose intolerance. Those participants who have a known lactose intolerance will be supplied with an alternative low lactose protein supplement (whey protein isolate). If a reaction does occur, participants will no longer be required to consume the protein supplement, however, will be asked to consult with the dietician about alternative protein products to consume instead of the protein powder supplement after each supervised training session. Please see the Bulk Nutrients, Whey Protein Concentrate, Vanilla flavour website page for further nutritional content information (http://www.bulknutrients.com.au/products/whey-protein-concentrate.html).

As a participant, you should contact a member of the research team if you are concerned about the potential of any adverse effects or if you experience any adverse effects following any of the tests, exercise sessions and/or consumption of the protein supplement. If any major symptoms of concern do arise during the study, you will be referred to your GP for further consultation, remediation, and clearance to continue in the trial as needed.

What benefits do I gain from participating?
All study activities, including the exercise instruction and training, nutrition consultation, protein supplement, and exercise equipment provided for home use as well as all assessments are provided at no cost to the participants.

Confidentiality and privacy statement:
The conduct of this research involves the collection, access and/or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal, or other regulatory authority requirements. Your results will be kept as confidential as is possible by law. All data will be kept in the possession of the investigators and stored in locked filing cabinets and password restricted computers for a minimum of 25 years. If the results of the study are published in a scientific journal, your identity will not be revealed. Participants will not be referred to by name

during research reports or study discussions. A re-identified copy of this data may be used for future research projects. However, your anonymity will be safeguarded at all times.

Feedback:
All participants will be provided with test results at the end of the study. A summary of study results will be made available to all interested participants upon completion of the trial.

Voluntary participation:
Whether you decide to participate in the study or not, your decision will not prejudice you in any way. No explanation or justification is needed if you choose not to participate. If you do decide to participate, you are free to withdraw your consent and discontinue your involvement at any time.

Withdrawing consent to participate:
Participants are free to withdraw their consent to further involvement in the research project at any time. If you decide to withdraw after initial baseline assessment, then your data may still be useful to us and assist with our study. If you wish to withdraw all information from the study then you may do so by indicating this to us in writing.

Contacting the investigators:
We are happy to answer any questions you may have at this time. Please do not hesitate to contact either:

Ms Rebekah Wilson	Phone: [redacted]	Email: [redacted]
Prof Daniel Galvão	Phone: [redacted]	Email: [redacted]
Prof Rob Newton	Phone: [redacted]	Email: [redacted]

If you have any concerns or complaints about the research project and wish to talk to an independent person, you may contact

Human Research Ethics Officer	Phone: (08) 6304 2170	Email: research.ethics@ecu.edu.au

A4. Patient consent forms

Chapter 4:

Image is not available in this version of the thesis

First name (print) _____ Surname _____

Gender (circle) F M DOB _____ Age _____

Email address _____

1. Have you had a DEXA Body Composition scan before? YES NO

   If so, when and where?

   _____

2. Where did you hear about us/who referred you?

   _____

3. Why have you decided to have a body composition scan?

   _____

4. Is there any chance you could be pregnant? YES NO
5. I give consent for Trench Health and Fitness to retain a copy of this form for record keeping purposes in accordance with our privacy policy YES NO
6. I give consent for Trench Health and Fitness to use my age, gender and body composition results for scientific research purposes where my personal identifying information (name) will remain protected YES NO
7. Do you have any questions? YES NO

I have read the information & what the procedure entails and have had the opportunity to ask questions which have been answered to my satisfaction. I consent to this procedure to be performed.

Name (print)_____

Signature _____ Date_____/_____/_____

Consent to Release Information to my Health Providers

Please indicate if you consent to Trench Health and Fitness sharing your health information with any of your usual Health Care Providers. If you do not consent, we will not share any of your health results.

1. Profession(circle): GP Psychologist Physiotherapist Specialist Other
   Name: _____
   Practice: _____
   Phone: _____

2. Profession (circle): GP Psychologist Physiotherapist Specialist Other
   Name: _____
   Practice: _____
   Phone: _____

3. Profession (circle): GP Psychologist Physiotherapist Specialist Other
   Name: _____
   Practice: _____
   Phone: _____

4. DVA (circle if applicable)

Please note with clients presenting with eating disorders and/or mental health concerns it is a requirement that we communicate with your GP and psychologist.

Consent to Utilise Information for Research Purposes

No identifiable data such as your name, date of birth, address or contact details will be used. Only your body composition and blood pressure data may be used for research purposes.

Confirmation of Informed Consent

I (print name) _____ provide consent for Trench Health & Fitness to obtain information from and release information to my health care provider/s listed above and DVA (if required). I have read and understood the Consent Form and agree to these conditions for the dietetic services provided by Trench Health & Fitness.

☐ I consent to my data being used for research purposes.

☐ I do not consent to my data being used for research purposes.

Chapter 5, 6, 7:

CONSENT FORM

Project title: Effects of a combined exercise and diet intervention in obese prostate cancer patients on androgen deprivation therapy: a prospective study.

- I understand this study is being conducted as part of the requirement for a Doctor of Philosophy degree.
- I have read and understood the information sheet and this statement of informed consent.
- I understand that the study will be carried out as described in the information sheet, a copy of which I have retained.
- The nature and possible effects of the study have been explained to me.
- Any questions that I have asked have been answered to my satisfaction.
- I understand that all research data will be treated as confidential.
- I realise data gathered from this study may be used in future studies conducted by the Exercise Medicine Research Institute.
- I agree to participate in this study and give my consent freely.
- I realise that my participation in this research study is voluntary and whether or not I decide to participate is solely my decision.
- I also realise that I can withdraw from the study at any time and that I do not have to give any reasons for withdrawing.
- If I choose to withdraw from the study I understand that I also have the right to withdraw all information, but this must be provided in writing.
- I agree that research data gathered for the study may be published provided my name or other identifying information is not disclosed and may be used in future research studies.
- I understand that assessments conducted in this study could reveal information that may be significant for my health;
  - I would like to be informed ☐
  - I would not like to be informed ☐

I would like to receive any abnormal results via: (please note only your GP can provide a medical diagnosis and treatment advice)
Email: ☐
Letter: ☐
Phone call: ☐
My nominated GP: ☐

GP Name _____ GP Practice _____

Participant:

Name _____ Signature _____ Date _____

A5. Medical clearance form

MEDICAL PRACTITIONER CLEARANCE FORM

Project title: Effects of a combined exercise and diet intervention in obese prostate cancer patients receiving androgen deprivation therapy: a prospective study

Researchers: Ms Rebekah Wilson, Prof Daniel Galvão, Prof Robert Newton, Dr Nicolas Hart, Prof Dennis Taaffe, A/Prof Philippa Lyons-Wall

Contact: Ms Rebekah Wilson, **Email:** [redacted] **Phone:** ([redacted]

Institute: Exercise Medicine Research Institute – Edith Cowan University

Dear Doctor,

The Exercise Medicine Research Institute is undertaking a research study investigating the efficacy of a combined exercise and diet intervention to reduce fat mass in obese prostate cancer patients receiving androgen deprivation therapy (ADT). Obesity within the prostate cancer population has been identified as an area of concern, with obesity being associated with increased risk of prostate cancer-specific death, more aggressive prostate cancer stage, and biochemical recurrence. Current strategies recommend the use of the prostate cancer physical activity guidelines of 75-150 minutes of exercise per week. Although these guidelines have been shown to induce significant improvements in quality of life, fatigue levels, muscular strength, and aerobic fitness, they have been unable to show significant reductions in fat mass. Greater amounts of exercise with an energy deficit diet aligning more with the Australian weight loss guidelines has been proposed as a potential strategy to improve body composition by losing fat mass and maintaining skeletal muscle mass.

The purpose of this study, as part of the requirement for a Doctor of Philosophy degree, is to: 1) assess the efficacy of a 12-week combined exercise and diet intervention to reduce fat mass while maintaining skeletal muscle mass in obese prostate cancer patients receiving ADT; and 2) to assess the effect of the intervention on blood and inflammatory biomarkers, cardiorespiratory fitness, resting metabolic rate, muscle strength, and quality of life.

We require men who are 6 months post commencement of ADT but who are anticipated to remain on ADT for the course of the study period. Participation in the research project involves completion of a 12-week combined exercise and diet intervention designed and monitored by experienced exercise scientists/physiologists, and dieticians. Following the supervised training period, participants will complete a 12-week self-monitored home-based programme where they will be recommended to continue utilising the exercise and nutrition advice provided during the initial 12-week supervised training period. The exercise component will involve 300 minutes of combined aerobic and resistance exercise each week (~45 minutes per day), to be completed throughout the 12-week supervised training period and 12-week home-based programme. The 12-week supervised training period will include completion of three aerobic/resistance training sessions, under direct supervision, and daily self-monitored aerobic exercise of the participants own choice. The resistance training component will include exercises covering all major muscle groups that will gradually progress over the 12-weeks using 6-12 repetitions (the number of times the weight can be lifted per set before resting and is equivalent to a moderate-to-high intensity) for 1-4 sets. Each supervised session will last approximately 60-minutes commencing with a 5-minute warm up and concluding with a 10-minute cool down period to minimize the participant's risk of injury/harm. The resistance component is designed to improve muscular strength and develop muscle hypertrophy while assisting in the increased daily energy expenditure to assist fat loss. The aerobic component will be completed with researcher consultation and

initial familiarisation during the supervised sessions but will be mostly executed without supervision. The recommended intensity will be 50-90% of their predicted heart rate maximum (220 - age). The diet component of the intervention will provide individualised nutritional advice delivered via three nutritional counselling sessions at week 1, week 3 and week 12 of the 12-week supervised training period by an Accredited Practising Dietician. Although advice will be individualised, we will aim for a daily energy deficit of 2-4 MJ (500-1000 kcal), and reduced consumption of refined carbohydrates, saturated fats, and to optimise protein intake (protein = 1-1.2g/kg/day; aligns with Australian Healthy Eating Guidelines for older persons). To assist with protein intake, we will be providing participants with a whey protein concentrate shake after each supervised training session throughout the intervention period.

Participants will undergo Dual Energy X-ray Absorptiometry (DXA) and peripheral Quantitative Computed Tomography (pQCT) scans in order to assess body composition, bone mineral density (including hip and spine), and cross-sectional areas of the lower limb. Blood tests will also be conducted by a commercial pathology laboratory to assess blood and inflammatory markers. Participants will also provide a 24hr urine sample to assess protein intake. Participants will undergo several physical tests including a maximal treadmill aerobic capacity test, which will be supervised by a physician, a 400m walk test, and one-repetition maximum strength tests (chest press, leg press, seated row). All tests will be conducted by a trained researcher and will be terminated with signs of undue stress.

Participants must meet all the following criteria to participate:

- Be receiving ADT, however, must have commenced at least 6 months prior to study entry and must anticipate continuing to receive ADT for the remainder of the study period (that is, receiving at least one more dose of ADT).
- Have a body mass index between 25-50 kg/m^2, (however, only those with a body fat percentage ≥25%, as assessed by DXA in the first testing session, shall be accepted into the study).
- Do not have bone metastases or secondary cancer diagnosis.
- Not already performing regular exercise defined as undertaking structured resistance or aerobic training two or more times per week within the last 3 months.
- Not receiving professional dietary advice defined as seeking nutritional recommendations from an Accredited Practising Dietician.
- No acute illness, musculoskeletal, cardiovascular, kidney, thyroid, or neurological disorder that could place the participant at risk of injury or illness resulting from the exercise and/or diet.
- Be able to complete moderate-vigorous intensity exercise, including able to comfortably walk 400m.

The concern of the researchers is of past and/or present medical conditions that may compromise the individual's ability to participate in the exercise or diet component of this study. For these reasons, all potential participants have been asked to seek their medical doctor's approval prior to involvement in the study. As the participant's nominated doctor, you may be contacted if your patient receives any abnormal results that may require further medical advice. Also, if any symptoms of concern arise during the study period, your patient will be referred back to you for further consultation, remediation, and clearance to continue in the trial as needed.

The study has been approved by Human Research Ethics Committee at Edith Cowan University and subjects will be free to withdraw from the study at any time. Should you require further information, please feel free to contact us by phone or by email.

Sincerely,

Rebekah Wilson, Daniel Galvão, Robert Newton, Nicolas Hart, Dennis Taaffe, Philippa Lyons-Wall.

_____ is in sufficient health to participate in this study.

Participant's name

Doctor's Name	Doctor's Signature	Date

B. TESTING PROTOCOLS

B1. Testing sheets

REBEKAH PHD DATA COLLECTION SHEET – DAY ONE

Name: _____ Code: _____
DOB: _____ Age: _____ Date: _____

Testing time: Baseline Pre-intervention Post-intervention Post-follow up

1. **EQUIPMENT REQUIRED:**

- ○ Tape measure
- ○ Fitmate Pro (hood + attached flowmeter + analyser, machine + black cord + extension cord, pillow)
- ○ Automatic blood pressure cuff
- ○ Scales
- ○ DXA (pillow, 3x machine pillows, strapping tape)
- ○ pQCT (towel, chair, box)
- ○ Questionnaires (2x QoL, Godin PA, FFQ, Adherence (pre intervention/post follow-up), participant survey (baseline, post follow-up)
- ○ Participant clip board + pen
- ○ Off-site testing (actigraph, urine test, blood test, food record) – Will know before coming in if they need these now or next appointment.

2. **Arrive 45 minutes early.**
3. **Calibrate the DXA and pQCT – Select NHANES**
4. **Get out all the equipment required as per listed above.**
5. **Set up the RMR and make sure all good (are there any warning signs that come up? Battery? Memory? O2 sensor state – all must be GREEN to go ahead)**
6. **Participant arrives.**
7. **Introduce study and how things will work today (DXA, RMR, questionnaires, pQCT).**
8. **Have you received/checked:**

- ○ Informed consent received?
- ○ GP consent received?
- ○ Participant permission for GP to receive abnormal results?
- ○ Patient is fasted?
- ○ Did they take their morning medication? YES NO
- ○ Is the patient seeing a cardiologist? May require further consent for CPET.
- ○ Demographic/health questionnaire OR health changes form completed?
- ○ Received exercise log book (post-follow up)

NB: *Check to see that all questions were filled out. Go over questionnaires with participant and ask if there was anything they didn't understand.*

9. Body composition (anthropometrics/DXA):

NB: *If W/HC is more than 2mm different, repeat untill consistent.*
NB: *Feet together for hip circumference.*
NB: *Object length is measured from the bottom of malleolous (ankle bone) to the tibial plateau (gap on the medial side of the knee).*

Item	Result	Item	Result
Height	cm	Weight	kg
BMI	kg/m^2	Waist circumference 1	cm
Hip circumference 1	cm	Waist circumference 2	cm
Hip circumference 2	cm	Waist circumference 3	cm
Hip circumference 3	cm	W/H ratio	
Object length	mm		

NB: *RADIATION BADGE*
NB: *Ask participant to take off all metal and reflective clothing. This could include jewellery, zips, reflective logos.* _____
NB: *Ask if participant has any metal inside their body:* _____
NB: *Instruct participant to get on the plinth without touching the sides.*
NB: *Ask if they would like a pillow:* _____
NB: *Input participants details into the computer and answer the FRAX questions as appropriate.*
NB: *Set up participant in the centre of the plinth and tape feet together in an internally rotated position (ask if allergic to tape).*
NB: *Instruct participant that the bed moves and to remain STILL over the next 3-5 minutes.*

10. Complete DXA : WHOLE BODY LEFT HIP LUMBAR SPINE.
11. CHECK FAT %.

Notes:

12. Resting metabolic rate and resting blood pressure and heart rate (supine):

NB: *Participant to lie down with no equipment on for 10 minnutes – Lights off.*
NB: *Instruct participant to remain relaxed but to try and avoid a state of sleep.*
NB: *Set up machine just before 10minutes and once the calibration is done place the hood over participant (flowmeter at head) and tuck in all sheets.*
NB: *Turn off machine once you get a warning of "collected enough data."*
NB: *Complete BP and HR once finished.*

Item	Result	Item	Result
Blood pressure 1 (right)	mmHg	RMR	kcal/d
Blood pressure 2 (right)	mmHg	RMR	kcal/kg/d
Blood pressure 3 (right)	mmHg	RMR	kcal/lean kg/d
Blood pressure 1 (left)	mmHg	Heart rate 1	bpm
Blood pressure 2 (left)	mmHg	Heart rate 2	bpm
Blood pressure 3 (left)	mmHg	Heart rate 3	bpm
Dominant arm	Right left		

Notes:

13. **If still have time, set up the pQCT machine: participant details, and machine set.**
14. **Provide participants with the questionnaires, they may fill out what they can now but will need to complete the rest at home:**

- ○ Quality of life (SF36 and EORTC) questionnaires.
- ○ Godin physical activity questionnaire.
- ○ Food Frequency questionnaire.
- ○ Health changes questionnaire
- ○ Adherence questionnaire (pre-intervention/post-follow up)
- ○ Participant Survey (baseline/post-follow up)
- ○ Envelope to keep in the questionnaires.

15. **Complete tibia pQCT**

NB: *Feet flat on box (right height for chair). Have machine up high to start with.*
NB: *Laser aligns with distal malleolous. Looking for the gap between the tibia and talus bone.*
NB: *Participant may eat at this time while filling out the questionnaires*
NB: *Check leg is not going to touch the machine*

Notes:

16. **Clarify with participant all the instructions of any homebased testing/next appointments:**

- ○ Booking of the next 2 appointments.
  NB*: require 0 days between this and the second appointment. Require at least 4 days, including the weekend, for the third appointment.*
  _____
- ○ Preferred training times completed (pre-intervention): _____
- ○ Below instructions will depend on appointment timing – these are preferably given at 2nd appointment not 1st).
- ○ Provided participant with accelerometer + instructions
- ○ Provided participant with food diary + instructions
- ○ Provided participant with urine collection container + bottle + chilly bag + instructions (clarify if they will bring to you or you will pick up).
- ○ Provided participant with bloods form + instructions + day they will complete test (just to get an idea of when I will need to pick up bloods).

17. **Turn off heater – wait 5 minutes then turn off computer and met cart. Finish all equipment clean up.**

REBEKAH PHD DATA COLLECTION SHEET – DAY TWO

Name: _____ Code: _____

DOB: _____ Age: _____ Date: _____

Testing time: Baseline Pre-intervention Post-intervention Post-follow up

1. **EQUIPMENT REQUIRED:**

- ○ Met cart (3x mixing chamber attachments, hose, 7x mask attachments, mask, head strap)
- ○ Activated actigraph, instructions
- ○ Food record sheet, instructions, scales, cups, spoons
- ○ Urine collection container, funnel, bottle, chilly bag, 2x freezer bricks (to freeze)
- ○ Filled in bloods form, instructions
- ○ Blood pressure cuff/stethoscope
- ○ RPE scale
- ○ ECG (razor, alcohol wipes, scratchy sponge, sticky tabs)
- ○ Spirometer, tube
- ○ Oxygen saturation finger
- ○ Scales for height and weight
- ○ Medication list for doctor

2. **Arrive 45-60 minutes early. Turn on computer (ECG and met cart computers), treadmill, and met cart – Wait 5 minutes.**
3. **Get out all the equipment required for the met cart.**
4. **(after 5 minutes). Turn on the heater – Wait 30 minutes.**
5. **Set up the equipment required for the stress test (including BP, lung function, O2).**
6. **(after 30 minutes). Calibrate met cart. (Press "save" every time even if it's incorrect).**

- ○ Performed the gas calibration (-1.5% and +1.5%)? Calibration result: O2%: CO2%:
- ○ Flow metre calibration (-1.5% and +1.5%)? Calibration result: _____

7. **Participant arrives.**
8. **Run through how things are going to work today**
9. **Have you received/checked:**

- ○ Received 2x Quality of life questionnaires,
- ○ Received Godin physical activity questionnaire
- ○ Received FFQ
- ○ Received health changes form
- ○ Received participant survey (baseline/post follow-up)
- ○ Received adherence questionnaire (pre-intervention/post follow-up)

Supervising doctor (name): _____ (signature): _____

Assistant #1 (name): _____ (signature): _____

Assistant #2 (name): _____ (signature): _____

10. Update weight, use the same height from previous tests.

Item	Result	Item	Result
Weight	kg	Height	cm

11. ECG set up

NB: *Get the participant lying down with their shirt off*

NB: *Find points starting with V1, V2, V4, V3, V5, V6 arms, hips in that order. Then shave, scratch, alcohol swab, electrodes attach.*

NB: *Analyse resting ECG for 5 minutes.*

NB: *Take O2 saturation while lying down.*

NB: *Make note of BP supine/seated and HR after 5 minutes.*

Item	Result	Item	Result
Blood pressure left (supine)	mmHg	Blood pressure right (supine)	mmHg
Blood pressure left (seated)	mmHg	Blood pressure right (seated)	mmHg
Heart rate rest	bpm	O_2 saturation	%

12. Lung volume measures/oxygen saturation

NB: *Instruct participant (deep breath in and exhale until I say stop).*

NB: *Allow participant one practice – time each attempt for 6 seconds of exhaled breath.*

Item	Result	Item	Result
FVC – 1	L	FEV - 1	L
FVC – 2	L	FEV - 2	L
FVC - 3	L	FEV - 3	L
FEV/FVC - 1	%	FEV/FVC - 3	%
FEV/FVC - 2	%		

13. Maximal aerobic capacity test:

NB: *One assistant to complete RPE, treadmill. Other assistant to complete BP. Other jobs could include standing behind treadmill, stop watch.*

NB: *Blood pressure to be taken on the non-dominant side.* _____

NB: *Instructions to provide participant:*

a) *This is a walking test and requires you to keep going until you think you have reached your maximum.*
b) *We will do a 5 minute warm up at 2.7kph then go straight into the test and finish with a 5 minute cool down where you will continue walking.*
c) *During the test the treadmill gradient and/or speed will change every 3minutes.*
d) *The treadmill does start and stop quite abruptly so please have a hold on when it starts and stops.*
e) *When you think you have gone for as long as you can or you just want to stop the test because you don't feel good just raise your hand and this will let us know that you are finished.*
f) *However, we ask that you continue walking. We will reduce the treadmill speed and gradient to as low as possible but you need to keep walking as the treadmill will not stop moving.*
g) *You may hold on to the rail at any point if you need to but try not to rely on it.*

Minutes	Heart rate	Blood pressure	RPE (0-10)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
Finish			
R1			
R2			
R3			
R4			
R5			

NB:

- *The finish column is the values take at the point at which the participant chooses to stop/terminate test.*
- *Measures all taken in the 30 seconds leading up to stage change e.g. minute 2.30-3.00*
- *TEST SUCCESS CRITERIA: RPE ≥ 9 (RER ≥ 1.1, ± 10 bpm of HRmax).*
- *CRITERIA TO STOP: hypertension - >200/110, abnormal exercising ECG with complaints, severe cardiac arrhythmias, patient feels unwell or non-test specific pain.*

Item	Result	Item	Result
Time	min sec	Relative VO_{2max}	ml/kg/min
End RQ/RER		Absolute VO_{2max}	L/min
Warm up rate	km/hr	HR max	bpm
Face mask size			

Notes:

14. **Provide participant with:**

- ○ Clarify the dates they will complete actigraph and activate the device for those dates (Thursday, Friday, Saturday OR Sunday, Monday, Tuesday)
- ○ Actigraph, log book, instructions
- ○ Food diary, instructions, scales, cups, spoons
- ○ Urine collection container, funnel, bottle, chilly bag, 2x freezer bricks (to freeze), instructions
- ○ Filled in bloods form, instructions

15. **Check in before participant leaves**

- ○ Confirmed next appointment time (require at least 4 days, including the weekend, until next appointment)?
- ○ Remind of instructions of tests to complete at home.

16. **Turn off heater – wait 5 minutes then turn off computer and met cart. Finish all equipment clean up.**

REBEKAH PHD DATA COLLECTION SHEET – DAY THREE

Name: _____ Code: _____

DOB: _____ Age: _____ Date: _____

Testing time: Baseline Pre-intervention Post-intervention Post-follow up

- ○ Familiarisation?
- ○ Actual test?

1. **EQUIPMENT REQUIRED:**
   - ○ Heart rate monitor
   - ○ Blood pressure cuff/stethoscope
   - ○ 2x cones, 2x door stop
   - ○ Stop watch
   - ○ Tape measure
   - ○ RPE scale
2. **Arrive 30 minutes early. Prepare all paper work.**
3. **Participant arrives.**
4. **Run through how things will work today (400m walk, 3x 1RM, diet history if week 6).**
5. **Have you received/checked:**
   - ○ If familiarisation – have you provided patient with actigraph, food dairy, scales/cups/spoons with clear instructions for all?
   - ○ Received 2x Quality of Life questionnaires
   - ○ Received Godin PA questionnaire
   - ○ Received Food Frequency questionnaire
   - ○ Received adherence questionnaire (pre-intervention/post-follow up)
   - ○ Received actigraph with log book
   - ○ Received 3-day food diary, scales, cups, spoons.
   - ○ Received 24hr urine sample with log book (pre/post-intervention)
   - ○ Confirmed blood test has been done by Clinical Labs (pre/post-intervention)
   - ○ Identified if patient has any existing injuries/conditions that may prevent them from doing one of the tests?
6. **Place a heart rate monitor on participant**
7. **400 m walking test**

NB: *Place BP cuff on participant and take pre-test HR/BP sitting down*

NB: *Complete 20m of strides ("as if you were pacing something out"). Half a stride = 1 full count.*

NB: *Instruct participant on test and that they may stop at any time (walk around the cone, walk as fast as you can)*

Item	Result	Item	Result
Heart rate rest (seated)	bpm	Blood pressure pre-test	mmHg
Non-dominant hand	Right / Left	Warm up strides (20m)	#

NB: *When finished stop watch immediately, ask participant to read HR, take BP on the non-dominant side, ask what their RPE was once BP finished.*

NB: *make a note of 1min post HR*

NB: *Warm down*

NB: *Make a note of 2 min post HR*

Laps: 1 2 3 4 5 6 7 8 9 10

Item	Result	Item	Result
Heart rate end	bpm	Time	s
Heart rate 1min post	bpm	RPE end	
Heart rate 2 min post	bpm	Blood pressure post-test	mmHg
Average heart rate	bpm	Estimated VO_{2max}	ml/kg/min
Maximum heart rate	bpm	Stride length (< 1.2steps/m)	Yes / No
Notes: Blood pressure is taken in a seated position.			

8. Chest press

NB: *Place the participant into the correct position. 90* at arms, bar at nipple line, feet where comfortable and place tape/mark where his thumbs are to be placed each time. Mark down all the equipment position measurements.*

Item	Result	Item	Result
Bar Start (big/little)		Bench position	cm
Grip position	cm	Step height	
Bench angle	lowest		

NB: *Instruct technique and breathing (out on the effort)*

NB: *Complete each stage with 2 minutes rest between each one.*

NB: *F marks a failed attempt*

Item	Result	Item	Result
6 reps x 80% 1RM	kg	3 reps x 80% 1RM	kg
1RM attempt 1	kg	1RM attempt 2	kg
1RM attempt 3	kg	1RM attempt 4	kg
1RM attempt 5	kg	Actual 1RM	kg
Notes:			

9. Leg press

NB: *Place participant into the correct position. 90* legs, heels bottom of black on incline, toes at top in supine, hands on handles. Mark down the equipment position*

NB: *200kg is the limit of the incline leg press.*

Item	Result	Item	Result
Machine used	Incline / Seated	90° knee level (distance from floor to top of tape)	cm
Foot position	Heels in lie with bottom grip	90° supine seat position	
Back support (supine)	5		

NB: *Instruct technique and breathing (out on the effort).*

NB: *Complete each stage with 2 minutes rest between each one.*

NB: *F marks a failed attempt*

Item	Result	Item	Result
6 reps x 80% 1RM	kg	3 reps x 80% 1RM	kg
1RM attempt 1	kg	1RM attempt 2	kg
1RM attempt 3	kg	1RM attempt 4	kg
1RM attempt 5	kg	Actual 1RM	kg
Notes:			

10. Seated row

NB: *Place the participant into the correct position. 90* at legs, arms not over stretched, feet where comfortable. Mark down all the equipment position measurements*

Item	Result	Item	Result
Seat height		Handgrip position	cm
Chest pad		Feet position	Floor / Foot rest

NB: *Instruct technique and breathing (out on the effort)*

NB: *Complete each stage with 2 minutes rest between each one.*

NB: *F marks a failed attempt*

Item	Result	Item	Result
6 reps x 80% 1RM	kg	3 reps x 80% 1RM	kg
1RM attempt 1	kg	1RM attempt 2	kg
1RM attempt 3	kg	1RM attempt 4	kg
1RM attempt 5	kg	Actual 1RM	kg
Notes:			

11. Diet history (ONLY at week 6)

12. Final check in before participant leaves

○ Confirmed/booked next appointment time (could be – next testing time point, nutrition counselling, and/or exercise session)?

○ Remind of instructions of tests to complete at home (if familiarisation).

B2. Muscle strength one-repetition maximum (1RM) protocol

Equipment: Chest press (+ step), leg press (+ pillow), seated row, tape measure, stopwatch.

1. Record and measure all machine, hand, and feet positions – Machines then to be set the same for each subsequent measure. NB: the seat angles never change for chest or leg press, they are on the lowest incline always.
2. Legs or arms must be at 90 degrees at start of movement, for seated row the arms are outstretched but not over stretched.
3. Instruct the patient of the movement techniques by first demonstrating then instructing while demonstrating.
4. The patient completes 6 repetitions ~60% of 1RM
5. Rest 2 minutes
6. The patient completes 3 repetitions ~80% of 1RM
7. Rest 2 minutes
8. First attempt at 1RM
9. Rest 2 minutes.
10. If the patient says/looks like they can do more repeat 1RM with a higher weight until maximum reached or 5 attempts, whichever comes first.

B3. Cardiopulmonary exercise test protocol

Modified Bruce Treadmill Protocol			
Stage	**Time (minutes)**	**Speed (kph)**	**Grade (%)**
Warm up	3 – 5	2.5 - 2.7	0
1	0:00	2.7	0
2	3:00	2.7	5
3	6:00	2.7	10
4	9:00	4.0	12
5	12:00	5.5	14
6	15:00	6.8	16
7	18:00	8.0	18
Cool down	3 - 5	2.5 - 2.7	0

B4. 400m walk protocol

Equipment: 2x cones, stopwatch, blood pressure monitor, heart rate monitor, 2x door stopper, chair.

1. Ask patient to sit down in a chair while you set up the cones.
2. Get the patient's resting HR (HR monitor) and resting BP.
3. Instruct the patient that they are walking as fast as they can for 400m but must WALK. They will complete 10 laps (there and back = 1) of the course but they do not need to count (I will do that).
4. Demonstrate to the patient how to walk AROUND the cone and tell them if they kick it by accident to leave it and I shall pick it up.
5. Before starting, ask the patient to stride out one length (20m) (walks slightly longer than their everyday stride) and count how many steps they complete.
6. Get them to walk back to the start.
7. Ask the patient to stand next to the cone and count down 3, 2, 1 GO to start.
8. Give standard encouragement like "that's two, well done" "that's halfway" "three more laps to go, nice work"
9. On the final lap instruct the patient to walk straight past the cone (rather than around) and stop the stopwatch as their foot walks past the cone.
10. Record the time.
11. Record the final HR, average HR, maximum HR.
12. Sit the patient down immediately and take blood pressure.
13. Record the recovery HR at 1 and 2 minutes post finish.

B5. Blood collection and analysis protocol

FASTING BLOOD COLLECTION

Name: _____ Date collected: _____

From the blood samples, we will be analysing your lipid profile, insulin, HbA1c, C-reactive protein, testosterone, prostate-specific-antigen, insulin-like-growth factor-1, and interleukin-6. These markers provide us with information on a number of different aspects of your overall health. The blood samples will provide important data that has the potential to impact nutrition and exercise advice provided to prostate cancer survivors in the future.

Please follow the instructions below carefully:

1. Bloods are to be collected by **Australian Clinical Labs** ONLY (you do not need to make an appointment you can just turn up).
2. You may go to any Australian Clinical Labs pathology clinic that is convenient to you. For the locations please visit https://www.clinicallabs.com.au/location/.
3. Blood **MUST** be taken in a **fasted state**. This means no food or drink 10 hours prior to bloods being collected. Ideally you will have your blood collected in the morning after an over night fast (no food/drink, except water, after 10pm).
4. You are also asked to refrain from smoking during this fast.
5. The attached form is to be given to the nurse/phlebotomist that will be taking your blood.

Blood biomarker analysis completed at Edith Cowan University via ELISA:

1. Interleukin 6
   Dilution factor used: NA
   https://www.abcam.com/human-il-6-elisa-kit-ab46027.html
2. Adiponectin
   Dilution factor used: 30,000 fold
   https://www.abcam.com/human-adiponectin-elisa-kit-ab99968.html
3. Leptin
   Dilution factor used: 35 fold
   https://www.abcam.com/human-leptin-elisa-kit-ab100581.html
4. IGFBP-3
   Dilution factor used: 110 fold
   https://www.abcam.com/human-igfbp3-elisa-kit-ab100541.html
5. IGF-1
   Dilution factor used: 11 fold
   https://www.abcam.com/human-igf1-elisa-kit-ab100545.html

B6. ActiGraph

3-DAY ACTIVITY MONITOR LOG

Name: _____ Date started: _____

The activity monitor is a device that measures the amount of physical activity you do in your everyday life. Some of the information it records includes the duration and intensity of activity, energy expenditure, number of steps taken, and sleep quality. The information obtained from the activity monitor will provide us with important data that has the potential to impact exercise and nutrition advice provided to prostate cancer survivors in the future.

Please follow the instructions below carefully:

1. The monitor must be worn on 2 week days and 1 weekend day.
2. Please START wearing the activity monitor first thing in the morning on the discussed start date: _____
3. Please STOP wearing the activity monitor first thing in the morning on the discussed end date: _____
4. Please note the time you started wearing the monitor on the morning of day 1 and the time you took it off on the morning of day 4.
5. The monitor is to be worn around the hip area with the black circle facing upward. It can be worn above or under clothing and does not need to touch the skin to work. Please have the strap secure and snug around your waist to prevent any abnormal readings (i.e. the device ideally should not bounce or slide around). Please do not cut the straps.
6. The monitor must be worn for 3 days and 24 hours a day. This includes wearing it while you sleep.
7. The activity monitor is NOT water proof. Please take the monitor off while bathing/showering/swimming. The activity monitor needs to be put back on immediately afterwards.

8. In the log below, please make note of anytime you took the monitor off and for how long.

Day	Details of activity monitor
1	Time started wearing in the morning: Time took off:
2	Time took off:
3	Time took off:
4	Time finished wearing in the morning:

Thank you very much for your time in completing this activity log

B7. Three day weighed food record

3-DAY WEIGHED FOOD RECORD

Name: _____ Date: _____

A 3-day weighed food record is a complete record of everything that you eat and drink over a three day period. Some of the information we can assess from this record includes total energy intake, the proportion of fats, carbohydrates, and protein in your diet, and the vitamin and mineral content. By completing this record, it will provide us with important data that will assist with the development of your individualised nutrition plan as well as information that has the potential to assist with nutrition advice provided to prostate cancer survivors in the future.

Please follow the instructions below carefully:

1. Keep your food diary for **3 consecutive days** that suit you best. However, it must include 2 week days and 1 weekend day and **please try not to change your eating habits**:
   Thursday, Friday, Saturday OR Sunday, Monday, Tuesday.
2. It is best to write down the food to be consumed when being prepared or as soon as possible after eating.
3. Record **ALL** that you eat and drink from the time you get up in the morning until you retire at night: a glass of water; the different vegetables in a stir-fry; tea and biscuits; vitamin pills.
4. At the top of the page please note your name and start date.
5. In the first column note the time of day you consumed the food or drink.
6. In the second column state the food or drink consumed e.g. toast with jam, and tea. **Include any nutrition supplements, vitamins, or minerals**.
7. In the third column please describe everything about the dish (e.g. type of bread, margarine, sugar in tea, type of milk added) including brand names where applicable. Where possible, list **all ingredients** put into the dish consumed for example in mixed dishes, sandwiches, soups. Attaching a recipe or food label where available would improve the accuracy of your record and be appreciated.
8. **All food and drink should be weighed using the scales provided** and the weight written in the fourth column in **grams**. If food/drink is unable to be weighed, please estimate what you consumed in the fifth column and describe using cups or spoons, **avoid** subjective terms like “bowl” or “serving”. For example, when eating out, describe the

dish as best as possible using spoons and/or cups as a guide to how much you consumed.

9. If you do not consume everything then please re-weigh or provide an estimate of the leftovers in the sixth column.
10. At the end of the day please **go through the checklist below** to make sure you have included everything (these items are of particular interest for this study).

CHECKLIST:

Portion guide: ¼ cup = golf ball, ½ cup = tennis ball, 1 cup = small fist, 1 teaspoon = quarter of your thumb, 80g cooked meat = a deck of playing cards.

Please tick if you've considered whether you ate these today – if it reminds you of anything you haven't included please add it to the record.

Food	Day 1	Day 2	Day 3	Food	Day 1	Day 2	Day 3
Confectionary				Fruit			
Soft drinks/juice				Vegetables			
Alcohol				Milk			
Eggs				Yoghurt			
Nuts				Rice/pasta/bread			
Meat				Added sugar			
Fish				Supplements			

Example food record for part of the day

Time of day	Food and drink	Description of foods and drink	Weight (g)	Amount (cups or spoons)	Leftovers (g)
7.30am	Jam toast with tea	2 x whole grain bread (Coles brand)	88 g		
		Butter	13 g		
		Jam	26 g		
		Sugar in tea		1 teaspoon	
		Water/tea	250 g		
		Milk in tea (full cream)	20 g		
10am	Muffin and coffee	Flat white (large) (café bought)		Large	
		Raspberry and white chocolate muffin (café bought)		Medium (size of a cup)	
12.30pm	Green Thai Curry	White rice	288g		
		Green bean, chicken, red capsicum, curry paste (Valcom brand), coconut milk (recipe attached)	237g		
		Water	300 g		

Hint for weighing: Example of how to weigh the breakfast meal above:

1. Place plate on scales and tare it to zero (note: may help to place a bowl and then a plate on top so that you can see the screen).
2. Place cooked toast on and record weight.
3. Tare to zero.
4. Spread butter and record weight.
5. Tare to zero.
6. Spread jam and record weight.
7. For cup of tea place mug on scales and tare to zero.
8. Pour in water and record weight without tea bag.
9. Measure sugar with a teaspoon and describe amount.
10. Tare to zero.
11. Pour milk and record weigh

B8. Diet history template

Diet History Protocol

Protocol

AIM - To supplement the information provided by the food frequency questionnaire and weighed food record with a diet history that enables a more detailed assessment of longer term dietary intake, in terms of typical portion sizes and food patterns. A diet history also allows assessment of average energy intake.

The diet history asks: What sorts of foods do you eat in a typical day, how much and how often, starting from when you arise in the morning until you retire at night. It provides a means for validating the data supplied from the food frequency questionnaire and weighed record, thereby minimising error and enhancing the strength of the study.

A diet history is intended to provide an estimate of intake in a typical month over a specified time interval, for example, the last 6 months. Initial questions involve assessing whether the subject has changed their diet in any significant manner within that time or if it has remained stable from month to month. If the subject has had a stable diet then focus only on the last month as this will represent a typical month. If any significant changes have been made document the foods involved and the change in quantities consumed and frequency of intake.

The number of meals reported should be approximately equal to 28 each for breakfast, lunch and dinner. Indicate the frequency of intake for meals/foods eaten multiple times in a month. The total should also include foods or meals eaten less frequently (eg restaurants). A variety of tools are to be used in conduction with the diet history to optimise accuracy.

<u>Models</u>

- Food models (eg serves of meat) - ask how much would you have in comparison?
- Standard utensils (plates, bowls, cups, spoons) of varying sizes. Ask what size would you usually use?
- The display includes multiple quantities of vegetables and carbohydrate portions on a dinner plate. Ask subjects to indicate the portion size they would usually have.
- Three slices of bread with different amounts of margarine/butter (3g, 5g and 10g) will be provided. Ask men to indicate which amount they would usually have.

<u>Detail</u>

Obtaining detail is essential. This includes information such as:

- Dairy foods - fat percentage, calcium enriched
- Bread - type eg white, multigrain, fruit, foccacia, home sliced or pre-sliced
- Method of preparing foods - eg boiled, baked, fried, steamed
- Amount and type of fat used in cooking

- Use of fortified foods - eg iron enriched, fortified cereals
- Brand names wherever possible - especially for bread, cereal and yoghurt

Background questions

1. Weight history
What is your 'normal' weight?

Current weight? Recent weight gain and time interval since diagnosis of PrCa
How much? What time period?
What do you feel is the reason for the weight gain?
(eg hungrier, eating more, eating the same but gaining weight, hormone therapy)

2. Do you avoid certain foods or fluids, if so which ones?

3. Have you made any significant changes to your diet since your diagnosis? Yes / No
If so what changes and why? (types of foods, amounts, supplements)

4. Are you on any special 'diet', what type? eg heart healthy, general healthy, high protein, diabetes) Source of information (eg family, wife, friends, PrCa Support group).

5. Has your GP or specialist recommended that you make changes to your diet?

6. Who prepares your meals (eg prepares own, spouse or partner, shared)

7. How much water do you drink per day?

Diet History
Ask about the sorts of foods and drinks you have in a typical day, starting at beginning of the day, going through until you retire at night. Include water and alcohol. Focus on intake over the last month. Include what you eat on each eating occasion, how much and how often.

Starting with Week days

BREAKFAST
Beginning with weekdays. After you wake up, what is the first thing you usually have to eat and drink? Have you eaten anything else at this time during the last month? If so, how often?

Weekdays

Food
Quantity
Frequency

MORNING TEA When is the next time you have anything to eat or drink?

LUNCH/DINNER

On weekdays, what food or drinks do you eat for your main midday meal? Do you ever have anything different in a typical month?

Weekdays

Food
Quantity
Frequency

AFTERNOON TEA

When is the next time you have anything to eat or drink?

TEA/DINNER

On weekdays what foods and drinks do you usually have for your main evening meal?
In a typical month do you ever have anything different?

Food Quantity
Frequency
Meat/alt
CHO
Free veg
Dessert

SUPPER/ DURING NIGHT

Do you have anything else to eat or drink before you arise the next morning?

Do you eat differently over the weekends?

Takeaway

How often in a typical month do you eat takeaway food? What sorts of foods/drinks do you consume?

Restaurants/Coffee shops

How often in a typical month do you eat out at restaurants or coffee shops? What sorts of foods/drinks do you consume?

GLOSSARY

Food - Specify the type of food and drink and the brand name where possible
Amount - In standard measuring sizes: weights/teaspoons/tablespoons/metric cups/cm/mm measurements
Frequency - How often the food is consumed per day, per week, per month or per >1month, whatever is most appropriate
Meat/alternatives - red meats, chicken, fish, seafood, eggs, nuts, legumes
CHO - bread, rice, pasta, potato, sweet potato, corn
Free vegetables - all vegetables other than those listed in CHO and legumes
Dessert - any sweet food consumed after meal, includes fruit

CHECKLIST

Based on foods specified in the food frequency questionnaire

Assists in completion of written diet history - use as both a reminder of different foods to query and to summarise total daily or weekly intake

Intended as a reminder to obtain further detail regarding the form of different foods eg within vegetables - boiled vs. baked vs. steamed vs. canned

Breads & Cereals

- Cold breakfast cereal
- Cooked breakfast cereal
- Toast/bread
- Rolls
- Fancy breads eg foccacia, Lebanese
- Crackers, crispbread
- Sweet biscuits
- Couscous, polenta, barley, burghul, taco, tortilla
- Pancakes/waffles
- Pasta/noodles/lasagne
- Rice
- Crumpets
- English muffins
- Sprinkles eg LSA, bran
- Scones

Fruit

- Fresh fruit
- Cherry/berry/grapes
- Dried fruit
- Grapefruit
- Tinned fruit
- Olive
- Stewed fruit
- Avocado
- Fruit juice (g'fruit/apple/blackcurrant/grape)

Vegetables

- Raw/salad
- Herbs
- Steamed/microwave
- GLV
- Boiled
- Onions/garlic
- Baked - fat/no fat
- Stir-fried
- Asparagus
- Deep/shallow/pan fried
- Canned
- Soup
- Legumes

Milk

- Milk
- Flavoured/cocoa/milo
- Yoghurt
- Smoothie/milkshake
- Cheese
- Ice cream/dairy desserts
- Custard
- Soy milk

Meat/alternatives

- Cold/sandwich meats
- Gravy/white sauce
- Red meat - roast/steak/chops
- Red meat - stew/casserole/stir-fry
- Mince
- Chicken/stuffing
- Meat products eg sausages, pies, bacon
- Fish/ seafood
- Offal
- Soy products
- Other vegetarian products eg TVP
- Legumes
- Nuts
- Eggs

Other

- Muesli/nut and seed bars
- Pastry/croissant/quiche
- Packet/frozen meals
- Ethnic
- Cake
- Muffin (cake type)
- Iced/fruit buns/fruit loaf
- Lollies
- Chocolate
- Spreads (vegemite/PBut/hummus/marmalade/jam/honey)
- Sauces/salad dressing
- Fat – oils/dripping/marg/butter
- Pizza
- Deep-fried foods
- Soft drink/cordial (diet?)
- Crisps/hot chips
- Beer
- Desserts
- Spirits, liqueur
- Ice blocks
- Red wine, white wine
- Water (per day)
- Coffee, Tea

C. QUESTIONNAIRES

C1. Adherence questionnaire

	Questions	Criteria for 1 point
1	How many **days** this week did you consume starchy vegetables? e.g. potatoes, yams, sweet potato, taro.	≤ 1
2	On a given day, how many **serves** of starchy vegetables did you consume? (1 serve: ½ medium size potato).	≤ 1
3	On average, did you consume more than **3 serves** of non-starchy vegetables every day of the week? (1 serve: ½ cup cooked vegetables or 1 cup raw vegetables) e.g. vegetable salad, carrots, broccoli, cauliflower, avocado, green beans/peas.	Yes
4	On average, how many pieces of fruit and/or fruit juice with no added sugar did you consume **per day**? (1 medium size piece; 1 small glass or 125ml).	≥ 1
Nuts and beans		
5	How many **days** this week did you consume nuts (including peanuts)? (1 serve: 30g).	≤ 7
6	How many **days** this week did you consume cooked or canned beans? (1 serve: 150g or 1 cup cooked) e.g. baked beans, falafel, chickpeas, lentils, soy beans, tofu, kidney beans, or any other type of beans.	≤ 7
Meat, fish, and eggs		
7	How many **days** this week did you consume meat or meat products, seafood, or eggs?	≥ 6
8	What **type** did you consume? ☐ *Skinless chicken* ☐ Fried fish ☐ *Pork (fat cut off)* ☐ Coated chicken (e.g. skin, crumbed) ☐ *Baked/smoked fish* ☐ *Veal (fat cut off)* ☐ *Shellfish* ☐ Salami ☐ Ham ☐ Sausages ☐ *Lean mince* ☐ *Eggs* ☐ *Lamb (fat cut off)* ☐ Bacon ☐ *Kangaroo (fat cut off)* ☐ *Beef (fat cut off)* ☐ *Canned fish (low salt)* ☐ Other _____	*Italicised*

Spreads and oils		
9	On average, how many **serves** of butter or margarine did you consume per day (1 serve: 10g / approx.. 2tsp)	≤ 1
Dairy		
10	How many **days** this week did you consume cheese? (1 serve: 2 slices or 40g)	≥ 5
11	How many **days** this week did you consume milk or yoghurt? (1 serve: 250mL milk, 200mL yoghurt)	7
12	What **type** of milk or yoghurt did you consume? ☐ *Skim* ☐ *Reduced fat* ☐ Full fat ☐ Other _____	*Italicised*
Extras		
13	How many **times** this week did you consume sweets, ice cream, pastries, cakes, cookies, or biscuits?	≤ 2
Grains and cereals		
14	What **type** of bread, flat bread, or wraps did you consume? ☐ White ☐ *High fibre- white* ☐ Corn tortilla ☐ White wrap ☐ *Wholegrain, wholemeal or rye* ☐ Brown ☐ Multi-grain ☐ Flour tortilla ☐ *Wholemeal tortilla* ☐ *Wholemeal wrap*	*Italicised*
15	What **type** of carbohydrates did you consume this week? ☐ White pasta ☐ *Wholemeal pasta* ☐ White couscous ☐ *Wholemeal couscous* ☐ White rice ☐ *Brown rice* ☐ Flour based pizza base ☐ Noodles ☐ *Quinoa*	*Italicised*
16	What **type** of breakfast cereal did you consume? ☐ *Untoasted Muesli* ☐ Rice based cereals e.g. Rice Bubbles ☐ *Wheat biscuits/flakes* ☐ Corn flakes (no sugar) ☐ *Porridge* ☐ *Bran based cereals e.g. All-bran, Sultana Bran* ☐ Nutri-grain ☐ Sugary cereals e.g. Crunchy Nut ☐ *Special K* ☐ *Mixed grain cereals e.g. Just Right, Sustain* ☐ Other _____	*Italicised*

Fluids		
17	On average, how many energy drinks, cordials, or soft drinks did you consume **per day**?	0
18	On average, how many glasses of water did you consume **per day**?	≥ 2
19	How many days per week did you consume alcohol?	≤ 5
20	What **type** of alcohol did you consume? ☐ *Red wine* ☐ Beer ☐ Spirits with sugary mixer e.g. Bourbon and Coca-Cola ☐ White wine ☐ *Light beer* ☐ Bubbles ☐ *Spirits (straight)* ☐ *Spirits with non-sugary mixer e.g. gin and tonic*	*Italicised*
21	On a given a day, how many alcoholic drinks did you consume on **one occasion**?	≤ 2
22	On average, how many hot drinks do you drink **per day**?	≥ 2
23	What **type** of hot drink did you consume? ☐ *Coffee* ☐ *Tea* ☐ Hot chocolate ☐ Other _____	*Italicised*
Eating out		
24	How **often** did you eat take away food this week? e.g. fish and chips, pizza, hamburgers	0
Exercise		
25	Have you done at least 30 minutes of purposeful exercise **every day this week**?	Yes

1. What was your weekly nutritional goal? Did you achieve it?

2. What was your weekly exercise goal? Did you achieve it?

3. Was there any nutrition and/or exercise element that you struggled with this week?

Thank you very much for your time in completing this important questionnaire

C2. 36-Item Short-Form Health Survey

Form not available in this version of the thesis

C3. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module

Questionnaire not available in this version of the thesis

C4. Godin Leisure-Time Exercise Questionnaire

PHYSICAL ACTIVITY LEVEL

For this question, we would like you to recall your average weekly exercise in the **PAST MONTH**.

When answering these questions please:

- Only count exercise sessions that lasted 10 minutes or longer in duration.
- Only count exercise that was done during free time (i.e. not occupation or housework).
- Note that the main difference between the three categories is the intensity of the exercise.

1. Considering a typical week (7 days) how many times on the average did you do the following kinds of exercise in the past month?

	Average Frequency (times per week)	Average Duration (minutes)
a. **STRENUOUS EXERCISE** (HEART BEATS RAPIDLY, SWEATING) (e.g. running, jogging, aerobics classes, vigorous swimming, vigorous bicycling).	_____times/week	_____mins
b. **MODERATE EXERCISE** (NOT EXHAUSTING, LIGHT PERSPIRATION) (e.g. fast walking, tennis, easy bicycling, easy swimming, popular and folk dancing).	_____times/week	_____mins
c. **MILD EXERCISE** (MINIMAL EFFORT, NO PERSPIRATION) (e.g. easy walking, light yoga, lawn bowling, fishing from a river bank).	_____times/week	_____mins
d. **RESISTANCE EXERCISE** (MUSCLE STRENGTHENING) (e.g. repetitively lifting weights using dumbbells, weight machines or resistance bands, sit ups, squats)	_____times/week	_____mins

2. During a typical 7-Day period (a week), in your leisure time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

☐ 1. OFTEN ☐ 2. SOMETIMES ☐ 3. NEVER/RARELY

C5. Demographic and medical history questionnaire

EMRI
Exercise Medicine Research Institute
vario health clinic

AUSTRALIA ECU EDITH COWAN UNIVERSITY

DEMOGRAPH INFORMATION
AND
MEDICAL HISTORY QUESTIONNAIRE

First name:_____ Middle initial:____Last name: _____

Date of birth (dd/mm/yyyy):_____ Age:_____

Email:_____

Home phone:_____ Mobile:_____

Best time/day to get in touch: _____

Postal address:_____

_____

Family physician (GP) name:_____

Family physician (GP) phone number:_____

Family physician (GP) address/practice name:_____

_____

Emergency contact name:_____

Emergency contact phone number:_____

Relationship with emergency contact:_____

1. How did you find out about this study?

_____

2. What is your current marital status?

Single	Defacto	Divorced
Married	Separated	Widower

3. What is the highest level of education you have completed?

Primary	Trade	Bachelor degree
Secondary	Certificate/Diploma	Higher degree

Other:_____

4. **What is your current level of employment?**

Retired Casual Full-time Sick leave

Unemployed Part-time Volunteer

If employed, what is your current occupation?_____

If employed, how many hours/days do you work in a typical week?

_____ Hours/day _____ Days/week

5. **Are you or have you ever been a smoker?**

Yes No

If yes:

a) Are you a past or current smoker? _____

b) Age you started smoking: _____

c) Age you quit smoking (for past smokers only): _____

d) Average number of cigarettes smoked per day: _____

6. **How many alcoholic drinks do you usually have per week?** _____

7. **Has your weight fluctuated more than a few kilos in the last 12 months?**

Yes No

a) If yes, approximately how many kilograms? _____

8. **What is your current level of physical activity?**

Active (equal to or more than 90 minutes of structured exercise per week)

Inactive (less than 90 minutes of structured exercise per week)

a) Details:_____

_____

_____

_____

_____

9. **Do you experience shortness of breath while walking with others of your age?**

Yes No

10. **Do you experience sudden tingling, numbness, or loss of feeling in arms, hands, feet, or face?**

Yes No

11. Do you experience swelling of your feet and ankles?

Yes No

12. Do you get pains or cramps in your legs?

Yes No

13. Do you experience any discomfort in your chest?

Yes No

14. Have you ever been told that your blood pressure was abnormal?

Yes No

a) If yes, do you currently take any medication (please provide details)?_____

_____

15. Have you ever been told that your serum cholesterol or triglyceride level was high?

Yes No

a) If yes, do you currently take any medication (please provide details)?_____

_____

16. Do you have cardiovascular disease?

Yes No

a) If yes, please provide details of condition and how it is controlled?_____

_____

_____

17. Do you have diabetes?

Yes No

a) If yes, how is it controlled?_____

_____

_____

18. Do you have osteoporosis?

Yes No

a) If yes, how is it controlled?_____

_____

_____

19. How many medications/supplements are you currently taking?_____

a) Please list below ALL the medications/supplements you are currently taking. Fill out every column for each item you list.

Medication/supplement	How long have you been taking it (in years and months)	Reason for taking (i.e. which medical condition) and other comments
e.g. Aspirin 100mg	Approximately 2 years 3 months	e.g. cardiovascular disease prevention.

20. Has a doctor or nurse ever told you that you had any of the following conditions?

Heart attack	Yes	No	Kidney disease	Yes	No
Stroke	Yes	No	Arthritis	Yes	No
Emphysema	Yes	No	Thyroid disease	Yes	No
Chronic bronchitis	Yes	No	Peripheral vascular disease	Yes	No
Angina (chest pain)	Yes	No			

a) If yes, please provide details e.g. how it is controlled:_____

_____

_____

_____

21. Do you have any other medical conditions (chronic or serious illness)?

Yes No

a) If yes, please provide details_____

_____

_____

_____

_____

22. Have you ever had any surgery (unrelated to cancer)?

Yes No

a) If yes, please provide details about the type, date and reason for the surgery

Type of surgery	Date of surgery (month and year)	Reason for surgery and details of any continuing impairments
e.g. Hip replacement	e.g. June 2010	e.g. Severe arthritis. Cannot run.

23. When were you diagnosed with prostate cancer? Month: _____ Year: _____

24. What was the Gleason score (out of 10) given to your prostate cancer at diagnosis?

_____

25. Is your prostate cancer: (Please circle all that apply).
    a) localised to the prostate,
    b) Spread to the surrounding lymph nodes or tissue, and/or
    c) Metastasised to other organs

Please provide details:_____

_____

_____

_____

26. Which types of treatment have you undertaken OR are currently undertaking OR anticipate receiving for your prostate cancer (circle all that apply)?

Surgery Radiation Chemotherapy Androgen deprivation therapy

Other (please indicate the type of treatment):_____

_____

_____

27. Regarding your prostate cancer treatment/s selected above, please provide details of treatment type e.g. surgery type, radiation type, name of chemotherapy, name of androgen deprivation therapy, the month/year you received the treatment and the date finished and/or anticipated finishing date.

Treatment	Type of procedure and/or drug name and how often (if applicable)	Start date	End date or anticipated end date.
e.g. Androgen deprivation therapy	e.g. Lucrin every 3 months and Cosudex tablets daily	e.g. May 2017	e.g. Expect to finish February 2018

28. Please specify any side effects experienced from your prostate cancer treatment and/or cancer and how they were treated?

_____

_____

_____

_____

_____

_____

_____

_____

Thank you very much for your time in completing this important questionnaire

C6. Feedback questionnaires

PARTICIPANT'S FEEDBACK FORM (pre-study)

We thank you so much for your participation in this study. Your commitment and enthusiasm is important to the development of exercise and diet programmes to better improve the care of prostate cancer patients.
We would like to ask for your thoughts around exercise and nutrition and how they fit into your prostate cancer care plan.

1. Thinking about your overall health and prostate cancer health, why do you feel it is important to begin an exercise and diet programme?

_____
_____
_____
_____
_____

2. Thinking about your prostate cancer journey thus far, what barriers have prevented or discouraged you from completing exercise and/or seeking nutritional advice?

_____
_____
_____
_____
_____

3. Based on your current knowledge of the programme you are about to start, what benefits do you anticipate gaining that are not currently offered to you through your current prostate cancer care plan?

_____
_____
_____
_____
_____

4. Consider any experience you may have with receiving an exercise and/or diet programme or advice, what strategies do you anticipate will be helpful in assisting with successful completion of the current programme?

_____
_____
_____
_____
_____

I _____ give permission for my responses to be quoted in an academic journal publication, conference presentation, and/or programme advertisements. I understand that no identifying information will accompany published quotes.

Signed: _____ Date: _____

PARTICIPANT'S FEEDBACK FORM (post-study)

We thank you so much for your participation in this study. Your commitment and enthusiasm is important to the development of exercise and diet programmes to better improve the care of prostate cancer patients.
We would like to ask for your feedback on the programme.

1. Thinking about the physical and/or mental changes you may have experienced over the last 6 months, do you feel an exercise and diet programme is an important part of your prostate cancer care plan?

2. Thinking about the 3 month **supervised** training period, what barriers prevented or discouraged you from completing exercise and/or following the nutritional advice?

3. Thinking about the 3 month **home-based** training period, what barriers prevented or discouraged you from completing exercise and/or following the nutritional advice?

4. Thinking about the 3 month **supervised** training period, what strategies (self-implemented or researcher implemented) did you find helpful in assisting with successful completion of exercise and diet programme?

5. Thinking about the 3 month **home-based** training period, what strategies (self-implemented or researcher implemented) did you find helpful in assisting with successful completion of exercise and diet programme?

6. Thinking about the last 6 months, what benefits did you notice by following the exercise and/or diet programme?

_____
_____
_____
_____
_____

7. Would you change anything about the programme?

_____
_____
_____
_____
_____

I _____ give permission for my responses to be quoted in an academic journal publication, conference presentation, and/or programme advertisements. I understand that no identifying information will accompany published quotes.

Signed: _____ Date: _____

C7. Health changes form

EMRI
Exercise Medicine Research Institute
vario health clinic

AUSTRALIA ECU EDITH COWAN UNIVERSITY

HEALTH INFORMAITON SHEET

Name:_____Code:_____ DOB:_____ Date:_____

Testing time: Pre-intervention Post-intervention Post follow-up

The questions below relate to any changes to your health or adverse events that have occurred since we last saw you. Please fill in the form even if you have not experienced any significant changes to your health.

1. **How many medications/supplements are you currently taking?**_____

   a) Please list below ALL the medications/supplement you are currently taking. Fill out every column for each item you list.

Medication/supplement	How long have you been taking it (in years and months)	Reason for taking (i.e. which medical condition) and other comments
e.g. Aspirin 100mg	Approximately 2 years 3 months	e.g. cardiovascular disease prevention.

2. Have you had any health concerns since we last saw you?

   Yes No

   a) If yes, please provide details_____

   _____

   _____

   _____

3. Have you experienced any adverse events (non-cancer related) since we last saw you? E.g. an illness that resulted in extended bed rest, musculoskeletal injury etc.

   Yes No

   a) If yes, please provide details_____

   _____

   _____

   _____

4. Has there been any concerns with your cancer diagnosis since we last saw you?

   Yes No

   b) If yes, please provide details_____

   _____

   _____

   _____

5. Has your cancer treatment plan changed since we last saw you?

   Yes No

   c) If yes, please provide details_____

   _____

   _____

   _____

6. Have you experienced any severe side effects from your prostate cancer treatment and/or cancer since we last saw you and how they were treated?

   Yes No

   d) If yes, please provide details_____

   _____

   _____

   _____

Thank you very much for your time in completing this important questionnaire

D. INTERVENTION PRESCRIPTION

D1. Resistance training protocol (Chapter 5 and 6)

Name: _____ **Body mass:** 1) _____kg. 4) _____kg. 7) _____kg.

Adherence questionnaire completed during sessions: 1 4 7

Session #	1	2	3	4	5	6	7	8	9
Date									

WARM UP	1	2	3	4	5	6	7	8	9
Machine									
Time									

Exercise target week 1 (Sessions 1-3) = 12 repetitions x 1 set (R/S)

Exercise target week 2 (Sessions 4-6) = 10 repetitions x 2 sets

Exercise target week 3 (Sessions 7-9) = 10 repetitions x 3 sets

MONDAY AND FRIDAY SESSIONS:

Exercise	Monday		Friday		Monday		Friday		Monday		Friday	
	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt
Seated leg press												
Leg Extension												
Leg curl												
Seated chest press												
Seated row												
Bicep curl												
Tricep extension												
Ab/back												

WEDNESDAY SESSIONS:

Exercise	Wednesday		Wednesday		Wednesday	
	R/S	Wt	R/S	Wt	R/S	Wt
Seated leg press						
Hip ab/adduction						
Seated calf raise						
Seated chest press						
Lat pulldown						
Shoulder press						
Ab/back						

COOL-DOWN	1	2	3	4	5	6	7	8	9
Machine									
Time									
Stretching									

Please collect your protein powder from Rebekah after EVERY session.

Booked in Nutrition Counselling sessions:

Week 1 =

Week 3 =

Comments/Reasons for missing sessions:

Name: _____ **Body mass:** 10) _____kg. 13) _____kg. 16) _____kg.

Adherence questionnaire completed during sessions: 10 13 16

Session #	10	11	12	13	14	15	16	17	18
Date									

WARM UP	10	11	12	13	14	15	16	17	18
Machine									
Time									

Exercise target week 4 (Sessions 10-12) = 8 repetitions x 3 sets (Monday/Friday), 10 repetitions x 3 sets (Wednesday) (R/S)

Exercise target week 5 (Sessions 13-15) = 8 repetitions x 3 sets (Monday/Friday), 10 repetitions x 3 sets (Wednesday)

Exercise target week 6 (Sessions 16-18) = 8 repetitions x 3 sets (Monday/Friday), 10 repetitions x 3 sets (Wednesday)

MONDAY AND FRIDAY SESSIONS:

Exercise	Monday		Friday		Monday		Friday		Monday		Friday	
	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt
Supine leg press												
Hip ab/adduction												
Standing calf raise												
Seated chest fly												
Pulldown												
Bicep curl												
Tricep extension												
Ab/back												

WEDNESDAY SESSIONS:

Exercise	Wednesday		Wednesday		Wednesday	
	R/S	Wt	R/S	Wt	R/S	Wt
Seated leg press						
Leg Extension						

Leg curl						
Seated chest press						
Low seated row						
Dumbbell lateral raise						
Ab/back						

COOL-DOWN	10	11	12	13	14	15	16	17	18
Machine									
Time									
Stretching									

Please collect your protein powder from Rebekah after EVERY session.

Food record and actigraph measurement

Week 6 = Sunday Monday Tuesday OR Thursday Friday Saturday

Comments/reasons for missing sessions:

Name: _____ **Body mass:** 19) _____ kg. 22) _____ kg. 25) _____ kg.

Adherence questionnaire completed during sessions: 19 22 25

Session #	19	20	21	22	23	24	25	26	27
Date									

WARM UP	19	20	21	22	23	24	25	26	27
Machine									
Time									

Exercise target week 7 (Sessions 19-21) = 8 repetitions x 3 set (Monday), 10 repetitions x 3 sets (Wednesday), 12 repetitions x 3 set (Friday) (R/S)

Exercise target week 8 (Sessions 22-24) = 8 repetitions x 3 set (Monday/Friday), 10 repetitions x 3 sets (Wednesday)

Exercise target week 9 (Sessions 25-27) = 8 repetitions x 4 set (Monday/Friday), 10 repetitions x 4 sets (Wednesday)

MONDAY AND FRIDAY SESSIONS:

Exercise	Monday		Friday		Monday		Friday		Monday		Friday	
	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt
Incline leg press												
Leg Extension												
Leg curl												
Standing chest press												
Standing row												
Bicep curl												
Tricep extension												
Ab/back												

WEDNESDAY SESSIONS:

Exercise	Wednesday		Wednesday		Wednesday	
	R/S	Wt	R/S	Wt	R/S	Wt
Seated leg press						
Hip ab/adduction						

Seated calf raise						
Seated chest fly						
Rear dealt						
Shoulder press						
Ab/back						

COOL-DOWN	19	20	21	22	23	24	25	26	27
Machine									
Time									
Stretching									

Please collect your protein powder from Rebekah after EVERY session.

Comments/reasons for missing sessions:

Name: _____ **Body mass:** 28) _____kg. 31) _____kg. 34) _____kg.

Adherence questionnaire completed during sessions: 28 31 34

Session #	28	29	30	31	32	33	34	35	36
Date									

WARM UP	28	29	30	31	32	33	34	35	36
Machine									
Time									

Exercise target week 10 (Sessions 28-30) = 6 repetitions x 4 sets (Monday/Friday), 10 repetitions x 4 sets (Wednesday) (R/S)

Exercise target week 11 (Sessions 31-33) = 6 repetitions x 4 sets (Monday/Friday), 10 repetitions x 4 sets (Wednesday)

Exercise target week 12 (Sessions 34-36) = 10 repetitions x 3 sets (Monday), 8 repetitions x 3 sets (Wednesday), 6 repetitions x 3 sets (Friday)

MONDAY AND FRIDAY SESSIONS:

Exercise	Monday		Friday		Monday		Friday		Monday		Friday	
	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt	R/S	Wt
Incline leg press												
Leg Extension												
Leg curl												
Smith chest press												
Seated row												
Bicep curl (grip change)												
Tricep extension (grip change)												
Ab/back												

WEDNESDAY SESSIONS:

Exercise	Wednesday		Wednesday		Wednesday	
	R/S	Wt	R/S	Wt	R/S	Wt
Incline leg press						

Hip ab/adduction						
Standing calf raise						
Seated chest press						
Lat pulldown						
Dumbbell lateral raise						
Ab/back						

COOL-DOWN	28	29	30	31	32	33	34	35	36
Machine									
Time									
Stretching									

Please collect your protein powder from Rebekah after EVERY session.

Booked in Nutrition counselling session:

Week 12 =

Booked in post-intervention testing:

Testing session 1 =

Testing session 2 =

Testing session 3 =

Comments/reasons for missing sessions:

D2. Diet prescription template (Chapter 5 and 6)

Weight loss programme for prostate cancer patients

Name: _____

Food groups	Examples of food items	Daily recommended consumption
Vegetables	• Cooked vegetables e.g. greens beans, peas, pumpkin, carrot, cauliflower, mushrooms • Cooked dried or canned beans, lentils • Green leafy salad, tomato, cucumber, onions, celery • Sweet corn, potato or other starchy vegetables	
Fruit	• Apple, banana, orange • Apricots, kiwi fruits, plums • Diced or canned fruit (no added sugar) • Fruit juice (no added sugar) • Dried fruit	
Grains (cereals)	• Bread, flat bread, bread roll • Cooked rice, pasta, noodles, quinoa • Oats • Wheat cereal flakes • Muesli • Crumpet • English muffin or scone	
Sources of protein	• Lean red meats e.g. beef, lamb, veal, pork • Lean poultry e.g. skinless chicken • Fish fillet or one small can e.g. tuna • Eggs • Cooked or canned beans e.g. chickpeas • Tofu • Nuts, seeds, peanuts	
Dairy	• Milk • Hard cheese e.g. cheddar • Ricotta cheese • Yoghurt	
Discretionary items	• Alcohol • Soft drinks • Confectionery • Hot chips, potato crisps • Process meats e.g. salami, bacon • Puddings, desserts • Cake, biscuits • Take away food • Honey, jam	

Nutrition goals:

1.

2.

3.

Meal example:

BREAKFAST

MORNING TEA

LUNCH

AFTERNOON TEA

DINNER

DESSERT

E. EXERCISE AND NUTRITION INFORMATION BOOKLETS

E1. Weight loss intervention booklet (Chapter 5 and 6)

Weight loss programme for prostate cancer patients

Guide to exercise and nutrition intervention

Developed by
Rebekah Wilson, MPhysEd
Ph.D Candidate

NHMRC Centre for Research Excellence
PROSTATE CANCER SURVIVORSHIP

Exercise Medicine Research Institute

AUSTRALIA ECU EDITH COWAN UNIVERSITY

vario health clinic

Contents

WELCOME!

Congratulations on taking the first steps to a healthier lifestyle and thank you for your participation in Rebekah's PhD project of an exercise and nutrition programme for men with prostate cancer on androgen deprivation therapy (ADT). This project has been designed and will be monitored by our team of medical, exercise, and nutrition experts from the Exercise Medicine Research Institute at Edith Cowan University.

This programme has been developed specifically for men with prostate cancer on ADT as a strategy to improve body composition. Changes to body shape are very common when receiving ADT with most men typically experiencing a loss in lean muscle mass and a gain in fat mass. This programme has been designed to reduce fat mass and build muscle mass that will lead to improved physical function and general state of well-being.

This manual was written to help with the home-based section of the programme and will assist with any initial questions or concerns you may have. You will receive 12 weeks of contact time with the Research Team who will help with all your queries. This manual will act as a reminder and keep you on track with your home-based exercise and nutrition plan as well as provide extra information on prostate cancer, exercise, and nutrition.

Why exercise and diet?

Exercise improves health…. It is as simple as that. In fact, a number of the world's leading doctors and scientists have said that ***if exercise could be encapsulated in a pill it would be among the most powerful medications ever developed***.

This is because exercise works all the major systems in your body simultaneously. Through improving the structure and function of the body's systems, exercise and eating a balanced diet acts as a shield against disease as well as the declines in physical and mental function that can occur as we age.

There is a long list of benefits of exercising and eating the right foods such as:

- Help you feel good both physically and mentally
- Improve your health
- Improve your quality of life
- Help you live longer
- Reduce risk of developing diseases such as heart disease, diabetes, and osteoporosis (being on ADT places one at increased risk of these conditions)
- Reduce risk of other cancers
- Reduce risk of cancer recurrence or progression
- Improve function of your heart and lungs
- Improve strength and build muscle
- Improve the strength of bones and function of joints
- Improve balance and reduce the risk of falls
- Increase energy levels and reduce fatigue
- Improve your state of mind and relieve stress
- Reduce the severity of anxiety and depression
- Improve your self-esteem
- Improve the quality of your sleep
- Help you lose weight and keep it off
- Help maintain your physical function and make everyday activities easier to do

But why exercise and diet while I am receiving treatment.... Many of the cancer treatments can be quite harsh on your body with a number of adverse side effects. Common side effects of ADT include:

- Loss of muscle mass/strength
- Increase in fat mass and body weight
- Loss of energy levels (fatigue)
- Hot flushes
- Loss of bone mass
- Impotence

Exercise and a balanced diet offer the greatest potential to prevent and reverse treatment related side effects in men with prostate cancer. This is why many health organisations advise people with cancer to **avoid inactivity** even while undergoing difficult treatment regimes. Exercise and healthy nutrition choices are also known to reduce a number of risk factors and help control conditions such as cardiovascular disease, diabetes, and depression, which men on ADT are at increased risk of developing.

Exercise increases testosterone levels, is it safe to exercise while on ADT…. **YES!** There is much scientific evidence showing exercise, and even high-intensity exercise, is safe for men with prostate cancer while on ADT and after treatment has finished. Getting involved with exercise can help reduce long-term side effects that may occur after treatment has stopped and as an added bonus can even help get your mind off your treatment and the stresses of everyday life.

Obesity and prostate cancer

Obesity is a heavily targeted condition in Australia (and worldwide) with more than 60% of Australia's adult population considered overweight or obese. However, it is only in the last few years that obesity has become a concern in the cancer population. Studies have shown that almost 90% of men on ADT are overweight or obese. This places a larger burden on prostate cancer survivors with not only having to worry about their cancer-related health but the potential of other issues evolving from being overweight.

Why is being overweight or obese an issue if I have cancer… The combination of being overweight or obese and having a prostate cancer diagnosis has been associated with a higher risk of poor prostate cancer prognosis. What this means is if you are overweight or obese, you are at an increased risk of recurrence (your PSA increasing again after treatment which could indicate cancer progression), developing other conditions such as cardiovascular disease, and diabetes (which are commonly developed in men on ADT), and your cancer becoming more aggressive.

The good news is…. Increasing your activity levels and eating a balanced diet (even without significant changes to your body shape) can improve these risks!!!! Not to mention that exercise and diet will also provide other benefits that have already been referred to on the previous page.

Goal setting

The aim of this programme is to help you lose fat mass by providing a supervised exercise programme, an individualised nutrition programme, and advice for how to manage your own exercise and nutrition habits. Ultimately, we are aiming for 300 minutes of aerobic and resistance exercise per week, and a diet consisting of smaller portion sizes and healthy choices. These guidelines are in line with what is currently recommended in clinical practice for obesity management (http://www.health.gov.au). In this study, you will be prescribed an exercise and nutrition programme specific to the needs of prostate cancer patients and yourself.

Although you will be coming to the Vario Clinic three times a week for 12 weeks, you will also be asked to complete exercise outside of the Clinic and monitor your own nutritional intake. One way to implement these changes and monitor your progress is by having weekly goals. Sometimes the "big picture" is too much to take on board all at once so one way to set goals is to break down the big goal into smaller steps.

For example:

> Study goal: "For 12 weeks you will be walking briskly for 30 minutes on 4 days, and attending supervised training sessions on 3 days each week."
> My goal 1: "During week one of study I will complete 20 minutes of low intensity walking on 4 days and attend 3 supervised training sessions."
> My goal 2: "During week one of study I will have one piece of multi-grain toast and a piece of fruit for breakfast and consume smaller portions of all foods at lunch and dinner meals."

Learning to set your own goals will help you be successful. Here are some tips about how to set **SMART** goals:

S – Specific:

Describe what you will do and how you will do it:

- I will walk 30 minutes a day, 4 days a week. I will walk quickly enough that I am breathing heavily.

M – Measurable:

Keep track of your progress:

- Set goals that are measured in minutes per session, heart rate intensity, amount of food, or food selection.
- We will be asking you to keep a record of your exercise and intensity in the log book at the back of this booklet. Hopefully this will help you to stick with your goals.

A – Achievable:

Can you meet this goal?

- Pick a goal you think you can meet.
- By gradually increasing the amount and intensity of exercise and food items replaced/removed, this should help in achieving the study aims described, rather than trying to change everything at once.

R – Rewarding

Is this goal meaningful or rewarding for me?

- Try to consider the health benefits that are important to you as a male with prostate cancer.
- Remember that good things take time, and you may not see changes immediately. However, you may start noticing that you feel better i.e. less fatigued.

T – Timeline

How long will this goal take? What is my timeline?

- Think short term and long term, for example:
  - This week I will add 5 minutes to every walking session.
  - By the end of 3 months I will be walking briskly for at least 30 minutes.

Barriers to exercise and dieting

There are many things that can keep us from exercising regularly or making healthy food choices. Especially while on treatment, exercising and making changes to your nutrition intake may not be a priority as you are trying to take on board all this new information about your cancer and treatment. However, try to remember that increasing your activity levels and improving your food choices may make your cancer journey easier.

Here are some common barriers as well as suggestions for getting around those concerns:

I'm too busy and exercise is not a priority:

- You are likely to have work commitments, family responsibilities, cancer-related appointments, seeing friends, holidays, and making time to relax. That's just for starters! But there are always little ways that we can fit things in.
- Try taking a walk around the block at lunch time.
- Meeting a friend for coffee? Take a walk along the beach instead (or as well as).
- Schedule in exercise. Make an appointment with yourself.
- Going to an appointment? Try leaving a little earlier and park further away so you have to walk a little longer.
- Use the stairs instead of the lift or escalator.
- Sometimes it is just about adding in incidental activity on those busy weeks.

Where does exercise and nutrition fit in to my cancer treatment?

- Try to remember all the important benefits of exercise and healthy food choices such as: Feeling less tired, less depression, reduced risk of cancer coming back, and reducing risk of other diseases such as diabetes. It can also take your mind off the cancer!
- Keep in mind that your exercise and healthy eating plan is an important aspect of your recovery and is actively encouraged by many doctors as part of a prostate cancer patient's care plan.

My family likes to eat these other things:

- Our aim is to provide a meal plan for you that works within your home situation.
- Eating out? Not a problem! There are healthy choices within takeaway shops. Take the time to look at the menu and consider ordering less food e.g. only consume a main meal with no entrée.

Feeling tired?

- Fatigue is a common side effect of cancer treatment, so it is important to consider ways that you can adjust your exercise plans to work when you are feeling tired.
- Remember that something is always better than nothing!

It's expensive:

- Particularly good quality fruit, vegetables, and meat can be expensive. Consider cooking meals with seasonal foods.
- Try shop around! There are many farmers markets and supermarkets to choose from. See which have the best offers for you.
- Gyms can also be expensive. We will be providing you with a gym stick and this will help with completing exercises at home. But being outside is free! Take the time to find walking/cycling tracks around Perth, and swimming in the ocean in summer time is very refreshing on those hot days.

I have another illness that makes it difficult to exercise:

- Exercise has been shown to be beneficial for many conditions such as arthritis, diabetes, and heart disease.
- Exercise within your limits (e.g. stop if you experience pain).
- Ask your doctor or Rebekah for advice if you are unsure.

I don't want to make these changes by myself:

- Getting your friends and family on board can really help with achieving your goals.
- Ask friends and family to exercise with you or cut out certain foods. Having someone you are accountable to can be very encouraging.

Study timeline

This is an outline of the study commitments. The study is ~30 weeks in total.

Part 1: BASELINE TESTING + 6 WEEK CONTROL PERIOD

What	When	Approximate time	Where	What does it involve?
Testing day 1	Week 0	2 hours	Joondalup Campus (ECU)	・Background health information ・Body composition (DXA, pQCT) ・Resting metabolic rate (fasting) ・Quality of life questionnaire (x2) ・Physical activity questionnaire ・Food frequency questionnaire
Testing day 2	Week 0	1 hour		・Strength testing familiarisation session
Off-site testing	Week 0	3 days		・3-day weighed food record ・3-day physical activity monitoring
Testing day 3	Week 0	1-2 hours		・400m walk ・Strength testing
Start of 6-week control period	Week 1		Home	You will be asked to continue with life as normal. Eat and exercise the same as you have been doing for the past few months.
End of 6-week control period	Week 6			

Part 2: PRE-INTERVENTION TESTING + 12 WEEK SUPERVISED INTERVENTION

What	When	Approximate time	Where	What does it involve?	
Testing day 1	Week 6	2 hours	Joondalup Campus (ECU)	・Body composition (DXA, pQCT) ・Resting metabolic rate (fasting) ・Quality of life questionnaire (x2)	・Physical activity questionnaire ・Food frequency questionnaire
Testing day 2	Week 6	1-2 hours		・Maximal aerobic capacity test	
Off-site testing	Week 6	3 days	Australian Clinical Labs (bloods only) Home	・Blood test (fasting) at your local Australian Clinical Labs ・24 hr urine sample	・3-day weighed food record ・3-day physical activity monitoring
Testing day 3	Week 6	2-3 hours	Joondalup Campus (ECU)	・400m walk ・Strength testing ・Diet history (this may be required to be on a separate day depending on availability)	
Start of 12-week training programme (supervised intervention)	Week 7	Each supervised exercise session will be 1 hour.	Joondalup or Mt Lawley Campus (ECU)	All sessions will be conducted by Rebekah Wilson. You will complete 3 supervised training sessions at the Exercise Clinic of your choice (Joondalup or Mt Lawley Campus, ECU), plus at least 30 minutes of aerobic exercise on the days when you don't attend a clinic session, totalling 300 minutes of exercise each week. The exercise sessions will be run in a group setting (however, times will be flexible). You will also be required to fill out a short weekly questionnaire about your eating and exercise habits for the past week. During the 12 weeks you will also be asked to follow an individualised nutrition plan.	

Nutritional counselling session 1	Week 7	1-2 hours	Joondalup or Mt Lawley Campus (ECU)	These will be individual sessions conducted by A/Prof Philippa Lyons-Wall and Rebekah Wilson. The main aim of the nutrition intervention is to choose smaller portion sizes at meals, while optimising protein intake. Then have a plan to reduce intake of refined carbohydrates and saturated fats. Please see *Nutrition Element* section for more information.
Nutritional counselling session 2	Week 9	1 hour		During this session you will be provided with an example meal plan for you to use as a guide for your daily nutrition to help optimise loss of body fat.
Off-site testing	Week 12	3 days	Home	・3-day weighed food record ・3-day physical activity monitoring
End of 12-week training programme	Week 18		Joondalup or Mt Lawley Campus (ECU)	All supervised exercise sessions stop
Nutritional counselling session 3	Week 18	1 hour	Joondalup or Mt Lawley Campus (ECU)	This session will assist with advice moving into the home-based intervention.

Part 3: POST-INTERVENTION TESTING + HOME-BASED PROGRAMME + FINAL TESTING

What	When	Approximate time	Where	What does it involve?
Testing day 1	Week 19	2 hours	Joondalup Campus (ECU)	・Body composition (DXA, pQCT) ・Resting metabolic rate (fasting) ・Quality of life questionnaire (x2) ・Physical activity questionnaire ・Food frequency questionnaire
Testing day 2	Week 19	1-2 hours		・Maximal aerobic capacity test
Off-site testing	Week 19	3 days	Australian Clinical Labs (bloods only)	・Blood test (fasting) at your local Australian Clinical Labs ・24 hr urine sample ・3-day weighed food record ・3-day physical activity monitoring
Testing day 3	Week 19	1-2 hours	Home	・400m walk ・Strength testing
Start of 12-week follow-up (home-based intervention)	Week 19		Home	You will be asked to continue completing 300 minutes of aerobic and resistance exercise at home. You will be provided with a GYMSTICK to assist with completing the resistance exercises at home. You will also be asked to continue utilising the nutritional advice.
Phone call check up	Week 24	15-20 minutes		This will be a phone call to ask the nutrition and exercise questionnaire that you would have filled out every week during the supervised training session.
End of 12-week follow-up	Week 30			Other than final testing described below, study contact time has now finished.
Testing day 1	Week 30	2 hours	Joondalup Campus (ECU)	・Body composition (DXA, pQCT) ・Resting metabolic rate (fasting) ・Quality of life questionnaire (x2) ・Physical activity questionnaire ・Food frequency questionnaire
Off-site testing	Week 30	3 days	Home	・3-day weighed food record ・3-day physical activity monitoring
Testing day 2	Week 30	1-2 hours	Joondalup Campus (ECU)	・400m walk ・Strength testing

Nutrition element

Making healthy food choices can have a positive impact on your prostate cancer journey and the extent of treatment related side effects. For this study, our primary aim is to influence body shape which is commonly altered as a result of ADT. We will be providing individualised nutrition advice that aligns with the Australian Dietary Guidelines and the nutrition recommendations for prostate cancer patients.

What will the nutritional counselling sessions involve?

- You will be asked to attend three compulsory nutritional counselling sessions (~60 minutes each). The first one will be during week one of the supervised intervention, the second will be 2 weeks later, and the final session will be at the transition point between the supervised and home-based intervention periods. The sessions will be conducted by A/Prof Philippa Lyons-Wall (Accredited Practising Dietitian) and lead researcher Rebekah Wilson. You will be asked about your usual eating habits and from there we will work through some basic goals that will help align your eating patterns to meet our intervention requirements (described below) and assist in weight loss. You will not be provided with a strict diet, simply given advice and examples of how to easily alter your current eating habits to assist with weight loss.

Aims of nutrition intervention

All advice provided will be individually tailored (advice that suits your lifestyle and preferences). We do, however, have two aims to help standardise the advice given to each participant.

AIM ONE: To decrease your portion sizes resulting in a daily energy deficit of 2-4 MJ (500-1000 kcal).

What does this mean?

- A portion size is the amount of food that you choose to eat for a meal or snack. It can be large or small. To successfully lose weight we must consume less energy than we use. The Australian clinical practice guidelines for weight management recommend a 2-4 MJ (500-1000 kcal) energy deficit to lose weight.

How will I create this deficit?

- We will calculate your daily energy requirements (the amount of energy your body needs to function each day). To create an energy deficit, you will be asked to eat 2-4 MJ (500-1000 kcal) less than your daily energy requirements. Since your body will be receiving less energy than it is currently used to your body will generate energy from the fat stores you already have. This process is what will result in changes to your body composition. During the nutritional counselling sessions, we will develop your example meal plan (personal to you) that will give you an idea of the portion sizes and types of carbohydrates, fats, and protein you may consume each day. You do not have to follow this plan meal for meal, it simply gives you an idea of the amount and type of food you may consume that will assist in successful weight loss and meeting the study requirements.

How will I know how much to eat?

- The individual meal plan we develop with you will state the ideal amounts to consume per day of vegetables, fruit, grains, meats and alternative protein sources, dairy, and discretionary items. The meal plan will give you a clear guide to the types of food and how much you should be consuming to meet the study's nutrition aims. We use the Australian Dietary Guidelines (www.eatforhealth.gov.au) and prostate cancer specific nutrition guidelines for the advice provided.

Food groups	Examples of food items	Daily recommended consumption
Vegetables	· Cooked vegetables e.g. greens beans, peas, pumpkin, carrot, cauliflower, mushrooms · Cooked dried or canned beans, lentils · Green leafy salad, tomato, cucumber, onions, celery · Sweet corn, potato or other starchy vegetables	
Fruit	· Apple, banana, orange · Apricots, kiwi fruits, plums · Diced or canned fruit (no added sugar) · Fruit juice (no added sugar) · Dried fruit	
Grains (cereals)	· Bread, flat bread, bread roll · Cooked rice, pasta, noodles, quinoa · Oats · Wheat cereal flakes · Muesli · Crumpet · English muffin or scone	
Sources of protein	· Lean red meats e.g. beef, lamb, veal, pork · Lean poultry e.g. skinless chicken · Fish fillet or one small can e.g. tuna · Eggs · Cooked or canned beans e.g. chickpeas · Tofu · Nuts, seeds, peanuts	
Dairy	· Milk · Hard cheese e.g. cheddar · Ricotta cheese · Yoghurt	
Discretionary items	· Alcohol · Soft drinks · Confectionery · Hot chips, potato crisps · Process meats e.g. salami, bacon · Puddings, desserts · Cake, biscuits · Take away food · Honey, jam	

Nutrition Counselling meeting goals:

1. _____

_____

_____

2. _____

_____

_____

3. _____

_____

_____

Meal example:

BREAKFAST

MORNING TEA

LUNCH

AFTERNOON TEA

DINNER

DESSERT

AIM TWO: To optimise protein intake and reduce consumption of refined carbohydrates and saturated fats.

What are refined carbohydrates?

- These are plant based foods that have had the fibre and much of the nutritional value removed during the processing phase. We often refer to carbohydrates as grains and/or cereals.
- Below are some examples of refined carbohydrates to **limit or avoid**:

Refined Carbohydrates	
・White bread	・Biscuits
・Lollies/chocolate	・Quick-cook rice packets (white rice specifically)
・Cakes	・Potato chips
・Sugary beverages	・Sugary cereals
・White pasta	・Sweeteners e.g. white/brown sugar
・Pastries	・Muffins

What are saturated fats?

- Saturated fats are not considered essential for good health. They are solid at room temperature and mainly found in animal products although some plant products as well.
- Below are some examples of foods containing saturated fats to **limit or avoid**:

Foods containing saturated fats	
・Butter	・Fatty cuts of beef/pork/lamb
・Cream	・Processed meats e.g. salami, sausages, chicken with skin/coating
・Full-fat milk	・Palm oil
・Cheese	・Cooking margarine
・Coconut oil	・Cakes
・Pies	・Biscuits
・Deep fried take away food e.g. fish ‘n’ chips	

What do you mean by optimising protein?

- Protein consumption is important for lean muscle development. We will be asking you to optimise your protein intake by consuming ~1-1.2 g/kg/day which is what the Australian Healthy Eating Guidelines and cancer nutrition guidelines recommend. For an 80kg male this would involve consuming ~80 grams of protein which may equate to - two serves of oats, and a single serve of milk, steak, and fish and half a serving of cheese over the period of a day.
- We will provide a vanilla whey protein shake after every supervised training session (40g protein) which will optimise muscle adaptations from the resistance workout and assist in your daily protein consumption.
- Below are examples of foods containing protein and should be **regularly consumed** in moderation:

Foods containing protein	
・Beef (fat cut off) ・Pork (fat cut off) ・Lamb (fat cut off) ・Kangaroo (fat cut off) ・Skinless Chicken ・Fish/shellfish	・Nuts and seeds ・Dried beans and lentils ・Milk (low fat) ・Yoghurt (low fat) ・Cheese (low fat) ・Soy products

What about my vegetable and fruit intake?

- We will be recommending that you consume > 5 serves of vegetables and fruit per day and consume vegetables of many colours. This aligns with the Australian Dietary Guidelines.

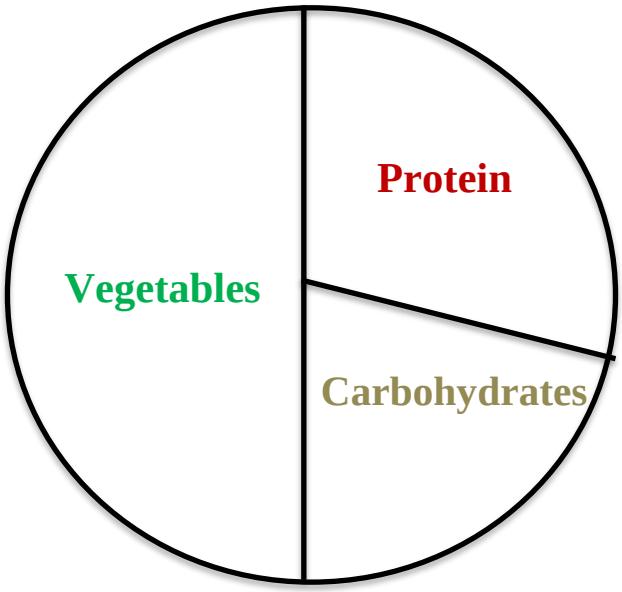
What about alcohol?

- We will be recommending that you limit your alcohol intake by consuming no more than 2 standard drinks at a time with at least 2 alcohol free days during the week. These align with the Australian Guidelines to reduce health risk from drinking alcohol.
- Below are some examples of alcoholic beverages to be consumed in moderation:

Alcoholic beverages	
・Light beer ・Red wine	・Straight spirits e.g. whisky ・Spirits with a non-sugary mixer e.g. Gin and Tonic.

What should my plate look like?

- Based on the above described Aim Two (optimise protein and reducing refined carbohydrates and saturated fats) the below diagram gives an idea of what your lunch and dinner meal should look like.



Exercise element

Cancer patients are actively recommended to **avoid inactivity** during their treatment. Exercise has been shown to have a positive effect on many treatment related side-effects, even going as far as reversing or preventing side effects from developing. As described, the primary aim of this study is to alter body shape. The exercise programme we have developed aligns with the Australian clinical practice guidelines for weight management and American College of Sports Medicine prostate cancer exercise guidelines. We will be aiming to induce fat mass loss, develop muscle size and strength, and improve general fitness. You will attend a 12-week supervised programme where you will be taken through an aerobic and resistance training workout and also provided with recommendations of home-based activities to complete throughout the 6-month intervention.

Aim of exercise intervention

Although a set workout will be provided during the supervised training sessions, all exercises will be individually tailored to your needs and fitness level. Exercise completed at home will also be individually tailored giving you the ability to select any aerobic exercise type you wish. However, we do have a study aim and outlines that will help standardise exercise prescription provided to all participants.

AIM: To complete a minimum of 300 minutes of combined aerobic and resistance exercise each week.

Exercise training outlines:

- Aerobic exercise intensity to be completed between 50-90%
- Resistance training exercises will progress from 6-12 repetitions and 1-4 sets.
- Resistance (weight) lifted will be individually prescribed based on participant fitness but will be ~60-85% of maximum lifting ability.

What type of exercise will you be required to do?

- When you are in the Vario Clinic exercise facilities you will be completing mostly resistance training. This involves doing exercises using machine and handheld weights that will target all major muscle groups.
- You will complete some aerobic exercise during the supervised sessions e.g. walking, cycling, rowing, to introduce you to the types of aerobic exercise and help you understand what the ideal intensity is to work when completing aerobic exercise outside of the clinic.
- At home, you will be asked to complete aerobic exercise of your choice. This may involve walking, jogging, cycling, swimming, rowing or playing a sport. Home-based exercises will be prescribed after consultation with Rebekah. However, you will simply be encouraged to select an activity you enjoy.
- In total, you will be asked to accumulate at least 300 minutes of exercise a week. For example, your week may contain 3 x 1hr supervised training sessions (180 minutes) (**compulsory**) plus you may complete 30 minutes of walking every other day of the week (120 minutes). Your total week will result in 300 minutes of exercise.
- 300 minutes of exercise a week is recommended for weight loss by the Australian clinical practice weight management guidelines.

What is aerobic exercise?

- Aerobic exercise (also known as cardio or endurance exercise) is a form of exercise which involves repetitive movements of large muscle groups that can be maintained for a prolonged period of time. Completing aerobic exercise has many benefits for your health and lifestyle.
- Types of aerobic exercise include but are not limited to:
  - Walking
  - Jogging/running
  - Riding a bicycle
  - Using a stationary bicycle
  - Rowing
  - Gym cardio fitness classes e.g. Spin
  - Cross trainer
  - Soccer
  - Basketball
  - Golf
  - Tennis
  - Swimming

How hard should I be exercising?

- During the supervised exercise sessions, we will show you how to judge your exercise intensity using a heart monitor and rate of perceived exertion (RPE).
- Heart rate is strongly associated with exercise intensity. Generally, the higher the heart rate, the harder you are working. We will be recommending that you exercise between 50-90% of your heart rate maximum. What we do is we work out your maximum heart rate (220-age) e.g. 220-65 = 155. From here, just say you want to work at 70%, we would ask that you exercise at an intensity where your heart rate is around 109 beats per minute (109 = 70% of 155).
- The other option is to work on a rate of perceived exertion scale. Below is a scale out of 10 that describes how hard you felt you worked throughout the session. We will be recommending that you exercise from 2 to 8 out of 10 which equates to ~50-90% intensity. The follow page is a table from Exercise and Sports Science Australia (https://www.essa.org.au/) that may also assist with describing the intensity of your exercise session.

Rating	Descriptor
0	Rest
1	Very, very easy
2	Easy
3	Moderate
4	Somewhat hard
5	Hard
6	*
7	Very Hard
8	*
9	*
10	Maximal

EXERCISE INTENSITY GUIDELINES

INTENSITY CATEGORY	HEART RATE MEASURES	PERCEIVED EXERTION MEASURES	DESCRIPTIVE MEASURES
SEDENTARY	< 40% HRmax	Very, very light RPE# < 1	• Activities that usually involve sitting or lying and that have little additional movement and a low energy requirement
LIGHT	40 to <55% HRmax	Very light to light RPE# 1-2	• An aerobic activity that does not cause a noticeable change in breathing rate • An intensity that can be sustained for at least 60 minutes
MODERATE	55 to <70% HRmax	Moderate to somewhat hard RPE# 3-4	• An aerobic activity that is able to be conducted whilst maintaining a conversation uninterrupted • An intensity that may last between 30 and 60 minutes
VIGOROUS	70 to <90% HRmax	Hard RPE# 5-6	• An aerobic activity in which a conversation generally cannot be maintained uninterrupted • An intensity that may last up to about 30 minutes
HIGH	≥ 90% HRmax	Very hard RPE# ≥ 7	• An intensity that generally cannot be sustained for longer than about 10 minutes

= Borg's Rating of Perceived Exertion (RPE) scale, category scale 0-10

What is resistance exercise?

- Resistance exercise or weight training is a form of exercise involving the repetitive lifting or moving against a force or weight. Some examples include using a GYMSTICK (which you will be provided with at the end of the supervised sessions to use at home), dumbbells, weight machines or your own body weight. Regular resistance exercise is extremely beneficial to your health and will enhance your physical function.

How do I complete resistance exercises at home?

- For the home-based intervention, you will be asked to continue completing resistance training exercises on a weekly basis, you will be provided with a GYMSTICK to assist with this. The GYMSTICK will come with a DVD for you to follow if you wish but Rebekah will show you how to use the GYMSTICK to replicate the exercises you would have completed during the 12 week supervised intervention period.

What is flexibility exercise?

- Flexibility exercise is a form of exercise that involves stretching of the muscles in order to improve range of motion. Flexibility exercises are typically done in a dynamic form e.g. moving through a range of motion, or a static form e.g. holding a position. Flexibility exercise will be completed during the warm up and cool down periods of the supervised exercise sessions.

<u>Unintentional exercise</u>

It's amazing how much of a difference the little things in life can make. Here are some ideas of the little things you can do to help increase your daily activity:

- *Take the stairs.* You can build up your fitness by taking the lift up but walking down the stairs or vice versa. If you work in a tall building maybe you walk up the first few flights and take the lift the rest of the way and slowly build up the number of flights of stairs you take.
- *Park further away.* Stop looking for that 'perfect car park.' Yes, sometimes we are in a rush and need to get things done but think of how much time you might save taking the first car park and walking then driving around and around looking for the closest car park.
- *House work.* Use the house chores as an opportunity to get up and do some exercise.
- *Use the TV ads to get up and move*. Ads on TV are a great opportunity to give your eyes a break from the screen and use your legs. You may use the 3 minutes to clear the dishes or bring in the washing or simply just stand and stretch.
- *Ten minutes here, ten minutes there.* The exercise completed at home does not have to be done in one go. If time is a concern try for a 10 minute brisk walk around the block in the morning, 10 minute brisk walk at lunch time, and 10 minute brisk walk in the evening.
- *Change your form of transport.* Parking, especially in the city, can be a nightmare. Try taking the bus or train, or even walk/cycle to your destination.

How do I include my family/friends?

For some it may be easy to make these changes by themselves for others the support of their children, grandchildren, friends, partner or wife will be important to the success of this programme. With the exercise and nutrition changes we are encouraging we do not want you to feel like you have to do or eat something different from the rest of your family. As well as your set 3 sessions in the clinic gym we are also encouraging you to exercise outside of these sessions. These sessions do not have to be organised walks by yourself (although sometimes the alone time can be welcomed!) they can be weekend outings or romantic walks on the beach! Some ideas include:

- Picnic on the beach. Take the time to walk up and down the sand or throw a ball around.
- Take the dog out for a walk.
- Take your children or grandchildren to the playground and get involved!
- Get your wife, partner or a friend on board and organise weekly active outings so that you have someone else to be accountable to.
- Catching up with a friend for coffee? Catch up with them for a walk instead! Or find a nice spot near a park or beach and do both.
- Have you been constantly thinking about re-joining a sporting club? Go for it! Take a friend or family member and play together. Tennis, squash, bowels, soccer, golf… the sky is the limit.

Exercise log book

We recommend that you either leave in the booklet or rip these pages out and place them somewhere you will look at them constantly e.g. kitchen fridge, by the front door, or on your night stand. The information you provide in this logbook will help with our overall analysis of exercise completed during the study period.

When to fill this in?

- Any non-supervised exercise you complete e.g. exercise completed away from the Vario Clinic exercise facilities, we ask that you write the type of exercise performed, how long you exercised for, and provide a value out of 10 of how hard you felt the exercise session was (see page 14 and 15).
- There is also a space that if you wish you can create a weekly exercise goal to help you meet the required 300 minutes of exercise. See page 3 for further information on how to develop a goal. Please take the time to discuss with Rebekah during your clinic exercise sessions if you wish.
- We would also like to know if you have any adverse events as a result of the programme or health concerns that stopped you from completing any exercise. For example, you may develop the flu and may do no exercise for a few days, or you may injury yourself while completing an exercise session. Please make note of any adverse events that may occur as a result from the programme or health concerns and how they affected you.

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
1	What type of exercise did you do?								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal

2	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**	**Weekly exercise goal**
3	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**	**Weekly exercise goal**
4	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
5	What type of exercise did you do?								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
6	What type of exercise did you do?								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
7	What type of exercise did you do?								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
8	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
9	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
10	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
11	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
12	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
13	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
14	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
15	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
16	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
17	What type of exercise did you do?								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
18	What type of exercise did you do?								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
19	What type of exercise did you do?								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
20	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
21	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
22	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
23	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Week		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Weekly exercise goal
24	**What type of exercise did you do?**								
	How long did you exercise?								
	How hard was the exercise 1= easy, 10 = maximal effort								
Adverse events/health concerns:									

Individualised meal plan example

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Breakfast							
Lunch							
Dinner							
Snacks							
Week nutrition goal							

E2. Home-based intervention booklet (Chapter 7)

NHMRC Centre for Research Excellence
PROSTATE CANCER SURVIVORSHIP

EMRI
Exercise Medicine Research Institute
vario health clinic

AUSTRALIA ECU EDITH COWAN UNIVERSITY

EXERCISE AND NUTRTION INFORMATION FOR HOME-BASED PROGRAMME

Developed by
Rebekah Wilson, MPhysEd
Ph.D Candidate

CONTENTS

Congratulations again on taking the first step to a healthier lifestyle and completing the supervised stage of Rebekah's PhD project (HREC ID: 18832) of an exercise and nutrition based weight loss programme for men with prostate cancer on androgen deprivation therapy (ADT).

The achievements made and progress gained has been incredible and we hope you have found a sense of accomplishment in completing the exercise sessions and taking on board the nutrition advice. Our hope is that you will take this advice and experiences and develop your own exercise and nutrition routine that will continue to develop and maintain your strength and general well-being as you continue with your treatment and beyond.

Our main message to you as you move on from the supervised sessions is to:

1. Be mindful of what and how much you are consuming and,
2. STAY ACTIVE on a daily basis.

This booklet is designed to provide exercise and nutrition ideas, advice, and reminders to complement what has already been provided throughout the 12-week supervised programme. Although this booklet focuses on resistance based exercises, don't forget that staying active can be as simple as getting off the couch and doing chores around the house, taking trips to the shopping centre, and being active and engage in physical activity with your family and friends. However, for ongoing results, purposeful exercise is encouraged in the form of aerobic training e.g. walking, biking, swimming, and resistance training e.g. lifting weights, GymStick©. Completing purposeful exercise will assist with continued development and maintenance of your overall fitness and strength and help keep your desired weight which are all commonly altered with cancer treatment.

We hope you will find this compilation of exercises and basic nutrition advice/reminders useful as you begin to create your own exercise and nutrition routine beyond that of the research study's programme.

EXERCISE HOME-BASED PROGRAMME IMPLEMENTATION

Now that the 12-week supervised programme is finished, it is time to create your own exercise routine. You have already been completing aerobic based exercise at home whether that was walking, biking, or swimming and so on. We encourage you to continue with this routine and maintain 30+ minutes of aerobic based exercise completed 3-5 days a week. However, you will now need to implement your own resistance based workouts to replace the now finished supervised sessions. Structured resistance exercises are recommended for men with prostate cancer to be completed a minimum of 2 times per week (but ideally 3 to continue with the exercise routine that has been completed over the last 12 weeks). These sessions should utilise 6 to 8 exercises covering all major muscle groups of your whole body each session (legs, chest, back, arms, and abdominals). Exercise (either resistance or aerobic training) should be completed on a daily basis for ongoing results.

Exercise Medicine Research Institute – Vario Health Clinic

To keep up your resistance training we would like to encourage you to continue your exercise with us at the Vario Health Clinic, Joondalup, as a paying client costing only $10 a session. Unlike local gyms, the Vario Health Clinic provides a casual membership (you pay when you come) and sessions are supervised by Exercise Physiologists specialised in working with cancer patients. You will be joining our "Living Longer Living Stronger" programme. These are group sessions run in one hour slots (see next page) where you will be provided with an individualised exercise programme by one of our Exercise Physiologists who supervise the sessions. Although these sessions are supervised you are given independence to move through your exercise programme. If you feel you still require close supervision while exercising we do have other groups and one on one sessions with greater level of supervision. Please speak to Rebekah, [redacted] if you are interested in attending the Vario Health Clinic or call the Vario Health Clinic reception (08) 6304 3444 for more information and to see what option is right for you.

See website for further details
https://www.exercisemedicine.org.au/

LIVING LONGER, LIVING STRONGER EXERCISE TIMES

Monday	Tuesday	Wednesday	Thursday	Friday
7.00am – 8.00am		7.00am – 8.00am	7.00am – 8.00am	
8.00am – 9.00am	8.00am – 9.00am	8.00am – 9.00am	8.00am – 9.00am	8.00am – 9.00am
	9.00am – 10.00am	9.00am – 10.00am		9.00am – 10.00am
	11.00am –12.00pm			
12.00pm – 1.00pm		12.00pm – 1.00pm		12.00pm – 1.00pm
1.30pm – 2.30pm	1.30pm – 2.30pm	1.30pm – 2.30pm	1.30pm – 2.30pm	1.30pm – 2.30pm
2.30pm – 3.30pm			2.30pm – 3.30pm	
3.30pm – 4.30pm			3.30pm – 4.30pm	

NOTE: *At this time the red time slots are not available due to full capacity reached.*

If membership costs or travel distance is an issue, we would recommend coming to the Vario Health Clinic once a week (remember our membership is a pay when you come, unlike local gyms where it is often a set 6 or 12 month membership) to complete a more intense resistance exercise session then complete 1 or 2 more resistance based sessions at home.

Edith Cowan University Sport and Fitness Centre – Mt Lawley and Joondalup

For those exercising at Mt Lawley you may like to take on a membership with the Edith Cowan University (ECU) Sport and Fitness Centre where you have been exercising for the 12-week supervised sessions. As part of your membership you will have access to Group Fitness including yoga, Pilates, BodyPump and more, plus individualised exercise programmes every 6-12 weeks (please note the individual programmes are not actively supervised, a staff member of the ECU Sports and Fitness Centre will provide a written exercise programme for you to complete). Memberships start at $30.60 per fortnight for an ongoing membership (6 months minimum) or you may like to try a fixed pay up front membership: 3 months = $273, 6 months = $426, 12 months = $571. Memberships may also be used at the ECU Sports and Fitness Centre at the Joondalup Campus if you wish (these prices are as of October 2018).

Local Gym

If a membership at the Vario Health Clinic or ECU Sports and Fitness Centre does not work for you but you are still interested in maintaining a gym-based exercise routine there are many local gym memberships available. Please speak to Rebekah if this is an option for you and what memberships/gyms would suit you best.

Cancer or senior specific programmes

Living longer living stronger: This is an evidence-based supervised progressive strength training exercise programme designed for those 50+ years. We run this programme at the Vario Health Clinic, however, there are over 50 sites throughout WA. Refer to their website http://www.lllswa.org.au/ for more details and site locations. Each site has a different cost (but are around $10 for a casual session) and programmes offered. Please speak to Rebekah about the best option for you.

PROST!: This is a prostate cancer support group who run exercises session at the Subiaco football club (Tuesday and Thursday 9am) in Leederville and at the University of Western Australia (Wednesday and Friday 1.30pm). All sessions are supervised by an exercise physiologist incur a cost of $10 a session. Please see website for contact details: http://www.prostate.org.au/support/list-of-support-groups/wa-support-groups/prost-exercise-4-prostate-cancer-inc/ or contact Ross Campbell: arcampbell@iinet.net.au or 0407886823.

Cancer council WA: This organisation provides a number of different services for cancer patients and caregivers covering all aspects of a cancer patient's journey. They run 6-12 week exercise programmes at various venues throughout WA. However, please note that there are restrictions on participation based on time of diagnosis and treatment. Please see website for more details: https://www.cancerwa.asn.au/patients/support-and-services/life-now/

Home-based exercise using GymStick©

As part of this study we have provided you with a GymStick© to assist you with maintaining resistance exercises at home if continuing with a membership at the Vario Health Clinic, ECU Sport and Fitness Centre, or a local gym is not an option for you. The GymStick© comes with a DVD and poster of exercises that you may follow as well as the example exercises provided within this booklet. Also see https://www.gymstick.com/training-videos/gymstick-original.html for more exercise options. For those who choose to use the GymStick© as their predominant form of resistance training or would like to learn more with the GymStick©, Rebekah will complete 2 exercise sessions (after the 12-week programme) to demonstrate how to use it.

Home-based exercise programme using own exercise equipment

Finally, if you have a gym within your residence and/or exercise equipment (such as dumb-bells, exercise ball) at home, please let Rebekah know what equipment is available to you and she will provide an individualised home programme in addition to the below example exercises to get you started. A home-based resistance session may also be completed in conjunction with an exercise session at the Vario Health Clinic.

HOW WERE THE SUPERVISED EXERCISE SESSIONS STRUCTURED?

Each exercise session was structured in a similar way that exercised the whole body. We started with an aerobic based exercise (such as stationary cycling) and then we began the resistance exercises starting with the larger muscles (such as those in the legs) and progressing to the smaller muscles (such as those in the arms). Over the 12 weeks we changed how many repetitions (one complete motion of an exercise) and sets (group of consecutive repetitions) we completed but these remained within the ranges of 6 to 12 repetitions and 1 to 4 sets for each exercise. When selecting how many sets and repetitions you complete during your resistance exercise sessions, change it up, as the body responds better when it receives different stimulations e.g. one week complete 3 x 10, the next week change it to 3 x 8 but maybe increase the weight or intensity of the task. Please note: if you choose to take on a membership at the Vario Health Clinic an exercise programme will be provided.

BEFORE YOU START EXERCISING - WHAT YOU NEED TO KNOW:

1. *If you experience any chest pain, radiating pain, extreme breathlessness or rapid or irregular heartbeat during exercise please stop exercising immediately and seek medical advice by calling 000 if it is an emergency or contact your local GP.*
2. *If any exercise causes excess discomfort stop performing that exercise immediately. Injuries such as muscle tears or strains are likely to occur if you push your body too hard and/or too quickly. If you feel any excessive or ongoing tightness, spasms, pain or cramps that cannot be relieved with rest or stretching the affected area, please seek medical advice from your GP or physiotherapist.*
3. *In the unlikely event of an injury or fall while completing exercise during the 12-week home-based period of the study please seek medical advice (GP or physiotherapist) for how/when to continue with exercise. We also ask that if an injury/fall does occur due to structured exercise during the unsupervised 12-week period that you please make a note of it in the exercise log you are required to keep during this time.*
4. *If you are not attending the Vario Health Clinic or do not have the ability to discuss your exercise with a trained professional at a local gym, please feel free to contact Rebekah at any stage for advice on exercise progression, concerns regarding completion of exercises, or concerns with injury.*

   Rebekah Wilson:

   Email: [redacted]

   Phone: [redacted]

EXERCISE TIPS

WHEN COMPLETING EXERCISES: In all exercises think about what muscle group you are supposed to be working and actively engage that area. Also engaging the abdominal muscles across each exercise provided will assist with a more controlled movement.

TIMING: Choose to exercise at a time of the day that you feel at your best. If you find you get quite tired in the afternoons try exercising in the mornings. You may also find you have good days and bad days, particularly with the treatment you are currently receiving. We encourage you to complete more activity on the good days, whereas the days you feel exhausted simply do as much as you can but we still encourage you to get active even if 5-10 minutes of low intensity exercise is all you can manage (you may even find this helps improve your fatigue levels).

GYMSTICK: To make an exercise more challenging rotate the elastic bands around the stick as this will provide more resistance making the band harder to pull and push.

GymStick© anatomy:

Image not available in this version of the thesis

EXAMPLE EXERCISES

NOTE: If attending the Vario Health Clinic, ECU Sports and Fitness Centre or a local gym is not a viable option, the following exercises are examples to prompt ideas for home based resistance workouts where you do not have access to machine weights. These exercises are EXAMPLES ONLY and may not be appropriate for all participants. Please take the time to discuss your proposed exercising routine with Rebekah as additional material may be given on request.

5-10 minute warm up:

Complete an aerobic based exercise at a light-moderate intensity. A warm up is designed to "kick-start" the muscles and get the blood flowing. Examples may include walking or cycling (stationary or push bike).

Leg exercises:

Select 3 different leg exercises that target different muscle groups each resistance exercise session. These were the main muscle groups targeted during the supervised sessions.

Image not available in this version of the thesis

Examples:

a) Squat (targeting mainly gluteus and quadriceps muscle groups).

This exercise may be completed free standing (Picture A). To progress this exercise you may wish to use hand held weights while completing the movement (Picture B) or use the GymStick© provided (Picture C).

Picture A:

Picture A is not available in this version of the thesis

Start position:

Place feet just wider than hips.

End position:

Make sure your knees line up over your toes as you bend and you keep your upper body as upright as possible.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Place feet just wider than hips. A power bag is pictured but any form of weighted object may be used e.g. dumbbell, kettle bell, weighted item from around the house.

End position

Make sure your knees line up over your toes as you bend and you keep your upper body as upright as possible. Only bend as far as is comfortable for you.

Picture C:

Picture C is not available in this version of the thesis

Start position:

Bar of the GymStick© is placed across the shoulders with one foot loop around each foot. Place feet just wider than hips.

End position:

Make sure your knees line up over your toes as you bend and you keep your upper body as upright as possible. Only bend as far as is comfortable for you.

b) Lunges (target gluteus, hamstring and quadriceps muscle groups) (Picture A)

This is a great all-round leg exercise. If balance is an issue please complete exercise close to a wall or chair for support. This exercise may be done stationary (movement completed on the spot) or walking if balance allows (complete the lunge movement and then bring the back leg forward to step into next lunge). To progress this exercise use hand held weights (Picture B) or GymStick© (Picture C) – a twist may be completed for added abdominal engagement.

Picture A:

Picture A is not available in this version of the thesis

Start position:

Place feet in a wide stance with the back heel off the ground. Keep weight in the centre of both legs.

End position:

Make sure your knees line up over your toes as you bend keeping weight centred between legs. Only bend as far as is comfortable for you.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Place feet in a wide stance with the back heel off the ground. Keep weight in the centre of both legs.

End position:

Make sure your knees line up over your toes as you bend keeping weight centred between legs. Only bend as far as is comfortable for you.

Picture C:

Picture C is not available in this version of the thesis

Start position:

Place one loop on each foot and bar across the shoulders. Place feet in a wide stance with the back heel off the ground. Keep weight in the centre of both legs.

Middle position:

Make sure your knees line up over your toes as you bend keeping weight centred between legs. Only bend as far as is comfortable for you.

End position:

Twist torso towards front leg for an added core rotation exercise. Twist back to "*middle* position" and then rise to "*start position" before completing next repetition.*

c) GymStick© seated leg extension (targeting the quadriceps muscles)

Image is not available in this version of the thesis

Start position:

You will likely have to wrap the band around the bar for added resistance. Place GymStick© behind the body on the chair with loop around the exercising foot.

End position:

Extend knee out but do not lock knee in a straight, stiff position.

d) Rear kick with GymStick© (targeting gluteus, hamstring and quadriceps muscle groups).

In order of difficulty, start kneeling on the floor (Picture A). Ensure something is placed under the knees to cushion the knee joint. When standing, complete the movement while using the wall to assist with balance (Picture B). To progress complete exercise balancing on one leg and adding in a chest press (Picture C).

Picture A:

Start position:

Have both loops around the working foot. Place GymStick© on floor directly under shoulders. Bring working leg into chest if flexibility allows or just off the floor as pictured.

Picture A is not available in this version of the thesis

End position:

Extend leg behind body making sure the leg is directly in line with the working side shoulder creating a flat line from head to foot.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Have both loops around the working foot. Place GymStick© at chest height on a flat wall. Start with foot close to the supporting knee.

End position:

Extend leg behind body making sure the leg is directly in line with the working side shoulder. Do not take leg any higher than knee height.

Picture C:

Picture C is not available in this version of the thesis

Start position:

Have both loops around the working foot. Place GymStick© at chest height with working foot close to supporting knee.

End position:

Extend leg behind body making sure the leg is directly in line with the working side shoulder creating a flat line from head to foot. Arms complete a chest press with bar finishing no higher than nose.

d) Standing calf raise (targeting gastrocnemius and soleus as well as balance) (Picture A).
Have a wall or chair handy to assist with balance. To progress this exercise use handheld weights (Picture B) or complete with balls of feet on a step (Picture C). To target the soleus muscle complete same motion but with knees bent (Picture D). All exercise may be done one foot at a time for added challenge.

Picture A:

Picture A is not available in this version of the thesis

Start position

Place feet together or shoulder width apart depending on balance.

End position:

Make sure your weight is over the big toe (do not roll your feet towards the little toe).

Picture B:

Picture B is not available in this version of the thesis

Start position

Place feet together or shoulder width apart depending on balance. Weights held in hands at sides.

End position:

Make sure your weight is over the big toe (do not roll your feet towards the little toe).

Picture C:

Picture C is not available in this version of the thesis

Start position

Place balls of the feet on step. Heels lowered just below the step line. You should feel a slight calf muscle stretch.

End position:

Make sure your weight is over the big toe (do not roll your feet towards the little toe).

Picture D:

Picture D is not available in this version of the thesis

Start position

Bend knees. This may be done on a step as pictured or on the ground.

End position:

Raise heels while keeping knees bend and ensuring weight is over the big toe (do not roll your feet towards the little toe).

e) GymStick© outer thigh exercise (targeting the iliotibial tract).

Have a chair or wall handy to assist with balance.

Image is not available in this version of the thesis

Start position

Place one loop on each foot. Twist the bar so that the bands are crossed over. Place the opposite side of the stick from the working leg on the ground for stability.

End position:

Raise the leg, no higher than knee height as pictured, to the side of the body. Complete a pulsing action – try not to let the working foot touch the ground after each repetition.

f) Wall squat (targeting gluteus, quadriceps, hamstrings, adductor muscles and iliotibial band).

This exercise is completed using your own body weight against a wall (Picture A). To engage the adductor muscles squeeze a ball between the knees (Picture B). The iliotibial band may be targeted by wrapping one of the GymStick© bands around the knees and pressing the knees outward (Picture C). This is an isolated movement meaning you simply hold this position for a set time (e.g. 15 seconds). Have a chair handy to assist with balance.

Picture A:

Picture A is not available in this version of the thesis

Start position

Have back straight against the wall and slide down pressing your weight into the wall. Only bend knees as far as you feel comfortable. Hold this bent position for a set length of time e.g. 15 seconds.

Picture B:

Picture B is not available in this version of the thesis

Start position

Have back straight against the wall and slide down pressing your weight into the wall. Only bend knees as far as you feel comfortable. Once in bent position place ball between knees, squeeze and hold or complete small pulsing movements keeping the ball between knees.

Picture C:

Picture C is not available in this version of the thesis

Start position

Have back straight against the wall and slide down pressing your weight into the wall. Only bend knees as far as you feel comfortable. Once in bent position wrap one GymStick© around knees and lightly press knees outwards, and hold or pulse.

Chest exercises:

Select one chest exercise to complete each resistance session. The pectoralis major was the main muscle targeted during the supervised exercise sessions.

Image is not available in this version of the thesis

Examples:

a) Chest fly

This exercise may be completed standing, sitting or lying down. Progress this exercise using handheld weights (Picture A) or GymStick© (Picture B).

Picture A:

- Lying down:

Image is not available in this version of the thesis

Start position:

Lie down on a bench with knees up as pictured. Hold weights above the body at chest height, arms slightly bent.

End position:

Arms move to the sides staying in a slightly bent position. Do not take arms lower than bench.

- Standing up

Image is not available in this version of the thesis

Start position:

Have arms slightly bent in front of the body at chest height.

End position:

Open arms to side keeping arms slightly bent (W shape). Do not take arms behind or above shoulder level.

NOTE: This exercise may also be done seated

Picture B:

Picture B is not available in this version of the thesis

Start position:

Stand on GymStick© and hold a loop in each hand. Have arms slightly bent out wide at shoulder height.

End position:

Bring arms together at the same time as completing a squat for added challenge (see leg exercises). This may be done with or without the squat movement.

b) Push up

In order of difficulty, a push up may be completed on a bench (Picture A), on knees (Picture B) or on toes (Picture C).

Picture A:

Picture A is not available in this version of the thesis

Start position:

Make sure head, hips and legs make a straight line as pictured. Hands should be a little wider than shoulders.

End position:

Lower chest to bench making sure hips do not drop.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Place a mat or pillow under knees. Place hands a little wider and slightly forward of shoulders.

End position:

Lower chest to ground making sure hips do not drop.

Picture C:

Start position:

Make sure head, hips and legs make a straight line as pictured. Hands should be a little wider and slightly forward of shoulders.

Picture C is not available in this version of the thesis

End position:

Lower chest to ground making sure hips do not drop.

c) Chest press

This exercise may be completed lying down using handheld weights (Picture A) or standing using a GymStick© (Picture B).

Picture A:

Picture A is not available in this version of the thesis

Start position:

Lie down on a bench. Place a step under feet if this position places strain on your back. Hold weights near shoulders.

End position:

Raise weights straight into air keeping in line with shoulders.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Place both loops around one foot and step through into a lunge position (front leg bent, back leg straight – back foot may be flat or heel raised depending on flexibility). Bar is held at chest height with arms positioned slightly wider than shoulders.

End position:

Press bar forward of body, no higher than nose line.

Back exercises:

Select one back exercise per session. Change the exercise each session to target different areas of the back. The main targeted muscle groups during the sessions were:

Image is not available in this version of the thesis

Examples:

a) Upright row (targets the trapezius).

To complete this exercise use hand held weights (Picture A) or GymStick© (Picture B).

Picture A:

Picture A is not available in this version of the thesis

Start position:	*End position:*
A kettle bell is pictured but any weighted object may be used e.g. dumbbell.	Raise weight to sternum, arms will make a "V shape" as pictured.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Have one loop around each foot, hold bar at hip height.

End position:

Raise bar to armpits but do not bring the bar any higher than shoulders.

b) Bent over row (targets the latissimus and lower trapezius).

To progress this movement use hand held weights (Picture A) or GymStick© (Picture B).

Picutre A:

Picture A is not available in this version of the thesis

Start position:

Bend knees. With a straight back lean forward slightly so that the weights are touching the knees and are straight down from shoulders.

End position:

With the elbows going towards the ceiling, raise the weights to your waist line ensuring knees stay bent and back tilted forward.

Picture B:

Picture B is not available in this version of the thesis

Start position:

You will need to shorten the bands for this exercise – roll over bar. Bend knees. With a straight back lean forward slightly so that the bar is touching the knees and arms are straight down from shoulders.

End position:

With the elbows going towards the ceiling, raise the bar to your belly button ensuring knees stay bent and back tilted forward.

c) GymStick© rear dealt (targets the rear deltoid (shoulder muscle), trapezius, rhomboids).

Image is not available in this version of the thesis

Start position:

Place bar under feet, bend knees, hold one loop in each hand with bands in a crossed position. Arms are pictured bent, for a more challenging exercise start with arms straight.

End position:

Extend arms to side making sure arms do not go behind body.

Arm and shoulder exercises:

Select two arm/shoulder exercises to complete each resistance training session. Rotate the exercises to target different muscle groups each time. The main muscle groups targeted during the supervised sessions were:

Image is not available in this version of the thesis

Examples:

a) Bicep curl (targets the biceps brachii).

This exercise may be completed standing or sitting with either handheld weights (Picture A) or GymStick© (Picture B).

Picture A:

Picture A is not available in this version of the thesis

Start position

Hold weights in hands down by sides.

End position:

Bring weights towards shoulders. Make sure the movement comes only from the elbows, the back should not tip.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Place a band around each foot. Hold bar at hip height.

End position:

Raise bar to just below chin height. Make sure the movement comes only from the elbows, the back should not tip.

b) Triceps extension (targets the triceps brachii).

To complete this movement use handheld weights with a combined bent over row for an added challenge (Picture A) or GymStick© (Picture B).

Picture A:

Picture A is not available in this version of the thesis

Start position:

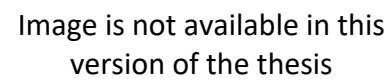
Place knee on cushioned chair/bench with same hand used as support. Have working arm (opposite to kneeling leg) hang straight down from shoulder holding weight.

Middle position:

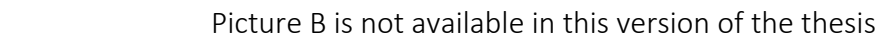
Bend elbow to bring weight up to near the shoulder.

End position:

Extend elbow behind body. To finish movement bring weight back into "*Middle position*" then down to "*starting position*" to begin second repetition.



Picture B:



Start position:

Wrap one band around the bar so that a suitable resistance is achieved. Facing the elbow behind the body, hold the band at hip height.

End position:

Extend the working arm behind the body. The elbow should not lift.

c) Shoulder press (targets the deltoids).

To complete this movement use hand held weights (Picture A) or GymStick© (Picture B). This exercise may be done seated or standing.

Picture A:

Picture A is not available in this version of the thesis

Start position:

Hold weights near shoulders.

End position:

Raise weights above the head. Make sure weights are kept slightly in front of the body and not behind the head.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Place a band around each foot and have hands holding the bar near shoulders.

End position:

Raise bar above the head. Make sure bar is kept slightly in front of the body and not behind the head.

Abdominal exercises:

Select one abdominal exercise each resistance training session. Change the selected exercise each session so that all abdominal muscles are targeted. Main muscled targeted during supervised sessions:

Image s not available in this version of the thesis

Examples:

a) Plank (targets rectus and transverse abdominal muscles).

In order of difficulty this exercise may be completed using a bench (Picture A) or on the floor (Picture B). When on the floor, similar to above demonstration of the push up, this exercise can be completed on either the knees or toes depending on ability.

Picture A:

Picture A is not available in this version of the thesis

Start position:

Make sure head, hips and legs make a straight line as pictured. Hands should be a little wider than shoulders.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Make sure head, hips and legs make a straight line as pictured. Hands should be a little wider and slightly forward of shoulders.

NOTE: Position may be held resting on the elbows if this is more comfortable on both the floor and bench.

b) Single leg lowers (targets the rectus abdominis).

In order of difficulty this exercise may be completed using just the legs (Picture A), by adding an arm movement (Picture B), or using a GymStick© for added resistance (Picture C).

Picture A:

Start position:

Lay on ground or bed and raise legs off the floor into a 90° position. Back should be flat on the floor. Engage abdominal muscles before a movement is completed.

Picture A is not available in this version of the thesis

End position:

Keeping the abdominal muscles engaged and back flat on the floor, extend one leg out. The closer the leg is extended to the floor, the more challenging the exercise.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Lay on ground or bed and raise legs off the floor into a 90° position and arms held in air in line with shoulders. Back should be flat on the floor. Engage abdominal muscles before a movement is completed.

End position:

Keeping the abdominal muscles engaged and back flat on the floor, extend one leg and opposite arm. The closer the leg is extended to the floor, the more challenging the exercise.

Picture C:

Picture C is not available in this version of the thesis

Start position:

Place a loop around each foot. Lay on ground or bed and raise legs off the floor into a 90° position with arms holding bar above the head (bands may also be wrapped around bar and held at hips if shoulder flexibility is minimal). Back should be flat on the floor. Engage abdominal muscles before a movement is completed.

End position:

Keeping the abdominal muscles engaged and back flat on the floor, extend one leg holding the arms above the head (or at hip is flexibility does not allow arms over the head). The closer the leg is extended to the floor, the more challenging the exercise.

c) Core rotations (targets all abdominal muscles).

This exercise may completed standing or sitting down. To complete exercise use handheld weights (Picture A) or GymStick© (Picture B).

Picture A:

Picture A is not available in this version of the thesis

Start position:

A dumbbell is pictured but any weighted object may be used. Hold weight in line with chest, have arms slightly bent to take strain off the upper back and neck. Engage abdominal muscles before movements begins.

End position:

Keeping the abdominals engaged and weight centred between two feet e.g. when twisting have weight equal on two feet, twist to the side holding weight at chest height. Arms may be kept slightly bent throughout movement to take strain off upper back and neck.

Picture B:

Picture B is not available in this version of the thesis

Start position:

Stand on bar holding both loops in both hands at chest height. Engage abdominal muscles before movement begins.

End position:

Keeping the abdominals engaged and weight centred between two feet e.g. when twisting have weight equal on two feet, twist to the side holding arms at chest height.

5-10 minute Cool-down:

Complete an aerobic based exercise at a light-moderate intensity. A cool down is designed to relax the muscles. Examples may include walking or cycling (stationary or push bike).

Stretching:

Take the time to stretch out the major muscle groups worked during the resistance session. Hold each stretch for ~15 seconds.

EXAMPLE WEEKLY EXERCISE PLAN

During the study, we encouraged a total of 300 minutes of exercise a week to encourage weight loss. Now that the supervised component is completed we recommend that you complete at least 150 minutes of purposeful exercise each week – a total of 30 minutes each day (although 300 minutes is still good to maintain – a total of 45 minutes each day) which includes aerobic based training and a minimum of two resistance based sessions. When the term "purposeful exercise" is used it means to complete an organised exercise session (not walking around the shops, but going for a purposeful walk around the block or in the park). These are the prostate cancer exercise guidelines as recommended by the American College of Sports Medicine and endorsed by Exercise and Sport Science Australia.

Please note – although 30 minutes per day is the recommendation you must listen to your body. Stay as active as possible but do complete low-intensity activities on the days you do not feel great and save the moderate-high intensity tasks for the good days.

EXAMPLE	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Exercise	1 hour Vario Health Clinic resistance training session	30 minute brisk walk	30 minute GymStick© workout at home	1 hour bike ride	30 minute GymStick© workout at home	30 minute pool session (walking or swimming)	30 minute low intensity walk

EXAMPLE LAYOUT	Week 1	Week 2	Week 3
3x leg exercises	2 sets 10 repetitions	3 sets 10 repetitions	3 sets 8 repetitions
1x chest exercise			
1x back exercise			
2x arm/shoulder exercises			
1x abdominal exercise			

NB: *Adjust weight/resistance as needed*.

HOW THE NUTRITION SESSIONS WERE STRUCTURED

Each participant's nutrition counselling sessions were individually tailored depending on personal goals and eating patterns. When providing advice, we aimed to make lifestyle adjustments that would be easy to maintain in the long-term to assist with ongoing weight maintenance and initial weight loss rather than implementing drastic measures to result in rapid weight loss. Associate Professor Philippa Lyons-Wall made nutrition-related goals with each person. We recommend that you continue working on these personal goals in order to continue with weight loss or maintain your current weight. Although personal goals were made, these were developed based on 2 over-arching aims of the study and we encourage you to continue thinking about these when making food choices to continue with a balanced diet.

The FIRST AIM of the study focused on reducing portion sizes to create an energy deficit diet. To completely simplify weight loss, it is a balance of energy intake versus energy expenditure. You must take in LESS and expend MORE as demonstrated in the figure below to result in weight loss.

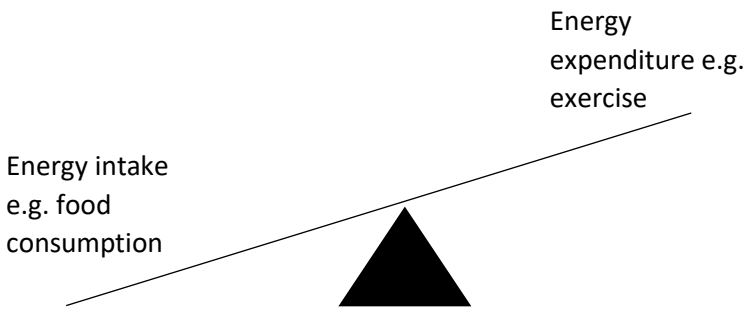


Figure 1: To lose weight consume less energy and expend more.

Adjusting portion sizes may be completed by using a smaller plate, sharing an item of food rather than having one each, or simply actively placing less food on your plate. Continue consuming smaller portions of food for ongoing weight loss.

However, in general, yes, consuming less food will assist is weight loss but this is a balancing act of making sure you are still consuming a balanced diet across all food groups, vitamins, and minerals and consuming at least 3 meals a day. Therefore……

The SECOND AIM was to ensure a well-balanced diet was consumed. We focused predominantly on three areas – increasing fruit and vegetables, optimising protein, and reducing refined carbohydrates and saturated fats.

1. Vegetable and fruit intake: It is important to have 2 serves of fruit e.g. medium size apple and banana, and a minimum of 5 serves of vegetables e.g. ½ cup of cooked carrots, ½ cup peas, ½ cup of sweet corn, ½ cup of green leafy salad and ½ medium potato (Figure 2), over the day, every day. Making sure you are consuming adequate fruits and vegetables is important as most have little calories and contain many essential vitamins and minerals. When eating vegetables, it is recommended to cook with lots of different colours. However, please bear in mind that starchy vegetables such as potato, sweet potato, corn, yams, pumpkin, have a higher carbohydrate content and should be consumed as the "carbohydrate" item on the plate e.g. when having potatoes there is no need to also consume pasta or rice or bread, the potatoes will be a large enough source of carbohydrate on their own (see below for further advice on why carbohydrates are important to cut back for weight loss/maintenance).

Figure 2 is not available in this version of the thesis

Figure 2: Example of 2 servings of fruit and minimum of 5 servings of vegetables to consume every day.

2. Protein intake: During the programme you were provided with a protein powder shake (~40g of whey protein) after every exercise session. Protein is best consumed across the day e.g. egg for breakfast, beans at lunch, fish for dinner (Figure 3). After consumption, protein is slowly released and used for energy throughout the day so it makes you feel less hungry (this is why it is good to spread it throughout the day). Optimal protein intake will also help slow down or stop age-related or cancer/treatment-related loss of lean muscle mass. Meat is a commonly consumed source of protein, however, when selecting meat it is best to consume non-processed lean meat with no skin or crumb coating and the fat cut off e.g. fish, skin-less chicken.

Figure 3 is not available in this version of the thesis

Figure 3: Example of sources of protein to be consumed throughout the day– egg for breakfast, beans (chickpeas, lentils, black beans) for lunch, and fish (salmon) for dinner.

If you are looking to keep up with the protein ingestion after a resistance training session (it has been shown that consumption of protein within an hour after exercise helps with muscle growth and development) you may replace the protein powder supplement with wholesome foods. Foods that contain protein include unprocessed meat (e.g. fish, skinless chicken), dairy (e.g. plain or fruit yoghurt, milk), and beans (e.g. chickpeas). These would be good options for ingestion of protein after resistance exercise if a supplement is not wanted. If you would like to purchase a protein supplement these can be in a muesli bar or powder format. We used Bulk Nutrients (https://www.bulknutrients.com.au/), however, there are many protein supplement products available within your local supermarket.

3. Reducing refined carbohydrate and saturated fat intake: Carbohydrates are a high source of calories and are often the food group that is reduced in a diet to assist with weight loss. However, it is still important to consume some carbohydrates each day as part of a healthy balanced diet. This can be done by consuming smaller portions of unrefined carbohydrates (carbohydrates that have not been stripped of fibre) such as wholemeal pasta, brown rice, wholemeal/rye/multigrain bread and starchy vegetables (Figure 4). Unrefined carbohydrates should replace refined carbohydrates such as biscuits, confectionary, cakes, white bread, and ice-creams, for a well-balanced nutritional intake.

Figure 4 is not available in this version of the thesis

Figure 4: Examples of unrefined carbohydrates to be consumed in moderation – wholemeal pasta, brown rice, wholemeal bread, starchy vegetables.

Fats are important to consume as part of a healthy balanced diet as well but it is the saturated fats that are considered non-essential for good health and should be consumed in moderation. Items such as cheese, butter, meat pies, deep fried take away food, fatty meat cuts, cakes and biscuits should be limited in consumption or avoided.

F. PUBLICATION INFORMATION

F1. Co-author declaration

To Whom It May Concern,

I, Rebekah Wilson, was responsible for most of the data entry, analysis, and interpretation, and manuscript preparation for the publication:

Wilson, R., Shannon, T., Calton, E., Galvão, D., Taaffe, D., Hart, N., Lyons-Wall, P., Newton, R. (2020). Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer. *Surgical Oncology*.

28th Aug 2020

I, as a Co-author, endorse that this level of contribution by the Candidate indicated above is appropriate.

Name	Signature	Affiliation	Date
Tom Shannon		- The Prostate Clinic, Perth, WA, Australia. - Hollywood Private Hospital, Perth, WA, Australia.	31st Aug 2020
Emily Calton		- School of Public Health, Curtin University, Perth, WA, Australia	28th Aug 2020
Daniel Galvão		- Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia. - School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia.	28th Aug 2020

Dennis Taaffe	[redacted]	- Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia. - School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia.	28th Aug 2020
Nicolas Hart	[redacted]	- Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia. - School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia. - Institute for Health Research, University of Notre Dame Australia, Perth, WA, Australia.	28th Aug 2020
Philippa Lyons-Wall	[redacted]	- School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia.	28th Aug 2020
Robert Newton	[redacted]	- Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia. - School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia. - School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia.	28th Aug 2020

To Whom It May Concern,

I, Rebekah Wilson, was responsible for most of the data collection, analysis, and interpretation, and manuscript preparation for the publication:

Wilson, R., Newton, R., Taaffe, D., Hart, N., Lyons-Wall, P., Galvão, D. (2020). Weight loss for obese prostate cancer patients on androgen deprivation therapy. *Medicine & Science, Sport & Exercise.*

28th Aug 2020

I, as a Co-author, endorse that this level of contribution by the Candidate indicated above is appropriate.

Name	Signature	Affiliation	Date
Daniel Galvão	[redacted]	- Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia. - School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia.	28th Aug 2020
Dennis Taaffe	[redacted]	- Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia. - School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia.	28th Aug 2020
Nicolas Hart	[redacted]	- Exercise Medicine Research Institute, Edith Cowan	28th Aug 2020

		University, Perth, WA, Australia. - School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia. - Institute for Health Research, University of Notre Dame Australia, Perth, WA, Australia.	
Philippa Lyons-Wall	[redacted]	- School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia.	28th Aug 2020
Robert Newton		- Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia. - School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia. - School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia.	28th Aug 2020

F2. Publisher copyright permission

I warrant that I have obtained, where necessary, permission from the copyright owners to use any third party copyright material reproduced in the thesis, or to use any of my own published work in which the copyright is held by another party.

Surgical Oncology:

Dear Ms. Wilson,

Article reference: SO_1416

Title: *Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer*

I wish to inform you that authors can use their articles, in full or in part, for a wide range of scholarly, non-commercial purposes one of which is inclusion in a thesis or dissertation.

See the following link for further information on this
https://www.elsevier.com/about/our-business/policies/copyright/personal-use
As you will be able to see from the above link, our policy is to allow authors to use their work in their thesis or dissertation (provided that this is not to be published commercially).

Therefore, I can confirm that you can make it publicly available on your university web site/repository for non- commercial use.

If you require further clarification please contact permissions@elsevier.com who will be able to help.

Kind regards

Gherniel Rivas Salvador
Researcher Support
ELSEVIER

Medicine & Science in Sport and Exercise:

MSSE® permits authors to deposit—in their non-profit, institutional repositories—versions of their manuscripts, including dissertations, which were submitted for peer review without requiring authors to acquire specific permission from the journal office.

Authors wishing to deposit post-peer review manuscripts, or the copy-edited, laid-out, and proof-corrected versions of articles into a repository may do so once 1) they pay the article processing charge and submit a completed license-to-publish form and 2) the final version of the article has been published online as open access. Please note that the final version is the version that is published in the monthly issue and not "early online"/"ahead of print" version(s).

In all instances, any version of an article deposited into a repository/archive should provide a link back to the article's official version of record on the MSSE® website, https://journals.lww.com/acsm-msse/pages/default.aspx.

F3. Accepted publication proofs

A proof of the accepted publication to *Medicine & Science in Sport & Exercise* was not available at time of submission.

Surgical Oncology:

F3 is not available in this version of the thesis