
**THE ROLE OF ANDROGEN DEPRIVATION THERAPY:
PSYCHOLOGICAL FACTORS AND PHYSICAL ACTIVITY
IN THE TREATMENT OF PATIENTS WITH PROSTATE
CANCER**

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Table of Contents

Table of Contents	i
List of Tables.....	i
List of Figures	ii
List of Terms	iii
Copyright Notices	v
Abstract	vi
General Declaration	viii
Manuscripts and Presentations	x
Acknowledgements	xiii
Chapter 1. Rationale and Aims of the Study	1
1.1. Introduction.....	1
1.2. Rationale for the Current Research.....	1
1.3. Theoretical Framework.....	3
1.4. Content and Structure of the Thesis.....	5
1.5. Summary and Conclusion	7
Chapter 2. Introduction to Prostate Cancer	8
2.1. Introduction.....	8
2.2. Anatomy of the Prostate	8
2.3. Natural History of Prostate Cancer	10
2.3.1. Incidence and Mortality Rates	10
2.3.2. Risk Factors, Presenting Symptoms and Screening Methods	13
2.3.3. Histological Features	15
2.3.4. Treatment Options	18
2.4. Summary and Conclusion	19
Chapter 3. Androgen Deprivation Therapy	20
3.1. Introduction.....	20
3.2. Androgen Deprivation Therapy	20
3.2.1. Mechanisms of Action	20
3.2.2. Prevalence and Benefits of Use	21
3.2.3. Side Effects of Androgen Deprivation Therapy.....	22

3.3.	Summary and Conclusion	24
Chapter 4.	Psychological Implications of Prostate Cancer and Androgen Deprivation Therapy	25
4.1.	Introduction.....	25
4.2.	Depression and Anxiety in Patients with Prostate Cancer.....	25
4.2.1.	Prevalence Rates of Depression and Anxiety in Patients with Cancer	25
4.2.2.	The Impact of Anxiety in Men with Prostate Cancer.....	26
4.2.3.	The Association between Depression and Hormonal Changes in Men	27
4.2.4.	The Relationship between Androgen Deprivation Therapy and Depression and Anxiety Symptoms.....	28
4.3.	Quality of Life in Patients with Prostate Cancer	31
4.3.1.	Defining Quality of Life	31
4.3.2.	The Impact of Androgen Deprivation Therapy on Quality of Life in Men with Prostate Cancer	33
4.4.	Cognitive Function and Androgen Deprivation.....	36
4.4.1.	The Association between Testosterone and Cognitive Functioning	36
4.4.2.	Changes in Cognitive Functioning during Androgen Deprivation Therapy	37
4.5.	Summary and Conclusion	39
Chapter 5.	Physical Activity and Prostate Cancer.....	41
5.1.	Introduction.....	41
5.2.	The Physical Activity Construct	41
5.2.1.	Defining Physical Activity.....	41
5.2.2.	Measurement of Physical Activity	43
5.2.3.	The National Physical Activity Guidelines of Australia	45
5.2.4.	Physical Activity Recommendations for Patients with Cancer.....	46
5.3.	Physical Activity	47
5.3.1.	The Health Benefits of Physical Activity.....	47
5.3.2.	The Cost of Physical Inactivity.....	48
5.3.3.	Benefits of Physical Activity for Patients with Cancer.....	49
5.4.	Physical Activity and Prostate Cancer.....	53
5.5.	Summary and Conclusions	56
Chapter 6.	The Impact of Physical Activity on Psychosocial Outcomes in Men Receiving Androgen Deprivation Therapy for Prostate Cancer.....	56
6.1.	Rationale and Aims for Paper 1	56
6.2.	ABSTRACT.....	58
6.3.	INTRODUCTION	59

6.4.	METHOD	63
6.4.1.	Inclusion Criteria	63
6.4.2.	Literature Search Strategy.....	64
6.4.3.	Data Extraction and Synthesis	65
6.5.	RESULTS	66
6.5.1.	Quality of Life	72
6.5.2.	Depression	73
6.5.3.	Cognitive Function	74
6.6.	DISCUSSION	74
6.6.1.	Quality of Life	74
6.6.2.	Depression and Anxiety.....	76
6.6.3.	Cognitive Function	77
6.6.4.	General Limitations of the Evidence Base and this Review	78
6.7.	References.....	81
6.8.	Appendix A.....	86
6.9.	Summary and Conclusions	87
Chapter 7.	Methodology.....	88
7.1.	Introduction.....	88
7.2.	Research Design and Study Variables	88
7.3.	Participants.....	88
7.3.1.	Socio-demographic and Medical Profile of the Sample.....	89
7.4.	Measures	91
7.4.1.	Socio-demographic and Medical Information	91
7.4.2.	The International Physical Activity Questionnaire	91
7.4.3.	Hospital Anxiety and Depression Scale.....	92
7.4.4.	Functional Assessment of Cancer Therapy – Prostate	93
7.4.5.	Functional Assessment of Cancer Therapy – Cognitive – Version 3.....	94
7.5.	Procedure	95
7.5.1.	Ethics Approval	95
7.5.2.	Piloting the Questionnaire.....	95
7.5.3.	Recruitment.....	96
7.5.4.	Distribution of Questionnaires to Participants	97
7.5.5.	Accessing Patient Medical Records.....	99
7.6.	Data Entry and Screening	99
7.7.	Data Analysis	100
7.7.1.	Paper 2: Factors Associated with Adherence to Physical Activity Guidelines in Patients with Prostate Cancer.....	100

7.7.2.	Paper 3: Predictors of Depression, Anxiety and Quality of Life in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy	102
7.7.3.	Paper 4: Factors Associated with Cognitive Function in Men with Prostate Cancer Receiving Androgen Deprivation Therapy	105
7.8.	Participant Demographics and Medical Details.....	107
7.9.	Summary and Conclusion	109
Chapter 8.	Factors Associated with Adherence to Physical Activity Guidelines in Patients with Prostate Cancer	110
8.1.	Rationale and Aims for Paper 2	110
8.2.	ABSTRACT.....	115
8.3.	INTRODUCTION	116
8.4.	METHOD	119
8.4.1.	Participants and Procedure.....	119
8.4.2.	Measures	120
8.4.3.	Data Analysis.....	122
8.5.	RESULTS	123
8.6.	DISCUSSION	128
8.6.1.	Limitations and Future Research	131
8.6.2.	Conclusions.....	131
8.7.	References.....	133
8.8.	Summary and Conclusions	137
Chapter 9.	Predictors of Depression, Anxiety and Quality of Life in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy	138
9.1.	Rationale and Aims for Paper 3	138
9.2.	Paper 3: Predictors of Depression, Anxiety and Quality of Life in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy	141
9.3.	Summary and Conclusions	150
Chapter 10.	Factors Associated with Cognitive Function in Men with Prostate Cancer Receiving Androgen Deprivation Therapy	151
10.1.	Rationale and Aims for Paper Four	151
10.2.	ABSTRACT.....	156
10.3.	INTRODUCTION	157
10.4.	METHOD	160
10.4.1.	Participants and Procedure.....	161
10.4.2.	Measures	163
10.4.3.	Data Analysis.....	165

10.5.	RESULTS	166
10.5.1.	Cognitive Complaints	166
10.5.2.	Factors Associated with Cognitive Function	168
10.5.3.	Factors Associated with Cognitive Function	173
10.6.	DISCUSSION	174
10.6.1.	Limitations and Future Research	179
10.6.2.	Conclusions.....	180
10.7.	References.....	181
10.8.	Summary and Conclusions	187
Chapter 11.	Integrated Discussion.....	188
11.1.	Rationale for the Study	188
11.2.	Research Aims and Summary of Results.....	189
11.3.	Synthesis of Results	191
11.4.	Implications of the Results for Theory and Practice.....	197
11.5.	Limitations of the Current Research	200
11.6.	Strengths of the Research	202
11.7.	Directions for Future Research and Concluding Remarks	203
References	207
List of Appendices	240
Appendix A: Ethics Approval.....		241
Appendix B: Study Questionnaire		247
Appendix C: Invitation Letter		267
Appendix D: Participant Information Statement		268
Appendix E: Consent Form.....		274
Appendix F: Reminder Letter		276
Appendix G: Phone Call Script for Participants with a High HADS Score		277

List of Tables

<i>Table 2.1.</i>	TNM Staging System for Prostate Cancer (National Comprehensive Cancer Network, 2012).	16
<i>Table 2.2.</i>	Anatomic Grade and Prognostic Groups Associated with PSA and GS (National Comprehensive Cancer Network, 2012).	17
<i>Table 6.1.</i>	Inclusion and Exclusion Criteria for Systematic Search.....	64
<i>Table 6.2.</i>	Outcomes of Supervised and Non-Supervised Clinical Exercise Studies During ADT for Prostate Cancer.	69
<i>Table 7.1.</i>	William Buckland Radiotherapy Oncologists' Classification.	89
<i>Table 7.2.</i>	Four Treatment Categories and Number of Participants in Each Group.	90
<i>Table 7.3.</i>	Summary of Response Rates in Recruitment Process.	97
<i>Table 7.4.</i>	Participant Demographics and Medical Characteristics for Total Sample and Treatment Groups.....	107
<i>Table 8.1.</i>	Participant Demographics and Medical Characteristics of the Sample by Treatment Type.	124
<i>Table 8.2.</i>	Chi-square Analyses of Participants Meeting NPAGA by Socio-Demographic and Medical Variables.....	125
<i>Table 8.3.</i>	Correlation Matrix of Key Study Variables with Leisure-time Physical Activity.	126
<i>Table 8.4.</i>	Logistic Regression to Predict Variables Associated with Meeting the NPAGA.	128
<i>Table 10.1.</i>	Participant Socio-demographic and Medical Details for the Sample by Treatment Group.	162
<i>Table 10.2.</i>	Chi-square Analyses of Most Common Complaints Endorsed on the FACT-Cog by Treatment Type.....	167
<i>Table 10.3.</i>	Summary of Univariate Analyses.	170
<i>Table 10.4.</i>	Correlation Matrix of Examined Variables with FACT-Cog Subscale Scores.....	172
<i>Table 10.5.</i>	Summary of Multiple Regression Analyses for Variables Predicting FACT-CogPCI Scores (N = 352).	174

List of Figures

<i>Figure 2.1.</i>	Location of the prostate gland.....	9
<i>Figure 2.2.</i>	Comparison of a normal prostate to an enlarged prostate.....	10
<i>Figure 6.1.</i>	Flow diagram of literature search and study selection.	67
<i>Figure 8.1.</i>	Flow diagram of respondents and inclusion of participants in analyses.	120
<i>Figure 8.2.</i>	Median MET-minutes of physical activity within each activity domain by treatment category.....	127

List of Terms

ACSM	American College of Sports Medicine
ADT	Androgen Deprivation Therapy
CogQOL	Impact of Perceived Impairments on QoL
CogOTH	Comments from Others
CogPCA	Perceived Cognitive Abilities
CogPCI	Perceived Cognitive Impairments
DRE	Digital Rectal Examination
EBRT	External Beam Radiotherapy
EORTC-CF	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 Cognitive Functioning Scale
FACT-Cog	Functional Assessment of Cancer Therapy – Cognitive
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GS	Gleason Score
GnRH	Gonadotropin-releasing Hormone
HDR	High Dose Rate
HIFU	High-Intensity Focused Ultrasound
HADS	Hospital Anxiety and Depression Scale
IPAQ	International Physical Activity Questionnaire
LRH	Latrobe Regional Hospital
LDR	Low Dose Rate
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone-releasing Hormone
MAX-PC	Memorial Anxiety Scale for Prostate Cancer

MET	Metabolic Equivalent Task
NPAGA	National Physical Activity Guidelines of Australia
PA	Physical Activity
PCa	Prostate Cancer
PSA	Prostate-Specific Antigen
QoL	Quality of Life
RT	Radiotherapy
SF-12	Short-Form 12-Item Health Survey
TNM	Tumour-Node-Metastasis
WHO	World Health Organisation
WBRC	William Buckland Radiotherapy Centre

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Abstract

Depression, anxiety and cognitive dysfunction are common complaints in men with prostate cancer (PCa) receiving androgen deprivation therapy (ADT). Consequently, the quality of life (QoL) of these men is often compromised. The positive impact of physical activity (PA) interventions on psychosocial wellbeing in men with PCa has been demonstrated in several studies. Therefore, the overarching objectives of the present study were: to describe the PA behaviour of patients with PCa; to evaluate the effects of ADT on depression, anxiety, cognitive function and QoL in men with PCa; and to examine the relationship between meeting the National Physical Activity Guidelines of Australia (NPAGA) and the presence and severity of physical and psychological side effects of ADT. A cross-sectional study was conducted during 2010 and 2011, with data collected from 377 men with PCa (mean age = 67.6 years). The measures used were the International Physical Activity Questionnaire (IPAQ); the Hospital Anxiety and Depression Scale (HADS); the Functional Assessment of Cancer Therapy – Prostate (FACT-P); the Functional Assessment of Cancer Therapy – Cognitive (FACT-Cog); and socio-demographic items. Inclusion criteria were men aged 40 to 80 years, English speaking who had undergone radiotherapy (RT) between 9 and 30 months prior to the survey. Participants were categorised into four groups based on the treatment they had received at the time of survey completion. These were RT only ($n = 174$); RT + 6 months ADT ($n = 100$); RT + 2.5 years ADT ($n = 77$); and RT + ADT indefinitely ($n = 26$). Less than half of participants were meeting NPAGA (41.9%) and men treated with ADT were significantly less active in comparison to those treated with RT only. Logistic regression analyses indicated that the likelihood of meeting NPAGA significantly decreased with increases in depressive symptoms and lower levels of education. ADT use was associated with poorer QoL, depression, anxiety and cognitive dysfunction compared to those receiving RT only and long-term ADT use appeared to exacerbate these outcomes. Those meeting NPAGA had significantly lower levels of depression and anxiety and improved QoL compared to those not meeting NPAGA. Logistic regression analysis results revealed the odds of clinically significant depression and anxiety scores, increased with younger age and comorbid conditions. Not meeting NPAGA increased the likelihood of caseness for depression. Multiple regression analysis results revealed that comorbid conditions and treatment category predicted poorer QoL, while meeting NPAGA positively predicted QoL. Multiple regression analysis results indicated that depression was the strongest predictor of cognitive impairment. Anxiety, QoL, age, comorbid conditions, PA and treatment centre were also predictors of poor cognitive function. The use of ADT in the management of men

with PCa has a measurable effect on depression and anxiety symptoms, cognitive function and QoL. These findings support the utility of PA in rehabilitation programs for patients with PCa and indicate that meeting NPAGA may improve QoL and psychosocial wellbeing in this population.

General Declaration

Monash University

Monash Research Graduate School

Declaration for thesis based or partially based on conjointly published or unpublished work

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original and unpublished publications. The core theme of the thesis is the impact of physical activity on quality of life and psychosocial wellbeing in men receiving androgen deprivation therapy for prostate cancer. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Psychology and Psychiatry under the supervision of Dr Sue Burney, Ms Jane Fletcher and A/Prof Jeremy Millar.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 6, 8, 9 and 10 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
6	The impact of physical activity on psychosocial outcomes in men receiving androgen deprivation therapy for prostate cancer: A systematic review.	Revised and Resubmitted	Development of systematic review protocol and search strategy; registration and publication of protocol; implementation of literature review search; writing paper.
8	Factors associated with adherence to physical activity guidelines in patients with prostate cancer.	Accepted for Publication	Project design, ethics application, professional liaison, data collection, data analysis, writing paper.
9	Predictors of depression, anxiety and quality of life in patients with prostate cancer receiving androgen deprivation therapy.	Published	Project design, ethics application, professional liaison, data collection, data analysis, writing paper.
10	Factors associated with cognitive function in men with prostate cancer receiving androgen deprivation therapy.	Submitted	Project design, ethics application, professional liaison, data collection, data analysis, writing paper.

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed:

Date:

Manuscripts and Presentations

The following manuscripts and presentations resulted from the research presented in this thesis:

Manuscripts in Preparation:

Chipperfield, K., Fletcher, J., Brooker, J., & Burney, S. (2013). *The impact of physical activity on psychosocial outcomes in men receiving androgen deprivation therapy for prostate cancer: A systematic review*. Revised and resubmitted for publication in *Health Psychology*.

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Fletcher, J., Burney, S., Chipperfield, K., Madhavan, P., Kornhauser, I., & Lowthian, P. (2009.) Screening for distress in the private sector: Establishing a screening protocol and referral pathway for Cabrini Health. *Victorian Integrated Cancer Service Supportive Care Conference* (abstract).

Fletcher, J., Burney, S., Chipperfield, K., Madhavan, P., Kornhauser, I., & Lowthian, P. (2009.) Screening for distress in the private sector: Establishing a screening protocol and referral pathway for Cabrini Health. *Asia Pacific Journal of Clinical Oncology*, 5 (Supp 2) (abstract).

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Chapter 1. Rationale and Aims of the Study

1.1. Introduction

In this introductory chapter of the study the rationale for the current research is provided followed by an overview and structure of the thesis. The concept of psychological morbidity related to androgen deprivation therapy (ADT) in men being treated for prostate cancer (PCa) is introduced. The utility of physical activity (PA) as a rehabilitation tool to improve quality of life (QoL) in this patient group is also highlighted.

1.2. Rationale for the Current Research

The literature suggests that the impact of ADT on QoL and psychosocial wellbeing has become increasingly recognised. In several studies the results have indicated associations between ADT and the development of depression and anxiety (Almeida, Waterreus, Spry, Flicker, & Martins, 2004; Pirl, Siegel, Goode, & Smith, 2002; Rosenblatt & Mellow, 1995; Soyupek, Soyupek, Perk, & Ozorak, 2008). Cherrier et al. (2009) noted increases in fatigue, depression, moodiness, irritability, tension, anxiety and loss of vigour in patients receiving ADT, with these outcomes diminishing three months after ADT administration was ceased. Pirl et al. (2002) reported a prevalence rate of 12.8% for major depressive disorder in a sample of 45 men undergoing ADT, 8 times higher than the rate in the general United States male population (1.6%) and 32 times higher than the rate in U.S. men over 65 years (0.4%). Furthermore, deficits in several domains of cognition have been reported in patients with PCa receiving ADT including, spatial memory and spatial ability (Cherrier, et al., 2009; Jenkins, Bloomfield, Shilling, & Edginton, 2005); executive

function (Green et al., 2002); and information processing (Green et al., 2004). The reason for this decline is that testosterone is related positively to cognitive functioning and consequently, the significant and abrupt reduction of testosterone levels in men receiving ADT may contribute to cognitive difficulties (Jenkins, et al., 2005). The results of numerous studies indicate reduced QoL in patients receiving ADT as a result of both physical and psychological dysfunction and consequently, the need to identify interventions that may reduce the impact of this treatment is necessary (Fowler, McNaughton-Collins, Walker-Corkery, Elliott, & Barry, 2002; Shahinian, Kuo, Freeman, & Goodwin, 2006; Sharifi, Gulley, & Dahut, 2005).

Physical activity (PA) has been proposed as a behavioural intervention to improve health and wellbeing outcomes for patients with cancer (Conn, Hafdahl, Porock, McDaniel, & Nielsen, 2006). In a population of 2,705 men with PCa, Kenfield et al. (2011) reported a 33% lower risk of death from any cause and a 35% lower risk of PCa-specific death in men who exercised for approximately three hours per week. Furthermore, the results of several clinical trials implementing PA interventions in men receiving ADT for PCa have demonstrated improvements in QoL and psychosocial wellbeing (Culos-Reed et al., 2010; Galvão, Taaffe, Spry, Joseph, & Newton, 2010; Segal et al., 2003). However, few studies have included variables examining the association between psychological morbidity and adherence to PA guidelines and consequently, it remains unclear what frequency, intensity and duration of PA is effective and safe in improving QoL in this patient group.

Given the paucity of research in this area, determining whether adherence to the National Physical Activity Guidelines of Australia (NPAGA; 150 minutes of moderate-intensity activity or more per week) would improve symptoms of depression and anxiety, cognitive function and QoL in men receiving ADT for PCa,

was the primary aim of the current study. Another aim was to estimate the proportion of patients with PCa meeting the NPAGA and whether meeting PA recommendations was associated with a range of socio-demographic and medical factors. A final aim was to examine the prevalence and severity of psychological morbidity in this patient group and determine predictors of depression, anxiety, cognitive function and QoL. It was expected that the results of the current study would provide preliminary information about the level of PA required to improve QoL in this population and provide insight into potential socio-demographic, medical and psychological factors that may affect exercise adherence. Increasing awareness of the impact of ADT on QoL and psychosocial wellbeing will also enable clinicians to make informed treatment decisions and provide appropriate support.

1.3. Theoretical Framework

The biomedical model was formerly the most widely used model to represent the concept of health and illness. The premise of this model is that all illness can be explained in terms of irregular somatic processes, such as biochemical imbalances or neurophysiological abnormalities (Engel, 1980). The structure of this unidimensional model attempts to explain illness in terms of a biological malfunction rather than recognising that a variety of factors, only some of which are biological may be responsible for the development of illness (Smith & Nicassio, 1995). Furthermore, it is suggested that the mind and body are separate entities and the focus is on abnormalities that lead to illness rather than conditions that might promote health (Engel, 1980). According to Smith and Nicassio (1995) this model therefore has three major limitations. The processes described in the model have difficulty explaining why a particular set of somatic conditions need not inevitably lead to illness; the reason for success of treatment being substantially affected by

psychological and social factors cannot be explained; and the influence of the practitioner-patient relationship on therapeutic outcomes cannot be explained.

The biopsychosocial model was developed as an alternative to the biomedical model. It was recognised that health could no longer be defined purely in physical terms, as the absence of disease or disability, but must encompass both mental and social dimensions (Larson, 1996). Consequently, the structure of the biopsychosocial model attempts to conceptualise health in holistic terms. The biopsychosocial model assumes that health and illness are a consequence of interactions between biological, psychological and social factors (Engel, 1980). In this model, four assumptions are proposed (Smith & Nicassio, 1995). Firstly, both external processes, such as social support or financial stability, and internal processes, such as cellular disorders or chemical imbalances, interact to produce a state of health or illness. Secondly, health and illness are caused by multiple factors. Thirdly, the mind and body cannot be distinguished in matters of health and illness. Finally, both health and illness should be emphasised rather than regarding illness as a deviation from a steady state. The biopsychosocial perspective of health is supported as an inclusive and informative model of health.

The application of the biopsychosocial model is highly relevant to the clinician to develop appropriate and individualised treatment plans for the patient. When evidence of biological abnormality is found in an organ of the patient, its full meaning and impact on the patient's functioning must be understood in light of the patient's coping resources and relationships with significant others (Smith & Nicassio, 1995). Similarly, the culture of the patient may affect his or her interpretation of available coping resources and social adjustment. In particular, the treatment of patients with PCa requires consideration of a wide variety of biological,

psychological and social variables as the treatment associated with this form of cancer can be significantly debilitating. For example, ADT treatment incurs a range of physical and psychological side effects which can have a significant impact on several aspects of QoL, including depression, anxiety, fatigue, cognitive difficulties, loss of sexual and urinary function, and body image dissatisfaction (Fowler, et al., 2002; Harrington & Badger, 2009; Penson et al., 2003; Taylor, Canfield, & Du, 2009). ADT treatment for PCa and the associated side effects are discussed further in Chapter 3. However, it is important to note that a biopsychosocial approach to treatment has long been identified as a useful integrative perspective for behavioural medicine and clinical health psychology, having important implications for the conceptualisation and treatment of chronic illness and in particular PCa (Smith & Nicassio, 1995).

1.4. Content and Structure of the Thesis

This thesis is presented in 11 chapters. In *Chapter 2* (Introduction to Prostate Cancer), the anatomy of the prostate, incidence and mortality rates, symptoms and screening methods, and diagnosis and treatment of PCa are defined and discussed. In *Chapter 3* (Androgen Deprivation Therapy for Prostate Cancer), the developmental history of ADT is described, with the mechanisms of action and use and potential side effects of this treatment.

In *Chapter 4* (Psychological Implications of Prostate Cancer and Androgen Deprivation Therapy), prevalence rates and the importance of screening for depression and anxiety in patients with prostate cancer are discussed and the association between hormonal changes and symptoms of depression in men is introduced. Subsequently, the relationship between ADT and the development of

depression, anxiety and cognitive dysfunction is discussed and the impact of this on QoL in this patient group. In *Chapter 5* (Physical Activity and Prostate Cancer), the concept of physical activity (PA) is introduced. Definitions and measurement of PA are discussed and the National Physical Activity Guidelines of Australia (NPAGA) are presented. The health benefits of PA for the general population and patients with cancer are described, with the cost of physical inactivity, followed by a review of the literature in which the potential utility of PA as a rehabilitation tool for patients with PCa is investigated.

Chapter 6 takes the form of a paper prepared for publication. *Paper 1* (The Impact of Physical Activity on Psychosocial Outcomes in Men Receiving Androgen Deprivation Therapy for Prostate Cancer: A Systematic Review) is a systematic review, with the results evaluating the efficacy of PA as an intervention to improve depression and anxiety symptoms, cognitive function and QoL in patients receiving ADT for PCa.

In *Chapter 7* (Methodology of the Current Study), an overview of the research design and a description of the study variables and psychological outcome measures are provided. The methodology of *Paper 1*, the procedure of the study, and the statistical analyses conducted for each paper are also described in this section.

In *Chapter 8*, the second paper for publication is presented. In *Paper 2* (Factors Associated with Adherence to Physical Activity Guidelines in Patients with Prostate Cancer) the proportion of patients with PCa meeting NPAGA is estimated and the socio-demographic and medical factors associated with meeting these guidelines are examined. The results of *Paper 2* also examine the domains in which patients with PCa are most active, explore differences in activity level by treatment

type and assess factors predicting the likelihood that patients with PCa would meet NPAGA. In *Chapter 9, Paper 3* (Predictors of Depression, Anxiety and Quality of Life in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy) is presented. In this paper, the presence and severity of psychological sequelae and physical side effects associated with ADT are explored and the relationship between meeting NPAGA and depression, anxiety and QoL is evaluated. *Chapter 10* takes the form of the final paper for publication, *Paper 4* (Predictors of Cognitive Function in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy). In this paper, the types of cognitive difficulties reported in this patient group is established, differences in cognitive function with increases in duration of ADT are compared, and the relationship between meeting NPAGA and cognitive function is described.

Chapter 11 (Integrated Discussion) is the final chapter in which a summary of the research aims and study results are provided. A synthesis of the findings from the four papers is presented followed by discussion of the limitations, implications of the study findings for theory and practice, and directions for future research.

1.5. Summary and Conclusion

In this preface to the study, an overview of the current thesis was presented. The study concepts were introduced and defined as part of the rationale for undertaking the research, and the content and structure of the thesis were described. In the following chapter, PCa is introduced and the medical aspects of this disease including incidence, symptoms, diagnosis and treatment are described.

Chapter 2. Introduction to Prostate Cancer

2.1. Introduction

In this chapter, the aetiology of PCa is presented and the anatomy and function of the prostate gland are described. The natural history of PCa is discussed including the incidence and mortality rates, risk factors, presenting symptoms and screening methods. The histological features of the disease and treatment options are also described.

2.2. Anatomy of the Prostate

The prostate is a small gland positioned below the bladder in men (*Figure 2.1.*). It wraps around the urethra, the tube that carries urine and semen from the bladder to the end of the penis. A normal prostate is approximately the size of a golf ball and its main function is to produce fluid that protects and enriches sperm (Prostate Cancer Foundation of Australia, 2012a). However, as the prostate is found near the nerves, blood vessels and muscles needed to control the bladder and achieve an erection, these functions can be affected if irregularities in the prostate occur (Prostate Cancer Foundation of Australia, 2012a).

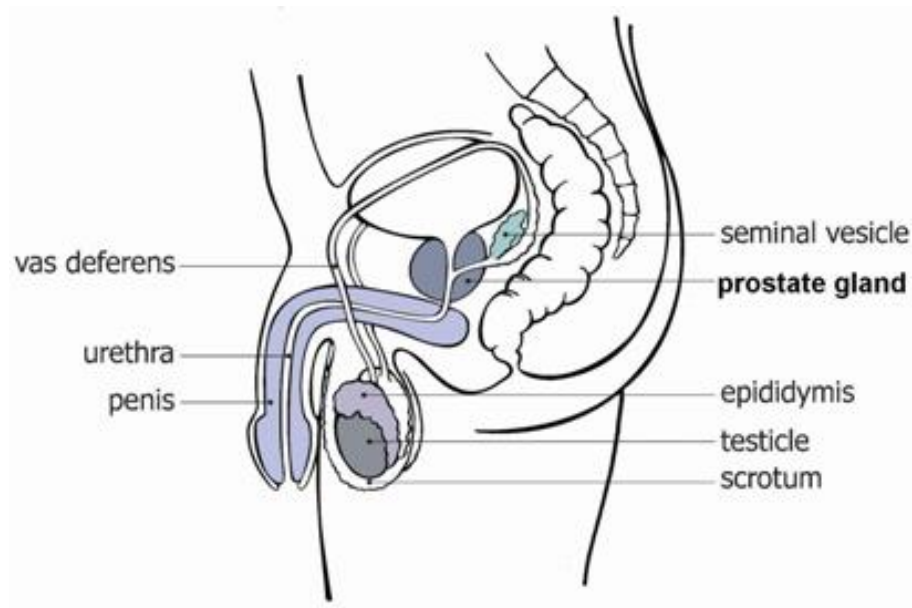


Figure 2.1. Location of the prostate gland.

The prostate begins to enlarge from 40 years of age and this is known as benign prostatic hypertrophy (BPH). An example of prostatic enlargement is presented in *Figure 2.1*. Changes in the balance of the male sex hormones, particularly testosterone, are generally the cause. There are three main conditions that come about as a result of prostate change. They are urinary symptoms, prostatitis and PCa. PCa is the abnormal growth of cells causing a malignant tumour of the prostate gland that is potentially life threatening (Kirby & Patel, 2008).

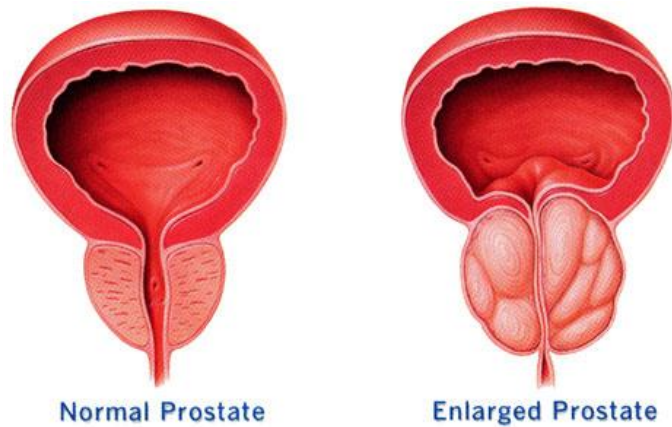


Figure 2.2. Comparison of a normal prostate to an enlarged prostate.

2.3. Natural History of Prostate Cancer

2.3.1. Incidence and Mortality Rates

PCa is the second most commonly diagnosed cancer worldwide, accounting for 14% (903,500) of the total new cancer cases in 2008 (Jemal et al., 2011).

Incidence rates vary significantly across the world with the highest rates recorded primarily in the developed countries of Europe, North America and Oceania (Jemal, et al., 2011). In men living in Australia, it is the most common internal cancer, with approximately 20,000 cases diagnosed every year (Prostate Cancer Foundation of Australia, 2012b).

Underpinning the increase in PCa diagnoses in developed countries is the wide utilisation of prostate-specific antigen (PSA) testing (Jemal, et al., 2011; Jemal, Siegel, Xu, & Ward, 2010; Prostate Cancer Foundation of Australia, 2012b). With the introduction of PSA testing in Australia in 1987 and listing of this service on the Medicare Benefits schedule in 1989, sharp increases in the incidence rate of PCa were observed in the early 1990s (Australian Institute of Health and Welfare, 2012). The age-standardised rate increased from 110 per 100,000 males in 1991 to a peak of

184 per 100,000 in 1994, with the actual numbers diagnosed increasing from 6,746 to 13,064 per annum (Australian Institute of Health and Welfare, 2007). This increase is the result of a large pool of undiagnosed cases that were found using the PSA test. After 1994 incidence rates declined to 128 cases per 100,000 males in 1998, then increased slowly to 135 per 100,000 in 2002 (Australian Institute of Health and Welfare, 2012).

In 2003 there were 13,526 new cases of PCa diagnosed in Australia and it is estimated that 18,700 new cases were diagnosed in 2006 (Australian Institute of Health and Welfare, 2007). Hospital admissions for a primary diagnosis of PCa almost doubled from 13,715 in 2001 to 25,429 in 2006. In the same period, radical prostatectomies (surgical removal of the prostate) with a primary diagnosis of PCa increased by 56% from 6,088 to 9,478 (Australian Institute of Health and Welfare, 2007). Since 2002 there has been a further rapid increase in the number of new cases diagnosed, with rates climbing to 183 per 100,000 in 2007 (Australian Institute of Health and Welfare, 2012). This second increase is most likely due to changes in diagnostic procedures and a reduction in investigation thresholds. In the past, a PSA of 4.0 ng/mL has been used as the threshold for consideration of prostate biopsy (National Comprehensive Cancer Network, 2012b). However, a study involving 332 men with PSA in the range of 2.5 ng/mL to 4.0 ng/mL revealed a 22% incidence of PCa by biopsy (Catalona, Smith, & Ornstein, 1997). It was suggested that lowering the PSA threshold to 2.5 ng/mL would significantly increase the rate of detecting PCa in men younger than 60 years with little loss of specificity (National Comprehensive Cancer Network, 2012b). Consequently, the number of biopsies taken increased and resulted in early detection of slow-growing cancers that may

have otherwise escaped diagnosis (Australian Institute of Health and Welfare, 2012; Jemal, et al., 2011).

PCa is a disease associated with ageing, primarily affecting men over the age of 50 years (Kirby & Patel, 2008). Thus the main reason for this observed increase in the incidence of PCa is the ageing of the Australian population, with the number of men aged 65 years and over increasing by approximately 2.8% per year (Australian Institute of Health and Welfare, 2007). With the worldwide trend towards an ageing population combined with increased use of PSA screening and continual advancement in treatment options prolonging survival, the number of men living with PCa is predicted to increase over the next two decades (Galvao, Taaffe, Spry, & Newton, 2007; Kirby & Patel, 2008). In 2003, the incidence rate for PCa was 86 per 100,000 for males aged 50-54 years old, increasing to 999 per 100,000 for males aged 85 years and over. In the same year, the age-standardised incidence rate was 144 new cases per 100,000 (Australian Institute of Health and Welfare, 2007). Linear extrapolation of data from 1982 to 2007, supplemented by PSA testing data from 2008 to 2010, suggests that age-standardised incidence rates of PCa will continue to increase by approximately 3 cases per 100,000 males per year to 200 new cases per 100,000 males. Based on expected population changes, this equates to approximately 31,000 new cases expected to be diagnosed in 2020 (Australian Institute of Health and Welfare, 2012).

With advancement in early detection methods and improved treatment options with curative intent, mortality rates for PCa have been decreasing in many developed countries, including Australia, Canada, the United Kingdom, the United States, Italy and Norway (Jemal, et al., 2011). Men can live up to 10 years post-diagnosis, depending on the severity of disease. However, untreated, PCa will

eventually cause death. Globally, PCa is currently the sixth leading cause of cancer death in males, accounting for 6% (258,400) of the total cancer-related deaths in 2008 (Jemal, et al., 2011). In Australia, the age-standardised mortality rate was 34 cases per 100,000 in 2003, with 84% of new cases occurring in men aged 60 years and over, and 84% of deaths occurring in men aged 70 years and over (Australian Institute of Health and Welfare, 2007). PCa accounted for 7.4% (2,938) of all cancer deaths in Australian men in 2007 and continues to contribute significantly to the high mortality rates in older men (Australian Institute of Health and Welfare, 2010).

2.3.2. Risk Factors, Presenting Symptoms and Screening Methods

Older age, race and family history remain the only well-established risk factors for PCa (Jemal, et al., 2011; Kirby & Patel, 2008). Some families carry a genetic mutation that increases their predisposition to cancer and is passed from one generation to the next. Women inheriting a mutation in the BRCA2 gene have been found to be at high risk of developing breast and ovarian cancer. However, it has recently been discovered that a male with a genetic fault in the BRCA2 gene has almost four times the risk of developing PCa than men in the general population and BRCA2 PCa tends to be more aggressive (Prostate Cancer Foundation of Australia, 2012c). A propensity to genetic vulnerability in black populations has been observed, with this group appearing to develop the disease earlier than white populations. Further, the highest PCa mortality rates in the world occur in males of African descent in the Caribbean region (Jemal, et al., 2011; Kirby & Patel, 2008). However, migration studies have shown that the incidence of PCa in men immigrating from a low- to a high-risk area increases to that of the local population within two generations, suggesting that environmental influences such as diet, nutrition and physical inactivity may have marked effects on the development of PCa (Kirby &

Patel, 2008). Of particular relevance to the present study, there is compelling evidence that routine physical activity is associated with reductions in the incidence of specific cancers and may reduce the burden of cancer-related diseases (Warburton, Nicol, & Bredin, 2006).

In the early stages of PCa, there may be no symptoms at all. As the disease progresses, however, symptoms can include the need to urinate frequently; sudden urges to urinate; difficulty in starting urine flow; a slow or interrupted flow and dribbling afterwards; incontinence; and pain during urination or blood in the urine or semen (Prostate Cancer Foundation of Australia, 2012d). However, these symptoms are not always indicative of PCa and may be the result of other forms of prostate disorder.

The two tests commonly used to detect possible signs of PCa are the PSA blood test and the Digital Rectal Examination (DRE). DRE is a manual examination of the prostate gland by the insertion of a gloved finger into the patient's rectum to check for abnormality in size, shape or texture in the prostate (Cancer Council Australia, 2012). It is the simplest, safest and most cost-effective means for detecting PCa. However, the tumour must be posteriorly situated and sufficiently large to be palpable (Kirby & Patel, 2008).

The measurement of PSA is currently the most effective single screening test for the early detection of PCa. PSA is a protein produced by the cells of the prostate gland and when enlarged, PSA levels in the blood tend to rise (Cancer Council Australia, 2012). However, PSA levels can rise due to cancer or benign (non-cancerous) conditions such as prostatitis and urinary tract infections and therefore, PSA test results cannot differentiate between benign prostate conditions and cancer

(Kirby & Patel, 2008). As a general rule, the higher the PSA result the greater the chance that PCa is present and where cancer is present, the volume of disease can be predicted by the PSA level (Prostate Cancer Foundation of Australia, 2012c). A PSA less than 10 ng/mL suggests that the tumour is likely to be confined to the prostate. However, a high likelihood of cancer spread beyond the prostate is indicated at a PSA level above 30 ng/mL, reducing the possibility of cure (Prostate Cancer Foundation of Australia, 2012c). Approximately 25% of men with PSA levels above the normal range (≥ 4 ng/mL) have PCa, with the risk increasing to more than 60% in men with PSA levels above 10 ng/mL (Kirby & Patel, 2008). However, a low PSA result does not necessarily mean that cancer does not exist and PSA elevations do not always indicate cancer. PSA determinations have been most useful in staging PCa and evaluating the response to treatment (Kirby & Patel, 2008).

2.3.3. Histological Features

The Tumour-Node-Metastasis (TNM) System is an internationally recognised cancer staging system that describes the extent of cancer in the patient's body or the patterns of disease spread (National Comprehensive Cancer Network, 2012a). T describes the size of the tumour and whether it has invaded nearby tissue; N describes the regional lymph nodes that are involved; and M describes distant metastasis (spread of cancer from one part of the body to another). According to Kirby and Patel (2008), PSA levels above 20 ng/mL are often indicative of tumour expansion beyond the prostatic capsule, while levels above 40 ng/mL suggest a high likelihood of bony or soft tissue metastases. In Table 2.1, the TNM staging system for PCa is presented.

Table 2.1.

TNM Staging System for Prostate Cancer (National Comprehensive Cancer Network, 2012).

Primary Tumour (T)		Regional Lymph Nodes (N)	
Tx	Primary tumour cannot be assessed	NX	Regional lymph nodes were not assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis
T1	Clinically unapparent tumour neither palpable nor visible by imaging.	N1	Metastasis in regional lymph nodes
<i>T1a – T1b</i>	<i>Tumour incidental histologic finding in 5 % or less of tissue resected.</i>		
<i>T1c</i>	<i>Tumour identified by needle biopsy (ie. Due to elevated PSA)</i>	Distant Metastasis (M)	
T2	Tumour confined within prostate	M0	No distant metastasis
<i>T2a</i>	<i>Tumour involves one-half of one lobe or less</i>	M1	Distant Metastasis
<i>T2b</i>	<i>Tumour involves more than one-half of one lobe but not both lobes</i>	<i>M1a</i>	<i>Non-regional lymph nodes</i>
<i>T2c</i>	<i>Tumour involves both lobes</i>	<i>M1b</i>	<i>Bones</i>
T3	Tumour extends through the prostatic capsule	<i>M1c</i>	<i>Other sites with or without bone disease</i>
<i>T3a</i>	<i>Extracapsular extension (unilateral or bilateral)</i>		
<i>T3b</i>	<i>Tumour invades the seminal vesicles</i>		
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder, levator muscles, and/or pelvic wall.		

In conjunction with the TNM system, the Gleason System is the most widely used measure for grading PCa. This system is based on the extent to which the tumour cells are arranged into visibly glandular structures and five levels of increasing aggressiveness are recognised (Prostate Cancer Foundation of Australia, 2012c). Grade 1 tumours form almost normal glands, whereas Grade 5 tumours are

characterised by sheets of undifferentiated cancer cells. The progressive loss of glandular differentiation is indicative of poor prognosis (Kirby & Patel, 2008; National Comprehensive Cancer Network, 2012a). As PCa is usually heterogeneous, the numbers of the two most widely represented grades are added together to produce the Gleason Score (GS) which yields a total score between 2 and 10 and can provide useful prognostic information (National Comprehensive Cancer Network, 2012a). Kirby and Patel (2008) suggested that a GS above 4 is associated with a progressive risk of more rapid disease progression, increased metastatic potential and decreased survival. In Table 2.2, the anatomic stage and prognostic groups associated with PSA levels and GS is presented.

Table 2.2.

Anatomic Grade and Prognostic Groups Associated with PSA and GS (National Comprehensive Cancer Network, 2012).

Stage	T	N	M	PSA	GS
I	T1a-c	N0	M0	< 10	≤ 6
	T2a	N0	M0	< 10	≤ 6
	T1-2a	N0	M0	X	X
IIA	T1a-c	N0	M0	< 20	7
	T1a-c	N0	M0	≥ 10 and < 20	≤ 6
	T2a	N0	M0	< 20	≤ 7
	T2b	N0	M0	< 20	≤ 7
	T2b	N0	M0	X	X
IIB	T2c	N0	M0	Any PSA	Any GS
	T1-2	N0	M0	≥ 20	Any GS
	T1-2	N0	M0	Any PSA	≥ 8
III	T3a-b	N0	M0	Any PSA	Any GS
	T4	N0	M0	Any PSA	Any GS
	Any T	N1	M0	Any PSA	Any GS
	Any T	Any N	M1	Any PSA	Any GS

T = Tumour; N = Node; M = Metastasis; PSA = Prostate-specific Antigen; GS = Gleason Score; X = cannot be processed.

2.3.4. Treatment Options

The GS, PSA level and TNM staging are all taken into account when determining which form of treatment will be most effective for the individual patient with PCa. These measures are considered with patient age and comorbid medical conditions. Treatment options for the management of localised PCa include: Radical prostatectomy (surgical removal of the prostate); External-beam radiotherapy (EBRT); Low-dose seed brachytherapy (inserting either iodine-125 or palladium-103 seeds into the prostate); Active surveillance (treatment options deferred until objective signs of biological activity are observed); High-intensity focused ultrasound (HIFU) (probe delivering HIFU transrectally to the prostate to achieve focal tissue destruction); and Cryoablation (freezing temperatures used to destroy prostatic tissue) (Kirby & Patel, 2008; National Comprehensive Cancer Network, 2012a). The management of high-risk PCa is more complex. The term ‘high risk’ refers to men with PCa whose cancer is confined to the prostate gland but have a high GS (>7) or high PSA level ($>20\text{ng/mL}$) or men with T3/T4N0M0 disease, in which the tumour is no longer confined to the prostate but there is no clinical evidence of spread to local lymph nodes or more distant sites (Kirby & Patel, 2008). Hormonal therapy, also known as Androgen Deprivation Therapy (ADT) is commonly incorporated into the treatment of high-risk PCa. ADT may be combined with surgery and/or radiotherapy depending on the severity of the cancer. However, it is now common practice for oncologists to integrate ADT into the treatment of low and intermediate risk cancers as well ($\text{GS} < 7$; $\text{PSA} \leq 10\text{ng/mL}$).

2.4. Summary and Conclusion

In this chapter, an overview of PCa was provided and the grading and staging system utilised to determine the most appropriate course of treatment was highlighted. A range of treatment options for PCa were described. In the next chapter, the concept of ADT is introduced as it is the focal treatment in the current study.

Chapter 3. Androgen Deprivation Therapy

3.1. Introduction

In this chapter, an overview of ADT is provided. Change in the prevalence of ADT use is discussed and the mechanisms of action are described. Subsequently, the physical side effects of ADT are highlighted and the concept of psychological disturbance associated with ADT is introduced.

3.2. Androgen Deprivation Therapy

3.2.1. Mechanisms of Action

ADT is a hormone treatment designed to reduce prostate and tumour volume, testosterone and PSA levels by suppressing testicular androgen production (Sharifi, et al., 2005). ADT can take the form of either surgical castration (orchidectomy) or chemical castration. This is normally achieved with luteinizing hormone-releasing hormone (LHRH, also known as gonadotropin-releasing hormone (GnRH)) analogues together with an antiandrogen (Kirby & Patel, 2008; National Comprehensive Cancer Network, 2012a). After administration, there is a transient initial increase in luteinizing hormone (LH) and testosterone secretion, potentially causing ‘tumour flare’ or initial androgen stimulation. However, this is followed by desensitisation or downregulation, resulting in a fall in LH and testosterone secretion (Kirby & Patel, 2008; Taylor, et al., 2009). There are currently newer classes of LHRH antagonists available to patients with PCa that rapidly and directly inhibit the release of androgens. There is no initial tumour flare with these agents and co-administration of an antiandrogen is not necessary (National Comprehensive Cancer Network, 2012a). ADT is primarily administered in combination with radiation in

localised or locally advanced cancers and as primary systemic therapy in advanced disease.

3.2.2. Prevalence and Benefits of Use

In the past, ADT was incorporated into the treatment of patients with metastatic disease to palliate symptoms and delay disease progression. However, as mentioned previously, it has become common practice for oncologists to integrate ADT into the treatment of localised disease with ADT use increasing steadily over the past decade (Bria et al., 2009; Scherr, Swindle, & Scardino, 2003). For example, in a large population based study, Shahinian and colleagues (2005) demonstrated substantial increases in the use of ADT for patients with PCa over the period 1991 to 1999, occurring across all cancer stages and grades. Cooperberg et al. (2003) found that the rates of ADT use as the primary form of treatment in high-risk patients were stable from 1996 through 2001. However, rates in low- and intermediate-risk patients increased sharply from 4.6% and 8.9% respectively, in 1989 and 1992, to 14.2% and 19.7% in 1999 and 2001. Overall, patients were nearly three times as likely to receive ADT as the primary form of treatment from 1999 to 2001 as they were from 1989 to 1992. This increase in the use of ADT in PCa patients with localised disease has occurred despite the benefits of treatment with this stage and grade of cancer remaining unclear (Shahinian, et al., 2005).

Research evidence suggests that ADT is effective at alleviating disease-specific symptoms (Kirby & Patel, 2008; National Comprehensive Cancer Network, 2012a; Shahinian, et al., 2006; Taylor, et al., 2009). The authors of several studies have suggested that ADT may prolong survival when used in combination with radiation therapy in patients with locally advanced PCa (Bolla et al., 2002).

However, other research evidence indicates no survival advantage (Lu-Yao, 2008). With confirmation of the debilitating side effects of ADT (Shahinian, et al., 2006; Taylor, et al., 2009) and little evidence to suggest improvements in overall survival by the early introduction of various forms of hormonal therapy (Wilt, Nair, MacDonald, & Rutks, 2011), the potential harm may outweigh the benefit for men with lower risk disease treated with ADT.

As a result of ADT treatment, testosterone deficiency (also referred to as hypogonadism) is common and often reflects a decline in hypothalamic and testicular function (Harman, Metter, Tobin, Pearson, & Blackman, 2001; Shores et al., 2004). The gradual decreases in bioavailable testosterone (testosterone that is not bound to sex hormone-binding globulin) as men age is reportedly associated with decreased muscle mass and strength; osteoporosis; reduced sexual activity; changes in cognition; and depression (Jenkins, et al., 2005; Shores, et al., 2004). However, it has been proposed that the sudden, sharp decrease in testosterone levels as a consequence of ADT treatment exacerbates these negative side effects with a consequent impact on quality of life (QoL) and psychosocial wellbeing (Almeida, et al., 2004).

3.2.3. Side Effects of Androgen Deprivation Therapy

Despite its effectiveness in treating PCa, ADT can induce a range of health related complications with the results of studies documenting detrimental effects on muscle, fat and bone mass, exacerbating the risk of sarcopenia which is the age-related loss of muscle mass and strength, osteoporosis and obesity (Galvao, et al., 2007; Taylor, et al., 2009). In a study by Taylor et al. (2009) it was revealed that individuals with PCa who undergo ADT have an approximately 23% increase in overall skeletal fracture risk. This is accompanied by bone mineral density loss and osteoporosis, with longer duration of ADT associated with greater risk. Furthermore,

the additional side effect of ADT including hyperglycaemia and increased insulin resistance can lead to diabetes with study results indicating increased risks between 36% (Keating, O'Malley, & Smith, 2006) and 49% (Lage, Barber, & Markus, 2007). An increased risk of cardiovascular related mortality of 17% was also reported by Taylor and colleagues (2009).

In a recent review of 13 studies assessing the safety and tolerability of ADT, the early and long term side effects of continual and intermittent ADT use were compared (Gruca, Bacher & Tunn, 2012). Side effects observed almost immediately after the initiation of ADT included hot flushes, fatigue and sexual dysfunction which encompassed both libido loss and erectile dysfunction. Gruca et al's (2012) results indicated that 42% of studies reported a decreased occurrence of hot flushes and increased sexual function during off-treatment periods, suggesting QoL may be improved with intermittent rather than continual ADT use. Gruca et al's (2012) results comparing the long term consequences associated with continual and intermittent ADT were inconclusive. However among the 13 studies reviewed, long term consequences and health risks of ADT consistently included anemia, bone loss, metabolic changes comprising increased fat mass, triglycerides, high- and low-density lipoproteins and decreased insulin sensitivity, while significant heart rate elevations increased the risk of cardiovascular disease, coronary heart disease, myocardial infarction and sudden cardiac death. Aside from the physical consequences associated with ADT, there has been increasing recognition of adverse psychological effects such as depression, anxiety and cognitive difficulties, which some authors have termed the *androgen deprivation syndrome* (Shahinian, et al., 2006; Taylor, et al., 2009). These adverse effects can have a significant impact on QoL and psychosocial wellbeing in this population. Furthermore, depression, anxiety

and distress often goes undetected and consequently, many cancer patients do not receive treatment for this often significant problem that can be alleviated through pharmacologic and psychological interventions (National Breast Cancer Centre (NBCC) and National Cancer Control Initiative (NCCI), 2003). To resolve this issue for patients with PCa, it is important to gain a thorough understanding of the psychological side effects of ADT to implement appropriate routine screening measures for distress, anxiety and depression.

3.3. Summary and Conclusion

In this chapter, the method of ADT use in the treatment of PCa and the potential benefits and caveats associated with its use was briefly described. In the next chapter the psychological implications of PCa and ADT are discussed in detail, specifically focusing on the concepts of depression, anxiety, quality of life (QoL) and cognitive function.

Chapter 4. Psychological Implications of Prostate Cancer and Androgen Deprivation Therapy

4.1. Introduction

The purpose of this chapter is to review previous research on depression, anxiety, QoL and cognitive function in individuals diagnosed with PCa and specifically as a result of ADT use. This chapter is divided into three major sections. In the first of these, depression and anxiety in patients with PCa is discussed, including prevalence rates, the importance of screening and the relationship between depression, hormonal changes and ADT. In the second section, QoL is defined and previous research examining the impact of ADT on QoL is considered. In the final section, changes in cognitive function associated with ADT are examined and the relationship between testosterone and cognitive function is explored.

4.2. Depression and Anxiety in Patients with Prostate Cancer

4.2.1. Prevalence Rates of Depression and Anxiety in Patients with Cancer

Many people diagnosed with cancer suffer high levels of distress, anxiety and depression, which can pose a threat to their psychosocial wellbeing and QoL (Turner, McAvoy, Luxford, & Fletcher, 2004). In fact, research has shown that prevalence rates for depression in cancer patients range from 20% to 35% with up to 35% experiencing long term psychological distress and/or clinically significant anxiety problems (Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Further, reactive anxiety is the most common reason for psychiatric referral in cancer patients (Kunkel, Bakker, Myers, Oyesanmi, & Gomella, 2000). Many cancer patients also

routinely suffer from tension, anxiety and feelings of helplessness prior to and upon commencement of treatment (DeVries et al., 1998; Munro & Potter, 1996). For example, in a Melbourne based study conducted with a sample of early stage breast cancer patients it was indicated that 42% of patients experienced anxiety, depression or adjustment disorders upon commencement of treatment, providing evidence that a significant proportion of cancer patients may be affected by psychological difficulties (Kissane et al., 1998). In a 2006 to 2007 trial at St. Vincent's Hospital Melbourne, Lethborg (2007) screened for psychological distress and anxiety in cancer patients and found that almost half (48%) of participants were experiencing possible clinical levels of psychosocial distress. Similarly, in a survey conducted by Sanson-Fisher and colleagues (2000) of 888 people undergoing cancer treatment it was revealed that 5 of the 10 highest unmet needs were in the psychological domain. Further, 40% of the sample reported that they had a 'moderate' or 'high' unmet need related to 'fears about the cancer spreading'.

4.2.2. The Impact of Anxiety in Men with Prostate Cancer

While little previous research has been undertaken into levels of distress and anxiety in men with PCa (Dale, Bilir, Han, & Meltzer, 2005; Steginga & Occhipinti, 2006), the results of these studies suggest that anxiety and aversive mood states may play a role in both disease onset and disease progression (Balderson & Towell, 2003; Steginga & Occhipinti, 2006; Turner et al., 2009). In the context of cancer, much of the work has focused on women with breast cancer where there is mixed support for the role of psychological distress in influencing onset and progression (Metcalf, Davey Smith, Macleod, & Hart, 2007). In contrast, relatively little research has been undertaken in malignancies known to affect men. However, like breast cancer, the pathogenesis of PCa includes hormonal involvement, thus making it biologically

plausible for psychological distress and anxiety to influence the course of the disease (Turner, et al., 2009).

As PSA level is a biological marker of prostate malignancy, there are three studies in which the relationship between indices of anxiety and this marker has been examined (Cohen et al., 2003; Stone, Mezzacappa, Donatone, & Gonder, 1999; Turner, et al., 2009). Stone et al. (1999) found that both high stress and low satisfaction with support were associated with higher PSA levels in men undergoing screening for PCa. Similarly, Cohen et al. (2003) reported that increased cancer-related worries were associated with elevated PSA levels (>4 ng/mL), a relationship that persisted after controlling for the effects of age, previous PSA testing, and cancer-related symptoms. In a more recent study, Turner and colleagues (2009) failed to find an association between distress, anxiety and depression and PSA level. However, scores indicative of clinical depression on the Hospital Anxiety and Depression Scale (HADS) in this study were associated with a 23% increase in the likelihood of a cancer diagnosis. These results highlight the potentially important role of depressed mood in the onset of PCa. Given the evidence suggesting there may be an association between disease onset and progression and distress/anxiety in PCa patients, screening for and alleviating psychological distress and anxiety in this population may be an important aspect of treatment that is currently neglected.

4.2.3. The Association between Depression and Hormonal Changes in Men

Depression is a common condition faced by the elderly (Steffens et al., 2000). In men, it has been proposed that this may be a side effect of the hormonal changes associated with ageing (Barrett-Connor, Von Muhlen, & Kritz-Silverstein, 1999; Seidman et al., 2002). This is commonly known as hypogonadism (diminished sex

hormone production). While the association between hypogonadism and depression is unclear, the results of a number of studies suggest there may be a relationship. For example, in a longitudinal analysis comparing men with eugonadal (normal) and hypogonadal testosterone levels, an increased incidence of depressive illness was observed in men considered to be hypogonadal, with total testosterone levels of 200 ng/dL or less related to an approximate 4-fold increase in the risk of incident depression (Barrett-Connor, Von Muhlen, et al., 1999). In this cross-sectional population-based study of 856 older men it was also found that testosterone levels were inversely associated with scores on the Beck Depression Inventory (Barrett-Connor, Von Muhlen, et al., 1999). Similarly, Seidman et al. (2002) found that elderly men with dysthymic disorder (chronic depression with less severe but longer lasting symptoms than major depressive disorder) had significantly lower testosterone levels than men with major depressive disorder and men without depression. In this study the authors also found that the majority of the elderly men with dysthymic disorder had total testosterone levels in the hypogonadal range (300ng/dL). However, in other studies no relationship between testosterone level and depression in young and middle-aged men has been reported (Levitt & Joffe, 1988; Rubin, Poland, & Lesser, 1989).

4.2.4. The Relationship between Androgen Deprivation Therapy and Depression and Anxiety Symptoms

Previous studies and measures assessing depression outcomes typically include anxiety outcomes as well and vice versa, as these psychological symptoms often occur together. Therefore, this section combines the results of previous research assessing the relationship between ADT use and the presence of anxiety, depression, or both outcomes. There have been few previous studies in which the

relationship between depression and/or anxiety and ADT use in men with PCa has been examined. Although this section may not represent the entire literature examining these relationships, the studies included were selected on the basis of most recent or highly cited.

DiBlasio et al. (2008) retrospectively reviewed 395 patients receiving ADT for PCa between 1989 and 2005, dividing the cohort into three groups: pre-ADT psychiatric illness, de novo (post-ADT initiation) psychiatric illness, and no psychiatric illness. Thirty-four men (8.6%) were diagnosed with pre-ADT psychiatric illness and 101 (27.9%) men were diagnosed with de novo psychiatric illness at 87.4 months follow-up, most commonly including: depression ($n = 57$; 56.4%), dementia ($n = 14$; 13.9%), and anxiety ($n = 9$; 8.9%). Furthermore, increasing PSA was associated with de novo anxiety. Dale et al. (2009) used the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) and the HADS to evaluate the contribution of cancer-specific anxiety to earlier initiation of ADT in 67 men with PCa who experienced biochemical cancer recurrence. Results of this study indicated that PCa-specific anxiety, measured with the MAX-PC, was the most robust predictor of early ADT initiation. Furthermore, anxious patients started ADT within the first year of presentation, whereas the average time to initiation in non-anxious patients was greater than 2 years. More recently, Sharpley, Bitsika and Christie (2012) investigated the relationship between ADT side effects and symptoms of depression and anxiety in 147 patients with PCa. Self-reported ADT side effects were significantly associated with elevated anxiety and depression scores and with the presence of “clinically significant” anxiety, as measured by the Self Rating Anxiety/Depression Scales. Furthermore, there was a direct and significant

relationship between the number of ADT side effects reported and anxiety scores, suggesting the potential for a cumulative outcome of ADT side effects on anxiety.

With the sharp decrease in testosterone levels and consequent hypogonadism associated with ADT treatment, the results of previous research have suggested there may be a link between ADT and the development of depression (Almeida, et al., 2004; Pirl, et al., 2002; Rosenblatt & Mellow, 1995; Soyupek, et al., 2008). For example, in a pilot study of three patients undergoing leuprolide therapy (i.e., hormonal therapy aimed at lowering testosterone levels), Rosenblatt and Mellow (1995) discovered that they all developed depression after the initiation of hormonal therapy. Furthermore, the timing of the onset of the depression suggests that it was related to hormonal therapy rather than to the patient receiving a cancer diagnosis. Depressive symptoms subsided in all men upon cessation of leuprolide despite ongoing or increasingly severe medical problems. It should also be noted that depressive symptoms recurred in two of the three cases when hormonal therapy was reinstated, strongly supporting the role of this hormonal manipulation in precipitating depression.

The results of another study indicated that ADT treatment was associated with increased Beck Depression (BDI) and Anxiety Inventories (BAI) scores (Almeida, et al., 2004). Further, men undergoing ADT treatment in the study by Cherrier et al. (2009) reported increases in fatigue, depression, moodiness, irritability, tension, anxiety and loss of vigour, which returned to near baseline, three months after ceasing ADT. Pirl et al. (2002) also found that major depressive disorder was present at a prevalence rate of 12.8% in a sample of 45 men undergoing ADT. The rate of depression observed in this study was 8 times higher than the rate

in the general male population of the United States (1.6%) and 32 times higher than the rate in men over 65 years old in this country (0.4%).

4.3. Quality of Life in Patients with Prostate Cancer

4.3.1. Defining Quality of Life

QoL is an abstract concept encapsulating a range of physical, psychological and social components, with many challenges apparent in the definition and operationalisation of this term (Farquhar, 1995; Felce, 1997). Although there is a lack of consensus as to which definition is most appropriate, improved QoL is perhaps the most desirable outcome of healthcare policies (Farquhar, 1995). Proposed components of QoL have included functional ability, including role functioning (e.g., occupation and/or domestic tasks); social interaction; community involvement; physical function; somatic sensation (e.g., pain); self-esteem; environmental circumstances (e.g., safety); financial stability; independence and engagement in activities of daily living; psychological wellbeing; and life satisfaction (Bosworth et al., 2000; Felce, 1997; Quek & Penson, 2005). However, it has been argued that such a broad definition of QoL is impractical in medical research and therefore operationalisation of QoL should be limited to those domains most relevant to health, including psychological and social wellbeing, physical function and disease- and treatment-related symptoms (Bosworth, et al., 2000). Irrespective of an agreed definition, what appears to be most important is that QoL is a patient centred outcome that should not be estimated from physician report, but rather regularly assessed through self-report (Quek & Penson, 2005).

Felce (1997) proposed a QoL model consisting of three elements in which personal values, life conditions, and personal satisfaction interact to determine

overall wellbeing. Herr (1997) also concluded that a person's QoL is influenced by individual experience, beliefs, expectations, and perceptions. Therefore, two important aspects should be considered when conceptualising QoL in patients with cancer. Firstly, expectations regarding health and the ability to cope with limitations and disability can have a substantial impact on a person's perceptions of health and satisfaction with life. Consequently, two individuals with the same health status may have very different qualities of life (Herr, 1997). For example, two men who have undergone treatment for PCa with curative intent may experience different levels of satisfaction if one is incontinent and the other is not. Secondly, an individual's satisfaction with the quality of their life varies over time (Herr, 1997). For example, the perceived QoL early after treatment might differ from perceived QoL years later, especially if side effects become more troublesome or the cancer recurs.

Consistent with Bosworth et al. (2000), the focus of the present research was psychological wellbeing (emotional and mental state including mood states, such as anxiety and depression); social wellbeing (capacity to engage in relationships and activities with others); physical functioning (ability to undertake activities of daily living, such as housework and self-care); and physical symptoms (PCa symptoms and treatment side effects). However, it is acknowledged that these components of QoL are related and therefore interact with each other as described in the biopsychosocial model of health. Therefore, in the present study the examination of physical symptoms in association with psychosocial wellbeing was the primary focus.

4.3.2. The Impact of Androgen Deprivation Therapy on Quality of Life in Men with Prostate Cancer

The negative physical side effects of treatment for PCa can be extremely debilitating, significantly impacting on QoL. Previous research indicates that impotence and incontinence are common, and these generally have a negative impact on QoL (Fowler, et al., 2002; Penson, et al., 2003; Sharifi, et al., 2005; Smith et al., 2009). Penson et al. (2003) noted that men with sexual and urinary dysfunction had significantly worse outcomes in the bodily pain, mental health, role limitation, vitality, and overall health status domains of general QoL. Furthermore, QoL is a particularly important consideration for PCa patients receiving ADT. The results of previous studies have shown that ADT significantly impairs QoL (Dacal, Sereika, & Greenspan, 2006; Fowler, et al., 2002; Herr, 1997; Herr & O'Sullivan, 2000; Quek & Penson, 2005). While available research on this issue is limited, the results of two studies have shown that patients who have been receiving ADT for six months experience decreases from baseline assessment in sexual, social and role functioning (Fowler, et al., 2002; Sharifi, et al., 2005). They also experience declines in cognitive ability and increases in depression and/or anxiety symptomatology. Dacal et al. (2006) examined the effects of ADT on several dimensions of QoL in patients with PCa. Men receiving short- and long-term ADT had significantly lower QoL in the dimensions of physical functioning and general health. Fowler et al. (2002) used Medicare files to compare QoL in PCa patients undergoing radical prostatectomy followed by ADT ($n = 220$) with those undergoing radical prostatectomy alone ($n = 810$). In this study, PCa patients who were androgen deprived after radical prostatectomy reported significantly worse scores on QoL measures than matched surgical patients who were not androgen deprived. The androgen deprived group

reported more negative effects of PCa and treatment on their lives; increased concern about body image; less energy; more worries about cancer and death; and poorer perceptions of general health, mental health, and activity level. These findings were similar to those of Herr and O'Sullivan (2000) who reported that men with locally advanced PCa who had received ADT had more fatigue, loss of energy, emotional distress, and lower QoL than men who deferred hormone therapy.

A common theme in the research literature appears to be that the negative side effects of radiotherapy and/or radical prostatectomy are intensified by the addition of ADT, exacerbating the impact of treatment on QoL and psychosocial wellbeing (Fowler, et al., 2002; Sharifi, et al., 2005; Smith, et al., 2009). For example, although erectile dysfunction is not uncommon after radical prostatectomy, men who undergo ADT have a further decline in ability for sexual intercourse and a decrease in sexual desire compared with men who are not treated with ADT (Fowler, et al., 2002; Sharifi, et al., 2005; Smith, et al., 2009). Testosterone plays an important role in normal male sexual function and consequently, decreasing testosterone to hypogondal levels as a result of ADT treatment has been associated with erectile dysfunction and a significant negative impact on QoL for patients receiving this form of treatment (Fowler, et al., 2002; Penson, et al., 2003; Smith, et al., 2009).

Hot flushes have also been noted as a factor significantly affecting QoL in men undergoing ADT. For example, in one study up to 80% of patients undergoing treatment with GnRH reported hot flashes and up to 27% said this was the most troublesome side effect (Sharifi, et al., 2005). Furthermore, testosterone levels reportedly have a negative correlation with fat mass and a positive correlation with muscle mass and consequently, the decrease in testosterone levels associated with ADT treatment can result in weight gain and loss of muscle mass. As previously

discussed, these metabolic changes can increase the risk of cardiovascular disease, diabetes, osteoporosis and obesity having a further negative impact on QoL. The psychological impact of these bodily changes and the implications this has for psychosocial wellbeing has become increasingly apparent in the research literature.

There is anecdotal evidence from medical specialists in the research team of the present study, that body image dissatisfaction is frequently reported in men with PCa receiving ADT. However, there has been little research to examine the effects of ADT on body image. Given the physical changes that take place secondary to the ADT-induced hypogonadal state, it has been hypothesised that ADT treatment may increase body dissatisfaction, further impacting on psychosocial wellbeing (Harrington & Badger, 2009). In the first study to describe differences in body image in men with PCa based on whether they had been receiving ADT or not, Harrington et al. (2009) demonstrated a significantly increased degree of body image dissatisfaction in men receiving ADT compared to those men who were ADT naive. In addition to the diverse range of ADT side effects discussed and the implications this has for QoL, the results of previous research suggest that the impact of ADT on QoL is persistent (Smith, et al., 2009). In a population-based study of 1642 PCa cases and 495 controls, Smith et al. (2009) reported that compared to those treated with radical prostatectomy and external beam radiotherapy, men with primary ADT treatment had poorer general physical or mental QoL than controls, persisting up to three years after the conclusion of treatment.

4.4. Cognitive Function and Androgen Deprivation

4.4.1. The Association between Testosterone and Cognitive Functioning

Few studies have included variables examining the association between testosterone and cognition in older men. However, the neuropsychological research literature suggests that testosterone is positively related to cognitive functioning. For example, Moffat et al. (2002) conducted a longitudinal assessment of 407 men aged 50 to 90 years. Using an objective cognitive test battery, the results suggested a beneficial relationship between higher testosterone levels and spatial ability. In this study, men classified as hypogonadal had a lower cognitive status on measures of visual and verbal memory, visuospatial rotation and visuomotor scanning. Furthermore, men with higher testosterone levels exhibited reduced rates of cognitive decline on visual memory tasks, whereas men classified as hypogonadal showed a faster rate of cognitive decline on these tasks. The results of the study by O'Connor et al. (2001) also suggested that hypogonadal patients may have persistent cognitive deficits in the spatial ability domain. In Barrett-Connor et al's (1999) population-based study of 547 men between the ages of 59 and 89 years, the association between baseline testosterone and neuropsychological performance was measured using a combination of objective cognitive tests and self-report measures. Findings indicated that higher bioavailable testosterone concentrations in men predicted better mental control and long-term verbal memory. Similarly, Cherrier et al. (2001) explored the relationship between exogenous testosterone administration and spatial ability and verbal memory in 25 healthy older men between 50 and 80 years of age. Using a battery of cognitive tests, results showed improvements in spatial and verbal memory and spatial abilities in response to short-term testosterone treatment. However,

improvements were not evident for attention and language cognitive domains, providing further evidence for the specific role of testosterone on spatial memory and spatial abilities.

4.4.2. Changes in Cognitive Functioning during Androgen Deprivation Therapy

The results of previous research suggests that ADT may interfere with cognitive functioning in PCa patients, as this particular form of treatment reduces the amount of bioavailable testosterone to castration levels (Jenkins, et al., 2005). However, the domains of cognition affected remain unclear. The effects of hormonal treatment on attention and information processing as well as memory function have been investigated in several studies, as these domains are considered vulnerable to changes in sexual hormone levels (Salminen, 2003). Salminen et al. (2003) conducted an observational study of 25 men receiving ADT together with radiation and found no decline in cognitive function after 12 months of therapy but, rather, noted an improvement in object recall. However, following this study, Salminen et al. (2004) observed significant associations between testosterone decline and impairments in cognitive processing efficiency, with the degree of change in cognitive performance related to the magnitude of testosterone decline. In another study, Cherrier, Rose and Higano (2003) compared the cognitive function of 19 patients with increasing PSA following intermittent ADT with that of 15 healthy controls. Results did not change significantly on measures of verbal and spatial memory, executive function or language after nine months of ADT and after three months post treatment. However, a significant decline in performance on a measure of spatial ability (mental rotation task) was observed. Furthermore, PCa patients in the study by Joly et al. (2006) failed to self-report more cognitive problems on the

Functional Assessment of Cancer Therapy – Cognitive (FACT-Cog) than controls. In a more recent study, Mohile and colleagues (2010) examined the neuropsychological functioning of a cohort of men with PCa prior to ADT administration and six months following ADT initiation to assess potential changes in cognitive abilities. No declines in any cognitive domains following ADT treatment were found, but rather improvements in visuospatial planning were observed post-treatment. However, in this study, practice effects were not explicitly controlled and the authors acknowledged that improvements in function could have represented learning or practice effects.

There have been numerous studies in which deficits in cognitive functioning have been identified in several domains of performance in men undergoing ADT treatment. Using a combination of both objective cognitive tests and self-report QoL instruments, Jenkins et al. (2005) found a notable pattern of deficit on tasks of spatial memory and spatial ability in 32 localised PCa patients receiving ADT. Using the Wechsler Memory Scale-Revised (WMS-R) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) on 50 men treated with ADT for localised and advanced PCa for 6 months, Green et al. (2002) also found significant decreases in memory, attention, and executive function. More recently, Green et al. (2004) found that androgen ablation was associated with decreased performance on several tasks requiring complex information processing. Cherrier, Aubin and Higano (2009) used a battery of objective cognitive tests to assess mood and cognition in 19 healthy controls and 19 non-metastatic PCa patients undergoing intermittent ADT. Findings indicated a decline in spatial reasoning and working memory abilities in men receiving ADT for PCa. In this study, however, verbal memory, verbal fluency and selective attention remained unchanged. Jim and colleagues (2010) compared

cognitive functioning of men receiving ADT with an age and education-matched comparison group of healthy men without cancer. Patients with PCa recorded lower scores and higher rates of impairment on five of seven individual tests of cognitive functioning compared to the controls. These authors recommended monitoring for cognitive changes while patients are on ADT as part of a comprehensive assessment of treatment-related toxicity.

Although the results of a number of studies have suggested that skills relating to spatial abilities may be influenced by declining testosterone levels with ADT treatment, the research literature also highlights the lack of consensus as to which cognitive domains are specifically affected. However, these equivocal findings may be a reflection of the different measurement techniques used in such studies. For example, the results of previous research have demonstrated a lack of relationship between patient self-reports and objective methods for assessing cognitive dysfunction (Klepstad et al., 2002). However, although consensus is difficult to determine, it is clear that testosterone may play some role in mediating cognitive ability, and therefore is of relevance when considering the potential side effects of ADT for PCa patients, particularly if it is prescribed long-term (Jenkins, et al., 2005). Furthermore, together with the broad range of negative side effects associated with ADT treatment previously discussed, loss of cognitive function may also have significant implications for QoL in patients with PCa.

4.5. Summary and Conclusion

In this chapter, a review of the literature highlighted that ADT can lead to a range of adverse psychological effects such as depression, anxiety and cognitive dysfunction, which can have a significant impact on QoL. In recognition of this, the

need for interventions aimed at improving QoL and psychosocial wellbeing in patients with PCa receiving ADT is apparent. In the next chapter, the literature considering physical activity as a complementary behavioural intervention to improve QoL in patients with PCa is reviewed. Based on the results of previous research, it is proposed that patients with PCa receiving ADT may benefit from physical activity interventions.

Chapter 5. Physical Activity and Prostate Cancer

5.1. Introduction

In this chapter, the concept of physical activity (PA) is defined and the methods of measuring PA are considered. Following this, the health benefits of PA and the cost of physical inactivity are discussed. Subsequently, the potential benefit of PA for patients with cancer is reviewed. Finally, intervention studies involving PA in patients with PCa are reviewed and the beneficial effects of PA on a wide variety of biopsychosocial outcomes for PCa patients undergoing ADT identified. The aim of this review of PA intervention studies with PCa patients receiving ADT is to highlight gaps in the existing literature and provide the rationale for the current study.

5.2. The Physical Activity Construct

5.2.1. Defining Physical Activity

According to the World Health Organisation (2012), PA is defined as ‘any bodily movement produced by skeletal muscles that results in energy expenditure’. Some examples of PA are walking, playing sport, work-related activity, gardening and walking upstairs. Exercise is a subset of PA defined as ‘planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness’ (Armstrong, Bauman, & Davies, 2000). Therefore, exercise has specific objectives of improving fitness, performance and health. PA is the focus of the present study and therefore this concept will be described in further detail. PA comprises four components including duration (length of time spent participating in PA); frequency (number of times PA was participated in e.g., over the last 7 days);

type (specific activities undertaken e.g., gardening, walking); and intensity (self-perceived energy exerted in a period of PA).

PA is categorised as light-, moderate- or vigorous-intensity depending on the energy expenditure of a specific activity. A metabolic equivalent, or MET, is a unit describing the ratio of the rate of energy expended during an activity compared with rest (United States Department of Health and Human Services, 2008). Light-intensity activities are defined as less than 3.0 METs (expending less than 3.5 calories per minute) and may include activities such as casual walking, sitting or stretching. Moderate-intensity PA is described as activity between 3.0 and 6.0 METs (expending between 3.5 and 7 calories per minute). For example, walking at a rate of 4.8km per hour requires 3.3 METs of energy expenditure and would therefore be considered a moderate-intensity activity. Other examples of moderate-intensity activity may include housework that involves intense scrubbing or cleaning, recreational swimming, yoga or low impact aerobics. Vigorous-intensity PA comprises activity greater than 6.0 METs (expending more than 7 calories per minute). For example, running at approximately 6 ½ minutes per kilometre is a 10 MET activity and is therefore classified as vigorous intensity. Other examples may include high impact aerobics, boxing and competitive team sports such as netball, football or rugby (Reiser & Schlenk, 2009; United States Department of Health and Human Services, 2008).

Distinguishing between aerobic and resistance training is also important when defining PA. Aerobic exercise involves substantial increases in heart rate and energy expenditure through dynamic activities using large muscle groups. Regular participation improves cardiovascular system and skeletal muscle functioning, leading to an increase in endurance performance (Howley, 2001). Conversely,

resistance exercise is designed specifically to increase muscular strength, power, and endurance by varying the resistance (intensity), the number of repetitions or times the resistance is moved in a single group of exercises (set), the number of sets completed, and the rest interval provided between sets. Muscular power, strength and endurance are measures of the rate at which work is performed, ability of the muscle to generate force, and ability of the muscle to make repeated contractions against constant resistance, respectively (Howley, 2001). Updated recommendations from the American College of Sports Medicine (ACSM) and the American Heart Association endorse the incorporation of both aerobic and resistance exercise in regular PA for the maintenance of health and physical independence (Haskell et al., 2007).

5.2.2. Measurement of Physical Activity

As outlined above, PA comprises several components (e.g., intensity, frequency, duration and type) and can be carried out in a variety of settings (e.g., leisure-time, occupational, transport and housework/gardening). Furthermore, there are several dimensions of PA related to health (e.g., fitness, strength, flexibility and energy expenditure). Consequently, the development of an appropriate tool to measure PA is challenging (Armstrong, et al., 2000). Methods for measuring PA include both self-report instruments and objective assessments of movement, fitness or energy balance.

While self-report methods of PA are more practical, less costly and easier to administer than laboratory PA measurements, their validity in individual assessment has some limitations. These caveats may include: reduced recall accuracy of PA over time; over estimation of intensity, frequency and duration of PA; and susceptibility to

socially desirable answers or feigning compliance (Reiser & Schlenk, 2009). The primary measurement goal of all self-report PA instruments is to estimate the proportion of respondents reaching an energy expenditure threshold that is sufficient to be of health benefit (Brown, Bauman, Chey, Trost, & Mummery, 2004). However, a range of self-report PA instrument formats are currently used to target specific populations (e.g., children, elderly or adolescents), requiring recall of PA levels over a range of time periods (e.g., past 24 hours, 7 days or 4 weeks) and measuring PA within different contexts or domains of activity. Consequently, results of previous research have demonstrated large differences across self-report PA instruments in reported PA levels and prevalence estimates of the proportion of individuals classified as reaching a particular PA threshold (Brown, et al., 2004). However, despite these limitations, the self-report PA method remains a valuable screening tool in clinical practice.

Objective PA methods include: direct observation (PA levels observed and recorded by a trained individual); pedometers (measure the number of steps taken through motion sensing mechanisms); accelerometers (measure movement in up to three dimensions to provide information on acceleration, accurately recording PA intensity); and heart rate monitors (device measuring the heart's response to physical demand) (Reiser & Schlenk, 2009). Although objective methods may enhance the accuracy of PA assessment, direct observation is time intensive and devices such as pedometers, accelerometers and heart rate monitors may vary greatly in accuracy and cost (Reiser & Schlenk, 2009). It has been suggested that combining self-report and objective PA measures may increase the accuracy of assessment (Vanhees et al., 2005).

5.2.3. *The National Physical Activity Guidelines of Australia*

The current National Physical Activity Guidelines of Australia (NPAGA) recommend achieving 150 minutes (i.e., 2 hours and 30 minutes) of moderate-intensity PA per week (Department of Health and Ageing, 2005). The ACSM has recommended that individuals accumulate at least 150 minutes of moderate-intensity PA per week and incorporate twice weekly resistance training (Schmitz et al., 2010). It is also recommended that between 8 and 10 exercises are performed on two or more non-consecutive days each week using the major muscle groups, allowing 8 to 12 repetitions for each exercise (Haskell, et al., 2007). However, the inclusion of resistance training is not mentioned in the NPAGA.

There has been debate in the research literature regarding the domains of activity considered suitable to incur health benefits. For example, Armstrong et al. (2000) reported a lack of evidence for determining whether gardening and household chores or walking at work contributes to achieving a sufficient level of activity for health benefit. Conversely, in a systematic review conducted by Dunn et al. (2001) it was concluded that both occupational and leisure-time PA were linked to declines in depression and anxiety symptoms. The ACSM proposed that routine activities of daily living, including domestic, transport and occupation related PA should be supplemented with the recommended level of aerobic activity (Haskell, et al., 2007). However, research evidence implies that measurement of PA conducted voluntarily in leisure-time may provide the most accurate measure of PA for health benefit (Armstrong, et al., 2000). Leisure-time PA includes exercise, sports, recreation, or hobbies that are not associated with activities as part of work, household duties or transportation (Reiser & Schlenk, 2009). The results of previous research have evaluated total leisure-time PA in isolation to determine whether participants are

meeting PA guidelines (Lynch, Cerin, Owen, & Aitken, 2007; Vallance, Courneya, Jones, & Reiman, 2005).

5.2.4. Physical Activity Recommendations for Patients with Cancer

Results of various studies support the contention that PA is essential in the prevention of chronic disease and premature death (Warburton, et al., 2006). However, in the past, there has been debate over the minimum volume of exercise required for health benefits in patients with cancer. The association between PA levels and QoL using different forms of exercise has been examined in several studies and consequently, it has been difficult to determine what frequency, intensity, type, and duration may be most effective and safe in improving QoL in patients with cancer (Bicego et al., 2009). A review of the literature has revealed that moderate PA for between 30 and 60 minutes per day had a stronger protective effect against colon and breast cancer compared to activities of low intensity (Thune & Furberg, 2001). Further, women who engaged in seven or more hours of moderate-to-vigorous activity per week had a lower incidence of breast cancer compared to women who were physically inactive (Thune & Furberg, 2001).

In patients with an established cancer diagnosis, PA equivalent to walking one or more hours per week was associated with improved survival compared to no exercise with the greatest benefit observed in cancer survivors engaging in three to five hours per week of moderate exercise (Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005). The results of two Canadian based studies found that ovarian cancer and non-Hodgkin's lymphoma survivors meeting PA guidelines (150 minutes of moderate-intensity PA per week) reported more favourable outcomes in relation to fatigue, psychosocial functioning and several QoL domains than those patients who

did not meet PA guidelines (Stevinson et al., 2009; Vallance, et al., 2005). Likewise, in an Australian population-based study of 1,966 colorectal cancer survivors, Lynch and colleagues (2007) found that participants who met the NPAGA had significantly higher overall QoL, and physical and functional wellbeing compared to colorectal cancer survivors not meeting NPAGA. In a study by Keogh et al. (2010), men with PCa receiving ADT who were meeting PA guidelines had significantly better QoL than participants not meeting PA guidelines. However despite this evidence, no specific PA recommendations have been established for patients with PCa.

5.3. Physical Activity

5.3.1. The Health Benefits of Physical Activity

The health benefits of PA are widely recognised with the results of hundreds of population-based studies published in peer-reviewed journals supporting this contention (Warburton, et al., 2006). Appropriate regular PA is a major component in preventing the growing global burden of chronic disease with physical inactivity a modifiable risk factor for cardiovascular diseases, including diabetes mellitus, cancer, obesity, hypertension, bone and joint diseases (e.g., osteoporosis and osteoarthritis) and depression (Warburton, et al., 2006). Furthermore, individuals who participate in moderate to vigorous levels of PA and/or have high levels of cardiorespiratory fitness have a lower mortality rate than those with a sedentary lifestyle or low cardiorespiratory fitness (Armstrong, et al., 2000). Results of studies have also indicated that engagement in regular PA is associated with increased self-esteem, improvements in activities of daily living, and improved cognitive and neuropsychological performance (Denkinger, Nikolaus, Denkinger, & Lukas, 2012; Kraft, 2012; Sieverdes et al., 2012; Sonstroem, 1984). Furthermore, it has been

consistently shown that participation in PA can reduce symptoms of stress, anxiety and depression (Dunn, et al., 2001; Glenister, 1996; Hassmen, Koivula, & Uutela, 2000; Paffenbarger, Lee, & Leung, 1994; Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991; Sieverdes, et al., 2012). PA is associated with increased mental health in population studies (Simonsick, 1991; Stephens, 1988) and is recognised as an evidence-based treatment for clinical anxiety and depression (Bauman & Owen, 1999). Results of studies have demonstrated that inactive people are twice as likely to develop depression compared with active people (Warburton, et al., 2006). PA has also been found to increase physical self-worth and body esteem (Harrington & Badger, 2009). Taylor and Fox (2005) found that participants randomised to an exercise intervention demonstrated evidence of improved physical self-worth, physical condition and physical health compared to the no exercise control group.

5.3.2. The Cost of Physical Inactivity

Despite the increasing awareness and understanding of PA and its benefits, this is not reflected in PA behaviours (Armstrong, et al., 2000). For example, the World Health Organisation (WHO) reported that at least 60% of the global population fails to achieve the minimum recommendations of 30 minutes of moderate intensity PA daily (Puska, Benaziza, & Porter, 2003). In 2007 to 2008, approximately 62% of adults did not meet PA guidelines, with 64% of women and 60% of men failing to achieve NPAGA (Australian Bureau of Statistics, 2011).

Coinciding with the increasing prevalence of physical inactivity, there has been a notable increase in the burden of chronic diseases. Physical inactivity represents a significant risk factor for several chronic and increasingly prevalent conditions including arthritis, coronary heart disease, depression, type 2 diabetes,

osteoporosis, stroke and obesity (Australian Institute of Health and Welfare, 2010).

In 1993-94, the estimated direct health care cost of six diseases attributable to physical inactivity was approximately \$377 million. This total consists of \$161 million for coronary heart disease, \$101 million for stroke, up to \$56 million for depressive disorders, \$28 million for type two diabetes, \$16 million for colon cancer and \$16 million for breast cancer (Stephenson, Bauman, Armstrong, Smith, & Bellew, 2000). In 1996, an estimated 13,019 deaths were due to chronic diseases linked to physical inactivity. Of these deaths, 53% were attributed to ischaemic heart disease, 22% to stroke, and 12% to colorectal cancer (Mathers, Vos, & Stevenson, 1999). Despite education and health promotion campaigns emphasising the importance of regular PA, current statistics indicate that the cost of physical inactivity continues to rise. Nationally in 2003, 6.7% of the disease burden was attributed to physical inactivity (Australian Institute of Health and Welfare, 2010). The direct cost of physical inactivity in Australia was estimated to be approximately \$1.5 billion in 2006 to 2007, with the largest components of this cost associated with falls (\$469 million) and coronary heart disease (\$372 million) (Econtech, 2007).

5.3.3. Benefits of Physical Activity for Patients with Cancer

There is evidence suggesting that participation in PA and high cardiorespiratory fitness reduces the risk of developing some forms of cancer, in particular breast and colon cancer (Armstrong, et al., 2000; Warburton, et al., 2006). The results of a number of studies have shown the protective effect of PA on risk of colon cancer (Colditz, Cannuscio, & Frazier, 1997) and on the prevention of precancerous polyps in the large bowel (Neugut et al., 1996; Slattery et al., 1997). Lee (2003) reported that physically active men and women exhibited a 30-40% reduction in the relative risk of colon cancer, and physically active women a 20-30%

reduction in the relative risk of breast cancer compared with their inactive counterparts. The results of other studies have revealed a reduction in the risk of breast cancer in physically active women (Gammon, John, & Britton, 1998; Latikka, Pukkala, & Vihko, 1998; Verloop, Rookus, Van der Kooy, & van Leeuwen, 2000). The evidence relating to PA and other cancers is less conclusive. There is, however, some evidence that vigorous activity protects men against PCa (Giovannucci et al., 1998), although other researchers have not found such a relationship (Liu et al., 2000).

In addition to the suggested link between engagement in regular PA and the prevention of some cancers, regular PA appears to confer a health benefit to patients with an established cancer diagnosis. For instance, the results of a number of studies have shown that engagement in regular PA after cancer diagnosis may reduce the risk of death from disease (Holmes, et al., 2005; Kenfield, et al., 2011; Meyerhardt et al., 2006; West-Wright et al., 2009). Furthermore, regular PA is associated with an improvement in overall QoL and health status in patients with cancer and cancer survivors (Bicego, et al., 2009; Courneya, 2009; Courneya et al., 2009; Hong et al., 2007; Kendall, Mahue-Giangreco, Carpentar, Ganz, & Bernstein, 2005; Lynch, et al., 2007; Mosher et al., 2009; Warburton, et al., 2006). In the survey of 1208 breast, colorectal and PCa survivors by Mosher et al. (2009) it was revealed that 150 minutes of moderate-to-vigorous exercise weekly was associated with better physical QoL, including less pain and role limitations associated with physical problems and better physical functioning, and vitality. However, 150 minutes of exercise weekly was not associated with any mental health outcomes, with the exception of better social functioning. In a long-term analysis of 371 breast cancer survivors, Kendall et al. (2005) found that positive change in PA was associated with higher QoL at least

10 years after cancer diagnosis compared to those who had not participated in regular PA. Similarly, healthy lifestyle practices, including regular moderate-to-vigorous exercise and consumption of a plant-based, low-fat diet, have been associated with better physical functioning in breast and PCa survivors over 60 years of age (Demark-Wahnefried et al., 2004). Furthermore, breast cancer survivors in the study by Pinto and Trunzo (2004) who reported regular PA participation demonstrated improved body esteem compared to sedentary breast cancer survivors.

PA has been proposed as a possible complementary behavioural intervention to improve health and wellbeing outcomes in cancer patients (Conn, et al., 2006). Recent attention has focused on the role of PA in improving fatigue and other symptoms such as mood, most notably depression, QoL and body composition or physical function (Conn, et al., 2006). For example, Bicego et al. (2009) conducted a systematic review of the impact of structured exercise programs, lasting a minimum of four weeks on QoL in women with all stages of breast cancer. Based on participants in nine randomised controlled trials meeting the inclusion criteria, exercise improved mood and QoL by increasing overall health through socialisation, goal setting, decreased body weight and/or decreased fatigue. Similarly, Hong et al's (2007) findings suggested that 30 minutes of moderate PA 4 days per week was associated with improved QoL. In this study the dose-response was such that 'highly active' survivors who reported vigorous PA for 30 minutes 5 days per week had even better QoL. In a recent randomised controlled trial including 122 lymphoma patients conducted by Courneya et al. (2009), results of a 12 week aerobic exercise program found significant improvement in physical functioning, overall QoL, fatigue, general health, happiness, depression, cardiovascular fitness and lean body mass of participants completing the exercise intervention compared to those patients

allocated to the usual care condition. Given the substantial evidence for the health benefits of PA, particularly for patients with cancer and survivors of cancer, engaging in regular PA may be essential in increasing QoL and psychosocial wellbeing.

Unfortunately, many cancer survivors do not adhere to various national guidelines regarding PA and diet. National surveys reveal few lifestyle differences between individuals diagnosed with cancer and the general population, and the vast majority of the population in general do not adhere to such guidelines (Eakin et al., 2007). Survivors of breast, colorectal and PCa cancers have been reported as having suboptimal dietary and exercise behaviours (Blanchard, Courneya, & Stein, 2008). For example, in Eakin et al.'s (2007) population-based survey investigating lifestyle improvements following a cancer diagnosis, including 968 cancer survivors and 5,808 comparison participants, no differences by cancer survivorship were reported for PA or the consumption of fruit and vegetables. Even more startling was the finding that cancer survivors were more likely to be current smokers than the comparison group. Bellizzi et al. (2005) reported similar levels of physical inactivity and overweight/obesity in cancer survivors and matched comparisons, with higher rates of smoking in younger cancer survivors. Findings indicate that unhealthy behaviours in large samples of cancer survivors in Australia are similar, if not worse, than those in a matched sample of individuals without cancer. This suggests that health promotion efforts regarding diet and PA need to be specifically targeted to cancer survivors (Eakin, et al., 2007).

5.4. Physical Activity and Prostate Cancer

A number of intervention studies involving PA in patients with PCa have demonstrated beneficial effects on a range of biopsychosocial outcomes. For example, Segal et al. (2003) concluded that a 12-week program of resistance training in men receiving ADT for PCa, reduced fatigue and improved QoL. Similarly, Segal et al. (2009) used a three-arm trial to compare the effect of resistance and aerobic exercise with usual care in men receiving RT for PCa. Both resistance and aerobic exercise were found to mitigate fatigue over the short term. In this study, however, resistance training was associated with longer term improvements in fatigue and additional benefits for QoL when compared with the effects of aerobic exercise. Furthermore, Galvao et al. (2006) showed that a 20-week high-intensity progressive resistance training program substantially improved muscle strength and endurance while preserving body composition and bone mass. This demonstrated the importance of PA in offsetting the harmful physical side effects associated with ADT in patients with PCa. Furthermore, in this study PA did not affect PSA levels, testosterone production or disease activity indicating that PA can be safely tolerated in men receiving ADT (Galvao et al., 2008; Galvão, et al., 2006). In a more recent study, Galvao et al. (2010) examined the impact of a combined resistance and aerobic exercise program to counteract the negative side effects of ADT. After 12 weeks, PCa patients undertaking the PA intervention showed significantly improved muscle mass, strength and physical function with vast improvements in several aspects of QoL including general health and reduced fatigue compared to control participants.

Patients with PCa involved in home-based, unsupervised PA programs have also shown improvements in QoL and psychosocial wellbeing (Carmack Taylor et

al., 2006; Culos-Reed, Robinson, Lau, O'Connor, & Keats, 2007; Culos-Reed, et al., 2010; Windsor, Nicol, & Potter, 2004). Culos-Reed et al. (2007) conducted a 12-week theory-based intervention program designed to promote daily PA. In this study, participants were able to successfully engage in a home-based PA program. Increases in weekly home-based activity levels were associated with significant improvements in physical functioning, fatigue and overall QoL. Similarly, Windsor et al. (2004) used a randomised controlled trial design to investigate the effects of a 4-week unsupervised home-based walking program on fatigue and QoL in men receiving EBRT for PCa. Home-based moderate-intensity walking produced a significant improvement in physical functioning with no significant increases in fatigue, suggesting that improving the physical functionality of PCa patients may be necessary to combat radiation fatigue and improve psychosocial wellbeing. Conversely, the results of a randomised trial evaluating the effectiveness of a 6-month group-based lifestyle PA program for PCa patients revealed no improvements in QoL or physical composition and no increases in PA participation in 134 PCa patients (Carmack Taylor, et al., 2006). However, this lifestyle approach, which emphasised cognitive behavioural skills, was effective in changing the way in which participants viewed activity and the strategies they used to be more active. Cancer survivors have reported a preference for unsupervised home-based walking as a mode of exercise in previous research (Hong, et al., 2007) and therefore this mode of exercise intervention may be a better option for this population.

In a number of observational studies significant improvements in QoL and psychosocial wellbeing in patients with PCa who are physically active while undergoing treatment have been found (Blanchard et al., 2004; Dahn et al., 2005; Demark-Wahnefried, et al., 2004). For example, in a cross-sectional survey of 107

PCa survivors, Blanchard et al. (2004) found that participants who reported being physically active for at least 30 minutes, 5 or more times a week, had significantly higher health-related QoL than those who did not. Similarly, Demark-Wahnefried et al. (2004) in a cross-sectional survey indicated that regular vigorous exercise was associated with increased physical function in PCa patients. Positive associations between regular PA and sexual functioning in PCa patients receiving EBRT have also been reported (Dahn, et al., 2005). In several cross-sectional studies the prevalence of PA in PCa survivors has been investigated (Bellizzi, et al., 2005; Blanchard, et al., 2004; Coups & Ostroff, 2005; Dahn, et al., 2005; Demark-Wahnefried, et al., 2004). In these studies, with all using self-report assessment of PA, the prevalence rate of PA ranged from less than 30% to more than 70% (mean 49.1%, median 50.2%). Sample size in the studies varied from 107 to 843 participants (Thorsen, Courneya, Stevinson, & Fossa, 2008). Coups and Ostroff (2005) and Bellizzi et al. (2005) compared PA prevalence rates of PCa survivors to non-cancer controls, with the results of both studies detecting higher PA prevalence rates in PCa survivors (29% and 30%, respectively) than non-cancer controls 65 years or older (22% and 26%, respectively). However, in this study potential confounders such as participant age were not controlled (Thorsen, et al., 2008).

In the observational and prevalence studies described in this chapter there was variation in the operational definitions of what constitutes adequate PA levels and consequently, it is difficult to compare QoL outcomes and those defined as ‘active versus inactive’ across studies. For example, in some of the prevalence studies, PCa survivors were defined as physically active if they met the ACSM recommendations. However, these guidelines include a number of criteria by which PA recommendations may be met (Thorsen, et al., 2008). For example, Denmark-

Wahnefried et al (2004) defined ‘active’ as those engaging in vigorous exercise for at least 20 minutes 3 times per week. Conversely, Blanchard et al (2004) defined ‘active’ as those engaged in moderate PA for at least 30 minutes 5 times per week. In other studies, both moderate and vigorous activity criteria have been used to define participants as ‘active’ or ‘inactive’ (Bellizzi, et al., 2005; Coups & Ostroff, 2005). In one study, the concept of ‘active versus inactive’ was not defined, and a mean score value of PA in METS was reported instead (Dahn, et al., 2005).

5.5. Summary and Conclusions

The results of a number of intervention and observational studies have demonstrated the utility of PA in alleviating the negative side effects associated with treatment for PCa. Previous clinical trials have shown the benefits of PA using structured, supervised exercise programs and have established the utility of both resistance and aerobic forms of exercise in reducing the adverse side effects of ADT. However, it is important to recognise that there may be a number of extraneous variables associated with the observed reduction in the negative side effects of treatment as a result of participation in a supervised PA program. For example, the concentrated attention patients receive when undergoing a clinical trial in the experimental condition may be associated with a reduction in negative side effects (i.e., the Hawthorne effect).

The results of a number of observational studies have revealed significant improvements in QoL and psychosocial wellbeing in patients with PCa undergoing treatment who are physically active in their daily lives. The results of previous studies have indicated that those classified as ‘active’ report fewer adverse side effects of treatment and better QoL than those classified as ‘inactive’. However, as

previously discussed, the definitions of ‘active’ and ‘inactive’ are quite diverse across the various studies, as are the PA guidelines used to determine this criterion. No previous studies could be located in which those meeting the NPAGA in their daily lives experience a reduction in the negative side effects associated with ADT. PA may be one of the few cost-effective interventions that can enhance functional wellbeing in patients with PCa and consequently, its incorporation into coping and rehabilitation programs may be essential (Courneya, 2003). However, it is first important to examine the association between patients with PCa receiving ADT who are classified as ‘sufficiently active’ and improvements in QoL and psychosocial wellbeing. Previous studies have not yet established whether moderate levels of PA or adherence to NPAGA will improve QoL in this population. This is essential to determine the utility of maintaining a regular exercise regime and the intensity and frequency of PA required to alleviate the negative side effects of treatment in patients with PCa undergoing ADT.

In the next chapter, the first paper for publication, *The impact of physical activity on psychosocial outcomes in men receiving androgen deprivation therapy for prostate cancer: A systematic review*, is presented. The purpose of this systematic review was to determine the effectiveness of PA as an intervention to improve depression and anxiety symptoms, cognitive function and QoL in patients receiving ADT for PCa.

Chapter 6. The Impact of Physical Activity on Psychosocial Outcomes in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

6.1. Rationale and Aims for Paper 1

In the paper featured in this chapter, a systematic review of the literature was conducted to evaluate the results of studies examining the utility of PA as an intervention to improve QoL and psychosocial wellbeing in men receiving ADT for PCa.

The research questions addressed in the current chapter were:

1. Does PA improve symptoms of depression and anxiety, cognitive function and QoL in men receiving ADT for PCa?
2. Does the impact of PA on depression, anxiety, QoL and cognitive function in this patient group differ according to length of time on ADT?

The following manuscript was submitted to *Health Psychology* in November 2012. The manuscript was reviewed by two referees with only minor revisions requested in January 2013. The revised version of the manuscript was resubmitted to *Health Psychology* in April 2013 and is currently being reconsidered for publication. The formatting of this paper is in accordance with the style specified by the editorial board.

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter 6

Declaration by candidate


In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Development of systematic review protocol and search strategy; registration and publication of protocol; implementation of literature review search; writing draft paper.	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Sue Burney	Guidance with review design and study inclusion; critical review of draft paper.	
Ms Jane Fletcher	Guidance with review design and study inclusion; critical review of draft paper.	
Dr Jo Brooker	Guidance with review design and study inclusion; critical review of draft paper.	

Candidate's
Signature

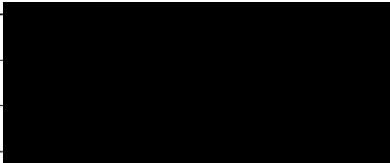
	Date 21/11/2012
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Declaration by co-authors

The undersigned hereby certify that:

- (1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- (2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- (4) there are no other authors of the publication according to these criteria;
- (5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- (6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) School of Psychology and Psychiatry, Clayton Campus, Monash University

Signature 1	Dr Sue Burney:		Date
Signature 2	Ms Jane Fletcher:		21/11/2012
Signature 3	Dr Jo Brooker:		26/11/12
			28-11-12

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**THE IMPACT OF PHYSICAL ACTIVITY ON PSYCHOSOCIAL
OUTCOMES IN MEN RECEIVING ANDROGEN DEPRIVATION
THERAPY FOR PROSTATE CANCER: A SYSTEMATIC REVIEW**

Authors:

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6.2. ABSTRACT

Objective: Depression, anxiety and cognitive dysfunction are common complaints in men with prostate cancer (PCa) receiving androgen deprivation therapy (ADT). Consequently, the quality of life (QoL) of these men is negatively impacted. This systematic review evaluated the effectiveness of PA as an intervention to improve depression and anxiety symptoms, cognitive function and QoL in patients receiving ADT for PCa. **Methods:** Inclusion criteria and search strategy were defined and documented in a protocol registered with the International Prospective Register of Systematic Reviews [Registration # CRD42012002666]. Due to the limited number of studies examining these outcomes in this patient group, no limitations were placed on study designs included. A systematic search of Ovid MEDLINE, PsycINFO, EMBASE, Informit, Scopus, Cochrane Library and CINAHL databases identified seven relevant studies: Four clinical PA interventions; two pilot studies; and one cross-sectional survey. Data extraction and risk of bias assessment tools developed by the Cochrane Collaboration were used to evaluate evidence. **Results:** Existing data suggest that PA improved QoL in men with PCa receiving ADT. The existing evidence, however, is not sufficiently robust to determine the adequacy of PA as an intervention to improve depression, anxiety and cognitive function outcomes in this patient group. **Conclusions:** Despite the lack of studies conducted, preliminary findings support the utility of PA in rehabilitation programs for improving QoL in men undergoing ADT for PCa. A clear gap in the current literature was identified, confirming the need for further clinical trials in which depression, anxiety and cognitive function are evaluated.

Keywords: Physical activity; Prostate cancer; Quality of life; Cognitive function; Depression; Anxiety.

6.3. INTRODUCTION

Prostate cancer (PCa) is the second most commonly diagnosed cancer worldwide, accounting for 14% (903,500) of the total new cancer cases in 2008, with the highest incidence rates recorded in developed countries including those in Europe and North America (Jemal et al., 2011). The increasing prevalence of PCa is attributed to the ageing population, with the disease primarily affecting men over the age of 50 years; increased use of screening tests such as prostate specific antigen (PSA) and digital rectal examination (DRE); and continual advancement in treatment options leading to extended survival (Kirby & Patel, 2008). A range of treatment options are available for PCa including radical prostatectomy, external beam radiotherapy (EBRT), brachytherapy, watchful waiting, active surveillance and androgen deprivation therapy (ADT) (Kirby & Patel, 2008).

The prevalence of ADT use has increased considerably with oncologists integrating ADT into the treatment of localised disease, whereas previously this form of treatment was used to palliate symptoms and delay disease progression in patients with metastatic disease (Bria et al., 2009; Scherr, Swindle, & Scardino, 2003). Furthermore, depending on the severity of disease, the duration of ADT treatment can be prolonged up to 3 years for patients treated with curative intent and indefinite use for those treated with palliative intent (National Comprehensive Cancer Network, 2012). This has prompted closer examination of the adverse effects of ADT to enhance treatment decisions and improve understanding of the impact of this therapy on quality of life (QoL) (Sadetsky et al., 2011; Sharifi, Gulley, & Dahut, 2005). While ADT effectively reduces prostate and tumour volume, testosterone levels and PSA levels (Kirby & Patel, 2008), the potential physiological side effects are widely documented. These include deleterious effects on muscle, fat and bone mass with

increased risk of osteoporosis, diabetes, obesity and cardiovascular related mortality (Keating, O'Malley, & Smith, 2006; Lage, Barber, & Markus, 2007; Taylor, Canfield, & Du, 2009). As well as the physical consequences, there has been increasing recognition of the psychological side effects of ADT, including depression, anxiety and cognitive dysfunction (Galvao, Taaffe, Spry, & Newton, 2007; Shahinian, Kuo, Freeman, & Goodwin, 2006; Sharifi, et al., 2005; Taylor, et al., 2009).

Links between ADT and multiple aspects of psychosocial functioning have been recognised in previous research (Almeida, Waterreus, Spry, Flicker, & Martins, 2004; Cherrier, Aubin, & Higano, 2009; Pirl, Siegel, Goode, & Smith, 2002; Rosenblatt & Mellow, 1995). For example, increases in fatigue, depression, moodiness, irritability, tension, and anxiety and loss of vigour have been reported by patients receiving ADT, with these outcomes reducing in severity three months after the cessation of ADT (Cherrier, et al., 2009). However, in other studies evaluating patients receiving intermittent or cyclical periods of ADT no difference has been found in QoL outcomes between on- and off-treatment phases, suggesting that the adverse effects of ADT may be long lasting and highlighting the importance of addressing psychosocial functioning during all stages of survivor trajectory (Alibhai, Gogov, & Allibhai, 2006). Pirl et al. (2002) reported a prevalence rate of 12.8% for major depressive disorder in a sample of 45 men undergoing ADT; 8 times higher than the rate in the general United States male population (1.6%) and 32 times higher than the rate in men over 65 years (0.4%). Prevalence rates for depression have not been compared across PCa treatment types. However, the results of two previous studies comparing the psychological impact of four treatments for PCa (active surveillance/watchful waiting; radical prostatectomy; radiotherapy; and ADT)

concluded that compared with other active treatments for PCa, ADT was associated with greater psychological distress and depression (Couper et al., 2009; Mols et al., 2006).

Furthermore, the results of previous research suggest that testosterone is related positively to cognitive functioning and consequently, the substantial and abrupt reduction of testosterone levels in men receiving ADT may contribute to cognitive difficulties (Jenkins, Bloomfield, Shilling, & Edginton, 2005). Higher testosterone levels have been found to have a beneficial effect on spatial ability and visual/verbal memory (Barrett-Connor, Goodman-Gruen, & Patay, 1999; Cherrier et al., 2001; Moffat et al., 2002; O'Connor, Archer, Hair, & Wu, 2001) with the degree of change in cognitive performance related to the magnitude of testosterone decline (Salminen, Portin, Koskinen, Helenius, & Nurmi, 2004). In addition, deficits in several domains of cognition have been reported in this patient group including, spatial memory and spatial ability (Cherrier, et al., 2009; Jenkins, et al., 2005); executive function (Green et al., 2002); and information processing (Green et al., 2004). Although there appears to be a lack of consensus in the literature as to which specific cognitive domains are affected, it is clear that testosterone may play some role in mediating cognitive ability, and therefore is of relevance when considering the impact of ADT on patient QoL, particularly if it is prescribed long-term (Jenkins, et al., 2005).

In numerous studies reduced QoL has been observed in patients receiving ADT compared to those not receiving ADT. In particular, decreases in sexual, social and role functioning (Fowler, McNaughton-Collins, Walker-Corkery, Elliott, & Barry, 2002; Sharifi, et al., 2005), lower physical functioning and general health (Dacal, Sereika, & Greenspan, 2006), and fatigue, loss of energy and emotional

distress (Herr & O'Sullivan, 2000) have been documented. Given the impact of ADT on physical functioning, psychological wellbeing and QoL, the identification of interventions that may reduce the impact of this treatment is critical.

Physical activity (PA) has been proposed as a behavioural intervention to improve health and wellbeing outcomes for patients with cancer (Conn, Hafdahl, Porock, McDaniel, & Nielsen, 2006). The results of research to date have indicated encouraging effects of PA on physical function, muscular fitness, fatigue, anxiety and depression, with these in turn influencing patient QoL and possibly survival (Kenfield, Stampfer, Giovannucci, & Chan, 2011; Thorsen, Courneya, Stevinson, & Fossa, 2008). In a sample of 2,705 men with PCa, Kenfield et al (2011) reported a 33% lower risk of death from any cause and a 35% lower risk of PCa-specific death in men who exercised for approximately 3 hours per week, with modest amounts of vigorous activity required to substantially improve PCa-specific survival.

Furthermore, PA has been found to have no effect on PSA levels, testosterone production or disease activity, providing evidence that PA can be safely tolerated in this patient group (Galvao et al., 2008; Galvão et al., 2006). Despite the potential benefits of PA for this patient group, the proportion of patients engaging in regular PA remains relatively low. For example, more than half of the participants in Keogh and colleagues' (2010) study were classified as insufficiently active with only 45% of men receiving ADT for PCa meeting current PA guidelines (i.e., 150 minutes of moderate intensity PA per week). The purpose of this review therefore was to evaluate the efficacy of PA as an intervention to improve depression and anxiety symptoms, cognitive function and QoL in patients receiving ADT for PCa. Another purpose was to compare the impact of PA on these outcomes in patients receiving ADT for varying lengths of time.

6.4. METHOD

6.4.1. Inclusion Criteria

Prior to the literature search, the inclusion criteria and search strategy were defined and documented in a protocol registered with the International Prospective Register of Systematic Reviews [Registration # CRD42012002666]. Given the limited number of studies in which these specific outcomes have been examined in this patient group, no limitations were placed on the study designs included. Randomised controlled trials, pre-post-test designs, and cross-sectional studies in which the impact of engagement in regular PA on psychosocial outcomes during ADT treatment for PCa was examined, were incorporated. Only peer-reviewed literature was included in this review to assure the quality of included manuscripts. The primary outcome measures of interest were depression, anxiety, QoL and cognitive function. Studies in which participants of any age had received ADT for PCa were also included. The eligibility criteria for inclusion and exclusion of studies are provided in Table 6.1.

Table 6.1.

Inclusion and Exclusion Criteria for Systematic Search

Inclusion Criteria	Exclusion Criteria
Physical activity interventions	Studies with the additional interventions of psychotherapy or nutritional consultation
Exercise interventions	
Supervised and non-supervised interventions	Studies about physical activity behaviour or motivation
Participants who were PCa patients receiving ADT only (or separate results according to cancer and treatment type)	Studies involving outcomes other than depression, anxiety, quality of life or cognitive function
All study designs	
Pilot studies (no sample size limitations)	Studies involving the impact of physical activity on PCa patients undergoing forms of treatment other than ADT
Published in English	

PCa = Prostate Cancer; ADT = Androgen Deprivation Therapy

6.4.2. Literature Search Strategy

The literature search strategy was developed by two of the authors [Chipperfield, K and Brooker, J] in conjunction with a Monash University Subject Expert Librarian [Young, A]. Studies were identified by searching electronic bibliographic databases. Reference lists of relevant articles were also examined however no new material was identified. The search strategy was applied to Ovid MEDLINE and PsycINFO and adapted for EMBASE, Informit, Scopus, Cochrane Library and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. The search was limited to articles published in English. No restrictions were imposed on publication dates. The last search was conducted on 8th March 2013. The following search terms were used to search MEDLINE and PsycINFO and the syntax was adapted to search all other databases: prostat* neoplasm*; prostat* cancer*; prostat* carcinoma; prostat* adenocarcinoma*; prostat* adj5 tumo*; androgen deprivation therapy; androgen ablation; androgen suppression; hormone*

therapy; androgen antagonist/; androgen agonist; gonadotropin; luteinising hormone-releasing hormone*; anti-androgen*; orchidectomy; surgical castration; chemical castration; physical activity; physical exercise; exercise; sport* therapy; sport*; endurance; aerobic training; resistance training; cardiac training; aerobic activity; resistance activity; and motor activity. See Appendix A for an example of the search strategy employed.

6.4.3. Data Extraction and Synthesis

An adapted version of the Cochrane Consumers and Communication Review Group's data extraction template was used (Cochrane Consumers and Communication Review Group, 2012). Information pertaining to study eligibility was extracted by one reviewer [Chipperfield, K]. Where there was any uncertainty about whether an article satisfied the inclusion criteria, the article was discussed by the group of co-authors to determine inclusion or exclusion from the review. The following information was extracted for each included study: 1) characteristics of participants (type of treatment and duration of ADT) and the inclusion and exclusion criteria; 2) type of intervention (supervised or unsupervised PA, duration and frequency); 3) type of outcome (including reduction in depression and anxiety symptoms and improvement in QoL and cognitive function scores, using validated scales). The terms "supervised clinical exercise" and "unsupervised clinical exercise" from Baumann and colleagues' (2012) systematic review were used to differentiate between studies in which PA interventions were supervised by a therapist/physiologist and studies in which PA interventions occurred without a therapist present (e.g., home-based programs). The risk of bias assessment tool developed by the Cochrane Collaboration (Higgins & Altman, 2008) was used to ascertain the validity and limitations of eligible studies. However, no formal

assessment of bias risk was undertaken because of the variability in research designs and the limited number of studies meeting the review inclusion criteria (Liberati, 2009). The limitations of individual studies and risk of bias across studies are discussed broadly.

6.5. RESULTS

The search of all databases after adjusting for duplicates provided a total of 867 citations. Of these, 829 articles were discarded due to titles and abstracts clearly not matching the eligibility criteria. A further 10 articles were excluded, as they were study protocols for PA intervention studies in progress. The full texts of the remaining 28 citations were examined in detail. Of these, 21 studies did not meet the inclusion criteria. Three studies were about physical function outcomes. In four studies PA was not assessed, eight studies involved interventions with a combination of PA, nutrition advice and/or psychotherapy, two studies combined cancer types and did not assess participants with PCa in isolation and four studies assessed self-efficacy and barriers to PA participation. Seven studies met the eligibility criteria and were included in the review (Culos-Reed, Robinson, Lau, O'Connor, & Keats, 2007; Culos-Reed et al., 2010; Galvao, Taaffe, Spry, Joseph, & Newton, 2011; Galvão, Taaffe, Spry, Joseph, & Newton, 2010; Hansen, Dechet, Porucznik, & LaStayo, 2009; Keogh, et al., 2010; Segal et al., 2003). See flow diagram *Figure 6.1* for a flow diagram of the literature search and study selection.

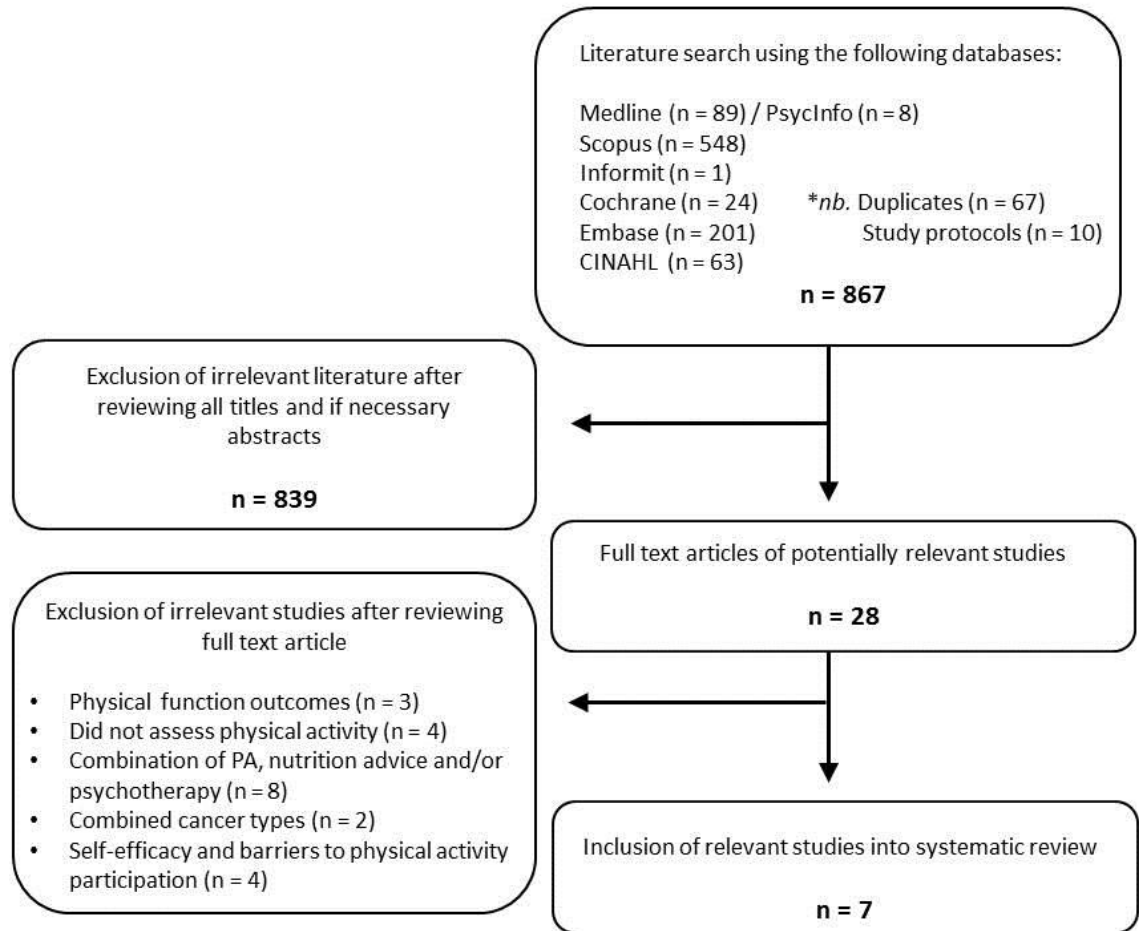


Figure 6.1. Flow diagram of literature search and study selection.

The seven studies selected for the review are presented in Table 6.2. In all of these studies the impact of PA during ADT administration for PCa was examined. Due to the limited amount of studies assessing the outcome variables of interest, two pilot studies were included in the review. Consequently, there was considerable variability in sample size across studies and the pilot studies used a pre-post-test design without a control group. The included studies involved 420 participants, 242 of whom participated in a PA intervention. The main inclusion criteria in these studies were those with histologically documented PCa of any disease stage and 1) scheduled to receive ADT at least 3 months after recruitment OR 2) minimum prior

exposure to ADT longer than 2 months OR 3) expected to receive ADT for at least 6 months.

In five studies a 12 week PA intervention was used, four of which involved supervised clinical exercise. In one study a 16 week, unsupervised clinical exercise intervention was used. Of the supervised clinical exercise intervention studies, two involved a resistance training program and two involved combined resistance and aerobic training, with outcomes measured at baseline and 12 weeks. The two unsupervised clinical exercise intervention studies involved home-based PA programs targeting both aerobic and resistance exercise, measuring outcomes at baseline, post-intervention and at two, four and six months follow-up. Finally, in one study a cross-sectional survey design was used to explore the relationship between meeting the American Cancer Society PA guidelines (i.e., at least 30 minutes of moderate-intensity PA on 5 or more days per week) (Schmitz et al., 2010) and QoL. QoL outcomes were examined in all seven studies. Depression was examined in one study (Culos-Reed, et al., 2010) and cognitive function was evaluated in another (Galvão, et al., 2010). Anxiety was not investigated in any of the seven identified studies.

Table 6.2.

Outcomes of Supervised and Non-Supervised Clinical Exercise Studies During ADT for Prostate Cancer.

Authors	Design	Intervention	Measuring Points	Outcome (Measures)	Results
Segal et al., 2003	<i>RCT</i> <i>n</i> = 155 IG = 82 CG = 73	<i>Supervised clinical exercise</i> 12 week PA program: 3x/week supervised resistance training program with 2 sets of 8-12 repetitions at 60-70% 1-repetition maximum for 9 full-body exercises	Baseline 12 weeks	Health-related QoL (FACT-P)	FACT-P scores for IG increased by 2.0 and CG decreased by 3.3 with a significant difference of change scores. Significant increase in FACT-P scores regardless of curative or palliative intent and < 1 year on ADT or ≥ 1 year on ADT.
Culos-Reed et al., 2007	<i>Pre-Post Test</i> <i>n</i> = 18 IG only – no CG	<i>Unsupervised clinical exercise</i> 12 week PA program: 3-5x/week home-based PA program with moderate intensity (walking, stretching, light resistance training) 1x/fortnightly 90 min group session	Baseline 12 weeks 4 months	QoL (EORTC QOL 30) <i>nb.</i> Used Global QoL scale only	12 weeks: Significantly increased PA behaviour; Increased QoL, but not significant. 4 months post intervention: Significantly decreased PA behaviour and QoL.
Hansen et al., 2009	<i>Pre-Post Test</i> <i>n</i> = 10 No CG <i>n</i> = 5 ADT <i>n</i> = 5 No ADT	<i>Supervised clinical exercise</i> 12 week PA program: 3x/week supervised resistance exercise using “a recumbent high-force eccentric ergometer”	Baseline 12 weeks	QoL (FACT-P)	ADT group: Increase of 8.2 points on the FACT-P, but difference not significant. However, change of 6 to 10 points is clinically relevant (Steffen, Hacker, & Mollinger, 2002).

Galvao et al., <u>RCT</u> 2010	<i>Supervised clinical exercise</i> 12 week PA program: 2x week supervised resistance and aerobic training; Resistance = 2-4 sets each from 12-16 repetition maximum, for 8 full- body exercises Aerobic = 15-20 min. of cardiovascular exercise at 65- 80% maximum heart rate.	Baseline 12 weeks	QoL (SF-36) QoL (EORTC QOL 30) Cognitive Function (2 item subscale of the EORTC QOL 30)	SF-36: IG compared to CG significantly increased in 3 subscales - general health; vitality; physical health composite. EORTC: IG compared to CG significantly increased in 6 subscales: role; cognitive; fatigue; nausea; dyspnoea; insomnia.
Culos-Reed et al., 2010	<u>RCT</u> <i>Unsupervised clinical exercise</i> 16 week PA program: 3-5x/week home-based PA program with moderate-intensity (walking, stretching, light resistance training) 1x/week 90 min group session – then 1x/monthly until 6 month follow-up	Baseline 16 weeks 2 months 6 months	QoL (EORTC QOL 30) – <i>nb.</i> Used QoL subscale (two items) only Depression (CES-D)	IG: Significantly increased PA behaviour; Increased QoL, but not significant; Decreased depression, but not significant. CG: Increased PA behaviour, but not significant; Decreased QoL, but not significant; Increased depression, but not significant.

Keogh et al., 2010	<u>Cross-Sectional</u> <i>n</i> = 84 PCa patients receiving ADT <i>n</i> = 82 healthy comparison participants	No Intervention	One time point	QoL (WHOQOL-BREF) PA (RAPA)	45% (<i>n</i> = 38) meeting PA guidelines. Those meeting PA guidelines had significantly higher levels of global and physical QoL and self-rated health than participants not meeting these guidelines.
Galvao et al., 2011	<u>RCT</u> <i>n</i> = 50 < 6 mths ADT = 16 ≥ 6 mths ADT = 34	As above	Baseline 12 weeks	QoL (SF-36)	No significant differences between < 6mths on ADT or ≥ 6 mths on ADT in QoL change. QoL significantly increased in ≥ 6mth ADT group on physical health composite score and 3 subscales: physical function; general health and vitality

RCT = Randomised Control Trial; IG = Intervention Group; CG = Control Group; PA = Physical Activity; QoL = Quality of Life; EORTC QOL30 = European Organisation for Research and Treatment of Cancer Study Group Quality of Life Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; SF-36 = 36-item Short Form Health Survey; FACT-P = Functional Assessment of Cancer Therapy – Prostate; ADT = Androgen Deprivation Therapy; PCa = prostate cancer; WHOQOL-BREF = World Health Organisation Quality of Life Questionnaire; RAPA = Rapid Assessment of Physical Activity Scale.

6.5.1. *Quality of Life*

In all seven studies the impact of PA on QoL was assessed. Of the supervised clinical exercise interventions, 12 week interventions of both resistance (Segal, et al., 2003) and combined resistance and aerobic training (Galvão, et al., 2010) improved several aspects of QoL. In particular, Segal et al (2003) observed a significant difference in QoL change scores between intervention and control groups ($p < .001$), with Functional Assessment of Cancer Therapy – Prostate (FACT-P) scores increasing 2.0 points in the intervention group and decreasing 3.3 points in the control group. Galvao et al (2010) found significantly larger change scores for the intervention group on the 36-Item Short-Form Health Survey (SF-36) subscales general health ($p = .022$), vitality ($p = .019$) and physical health composite score ($p = .020$) when compared with controls. Significantly better change scores were also observed for the intervention group on the role ($p < .001$), cognitive ($p = .007$), fatigue ($p = .021$) and dyspnea ($p = .017$) subscales of the European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (EORTC-30). Hansen et al. (2009) compared QoL change from baseline to 12 weeks following a resistance exercise intervention using a recumbent high-force eccentric ergometer in five men receiving ADT and five not receiving ADT. Participants receiving ADT demonstrated an improvement of 8.2 points on the FACT-P total score. Although this result did not reach statistical significance, a change of 6 to 10 points on the FACT-P is considered to be clinically relevant (Steffen, Hacker, & Mollinger, 2002). In this same study, participants not receiving ADT showed a significant improvement in the physical subscale scores, but not total scores, of the FACT-P pre-to-post intervention.

Of the unsupervised clinical exercise interventions, Culos-Reed et al's 12-week (Culos-Reed, et al., 2007) and 16-week (Culos-Reed, et al., 2010) home-based PA programs yielded trends toward positive change in overall QoL in participants undertaking PA, although these were not statistically significant. Culos-Reed et al's (2010) study yielded a 2.70 point increase in EORTC-30 scores in the intervention group, in contrast to a 2.33 point decrease in control participants. Culos-Reed et al (2007) also found a significant decrease in global QoL from immediate post-intervention to 4-month follow-up, suggesting that if exercise levels during an intervention are not maintained QoL diminishes. Further, participants meeting PA guidelines in Keogh et al's (2010) cross-sectional study reported significantly higher mean physical QoL ($p = .034$), global QoL ($p = .02$) and self-assessed health ($p = .04$) than participants classified as insufficiently active.

Differences in the impact of PA on QoL in men receiving short- and long-term ADT were examined in two studies. Segal et al. (2003) found no evidence of a differential response to resistance exercise between those who received ADT for < 1 or ≥ 1 year. Galvao et al (2011) also observed no difference between acute (< 6 months) and chronic (≥ 6 months) ADT recipients in QoL change.

6.5.2. *Depression*

Culos-Reed et al (2010) used the Center for Epidemiologic Studies Depression Scale (CES-D) to evaluate depression outcomes pre- and 16 weeks post-PA intervention. Total depression scores decreased from 8.62 to 8.22 in the PA intervention group and increased from 6.71 to 7.67 in the control group from pre- to post-intervention. These changes, however, were not significant.

6.5.3. Cognitive Function

Although not an explicit outcome evaluated by Galvao et al (2010), the QoL measure used in this study EORTC-30 provides a two item subscale assessing cognitive function. The study by Galvao et al (2010) was the only one identified in this review in which the impact of a PA intervention on subscale scores of the EORTC-30 was evaluated. Galvao et al (2010) found significantly better cognitive function change scores for participants in the PA intervention group compared to the control group after adjusting for between group differences in baseline cognitive function, time on ADT, use of anti-androgen, number of medications and education.

6.6. DISCUSSION

6.6.1. Quality of Life

Overall, the results of the seven studies included in this review indicate that supervised or unsupervised PA interventions administered as resistance or combined resistance and aerobic training formats, 2 to 3 times per week for 12 to 16 weeks, improved QoL in men with PCa receiving ADT. With findings that 55% of men receiving ADT for PCa were classified as insufficiently active (Keogh, et al., 2010), interventions promoting regular PA may significantly increase QoL in this patient group. Further, interventions should target PA adherence and the incorporation of regular PA into daily life, given the evidence that global QoL significantly decreases if exercise levels in an intervention are not maintained (Culos-Reed, et al., 2007). However, a number of caveats should be considered in the interpretation of these findings.

One such limitation is that substantial baseline differences between intervention and control groups on numerous QoL subscales were observed in Galvao et al's (2010) study. Although socio-demographic variables were not significantly different at baseline and analysis of covariance was used to compare QoL outcomes adjusted for baseline values and potential confounders, the interpretation of QoL data in this study may be limited. Furthermore, Culos-Reed et al (2010) reported an attrition rate of 34% and this reduction in statistical power may have resulted in inadequate numbers to detect significant changes in QoL outcomes.

Another issue to consider is that the comparability of QoL findings across the seven studies is confounded by the use of four different QoL measures. Furthermore, the internal consistency of several subscales of the EORTC-30 used to measure QoL in three of the studies (Culos-Reed, et al., 2007; Culos-Reed, et al., 2010; Galvão, et al., 2010) is poor (Culos-Reed, et al., 2010; Ringdal & Ringdal, 1993). Culos-Reed et al (2010) commented that the physical function scale of the EORTC-30 did not achieve adequate reliability and could not be examined in subsequent analyses and consequently, reliance on a two-item global QoL scale in this study may have attenuated findings. These authors also reported that the EORTC-30 may not have been as sensitive to changes in QoL over a short timeframe as the FACT-P (Culos-Reed, et al., 2010). Based on these findings it appears as though the FACT-P should be used in preference to the EORTC-30. However, to enhance comparability of findings across studies, consistent choice of QoL measures is required for future research. QoL measures typically used in cancer research may be superseded by efforts such as the Patient Reported Outcomes Measurement Information System (PROMIS) (United States Department of Health and Human Services, 2013). PROMIS is designed to enhance the reliability and validity of measures, while

allowing for comparisons across domains and diseases. Although PROMIS measures are yet to be used to examine the impact of PA on QoL, future research should examine the sensitivity of PROMIS tools to changes brought about by PA interventions.

A further caveat of the results from the studies in this review is associated with length of time on ADT. Findings from three studies included in this review suggested that improvements in QoL as a function of regular PA are observed regardless of ADT duration (Galvao, et al., 2011; Hansen, et al., 2009; Segal, et al., 2003). Furthermore, Keogh et al (2010) found no relationship between PA and time on ADT, suggesting that there is no critical timeframe for PA administration after ADT commencement. However, interpretation of these findings is restricted because of the limitations imposed by study design. Keogh et al's (2010) study was a cross-sectional, exploratory survey and Hansen et al's (2009) pilot study had a small sample size and no control group. Nevertheless, results from two well-designed RCTs indicated that both resistance training (Segal, et al., 2003) and combined aerobic and resistance training (Galvao, et al., 2011) improved QoL despite length of ADT administration, suggesting that PA is effective for men who have received ADT for short or longer periods of time. Further research assessing within-subject interactions between varying lengths of time on ADT and the impact of PA administration on psycho-social outcomes is required.

6.6.2. Depression and Anxiety

Among the few studies evaluating the benefits of PA in patients with PCa receiving ADT, outcomes relating to depression and anxiety appear to have been overlooked. Of the seven studies included in this review, none of them examined

anxiety outcomes and only one assessed depression. Consequently, the evidence is not sufficiently robust to determine the adequacy of PA as an intervention to improve these outcomes in this patient group. The one study in which depression was examined yielded non-significant results, suggesting that conclusions cannot be drawn in relation to this outcome (Culos-Reed, et al., 2010). Furthermore, in Culos-Reed et al's (2010) study there appears to be a considerable difference in baseline depression scores between intervention (8.62) and control (6.71) groups, which may affect the interpretability of findings relating to depression in this study. Another limitation of the studies in this review is that although both moderate and vigorous PA have been reported to reduce symptoms of depression (Dunn, Trivedi, & O'Neal, 2001), there are few studies in which an association between PA and a decrease in anxiety symptoms have been found. Furthermore, depression and anxiety have not been examined in previous studies as a function of ADT duration and this should be a focus for future research.

6.6.3. Cognitive Function

Only one study examined the impact of PA on cognitive function in men receiving ADT for PCa as a secondary outcome. In this study, an improvement in cognitive functioning was found in PA intervention participants when compared with controls (Galvão, et al., 2010). However, the cognitive functioning scale of the EORTC-30 has been reported as having unsatisfactory internal consistency (Ringdal & Ringdal, 1993) and consequently, the results relating to cognitive function reported by Galvao and colleagues (2010) may be unreliable. No prior studies have examined cognitive function relative to length of ADT treatment. Further research should assess the impact of ADT duration on psychological outcomes.

There is a great deal of evidence supporting the effectiveness of regular PA for improving cognitive function in other populations (Cotman & Berchtold, 2002; Cotman & Engesser-Cesar, 2002; Denkinger, Nikolaus, Denkinger, & Lukas, 2012; Kraft, 2012; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). In PA intervention studies involving neuroimaging techniques with human participants, it has been found that PA is associated with structural changes in the brain, including increases in gray matter volume in the frontal and temporal cortices (Kraft, 2012). A randomised controlled trial (RCT) involving a home-based walking exercise program in patients with PCa receiving ADT is currently underway, with the study protocol indicating that cognitive function, depression and anxiety are the primary outcome measures (Lee, Kilgour, & Lau, 2012). In the study protocol a comprehensive assessment of cognitive function using a battery of neurocognitive tests at baseline and 6 months is outlined, with administration of the CES-D and State-Trait Anxiety Inventory (STAI) measures of depression and anxiety at baseline, 3 and 6 months. The results of this RCT may provide valuable information regarding the management of men with PCa receiving ADT and the potential impact of regular PA on cognitive and psychosocial functions. There is certainly a clear need for further research on the benefits of regular PA for cognitive and psychosocial functions in this patient group.

6.6.4. General Limitations of the Evidence Base and this Review

This systematic review has several limitations. Publication bias may account for some of the effects observed and the quality of included studies varied. Only three RCTs implementing a PA intervention in men receiving ADT for PCa (Culos-Reed, et al., 2010; Galvão, et al., 2010; Segal, et al., 2003) were available for review and the primary outcomes for two of these studies were body composition and physical function (Galvão, et al., 2010; Segal, et al., 2003). Randomisation and

concealment was adequate in all trials and adherence to the intention-to-treat principle in data analyses was apparent.

Another limitation is that the potential for sample selection bias is evident across all studies as participants interested in or already achieving an active lifestyle may be more likely to participate. In support of this contention, the activity level of participants prior to study commencement was high in two studies (Hansen, et al., 2009; Segal, et al., 2003), with the majority of participants in Hansen et al's (2009) study performing at least 20 minutes of routine exercise 3 times per week, which was continued throughout the intervention. A further limitation was that there were three studies in which the comorbidities of participants were not reported (Culos-Reed, et al., 2007; Culos-Reed, et al., 2010; Segal, et al., 2003) and the exclusion criteria of all studies omitted potential participants with a range of comorbid conditions. It appears likely that patients with several comorbidities would be less likely to participate in a PA intervention, despite evidence that regular PA contributes to the primary and secondary prevention of several chronic diseases (Warburton, Nicol, & Bredin, 2006). Therefore, in future PA interventions with this patient group the potential selection bias imposed by inclusion/exclusion criteria should be carefully considered, and comorbid conditions should be controlled in all analyses.

Another concern is that the possibility of social support bias and attention effects is apparent in all but one study (Keogh, et al., 2010). It is possible that improvements in QoL in PA intervention groups were partly due to the fact that patients were seen two to three times per week in a structured environment by a fitness consultant and/or PA sessions conducted in small groups, fostering social interaction. In one study there were attempts to control for the potential confounds of social support by providing an individual PA intervention (Segal, et al., 2003). The

authors, however, commented that in some cases more than one participant in the intervention group attended the exercise facilities at the same time of day. Even the unsupervised, home-based intervention studies (Culos-Reed, et al., 2007; Culos-Reed, et al., 2010) were not immune to attention effects and social support bias with the inclusion of 90 minute group sessions once per week to enhance social support. The group sessions included in the studies by Culos-Reed et al. (Culos-Reed, et al., 2007; Culos-Reed, et al., 2010) were also multi-modal, incorporating PA, education and group support and consequently, the findings cannot be attributed to the effects of PA alone. In future research more rigorous measures should be used to control for these potential confounds and to isolate the impact of PA.

Despite the lack of studies undertaken in this area, preliminary findings suggest that PA interventions have beneficial effects on QoL in patients with PCa receiving ADT. Conclusions cannot be drawn in relation to depression, anxiety and cognitive function outcomes and thus a clear gap in the current literature has been identified. As a result of the variability of intervention types and methods of assessment, comprehensive PA recommendations cannot yet be defined for this patient group. Nevertheless, evidence thus far suggests that clinical exercise in the form of resistance and combined aerobic and resistance training programs may be important for the health status and rehabilitation of patients with PCa. This confirms the need for further studies, particularly clinical trials, to elucidate the relationship between regular PA engagement and psychosocial outcomes.

6.7. References

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6.8. Appendix A

Search Strategy: MEDLINE (OVID)

01. prostat* neoplasm*.mp
02. prostat* cancer*.mp
03. prostate cancer/
04. (prostat* adj5 cancer*).mp
05. prostat* carcinoma*.mp
06. prostat* adenocarcinoma*.mp
07. (prostat* adj5 tumo*).mp
08. prostatic neoplasms/
09. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. androgen deprivation therapy.mp
11. androgen ablation.mp
12. androgen suppression.mp
13. hormon* therapy.mp
14. androgen antagonist/
15. androgen agonist.mp
16. gonadotrop*in.mp
17. luteini#ing hormone-releasing hormone*.mp
18. luteini#ing hormone-releasing hormone analog*.mp
19. luteini#ing hormone-releasing hormone antagonist*.mp
20. anti-androgen*.mp
21. orchi*ectomy.mp
22. surgical castration.mp
23. chemical castration.mp
24. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. physical activity.mp
26. physical exercise.mp
27. exp exercise/
28. sport* therapy.mp
29. sport*.mp
30. endurance.mp
31. aerobic training.mp
32. resistance training.mp
33. aerobic activity.mp
34. cardi* training.mp
35. resistance activity.mp
36. motor activity/
37. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 9 and 24 and 37

6.9. Summary and Conclusions

In the paper presented in this chapter, a clear gap in the current literature was identified, with few previous studies evaluating the effectiveness of PA in improving depression, anxiety, QoL and cognitive function in men receiving ADT for PCa. Preliminary findings suggest that PA may be effective in improving QoL in this patient group. However, further studies are needed in which these specific outcomes are examined. In the next chapter, the methodology of the present study is described.

Chapter 7. Methodology

7.1. Introduction

In Chapter 7 the methodology for this cross-sectional study is described in detail. Although aspects of the methodology were discussed in the papers submitted for publication, the word limit and scope of those papers necessitated abbreviated descriptions of these aspects of the research.

7.2. Research Design and Study Variables

A cross-sectional survey design was used to collect quantitative data from patients with PCa attending for treatment at the Alfred, Cabrini and Latrobe Regional Hospitals (LRH) during October 2010 and August 2011. This study design was used to examine symptoms of depression and anxiety, cognitive function and QoL in this patient group. Specifically, the objectives of the present study were: to describe the PA behaviour of patients with PCa; to evaluate the effects of ADT on depression, anxiety, cognitive function and QoL in men with PCa; and to examine the relationship between meeting the National Physical Activity Guidelines of Australia (NPAGA) and the presence and severity of physical and psychological side effects of ADT.

7.3. Participants

Participants included in the current study were aged between 40 and 80 years old at the time of RT completion with a mean age of 67.6 ($SD = 7.5$) years. Participants were English speaking and had received RT for their PCa between 9 and 30 months prior to data collection. Previous research suggests a plateau in RT effects after 12 months, with the effects diminishing after 36 months, hence providing the

rationale for the latter selection criterion (Gore, Kwan, Lee, Reiter, & Litwin, 2009). No restrictions were placed on patient body mass index, weight, or level of PA prior to cancer diagnosis.

7.3.1. *Socio-demographic and Medical Profile of the Sample*

As described in Chapter 2, the type of treatment a patient with PCa receives is dependent on aspects of their disease. In the first part of the treatment decision-making process oncologists will consider the patients' TNM rating, GS and PSA level. This information is then used to classify the patients' disease risk level as high, intermediate or low. Table 7.1 presents the criteria by which disease status is categorised by oncologists at the centre from which patients were recruited.

Table 7.1.

William Buckland Radiotherapy Oncologists' Classification.

Low Risk	T1a – 2c and PSA \leq 10 and GS $<$ 7
Intermediate Risk	Not low or high risk
High Risk	$>$ T3a or PSA $>$ 20 or GS $>$ 7

The patients' age and other medical comorbidities must also be considered to tailor treatment to the individual. The Alfred Hospital guidelines suggest that those with low risk disease who are considered to be treated with curative intent receive RT only, in the form of EBRT or low dose rate (LDR) brachytherapy. Patients with intermediate risk disease typically receive six months of neo-adjuvant androgen deprivation followed by a course of RT. Patients classified as high risk generally

receive six months of neo-adjuvant androgen deprivation followed by EBRT +/- high dose rate (HDR) brachytherapy and a further two years of adjuvant androgen deprivation. Consequently, those patients classified as high risk usually receive 2 ½ years of ADT. Patients being treated with palliative intent are typically treated with ADT indefinitely. Information obtained from patient medical records was used to classify patients into one of four groups. In Table 7.2 the four treatment groups and number of participants falling within each category are described.

Table 7.2.

Four Treatment Categories and Number of Participants in Each Group.

	<i>n</i>	<i>% of Sample</i>
RT only	174	46.2%
RT + 6 months ADT	100	26.5%
RT + 2 ½ yrs ADT	77	20.4%
RT + ADT indefinitely	26	6.9%

Patients often do not fall neatly into these four categories as, for example, they may have to cease ADT earlier than expected due to side effects or their treating team may have decided to change their management plan during treatment. For the purposes of this study and with advice from the medical associate researchers, participants who had received ADT for less than or equal to one year were allocated to the RT + 6 months ADT group. Participants who had received ADT for more than one year were assigned to the RT + 2 ½ years ADT category.

7.4. Measures

7.4.1. Socio-demographic and Medical Information

Seven socio-demographic items were included in the questionnaire. These were age; marital status; level of education; ethnic background; employment status; and comorbid medical conditions. Other disease-related information was obtained from the patients' medical records and included date of diagnosis; treatment site; previous cancer diagnosis; disease risk level (high, intermediate or low); TNM rating; stage; GS; initial PSA test result; intent of treatment (curative, palliative or adjuvant); ADT status; start and finish date of ADT; ADT status at time of data collection; type of RT (EBRT, brachytherapy or EBRT + brachytherapy); type of brachytherapy (LDR or HDR); and radical prostatectomy status.

7.4.2. The International Physical Activity Questionnaire

The International Physical Activity Questionnaire (IPAQ; Craig et al., 2003) was designed to measure the frequency, intensity and duration of PA over the past 7 days. Designed specifically for use in adult populations, the IPAQ measures activity levels across four PA domains: (1) during transportation, (2) at work, (3) during household and gardening tasks and (4) during leisure time, including exercise and sport participation. For example, in the leisure-time activity domain participants are asked "during the last 7 days, on how many days did you walk for at least 10 minutes at a time in your leisure time?" Participants are required to state the number of days they walked in their leisure-time. The next item asks "how much time did you usually spend on one of those days walking in your leisure time?" Participants are required to record the hours and minutes spent walking in one day during leisure-time. These items are repeated for each activity type and intensity.

Two questionnaires have been developed, a short form (9 items) and a long form (31 items), both in self-report and telephone formats. The IPAQ short version is suitable for population studies, as it has a high variance and is not as sensitive to change when used in smaller intervention studies. However, the IPAQ long version is domain specific and more suitable for research, hence providing the rationale for its use in the present study (Hagstromer, Oja, & Sjostrom, 2006). The results of an evaluation of both reliability and validity of the instrument across 12 countries by the study authors produced repeatable data for all questionnaire versions, Spearman's ρ of 0.81 for the long form and 0.76 for the short form. The authors also assessed criterion validity against an accelerometer for the total amount of weekly PA, resulting in a median correlation of 0.33 and 0.30 (Spearman's ρ) for the long and short form, respectively. The IPAQ has acceptable properties for assessing PA in adult and elderly populations and provides a continuous measure of PA with respondents reporting hours and minutes of PA in each of the four domains (Hagstromer, et al., 2006; Tomioka, Iwamoto, Saeki, & Okamoto, 2011). As it is the only PA measure that provides normative data for residents of Australia (Craig, et al., 2003), it was considered most suitable for use in the current study. Scoring of the IPAQ is discussed later in the *Data Analysis* section.

7.4.3. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS; Snaith & Zigmond, 1994) is a 14-item self-report questionnaire, taking between two and five minutes to complete. It assesses the patient's emotional state during the previous 7 days and specifically measures anxiety and/or depression associated with physical illness. The measure does not include items assessing somatic symptoms related to depression and anxiety and therefore this instrument is suitable for use with those suffering from

physical conditions (Herrmann, 1997) or PCa (Mehnert, Lehmann, Graefen, Huland, & Koch, 2010; Nelson, Mulhall, & Roth, 2011). The instrument is divided into two subscales measuring depression (7 items) and anxiety (7 items). All items are presented alternately for the two scales. Some items are worded positively and some negatively. Participants are presented with statements and required to respond using four different response options for each item, rated on a Likert-type scale of 0 to 3. For example, participants are asked to respond to the statement “I have lost interest in my appearance” according to *Definitely* (scored as 3), *I don’t take as much care as I should* (2), *I may not take quite as much care* (1) or *I take just as much care as ever* (0). The combined scores for each subscale range from 0 to 21. Interpretation of mood state is based on the raw score of each subscale: normal (0-7); mild (8-10); moderate (11-14); severe (15-21). The total score can also be used as a general measure of distress. The HADS is widely used in hospital settings with previous research supporting its internal consistency with Cronbach’s alpha of 0.93 for the anxiety and 0.85-0.90 for the depression scale (Spinhoven et al., 1997).

7.4.4. Functional Assessment of Cancer Therapy – Prostate

The Functional Assessment of Cancer Therapy – Prostate (FACT-P; Esper et al., 1997) is a multi-dimensional, self-report QoL instrument specifically designed for use with PCa patients. It consists of 27 core items that assess patient function in four domains: Physical, Social/Family, Emotional, and Functional Wellbeing. Each item is rated on a 0 to 4 Likert type scale, and then combined to produce subscale scores for each domain, as well as a global QoL score. Developed as a disease-specific adjunct to the FACT measurement system, a 12-item prostate cancer subscale (PCS) was developed and tested in three independent samples (Cella, Nichol, Eton, Nelson, & Mulani, 2009). The 12 items ask about symptoms specific to

prostate cancer. For example, participants are required to respond to a statement such as “I am able to have and maintain an erection” according to *Not at all* (scored as 0), *A little bit* (1), *Somewhat* (2), *Quite a bit* (3), or *Very much* (4). Higher scores represent better QoL. These questions are added to the general (FACT-G) instrument. Internal consistency of the PCS ranged from 0.65 to 0.69, with coefficients for FACT-G subscales and aggregated scores ranging from 0.61 to 0.90 (Cella, et al., 2009; Esper, et al., 1997; Mehnert, et al., 2010). Concurrent validity was confirmed by the ability to discriminate patients by disease stage, performance status, and baseline PSA level (Esper, et al., 1997). Findings support the use of the FACT-P as a valid component of QoL evaluation in men undergoing treatment for PCa. The 12-item PCS was used in the current study as a measure of QoL concerns specific to patients with PCa.

7.4.5. *Functional Assessment of Cancer Therapy – Cognitive – Version 3*

The Functional Assessment of Cancer Therapy-Cognitive, Version 3 (FACT-Cog, (FACT-Cog; Wagner, Sweet, Butt, Lai, & Cella, 2009) is a 37-item measure designed to assess cognitive complaints in cancer patients. The FACT-Cog includes both negatively and positively worded items and yields four subscale scores: 1) Perceived Cognitive Impairments (CogPCI); 2) Impact of Perceived Impairments on QoL (CogQOL); 3) Comments from Others (CogOTH); and 4) Perceived Cognitive Abilities (CogPCA). Participants rate the frequency with which each statement occurred in the past seven days on a five-point Likert scale. For example, participants are asked to respond to the statement “I have had trouble concentrating” according to *Never* (scored as 0), *About once a week* (1), *Two to three times a week* (2), *Nearly every day* (3) or *Several times a day* (4). Higher scores reflect more cognitive

problems and poorer QoL. Wagner (2008) reported moderate to strong internal consistency for the FACT-Cog version 3 with Cronbach's alpha ranging from 0.67 (CogPCA) to 0.95 (CogPCI). Additional psychometric properties of the scale are currently being established. One of the most commonly used self-report measures of cognitive complaints, the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 Cognitive Functioning Scale (EORTC-CF), consists of only two items and has yielded mixed evidence of validity with cancer patients (Jacobs, Jacobsen, Booth-Jones, Wagner, & Anasetti, 2007; Ringdal & Ringdal, 1993). In general, the FACT-Cog and the EORTC-CF demonstrate similar psychometric properties. However, the FACT-Cog assesses broader aspects of cognitive complaints, thereby providing more information about the types of cognitive complaints patients are experiencing (Jacobs, et al., 2007).

7.5. Procedure

7.5.1. Ethics Approval

Ethics approval was obtained from the Human Research Ethics Committees at The Alfred Hospital (Melbourne), Cabrini Hospital (Melbourne) and LRH (Traralgon), as well as the Monash University Standing Committee on Ethics in Research involving Humans. Copies of the Ethics Approval Certificates can be found in Appendix A.

7.5.2. Piloting the Questionnaire

Prior to commencing data collection, the questionnaire was pilot tested on 10 healthy men aged between 55 and 60 years old to assess readability. The outcome of this pilot testing indicated that the questionnaire was acceptable to this group of men. The study questionnaire was composed of socio-demographic questions; the

International Physical Activity Questionnaire, IPAQ (Craig, et al., 2003); The Hospital Anxiety and Depression Scale, HADS (Snaith & Zigmond, 1994); The Functional Assessment of Cancer Therapy – Prostate, FACT-P (Esper, et al., 1997); The Functional Assessment of Cancer Therapy – Cognitive, Version 3, FACT-Cog (Wagner, et al., 2009); and the Short-Form 12-Item Health Survey, SF-12 (Ware, Kosinski, & Keller, 1996). Unfortunately, upon completion of data collection it was discovered that an incorrect version of the SF-12 was used with no scoring protocol available. Consequently, the SF-12 was excluded from data analyses and the current study. This is discussed further in the *Limitations of the Current Research* section. To reduce order effects associated with the sequencing of measures within the questionnaire, five versions were created, each with a unique sequence of instruments. A copy of the study questionnaire is included in Appendix B.

7.5.3. Recruitment

Participants included in the study were recruited through the William Buckland Radiotherapy Centre (WBRC), The Alfred Hospital, Melbourne. The WBRC database includes patients who initially attended for treatment at Cabrini and LRH and therefore it was possible to obtain data from those patients who attended for treatment at all three participating centres. Data were collected over a period of 12 months, using two separate mail-out processes. From the first mail-out in October 2010 including 477 patients, 292 men consented to participate in the study and returned questionnaires, yielding a response rate of 61%. A second mail-out in July 2011 including 161 patients conducted 8 months later returned 86 completed questionnaires, giving a response rate of 53%. The purpose of the second mail-out was to capture data from patients new to the Alfred database and who at this time met the inclusion criteria. In total, 378 patients consented to participate in the study

and returned questionnaires, giving an overall response rate of 59%. Two questionnaires were subsequently eliminated; one with less than 50% of the items completed and another because the participant had previously completed and returned a copy of the questionnaire. This left 377 questionnaires available for analysis. It was not possible to determine significant differences between responders and non-responders, in terms of medical and demographic details, because the research team did not have access to the medical records of non-responders. In Table 7.3 a summary of response rates for both stages of the recruitment process is provided.

Table 7.3.

Summary of Response Rates in Recruitment Process.

	Mail-out 1	Mail-out 2
Participants	292 (61%)	86 (53%)
Refusals	67 (14%)	16 (10%)
Deceased	10 (2%)	5 (3%)
Return to Sender (RTS)	9 (2%)	1 (1%)
Miscellaneous	99 (21%)	53 (33%)

7.5.4. Distribution of Questionnaires to Participants

A list of all patients meeting the inclusion criteria and who were currently receiving treatment or who had received treatment in the last 12 months at The Alfred, Cabrini or LRH was obtained from patient databases held by the medical associate researchers. Patients suitable for participation in the study were identified by the responsible treating clinician, Associate Professor Jeremy Millar and data manager Ms Robin Smith, using standard Radiation Oncology administrative processes.

The questionnaire package included an invitation letter from A/Prof Jeremy Millar (Director of Radiation Oncology, Alfred Hospital and Consultant Radiation Oncologist, Cabrini Health) endorsing the project and encouraging participation (Appendix C), the Participant Information Statement (Appendix D), Consent Form (Appendix E), self-administered questionnaire and a reply paid envelope. Questionnaires were ID coded according to patient medical records to track those receiving a questionnaire. This was necessary to enable matching of medical and socio-demographic information obtained from patient medical records with the patient's questionnaire and to facilitate the posting of reminder letters four weeks after the initial mail-out (Appendix F). Consequently, questionnaire data were confidential but not anonymous. Prior to participation patients were required to read the participant information statement and sign a consent form. The consent form highlighted that while the information collected was not de-identified, patient confidentiality would be protected by limiting data access to the Research Team; by ensuring appropriate security procedures for data handling including password protection; and not including identifiable information on any publications or reports. If the patient required further information about the study they were encouraged to contact the Principal Investigator, Dr Sue Burney or the doctoral candidate for more information. The reply paid envelopes for the consent form and questionnaire were returned directly to the Doctoral candidate at Monash University.

Nine participants scored in the severe range (15-21) on the HADS. These patients received a telephone call from Dr Sue Burney (Principal Researcher and registered Psychologist) suggesting that they contact their GP, medical specialist or one of the free support services listed on the Participant Information Sheet. The

phone call script used to contact participants with an elevated HADS score is included in Appendix G.

7.5.5. Accessing Patient Medical Records

The doctoral candidate acquired an appointment as an honorary staff member of the Alfred Hospital to access patient health records. The doctoral candidate read through the patient medical records of those patients who returned questionnaires and signed consent forms, to acquire disease-related information and to categorise patients into one of the four treatment groups. Dr Tracey Oh (WBRC registrar), assisted the doctoral candidate in accurately assessing patient disease-related information and categorising patients into the treatment groups.

7.6. Data Entry and Screening

Data from the questionnaires and medical records were entered into the Statistical Package for Social Sciences (SPSS) Version 18.0. Once data entry was complete, 10% of the paper questionnaires were verified against the SPSS data records. No errors were found. The data screening process was guided by the procedure outlined by Tabachnick and Fidell (2007). This included checking the dataset for accuracy, distribution of variables, outliers, and missing data.

Univariate descriptive statistics were checked for out-of-range values. Any errors found at the item level were checked against the original paper copy of the questionnaires for accuracy and any necessary corrections were made. The scale totals were computed twice to ensure the correct formulae were entered. No errors were found. The SPSS computed scores were then checked against hand-calculated values using a random sample (5%) of hard copy questionnaires. Missing values were inspected using SPSS frequencies. A considerable number of IPAQ total scores

were missing in the data set ($n = 57$) and therefore a missing values analysis was conducted. However, as no patterns were detected and given the large sample size it was assumed that missing data would not pose any serious threat to the interpretation of results (Tabachnick & Fidell, 2007).

7.7. Data Analysis

For papers 2, 3 and 4, descriptive statistics were calculated for variables investigated; the significance level for statistical tests was $p < .05$; and selected variables were examined for outliers, skewness and kurtosis. In the remainder of this section, the data analysis specific to the research questions addressed in each paper is described.

7.7.1. Paper 2: Factors Associated with Adherence to Physical Activity Guidelines in Patients with Prostate Cancer

As there were missing data on the dependent variable for this paper, IPAQ leisure-time PA score, 356 cases were available for analysis. Participants were categorised into two groups based on the treatment they had received at the time of survey completion. In total, 203 (53.8%) participants had received RT plus ADT and 174 (46.2%) had received RT only. As the HADS depression subscale score and PA variables violated assumptions of normality non-parametric statistical tests were used. The data analyses applicable to each research question for *Paper 2* are as follows:

1. What proportion of patients with PCa are meeting the National Physical Activity Guidelines of Australia (NPAGA)?

Each activity on the IPAQ is assigned a metabolic equivalent task (MET) value, which is the energy expended compared with sitting at rest (United States

Department of Health and Human Services, 2008). A total PA score including all activity domains is calculated in MET-minutes per week. However, the literature suggests that measurement of PA conducted voluntarily in leisure-time may provide a more accurate measure of PA for health benefit (Armstrong, et al., 2000; Merom, Phongsavan, Chey, Bauman, & Australian Bureau of, 2006; Tremblay et al., 2011). For consistency with previous research (Lynch, et al., 2007; Vallance, et al., 2005), in the present study the leisure-time PA domain score was used to evaluate whether participants were meeting the NPAGA.

Three levels of PA are proposed to classify populations using the IPAQ (low: < 600 MET-minutes per week; moderate: 600 - 1500 MET-minutes per week; and high: >1500 MET-minutes per week). It has been suggested that 150 minutes of moderate-intensity activity per week could be regarded as approximately equivalent to 500 MET-minutes per week (United States Department of Health and Human Services, 2008). Therefore, participants categorised as low PA according to IPAQ conventions in the leisure-time PA domain were considered not to be meeting NPAGA. Descriptive statistics were used to describe the proportion of the sample meeting NPAGA.

2. *What socio-demographic and medical factors are associated with meeting*

NPAGA and are patients who had ADT less physically active than those who had RT only?

Chi-square analyses were used to assess relationships between meeting NPAGA and employment status (full-time; part-time; retired; disability/sick leave; other), marital status (married/defacto/partner; divorced/separated; single; widow), education (school; tertiary; TAFE/apprenticeship; postgraduate), treatment category (RT only; RT + ADT), RT type (brachytherapy; EBRT; brachytherapy + EBRT),

radical prostatectomy (yes; no), currently receiving ADT (never received; yes; no), comorbid conditions (none; one or more), previous cancer diagnosis (yes; no) and treatment centre (Alfred Hospital; LRH). Spearman's rho correlations were calculated between leisure-time PA and age; time since diagnosis; comorbid conditions; HADS depression and anxiety subscale scores; and FACT-P PCS scores.

3. *What PA domains are patients with PCa most active and are there differences in activity level by treatment type?*

Mann-Whitney tests were computed to assess in which domains of PA (work; transport; domestic; leisure; total PA) participants were most active, by treatment category. Analyses related to PA at work included only participants who were currently working at the time of survey completion ($n = 175$).

4. *Which of the following factors were predictors of meeting NPAGA: Treatment category, education, comorbid conditions, age, depression, anxiety and QoL?*

Using the above predictors, logistic regression analysis was used to identify factors that predicted whether participants were meeting NPAGA or not. Variables significantly associated with meeting NPAGA guidelines in univariate analyses and variables found to be associated with level of PA in previous research were selected and entered into a multivariate logistic regression (Enter method).

7.7.2. *Paper 3: Predictors of Depression, Anxiety and Quality of Life in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy*

Participants were categorised into four groups for this paper based on the treatment they had received at the time of survey completion (RT only; RT + 6 months ADT; RT + 2 ½ years ADT; and RT + ADT indefinitely). The depression

variable violated normality assumptions and therefore non-parametric statistics were firstly used to investigate differences in this construct by treatment group. However, parametric statistics were then used to establish if there were any differences in level of depression by treatment group. As there was no difference between the non-parametric and parametric results, the parametric statistics were reported for consistency. The data analyses applicable to each research question for *Paper 3* are as follows:

1. What were the levels of depression, anxiety and QoL in patients with PCa by treatment category?

Scores for each subscale were classified as non-cases (0 to 7), mild (8 to 10), moderate (11 to 14) or severe (15 to 21) cases, as described in the HADS manual (Snaith & Zigmond, 1994). Descriptive statistics included means, standard deviations, medians and ranges. For anxiety and depression, the number and percentage of participants classified as non-cases, or mild, moderate or severe cases was calculated for the total sample and according to treatment category. Participants were also categorised into “cases” of depression and anxiety, referring to HADS subscale scores in the range of 8 to 21. Scores within this range are considered to be suggestive of clinically significant levels of depression or anxiety.

2. Did depression and anxiety levels and QoL differ based on:

- a. Treatment group?*
- b. Socio-demographic and medical factors?*
- c. Whether participants were meeting NPAGA?*

One way analysis of variance (ANOVA) was used to examine differences in levels of depression, anxiety and QoL by treatment category (RT only; RT + 6 months ADT; RT + 2.5 years ADT; RT + ADT indefinitely), RT type (EBRT;

brachytherapy; EBRT + brachytherapy) and employment status (full-time; part-time; retired; disability/sick leave; other). Pearson correlation coefficients were calculated to examine the relationships between independent variables (age; time since diagnosis; and co-morbid conditions) and outcome variables (depression, anxiety and QoL). Independent *t*-tests were used to assess differences between patients who met NPAGA and those who did not on levels of depression, anxiety and QoL.

3. *Which of the following factors were predictors of depression, anxiety and QoL: Treatment category, RT type, employment status, meeting NPAGA, age, time since diagnosis, and number of comorbid conditions?*

Multiple regression was considered the most appropriate statistical test for continuous anxiety and depression variables. However, logistic regression was chosen to analyse these variables for two reasons. Firstly, the research team agreed that predicting “cases” of depression and anxiety would create a more clinically meaningful representation of levels of depression and anxiety in this sample. Furthermore, logistic regression has been used to predict cases of depression and anxiety in similar previous research (Brooker et al., 2012). Secondly, the depression and anxiety variables were not normally distributed. The research team considered transforming the depression and anxiety variables so that multiple regression analyses could be performed. However, given the caveats associated with data transformation including interpretation of results in the context of a transformed outcome variable (Tabachnick & Fidell, 2007), logistic regression was used to provide a clinically meaningful representation of the data, that could be clearly interpreted.

Two logistic regression analyses were calculated to predict cases of anxiety and depression. After removing cases with missing data 319 and 318 cases were

available for logistic regression analysis of depression and anxiety, respectively. Variables significantly associated at a univariate level with depression and anxiety were selected and entered into a multivariate logistic regression model in one step, using the “Enter” function within SPSS.

To examine QoL, a multiple regression analysis, using the “Enter” function within SPSS, was conducted. The same predictor variables were included as in the logistic regressions conducted for depression and anxiety, with the addition of a dichotomous variable indicating whether patients had received a radical prostatectomy (yes or no). Finally, a forward stepwise multiple regression analysis was conducted with the same set of variables to determine whether a more parsimonious model could be developed.

7.7.3. Paper 4: Factors Associated with Cognitive Function in Men with Prostate Cancer Receiving Androgen Deprivation Therapy

Participants included 363 men with PCa categorised into the four treatment groups based on the treatment they had received at the time of survey completion. In total, 168 (46.3%) participants had undergone RT only; 94 (25.9%) RT + 6 months ADT; 77 (21.2%) RT + 2 ½ years ADT; and 24 (6.6%) RT + ADT indefinitely. All FACT-Cog subscale scores violated normality and therefore non-parametric statistical tests were used for bivariate analyses. The data analyses applicable to each research question for *Paper 4* are as follows:

1. What types of cognitive difficulties are reported by patients with PCa?

To specify the number and type of cognitive complaints, FACT-Cog scores were dichotomised by classifying responses as a complaint (2 or greater) or non-complaint (0 or 1). This method of analysis is consistent with Jacobs et al. (2007).

Chi-square tests were used to analyse relationships between treatment type (RT only; RT + ADT) and cognitive complaints.

2. *Are there differences in cognitive function based on socio-demographic and medical factors and PA level?*

Mann-Whitney and Kruskal-Wallis tests were used to examine differences in FACT-Cog subscale scores by centre (urban; rural), employment status (employed; not employed), radical prostatectomy (yes; no), NPAGA (yes; no), education (primary or secondary; technical and further education (TAFE)/apprenticeship; tertiary; postgraduate), treatment category (RT only; RT + 6 months ADT; RT + 2 ½ years ADT; RT + ADT indefinitely), and RT type (EBRT; brachytherapy; EBRT + brachytherapy). Spearman's rho correlation coefficients were calculated to assess the relationships between independent variables (depression, anxiety, QoL, leisure-time PA, age; comorbid conditions) and outcome variables related to cognitive function.

3. *Which of the following factors were predictors of cognitive function: Treatment centre, education, employment status, treatment category, RT type, depression, anxiety, QoL, comorbid conditions, age, and leisure-time PA?*

To examine predictors of cognitive function, a multiple regression analysis using the "Enter" function in SPSS was conducted. As the FACT-Cog, Version 3 does not allow for the calculation of a total cognitive function score, the developers of the FACT-Cog advised that the CogPCI subscale score be used as the outcome measure of cognitive function in regression analyses (email correspondence with Wagner, L. dated 26/6/2012). As the dependent variable was negatively skewed, a reflected square root transformation was applied (Tabachnick & Fidell, 2007). Variables significantly associated at a univariate level with CogPCI scores were selected and entered into the regression model.

7.8. Participant Demographics and Medical Details

Table 7.4.

Participant Demographics and Medical Characteristics for Total Sample and Treatment Groups.

Study Characteristic	RT Only	RT + 6mths ADT	RT + 2.5yrs ADT	RT + ADT indefinitely	Total Sample
<i>n</i> (% of total sample)	174 (46.2)	100 (26.5)	77 (20.4)	26 (6.9)	377 (100.0)
Mean age, years (SD)	65.1 (7.4)	68.9 (6.6)	70.2 (6.9)	71.1 (8.8)	67.6 (7.5)
Mean time since diagnosis, months (SD)	27.7 (15.2)	34.4 (16.6)	32.8 (26.8)	67.4 (48.9)	33.3 (24.0)
Mean PSA (SD)	5.6 (3.3)	10.1 (9.5)	21.0 (18.3)	80.2 (140.5)	15.0 (41.4)
Marital status, <i>n</i> (% of sample)					
Married/Defacto/Partner	150 (86.2)	85 (85.0)	61 (79.2)	25 (96.2)	321 (85.1)
Divorced/Separated	12 (6.9)	8 (8.0)	7 (9.1)	1 (3.8)	28 (7.4)
Single	5 (2.9)	4 (4.0)	4 (5.2)	0 (0.0)	13 (3.4)
Widowed	7 (4.0)	3 (3.0)	5 (6.5)	0 (0.0)	15 (4.0)
Educational level, <i>n</i> (% of sample)					
Primary school	2 (1.1)	5 (5.0)	8 (10.4)	2 (7.7)	17 (4.5)
Secondary school	84 (48.3)	42 (42.0)	33 (42.9)	11 (42.3)	170 (45.1)
Tertiary	67 (38.5)	43 (43.0)	30 (39.0)	9 (34.6)	149 (39.5)
TAFE/apprenticeship	15 (8.6)	8 (8.0)	5 (6.5)	1 (3.8)	29 (7.7)
Postgraduate	4 (2.3)	2 (2.0)	1 (1.3)	1 (3.8)	8 (2.1)
Missing	2 (1.1)	0 (0.0)	0 (0.0)	2 (7.7)	4 (1.1)
Employment status, <i>n</i> (% of sample)					
Full-time	57 (32.8)	17 (17.0)	13 (16.9)	3 (11.5)	90 (23.9)
Part-time	25 (14.4)	20 (20.0)	13 (16.9)	1 (3.8)	59 (15.6)
Retired	73 (41.9)	53 (53.0)	49 (63.6)	19 (73.1)	194 (51.5)
Disability/sick leave	9 (5.2)	4 (4.0)	1 (1.3)	1 (3.8)	15 (4.0)
Other	8 (4.6)	5 (5.0)	1 (1.3)	1 (3.8)	15 (4.0)
Missing	2 (1.1)	1 (1.0)	0 (0.0)	1 (3.8)	4 (1.1)

Study Characteristic	RT Only	RT + 6mths ADT	RT + 2.5yrs ADT	RT + ADT indefinitely	Total Sample
Number of co-morbidities, <i>n</i> (% of sample)					
0	38 (21.8)	22 (22.0)	11 (14.2)	9 (34.6)	80 (21.2)
1-2	110 (63.2)	54 (54.0)	47 (61.0)	11 (42.3)	222 (58.9)
>3	26 (14.9)	24 (24.0)	18 (23.4)	6 (23.1)	74 (19.6)
Missing	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.3)
Clinical risk category, <i>n</i> (% of sample)					
Low	76 (43.7)	3 (3.0)	0 (0.0)	0 (0.0)	79 (21.0)
Intermediate	87 (50.0)	84 (84.0)	2 (2.6)	3 (11.5)	176 (46.7)
High	11 (6.3)	13 (13.0)	75 (97.4)	23 (88.5)	122 (32.4)
Stage Category, <i>n</i> (% of sample)					
T1	23 (13.2)	3 (3.0)	1 (1.3)	1 (3.8)	28 (7.4)
T2	138 (79.3)	74 (74.0)	44 (57.1)	4 (15.4)	260 (69.0)
T3 or 4	12 (6.9)	22 (22.0)	30 (39.0)	21 (80.8)	85 (22.5)
Missing	1 (0.5)	1 (1.0)	2 (2.6)	0 (0.0)	4 (1.1)
Gleason Score, <i>n</i> (% of sample)					
< 7	72 (41.4)	12 (12.0)	3 (3.9)	0 (0.0)	87 (23.1)
7	97 (55.7)	83 (83.0)	27 (35.1)	11 (42.3)	218 (57.8)
> 7	5 (2.9)	5 (5.0)	47 (61.0)	15 (57.7)	72 (19.1)
RT Type, <i>n</i> (% of sample)					
Brachytherapy	136 (78.2)	9 (9.0)	0 (0.0)	0 (0.0)	145 (38.5)
EBRT	37 (21.3)	63 (63.0)	53 (68.8)	25 (96.2)	178 (47.2)
Brachytherapy + EBRT	1 (0.6)	28 (28.0)	24 (31.2)	1 (3.8)	54 (14.3)
Previous Cancer Diagnosis, <i>n</i> (% of sample)	12 (6.9)	10 (10.0)	6 (7.8)	0 (0.0)	28 (7.4)
Radical Prostatectomy, <i>n</i> (% of sample)	24 (13.8)	22 (22.0)	19 (24.7)	5 (19.2)	70 (18.6)
Currently receiving ADT, <i>n</i> (% of sample)	0 (0.0)	4 (4.0)	59 (76.6)	25 (96.2)	88 (23.3)

PSA = Prostate Specific Antigen; RT = Radiotherapy; EBRT = External Beam Radiotherapy; ADT = Androgen Deprivation Therapy

7.9. Summary and Conclusion

In this chapter the methodology used in the current study was presented. In the next chapter the second of the papers for publication, *Factors Associated with Adherence to Physical Activity Guidelines in Patients with Prostate Cancer* is presented.

Chapter 8. Factors Associated with Adherence to Physical Activity Guidelines in Patients with Prostate Cancer

8.1. Rationale and Aims for Paper 2

The results of prior research presented in Chapter 5 and findings of the systematic review reported in Chapter 6 suggest that PA may be an effective behavioural intervention to improve QoL and psychosocial wellbeing in men with PCa and in particular, for those receiving ADT. The aims of the study reported in this chapter were to describe PA behaviour in men receiving treatment for PCa and determine socio-demographic and medical variables associated with the ability to engage in regular PA.

The research questions addressed in the current chapter were:

1. What proportion of men with PCa are meeting NPAGA?
2. What socio-demographic and medical factors impact on the ability to meet NPAGA in this patient group?
3. Which domains of PA (work, transport, domestic and leisure) are men with PCa most active in and does activity level differ according to type of treatment?
4. What factors predict the likelihood that men with PCa would meet NPAGA?

The following manuscript was submitted to *Psycho-Oncology* in November 2012. The manuscript was peer-reviewed by four reviewers and required major revisions in January 2013. Amendments were made accordingly and the manuscript was resubmitted in March 2013. The revised manuscript was accepted for

publication in April 2013. The final version accepted for publication is included in this chapter. The formatting of this paper is in accordance with the style specified by the editorial board.

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter 8

Declaration by candidate

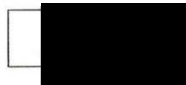
In the case of Chapter 8, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Research design, ethics applications, data collection, data analysis, writing draft paper and communication with participants.	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Ms Jane Fletcher	Guidance with research design, ethics application, data analysis, critical review of draft paper; duty of care for participants.	
A/Prof Jeremy Millar	Medical advice, data collection, critical review of draft paper.	
Dr Joanne Brooker	Guidance with data analysis, critical review of draft paper.	
Ms Robin Smith	Guidance with ethics application, data collection, critical review of draft paper; duty of care for participants.	
A/Prof Mark Frydenberg	Medical advice, critical review of draft paper.	
Dr Tracy Oh	Medical advice, critical review of draft paper.	
Dr Sue Burney	Guidance with research design, ethics application, data analysis, critical review of draft paper; duty of care for participants.	

Candidate's
Signature




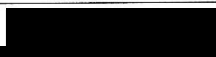
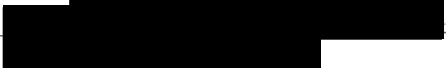
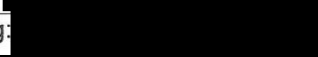



Date
21/11/2012

Declaration by co-authors

The undersigned hereby certify that:

- (1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- (2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- (4) there are no other authors of the publication according to these criteria;
- (5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- (6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) School of Psychology and Psychiatry, Clayton Campus, Monash University

Signature 1	Ms Jane Fletcher:		Date 26/11/12
Signature 2	A/Prof Jeremy Millar:		16.11.12
Signature 3	Dr Joanne Brooker:		28-11-12
Signature 4	Ms Robin Smith:		16/11/12
Signature 5	A/Prof Mark Frydenberg:		18/10/12
Signature 6	Dr Tracy Oh:		16.11.12
Signature 7	Dr Sue Burney:		21/11/2012

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FACTORS ASSOCIATED WITH ADHERENCE TO PHYSICAL ACTIVITY GUIDELINES IN PATIENTS WITH PROSTATE CANCER

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8.2. ABSTRACT

Objective: To estimate the proportion of patients with prostate cancer (PCa) meeting the National Physical Activity Guidelines of Australia (NPAGA) and determine socio-demographic and medical factors associated with meeting these guidelines. Secondary aims included examining physical activity (PA) levels by treatment type and domain (leisure, work, transport and domestic) and establishing a predictive model of the likelihood that men with PCa would meet NPAGA. **Methods:** A questionnaire was mailed to 638 men with PCa attending for treatment at the Alfred, Cabrini or Latrobe Regional Hospitals during 2010 and 2011, with a response rate of 59%. Measures included: International Physical Activity Questionnaire (IPAQ); Hospital Anxiety and Depression Scale (HADS); Functional Assessment of Cancer Therapy – Prostate (FACT-P); and socio-demographic items. Inclusion criteria were English speaking men aged 40 to 80 years, who had undergone radiotherapy (RT) between 9 and 30 months prior to the survey. **Results:** Of 356 men with PCa, less than half were meeting NPAGA (41.9%). Lower education and quality of life (QoL), a higher number of comorbid conditions, and symptoms of depression and anxiety were associated with decreased leisure-time PA. Patients treated with androgen deprivation therapy (ADT) were significantly less active than patients treated with RT only. Logistic regression analyses indicated that the likelihood of meeting NPAGA was significantly lower with higher levels of depressive symptoms and lower levels of education. **Conclusions:** Meeting NPAGA is associated with higher QoL and psychosocial wellbeing in men with PCa. These findings contribute important information for targeting PA interventions to PCa survivors.

Keywords: Physical activity; Prostate cancer; Oncology; Quality of life; Depression; Anxiety

8.3. INTRODUCTION

Prostate cancer (PCa) represents a significant global public health burden and is the most commonly diagnosed internal cancer in Australia, with approximately 20,000 cases identified per year [1]. Primary treatment alternatives for PCa include active surveillance, radical prostatectomy, external beam radiotherapy (EBRT), brachytherapy and androgen deprivation therapy (ADT) [2]. While the effectiveness of these treatments in increasing survival and delaying disease progression has been established [2-4], the negative impact of treatment for PCa on physical function, psycho-social wellbeing and quality of life (QoL) is widely recognised [5, 6]. Given the increasing prevalence of PCa [2] and the impact of treatment on both physical and psychological aspects of QoL, it is important to identify clinically beneficial and cost-effective interventions to improve wellbeing in this patient group.

Physical activity (PA) has been proposed as a behavioural intervention to improve health and wellbeing outcomes for patients with cancer [7]. There is evidence, albeit tenuous, that engagement in regular PA after cancer diagnosis may reduce the risk of death from disease [8, 9]. Furthermore, PA has been associated with an improvement in overall QoL and health status in patients with cancer and cancer survivors [10-14]. The results of numerous studies highlight the importance of PA in counteracting the negative side effects associated with treatment for PCa and demonstrate improvements in QoL and psycho-social wellbeing with regular PA participation [13-19]. Importantly, findings by Galvao et al [20] established that PA can be safely tolerated in this patient group, with no reported effect on PSA levels,

testosterone production or disease activity. Previous research indicates that patients with cancer recognise the benefits of PA and are interested in PA participation to improve QoL during and following treatment [21]. However, the proportion of patients engaging in regular PA remains low [11, 21-23].

The literature suggests that decrements in physical and psychological functioning associated with ageing and comorbid conditions may serve as barriers to physical inactivity [21, 24, 25], with cancer treatments likely to exacerbate pre-existing functional decrements [21, 26]. The side effects of cancer treatments may serve to obstruct PA participation, however, older patients engaging in regular PA during and following treatment have reported less severe symptoms [21]. Symptoms of depression and poor psycho-social wellbeing may also serve as significant barriers to PA participation, with depressed individuals less likely to engage in regular PA and physical inactivity associated with a higher risk of depressive symptoms [27]. Less education and lower socioeconomic status have also been associated with decreased PA participation in prior research [24, 28]. Of particular relevance to the present study, patients with PCa have previously reported a lack of knowledge about appropriate levels of PA following treatment [26].

Findings of previous research suggests that 150 minutes of moderate-intensity activity or more per week is associated with improvements in QoL in patients with cancer [8, 11, 22, 23, 29]. Two Canadian based studies found that ovarian cancer and non-Hodgkin's lymphoma survivors meeting PA guidelines (150 minutes of moderate-intensity PA per week) reported more favourable outcomes related to fatigue, psycho-social functioning and several QoL domains than those patients who did not meet the guidelines [22, 29]. In an Australian study conducted by Lynch and colleagues [11] it was found that colorectal cancer survivors meeting the National

Physical Activity Guidelines of Australia (NPAGA) [30] had significantly higher overall QoL and physical and functional wellbeing compared to those patients who did not meet these guidelines. In an American study, it was found that men with PCa who met the American Cancer Society PA guidelines [31] reported better QoL than participants classified as insufficiently active [23].

In addition to questions regarding the clinically appropriate level of PA for improvement in wellbeing, the domains of activity considered suitable to incur health benefits are also unclear. For example, Armstrong et al [24] reported a lack of evidence for determining whether gardening and yard work or walking at work contributes to achieving a sufficient level of activity for health benefit. Conversely, a systematic review concluded that both occupational and leisure-time PA was linked to declines in depression and anxiety symptoms [32]. The American College of Sports Medicine proposed that routine activities of daily living, including domestic, transport and occupation related PA should be supplemented with the recommended level of aerobic activity [33]. The importance of twice weekly resistance training for muscular strength and endurance in older adult populations has also been recognised [34]. For men with PCa receiving ADT, this may be an essential form of exercise to reduce the risk of bone fractures and osteoporosis and for maintenance of muscle mass, strength and physical function which may be negatively affected by the use of ADT [17, 18]. Nevertheless, research evidence implies that measurement of PA conducted voluntarily in leisure-time may provide a more accurate measure of PA for health benefit [24]. Lynch et al [11] and Vallance et al [22] used total leisure-time PA scores to evaluate whether colorectal cancer and non-Hodgkin's lymphoma survivors, respectively, were meeting PA guidelines. For consistency with previous

research, in the present study leisure-time PA was included as a measure of meeting NPAGA.

The purpose of the current study was to estimate the proportion of patients with PCa meeting the NPAGA and whether meeting PA recommendations was associated with socio-demographic and medical factors. Another aim was to examine the PA domains in which patients with PCa were most active and differences in activity level by treatment type. A final aim was to develop a model to predict the likelihood that patients with PCa would meet the NPAGA.

8.4. METHOD

Before data collection, approval for the research was received from the Human Research Ethics Committees at The Alfred, Cabrini and Latrobe Regional Hospitals (LRH) and Monash University.

8.4.1. Participants and Procedure

Participants were recruited through the William Buckland Radiotherapy Centre (WBRC) at The Alfred Hospital, Melbourne. The WBRC database includes patients who attended for treatment at Cabrini and LRH, making it possible to collect data from all three participating centres. Patients included in the study were English speaking, between 40 and 80 years at the time of radiotherapy (RT) completion and had received RT for PCa between 9 and 30 months ago. Data were collected over a 12 month period during 2010 and 2011. A flow diagram of respondents is included in *Figure 8.1*. As the research team did not have access to the medical records of non-responders it was not possible to examine differences between responders and non-responders in terms of medical and demographic factors.

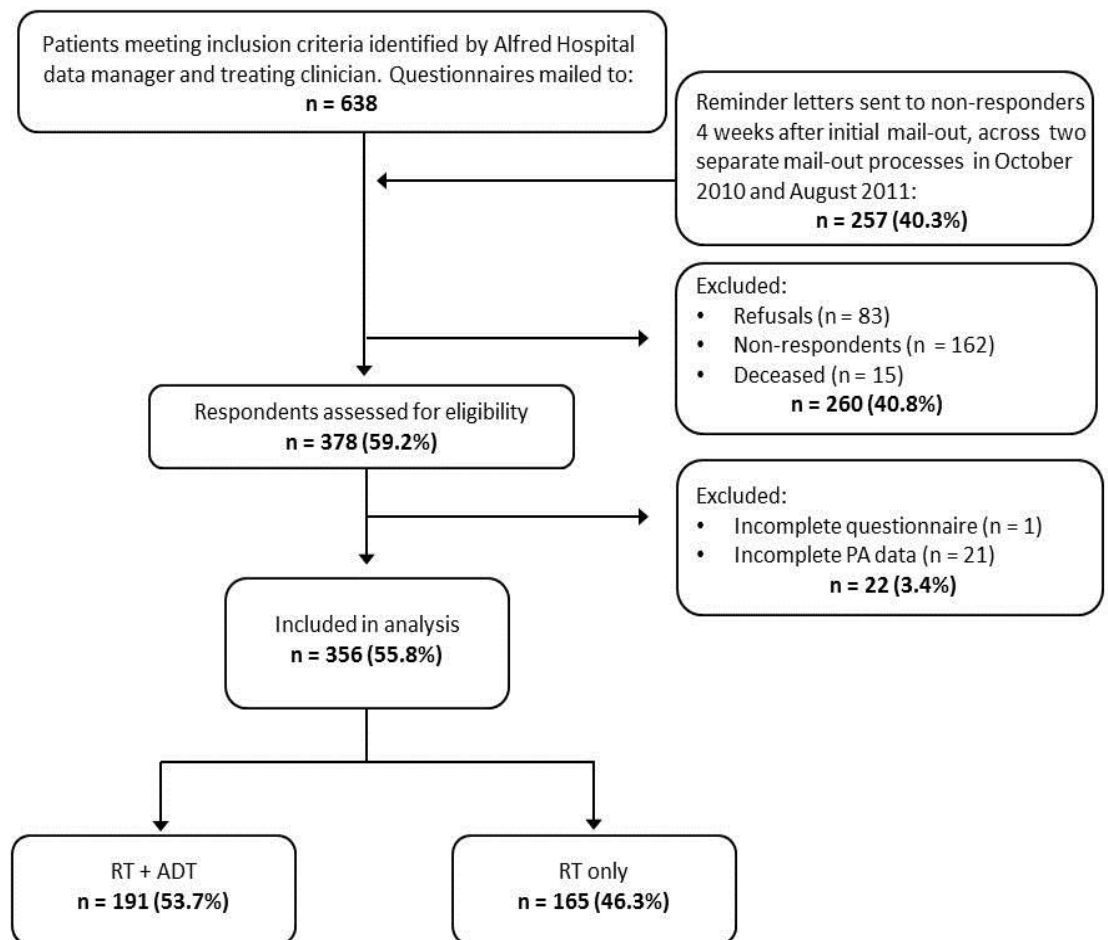


Figure 8.1. Flow diagram of respondents and inclusion of participants in analyses.

8.4.2. Measures

PA was measured with The International Physical Activity Questionnaire (IPAQ). The IPAQ consists of 31 items and assesses level of PA within four activity domains including work, transport, domestic and leisure-time. It includes the frequency, intensity and duration of PA over the past seven days. Craig and colleagues' [35] evaluation of reliability and validity of the IPAQ across 12 countries produced repeatable data (Spearman's ρ of 0.81) and a median correlation of 0.33 (Spearman's ρ) when assessing criterion validity against an accelerometer. The IPAQ provides a continuous measure of PA among young and elderly populations [36]. It

was considered appropriate for use in the present study as it is the only PA measure for which normative data from an Australian sample are available [35]. For comparability of findings with previous research the leisure activity domain of the IPAQ was used to evaluate participants meeting the NPAGA. Distinct activities on the IPAQ are assigned a metabolic equivalent task (MET) value, which are multiples of resting energy expenditure [37]. PA is classified into three levels using the IPAQ (low: < 600 MET-minutes per week; moderate: 600 - 1500 MET-minutes per week; and high: >1500 MET-minutes per week). Participants categorised as 'low' PA according to the IPAQ in the leisure activity domain were considered not to be meeting NPAGA.

Quality of life (QoL) specific to PCa and its treatment was measured using the 12-item prostate cancer subscale (PCS) of the Functional Assessment of Cancer Therapy - Prostate (FACT-P). Previous researchers have reported internal consistency of the PCS ranging from 0.65 to 0.69 [38, 39]. Each item is rated on a 0 to 4 Likert type scale, and then combined to produce a subscale score representative of PCa-specific QoL. Higher scores represent better QoL.

The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of depression and anxiety, over the past seven days with 7 items applicable to each construct [40]. The HADS is suitable for use with patients who have a physical illness [41], including PCa populations [42]. Each item is rated on a Likert-type scale of 0 to 3, with total scores for each subscale ranging from 0 to 21. Interpretation of anxiety and depression symptoms is based on the raw score of each subscale: normal (0-7); mild (8-10); moderate (11-14); and severe (15-21). Cronbach's alpha coefficients of 0.93 for the anxiety and 0.85-0.90 for the depression subscale have been previously reported [41].

8.4.3. *Data Analysis*

The significance level was set at $p < .05$. Data were analysed using IBM SPSS Statistics 18 (2010). Key study variables were examined for outliers, skewness and kurtosis. As the HADS depression subscale score and PA variables violated normality, non-parametric statistical tests were used for all analyses.

Chi-square analyses were used to assess relationships between meeting NPAGA and employment status; marital status; education; treatment category; RT type; radical prostatectomy; currently receiving ADT; comorbid conditions; previous cancer diagnosis; and treatment centre (urban or rural). Spearman's rho correlations were calculated between leisure-time PA and age; time since diagnosis; comorbid conditions; HADS depression and anxiety subscale scores; and FACT-P PCS scores. Mann-Whitney tests were computed to assess in which domains of PA (work; transport; domestic; leisure; total PA) participants were most active, by treatment category. Analyses related to PA at work included only participants who were currently working at the time of survey completion ($n = 175$).

Logistic regression analysis was used to identify factors that were associated with meeting NPAGA or not. Variables significantly associated with meeting NPAGA guidelines in univariate analyses (education; comorbid conditions; depression; anxiety; FACT-P PCS score) and variables found to be associated with level of PA in previous research (age; treatment category) were entered into a multivariate logistic regression.

8.5. RESULTS

Demographic and medical details of the sample are displayed in Table 8.1. Participants were categorised into two groups based on the treatment they had received at the time of survey completion, with 191 (53.7%) receiving RT plus ADT and 165 (46.3%) receiving RT only. In Table 8.2 a summary of chi square analyses for meeting NPAGA based on socio-demographic and medical factors is presented. In total, 41.9% of patients were meeting NPAGA. The proportion of participants meeting NPAGA differed according to education level ($\chi^2(3, N = 353) = 10.02$, $p < .05$), with a higher percentage of patients with tertiary level education meeting NPAGA. The proportion of patients with PCa meeting NPAGA did not significantly differ by employment status, marital status, treatment category, RT type, radical prostatectomy, currently receiving ADT, previous cancer diagnosis or treatment centre.

Table 8.1.

Participant Demographics and Medical Characteristics of the Sample by Treatment Type.

Study Characteristic	RT Only	RT + ADT	Total Sample
<i>N</i> (%)	165 (46.3)	191 (53.7)	356 (100.0)
Mean age, years (SD)	65.1 (7.4)	69.4 (7.1)	67.4 (7.5)
Mean time since diagnosis, months (SD)	27.1 (14.9)	37.3 (26.6)	33.1 (22.8)
Mean PSA (SD)	5.7 (3.3)	23.1 (56.6)	15.0 (42.5)
Marital status, <i>n</i> (%)			
Married/Defacto/Partner	143 (86.7)	161 (84.3)	304 (85.4)
Divorced/Separated	12 (7.3)	15 (7.9)	27 (7.6)
Single	5 (3.0)	8 (4.2)	13 (3.7)
Widowed	5 (3.0)	7 (3.7)	12 (3.4)
Education, <i>n</i> (%)			
Primary/Secondary School	85 (51.5)	94 (49.2)	179 (50.3)
Tertiary	62 (37.6)	78 (40.8)	140 (39.3)
TAFE/apprenticeship	13 (7.9)	13 (6.8)	26 (7.3)
Postgraduate	4 (2.4)	4 (2.2)	8 (2.2)
Missing	1 (0.6)	2 (1.0)	3 (0.8)
Employment status, <i>n</i> (%)			
Full-time	54 (32.7)	32 (16.8)	86 (24.2)
Part-time	25 (15.2)	31 (16.2)	56 (15.7)
Retired	68 (41.2)	113 (59.2)	181 (50.8)
Disability/sick leave	9 (5.5)	6 (3.1)	15 (4.2)
Other	8 (4.8)	7 (3.7)	15 (4.2)
Missing	1 (0.6)	2 (1.0)	3 (0.8)
Number of co-morbidities, <i>n</i> (%)			
0	37 (22.4)	40 (20.9)	77 (21.6)
1-2	104 (63.0)	106 (55.5)	210 (59.0)
>2	24 (14.5)	44 (23.1)	68 (19.1)
Missing	0 (0.0)	1 (0.5)	1 (0.3)
Clinical risk category, <i>n</i> (%)			
Low	74 (44.8)	3 (1.6)	77 (21.6)
Intermediate	81 (49.1)	86 (45.0)	167 (46.9)
High	10 (6.1)	102 (53.4)	112 (31.5)
Stage of Tumour, <i>n</i> (%)			
T1	23 (13.9)	5 (2.6)	28 (7.9)
T2	131 (79.4)	117 (61.3)	248 (69.7)
T3 or 4	10 (6.1)	66 (34.6)	76 (21.3)
Missing	1 (0.6)	3 (1.5)	4 (1.1)
Gleason Score, <i>n</i> (%)			
< 7	70 (42.4)	14 (7.3)	84 (23.6)
7	90 (54.5)	116 (60.7)	206 (57.9)
> 7	5 (3.0)	61 (31.9)	66 (18.5)
RT Type, <i>n</i> (%)			
Brachytherapy	129 (78.2)	9 (4.7)	138 (38.8)
EBRT	35 (21.2)	131 (68.6)	166 (46.6)
Brachytherapy + EBRT	1 (0.6)	51 (26.7)	52 (14.6)
Previous Cancer Diagnosis, <i>n</i> (%)	12 (7.3)	16 (8.4)	28 (7.9)
Radical Prostatectomy, <i>n</i> (%)	23 (13.9)	45 (23.6)	68 (19.1)
Currently Receiving ADT, <i>n</i> (%)	0 (0.0)	82 (42.9)	82 (23.0)

PSA = Prostate Specific Antigen; RT = Radiotherapy; EBRT = External Beam Radiotherapy;
ADT = Androgen Deprivation Therapy.

Table 8.2.

Chi-square Analyses of Participants Meeting NPAGA by Socio-Demographic and Medical Variables.

Variable	Meeting NPAGA		χ^2	<i>p</i>
	Yes	No		
<i>N</i> (%)	149 (41.9)	207 (58.1)	-	-
Employment status, <i>n</i> (%)			0.99	.32
Working	55 (38.7)	87 (61.3)		
Not Working	93 (44.1)	118 (55.9)		
Marital Status, <i>n</i> (%)			2.10	.15
Partner	132 (43.4)	172 (56.6)		
No Partner	17 (32.7)	35 (67.3)		
Education, <i>n</i> (%)			10.02	<.05
Primary/Secondary School	69 (38.5)	110 (61.5)		
Tertiary	71 (50.7)	69 (49.3)		
TAFE/apprenticeship	6 (23.1)	20 (76.9)		
Postgraduate	2 (25.0)	6 (75.0)		
Treatment Category, <i>n</i> (%)			0.18	.75
RT only	71 (43.0)	94 (57.0)		
RT + ADT	78 (40.8)	113 (59.2)		
RT Type, <i>n</i> (%)			0.32	.85
Brachytherapy	59 (42.8)	79 (57.2)		
EBRT	67 (40.4)	99 (59.6)		
Brachytherapy + EBRT	23 (44.2)	29 (55.8)		
Radical Prostatectomy, <i>n</i> (%)			0.94	.33
Yes	32 (47.1)	36 (52.9)		
No	117 (40.6)	171 (59.4)		
Currently Receiving ADT, <i>n</i> (%)			2.82	.24
Never received	71 (43.0)	94 (57.0)		
Yes	28 (34.1)	54 (65.9)		
No	50 (45.9)	59 (54.1)		
Previous Cancer Diagnosis, <i>n</i> (%)			0.26	.38
Yes	13 (46.4)	15 (53.6)		
No	136 (41.5)	192 (58.5)		
Treatment Centre, <i>n</i> (%)			0.04	.47
Alfred Hospital	116 (41.6)	163 (58.4)		
Latrobe Regional Hospital	33 (42.9)	44 (57.1)		

NPAGA = National Physical Activity Guidelines of Australia; RT = Radiotherapy; ADT = Androgen Deprivation Therapy; EBRT = External Beam Radiotherapy.

Correlations between leisure-time PA and examined variables are displayed in Table 8.3. Significant negative relationships were observed between leisure-time PA and comorbid conditions (r (355) = -0.14, $p < .01$), depression (r (356) = -0.23, $p < .001$) and anxiety (r (355) = -0.11, $p < .05$). A significant positive relationship was

detected between leisure-time PA and QoL ($r(354) = 0.18, p < .01$). No relationships were found between leisure-time PA and time since diagnosis or age.

Table 8.3.

Correlation Matrix of Key Study Variables with Leisure-time Physical Activity.

	1	2	3	4	5	6	7
1 IPAQ Leisure-time PA score							
2 HADS Depression subscale score	-0.23**						
3 HADS Anxiety subscale score	-0.11*	0.63**					
4 FACT-P PCa subscale score	0.18**	-0.51**	-0.35**				
5 Comorbid conditions	-0.14**	0.24**	0.13*	-0.33**			
6 Time since diagnosis (months)	-0.08	0.11*	0.02	-0.16**	-0.04		
7 Age	-0.04	0.09	-0.10*	-0.17**	0.15**	0.08	

* $p < .05$; ** $p < .01$

IPAQ = International Physical Activity Questionnaire; PA = Physical Activity; HADS = Hospital Anxiety and Depression Scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; PCa = Prostate Cancer.

In *Figure 8.2* median MET-minutes of PA in each PA domain by treatment category are presented. Mann-Whitney tests revealed that those who received ADT had significantly lower total PA scores than those who received RT only ($z = -2.11, p < .05$). No significant differences were found between treatment groups for the individual domains of work, domestic, transport or leisure-time PA.

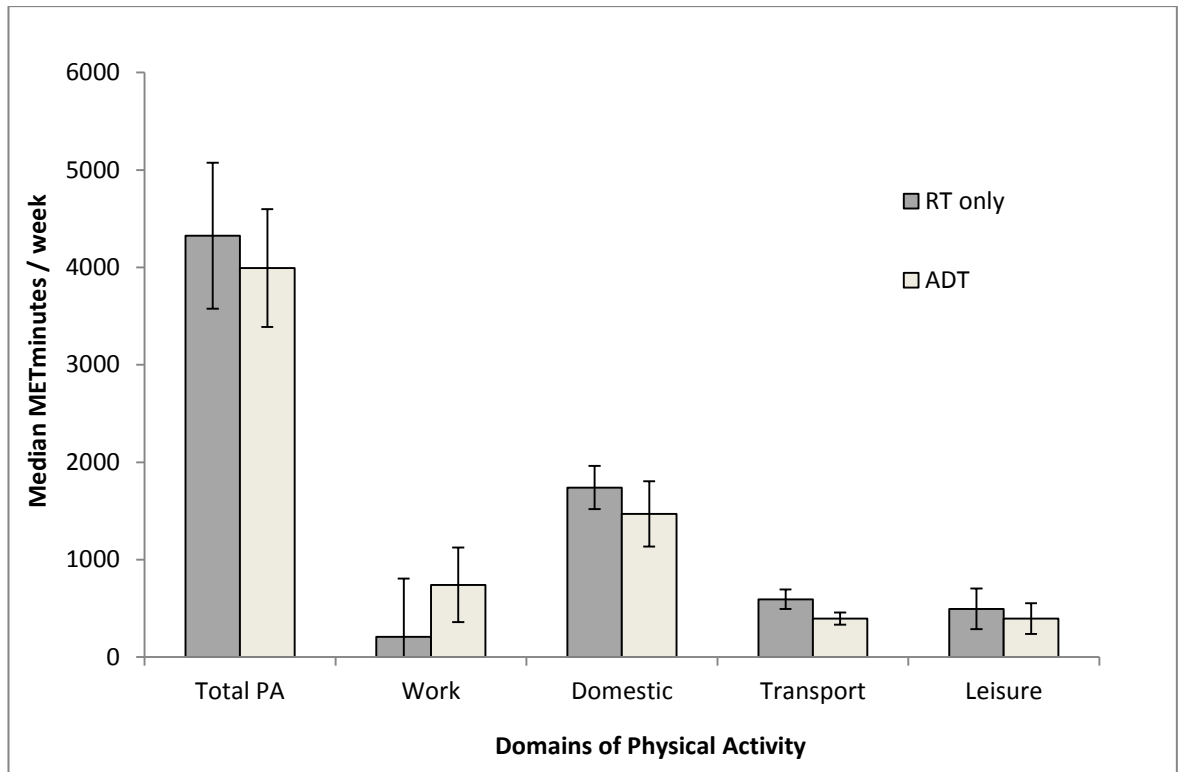


Figure 8.2. Median MET-minutes of physical activity within each activity domain by treatment category.

After automatic removal in SPSS of cases with missing data for variables included in the logistic regression model of meeting NPAGA, 349 cases were available for this analysis. Missing values analysis was undertaken and no patterns were detected, indicating that missing data posed a limited threat to the interpretation of results. The logistic regression model for meeting NPAGA with all predictors against a constant-only model was significant ($\chi^2 (9) = 33.23, p < .001$). The model accurately predicted 76.4% of participants not meeting NPAGA and 45.2% of participants meeting NPAGA, with an overall success rate of 63.3%. Table 8.4 shows that the odds of meeting NPAGA were significantly higher with lower depression scores. Furthermore, participants with a tertiary level education were significantly more likely to be meeting NPAGA than those with primary/secondary

school or TAFE/apprenticeship qualifications. Treatment category, comorbid conditions, age, anxiety and QoL were not significantly associated with meeting NPAGA.

Table 8.4.

Logistic Regression to Predict Variables Associated with Meeting the NPAGA.

Variable	Category	Intercept	Odds Ratio	(95% Confidence Interval)	p Value
Treatment Category	RT Only		1		
	RT + ADT	-0.07	0.93	(0.58, 1.51)	.78
Education	Tertiary		1		
	Primary/Secondary School	-0.50	0.61	(0.38, 0.97)	<.05
	TAFE/apprenticeship	-1.38	0.25	(0.09, 0.68)	<.01
	Postgraduate	-1.55	0.21	(0.04, 1.12)	.07
Comorbid conditions		-0.90	0.92	(0.76, 1.11)	.37
Age (yrs)		0.01	1.01	(0.98, 1.05)	.44
HADS depression score		-0.17	0.84	(0.76, 0.94)	<.01
HADS anxiety score		0.02	1.02	(0.94, 1.11)	.63
FACT-P PCa score		0.00	1.00	(0.97, 1.04)	.82

NPAGA = National Physical Activity Guidelines of Australia; RT = Radiotherapy; ADT = Androgen Deprivation Therapy; HADS = Hospital Anxiety and Depression Scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; PCa = Prostate Cancer.

8.6. DISCUSSION

The primary aim of the present study was to assess the proportion of patients with PCa meeting NPAGA and determine the medical and socio-demographic factors associated with meeting PA recommendations. Less than half of the participants met NPAGA (41.9%). This finding is comparable to previous research, with 45% of men with PCa receiving ADT found to be meeting PA recommendations [23]. Similarly, Sprod et al [21] reported that 46% of older patients

with cancer engaged in regular PA during RT and/or chemotherapy and 60% did so following treatment.

A larger proportion of participants with tertiary level education met NPAGA. This is consistent with previous research suggesting that less education is associated with decreased PA [24, 28]. Relationships between leisure-time PA and comorbid conditions, depression, anxiety and QoL were significant and in the directions consistent with prior research [21, 25, 26, 32, 43, 44]. However, correlations were weak and should be interpreted with caution, suggesting that there are other variables associated with leisure-time PA not measured in the current study. An extensive review of the literature by the current authors indicated that no prior studies have specifically examined the relationship between depression and PA in PCa populations and therefore the present findings are novel. Unlike prior findings, no relationship was found between age and leisure-time PA [21, 25, 26], perhaps reflecting the inability to observe such a relationship in the current sample, given the limited range in PA levels and age.

Domains of PA and differences in activity level by treatment type were examined. Participants receiving ADT were significantly less active in total PA compared with participants receiving RT only, although significant differences were not observed between treatment groups across individual PA domains (i.e., work, transport, leisure and domestic). The research evidence suggests that the negative side effects associated with ADT exacerbate the impact of other PCa treatments on QoL and psycho-social wellbeing [45, 46]. Consequently, with evidence suggesting that more severe treatment side effects are linked to a reduced likelihood of PA participation [21], it is plausible that the additional adverse effects associated with ADT affect the ability of patients to participate in regular PA. Furthermore, men

treated with ADT are likely to have more aggressive cancer with boney metastasis and regional spread of disease causing pain and discomfort, posing further limitations to regular PA engagement. However, it has been demonstrated that there are physical and psychological benefits of PA for PCa patients undergoing ADT [15, 17, 19, 23], highlighting the importance of engaging in regular PA for this patient group.

The current findings also suggest that men with PCa are most active in the domestic PA domain and least active in the transport and leisure PA domains, implying that PA is primarily undertaken involuntarily as part of household chores. However, it remains unclear whether domestic- and work-related PA contribute to achieving a sufficient level of activity for health benefit [24, 33]. In Armstrong and colleagues' [24] Australian population-based study of adult PA patterns, leisure-time PA was primarily reported, highlighting the element of personal choice in regular PA participation after work, travel and domestic chores are complete. PA recommendations for patients with PCa should therefore emphasise types of PA that would be considered sufficient to incur improvements in QoL.

The final aim of the study was to establish a model of factors associated with patients with PCa meeting NPAGA. Logistic regression analyses indicated that the likelihood of meeting NPAGA significantly diminished with lower levels of education and higher depression scores. Previous researchers have also found an association between education and PA [24, 28]. Consistent with the current findings, Sieverdes and colleagues' [43] found that a maximum reduction in the odds of depressive symptoms was reached with PA levels of approximately 150 minutes of moderate-intensity PA per week in the general population.

8.6.1. Limitations and Future Research

A widely-recognised problem with self-report PA measures is over estimation of PA levels [47], which is a key limitation in the current study. Furthermore, study design prevented the measurement of resistance based PA performed by this sample, which may be useful given the positive evidence for resistance training with this patient group [17, 18]. The lack of valid and accurate PA measures available is apparent [48], with further studies required using objective measurements of PA to establish whether meeting NPAGA is sufficient to yield improvements in QoL and psycho-social wellbeing in patients with PCa. Validation studies are also required to determine the energy expenditure of PA in domestic and occupational settings and to establish the utility of including these PA domains in self-report surveys. Further research to determine the effects of treatment type on PA levels would be beneficial to tailor appropriate PA interventions for adequate improvement of QoL and psycho-social wellbeing according to treatment type. Finally, given the cross-sectional design, longitudinal studies are required to examine change in PA levels prior to, during, and following treatment.

8.6.2. Conclusions

An extensive review of the literature suggests that this is the first study to examine the proportion of patients with PCa meeting NPAGA. The finding suggesting that less than 50% of patients with PCa are achieving optimal PA levels is cause for concern. However, this may be a reflection of treatment, disease and/or environmental factors, together with inadequate knowledge regarding appropriate levels of PA. The current findings provide helpful information to target PA intervention programs to PCa survivors, suggesting that 150 minutes of moderate-

intensity leisure-time PA weekly is sufficient to improve QoL in this patient group. Structured PA regimes including resistance training elements are likely to improve QoL and survivorship outcomes in men receiving treatment for PCa. Importantly, PA interventions need to include an education component emphasising the value, health benefits and optimal levels of PA for this patient group. Given the impact of treatment for PCa on physical and psychological functioning and evidence that meeting NPAGA is associated with a reduced likelihood of depressive symptoms, behavioural interventions targeted at meeting NPAGA should become an integral component of cancer rehabilitation programs. Such programs may contribute to reducing the burden of PCa on public health in terms of disability, QoL and financial cost.

8.7. References

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8.8. Summary and Conclusions

In this chapter, the first empirical paper from the study was presented. Taken with the results of previous research, the findings of this paper suggest that meeting NPAGA is sufficient to improve QoL and psychosocial wellbeing in men with PCa. Furthermore, the results indicated that depression was the strongest predictor of PA behaviour with the likelihood of meeting NPAGA diminishing with increases in depressive symptoms. Therefore, it was considered important to evaluate the effects of ADT on depression, anxiety and QoL to determine the barriers associated with PA participation in this patient group. Such an investigation was the concern of the third empirical paper arising from the study and this is presented in the next chapter.

Chapter 9. Predictors of Depression, Anxiety and Quality of Life in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy

9.1. Rationale and Aims for Paper 3

Results of the systematic review presented in Chapter 6 and the paper presented in Chapter 8 suggest that PA may be an effective intervention to improve QoL and psychosocial wellbeing in men with PCa, however only 41% of this patient group are meeting NPAGA. Additionally, symptoms of depression appeared to decrease the likelihood of PA participation in men with PCa. Given these results combined with the results of previous research suggesting an association between ADT and depression, anxiety and reduced QoL, it was considered important to investigate depression, anxiety and QoL in this patient group. Therefore, in the paper presented in this chapter, differences in depression, anxiety and QoL across treatment categories (RT only; RT + 6 months ADT; RT + 2.5 years ADT; and RT + ADT indefinitely) were examined.

The research questions addressed in the current chapter were:

1. What were the levels of depression, anxiety and QoL in patients with PCa by treatment category (RT only; RT + 6mths ADT; RT + 2.5yrs ADT; RT + ADT indefinitely)?
2. Do depression, anxiety and QoL levels differ based on medical and socio-demographic variables?
3. What is the relationship between PA, depression, anxiety and QoL?

4. Based on bivariate analyses and prior research, which of the following factors were predictors of depression, anxiety and QoL: Treatment category; RT type; employment status; comorbid conditions; radical prostatectomy; time since diagnosis; age; and PA?

Following is a manuscript which was submitted to *Psycho-oncology* in June 2012. The manuscript was reviewed by three referees with only minor revisions suggested. The revised version of the manuscript was resubmitted to *Psycho-oncology* in October 2012 and was accepted for publication in January 2013. The format of this paper was in accordance with the style specified by the editorial board and the final published version of the paper is included in this chapter.

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter 9

Declaration by candidate

In the case of Chapter 9, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Research design, ethics applications, data collection, data analysis, writing draft paper and communication with participants.	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Ms Jane Fletcher	Guidance with research design, ethics application, data analysis, critical review of draft paper; duty of care for participants.	
A/Prof Jeremy Millar	Medical advice, data collection, critical review of draft paper.	
Dr Joanne Brooker	Guidance with data analysis, critical review of draft paper.	
Ms Robin Smith	Guidance with ethics application, data collection, critical review of draft paper; duty of care for participants.	
A/Prof Mark Frydenberg	Medical advice, critical review of draft paper.	
Dr Sue Burney	Guidance with research design, ethics application, data analysis, critical review of draft paper; duty of care for participants.	

Candidate's
Signature




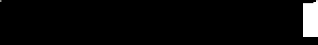
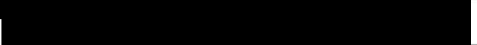
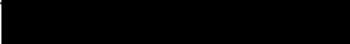
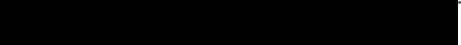
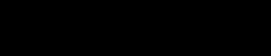
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21/11/2012

Declaration by co-authors

The undersigned hereby certify that:

- (1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- (2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- (4) there are no other authors of the publication according to these criteria;
- (5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- (6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) School of Psychology and Psychiatry, Clayton Campus, Monash University

Signature 1	Ms Jane Fletcher:		Date 26/11/12
Signature 2	A/Prof Jeremy Millar:		16-11-12
Signature 3	Dr Joanne Brooker:		28-11-12
Signature 4	Ms Robin Smith:		16/11/12
Signature 5	A/Prof Mark Frydenberg:		18/10/12
Signature 6	Dr Sue Burney:		21/11/2012

Predictors of depression, anxiety and quality of life in patients with prostate cancer receiving androgen deprivation therapy

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Abstract

Objectives: To evaluate the effects of androgen deprivation therapy (ADT) on depression, anxiety and quality of life (QoL) in patients with prostate cancer (PCa) and to examine the relationship between meeting the National Physical Activity Guidelines of Australia (NPAGA) and the presence and severity of both psychological sequelae and physical side effects associated with ADT. A secondary purpose was to examine the predictors of depression, anxiety and QoL in patients with PCa.

Methods: A questionnaire was mailed to English-speaking patients aged 40 to 80 years, who had received radiotherapy for PCa during 2010 and 2011, between 9 and 30 months prior to study initiation. Measures included the following: the International Physical Activity Questionnaire; the Hospital Anxiety and Depression Scale; the Functional Assessment of Cancer Therapy—Prostate; and sociodemographic items.

Results: Long-term use of ADT was associated with poorer QoL and psychosocial well-being. Those meeting NPAGA had significantly lower levels of depression and anxiety and improved QoL compared with those not meeting NPAGA. Logistic regression analyses showed the odds of clinically significant depression and anxiety scores, increased with younger age and comorbid conditions. Not meeting NPAGA increased the likelihood of caseness for depression. Multiple regression analyses revealed that comorbid conditions and treatment category predicted poorer QoL, whereas meeting NPAGA positively predicted QoL.

Conclusions: The use of ADT in the management of patients with PCa has a measurable effect on QoL. These findings support the utility of physical activity as an intervention for men undergoing ADT. Copyright © 2013 John Wiley & Sons, Ltd.

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Introduction

Prostate cancer (PCa) represents a significant burden of disease worldwide and is the most common internal cancer in men living in Australia, with approximately 20 000 diagnosed every year [1]. PCa is a disease associated with ageing, primarily affecting men over the age of 50 years, and therefore, the main reason for the observed increase in incidence relates to the ageing population [2]. The incidence of PCa is predicted to increase over the next two decades [2,3]. Primary treatment options for PCa include active surveillance, radical prostatectomy, external beam radiotherapy (EBRT), brachytherapy and androgen deprivation therapy (ADT) [2].

Androgen deprivation therapy is considered to be one of the standard treatment modalities for men with PCa [4]. This hormone treatment suppresses testicular androgen production and subsequently reduces testosterone and prostate-specific antigen (PSA) levels, and prostate and tumour volume [5]. ADT was formerly used in the treatment of patients with metastatic disease to palliate symptoms and delay disease progression. However, it is

now common practice to integrate ADT into the treatment of localised disease [4,6]. The increasing prevalence of ADT use has prompted a closer evaluation of its potential adverse effects to better inform treatment decisions and improve understanding of its impact on quality of life (QoL) [7].

The possible physiological side effects of ADT are widely documented and include detrimental effects on muscle, fat and bone mass with increased risk of osteoporosis, diabetes, obesity and cardiovascular-related mortality [3,8–10]. Hot flashes and loss of libido are also characteristic [11]. A common theme in the literature is that the negative side effects associated with ADT exacerbate the impact of other forms of treatment on QoL and psychosocial well-being [5,12,13]. For example, although erectile dysfunction is not uncommon after radical prostatectomy or radiotherapy (RT), men who undergo ADT experience a further decline in sexual functioning and decreased libido compared with men not treated with ADT [5,12,13]. Aside from the physical consequences, there has been increasing recognition of adverse psychological effects such as depression, anxiety and cognitive dysfunction [9,14].

The results of previous research have suggested that there may be a link between ADT and the development of depression [15–18]. For example, Almeida *et al.* [18] established that chemical castration as a result of ADT was associated with an increase in depression and anxiety. Furthermore, Cherrier and colleagues [19] reported post-baseline increases in fatigue, depression, moodiness, irritability, tension, anxiety and loss of vigour, which returned to near baseline levels, 3 months after ceasing ADT. Pirl *et al.* [17] found a prevalence rate of 12.8% for major depressive disorder in a sample of 45 men undergoing ADT. The rate of depression observed in their study was 8 times higher than the rate in the general male population (1.6%) in the USA and 32 times higher than the rate in men over 65 years (0.4%).

Research investigating the effects of ADT on QoL is limited. However, study results have shown a decrease in sexual, social and role functioning [5,12]. For example, Dacal and colleagues [20] demonstrated that men receiving short-term and long-term ADT had significantly lower physical functioning and general health compared with men with PCa not receiving ADT. Fowler *et al.* [12] compared QoL in PCa patients undergoing radical prostatectomy followed by ADT ($n=220$), with those undergoing radical prostatectomy alone ($n=810$). Patients who were androgen deprived after surgery reported significantly worse QoL than surgical patients who were not androgen deprived. Herr and O'Sullivan [21] also reported more fatigue, loss of energy, emotional distress and lower QoL in men who had received ADT for locally advanced PCa than men who deferred hormone therapy. Given the impact of ADT on physical functioning, psychological well-being and QoL, the need to identify effective interventions is warranted.

Physical activity (PA) has been associated with lower overall mortality and PCa-specific mortality [22], with PA proposed as a possible behavioural intervention to improve health and well-being outcomes for patients receiving ADT [23]. Intervention studies involving PA in patients with PCa have demonstrated beneficial effects on a wide variety of biopsychosocial outcomes during ADT. For example, in a physical exercise intervention conducted by Segal *et al.* [24], it was found that resistance and cardiovascular training reduced fatigue and improved QoL in this patient group. Furthermore, Galvao and colleagues [3,25–28] demonstrated the benefits of both aerobic and resistance exercise training programmes, noting vast improvements in muscle strength and body composition, as well as certain aspects of QoL. Home-based, unsupervised PA programmes have also led to improvements in QoL and psychosocial well-being in PCa patients undergoing ADT, demonstrating the benefits of promoting daily, moderate-intensity PA [29–32]. The results of these studies highlight the importance of PA in negating the harmful physical side effects associated with ADT and indicate that PA can be safely tolerated in this patient group, with no impact on PSA levels, testosterone production or disease activity [25,26].

On the basis of previous research examining the association between exercise interventions and QoL using both resistance and aerobic modes of PA, the American College of Sports Medicine has recommended that

patients with cancer and cancer survivors accumulate at least 150 min of moderate-intensity PA per week and incorporate twice weekly resistance training [33]. Similarly, the National Physical Activity Guidelines of Australia (NPAGA) recommends the accrual of 150 min of moderate-intensity activity or more per week [34]. However, the incorporation of resistance training is not highlighted. In a cross-sectional study by Keogh *et al.* [35], patients receiving ADT for PCa who were meeting the American Cancer Society PA recommendations had significantly higher QoL than those not meeting PA guidelines. Similar research with other cancer types has documented comparable findings. For example, two Canadian-based studies with ovarian cancer [36] and non-Hodgkin's lymphoma survivors [37] and one Australian-based study in colorectal cancer [38] revealed that those who were meeting PA guidelines reported more favourable outcomes related to fatigue, psychosocial functioning and several aspects of QoL than those patients who did not meet these guidelines. However, previous studies are yet to establish whether adherence to the NPAGA will improve psychosocial well-being in patients with PCa receiving ADT. The primary aim of the present study was to evaluate the effects of ADT on depression, anxiety and QoL in patients with PCa. An additional aim was to examine the relationship between meeting the NPAGA and the presence and level of psychological sequelae associated with ADT in this group. The final aim was to determine the predictors of depression, anxiety and QoL in these patients.

Method

Approval for the research was gained from the ethics committees at the participating institutions.

Participants and procedure

Participants were recruited through the Alfred Hospital, Melbourne. To be eligible to participate in the study, patients with PCa had to be 40 to 80 years at the time of RT completion, English speaking and received RT between 9 and 30 months ago. Previous research suggests a plateau in RT treatment effects after 12 months, with the effects diminishing after 36 months, providing the rationale for the latter selection criterion [39]. Data were collected between October 2010 and August 2011. An overall response rate of 59% was achieved, with 377 cases available for analysis. Participants were categorised into one of four groups on the basis of the treatment they had received at the time of survey completion. In total, 174 (46.2%) participants had undergone RT only; 100 (26.5%) RT+6 months ADT; 77 (20.4%) RT+2.5 years ADT; and 26 (6.9%) RT+ADT indefinitely. Demographic and medical details are displayed in Table 1.

Measures

Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS) [40]. This well-validated 14-item measure assessing depression and anxiety symptoms over the past 7 days is suitable for use with patients who have a physical illness [41] or

Table 1. Participant demographics and medical details for total sample and treatment groups

Study characteristic	RT only	RT + 6 months ADT	RT + 2.5 years ADT	RT + ADT indefinitely	Total sample
<i>n</i> (% of total sample)	174 (46.2)	100 (26.5)	77 (20.4)	26 (6.9)	377 (100.0)
Mean age, years (SD)	65.1 (7.4)	68.9 (6.6)	70.2 (6.9)	71.1 (8.8)	67.6 (7.5)
Mean time since diagnosis, months (SD)	27.7 (15.2)	34.4 (16.6)	32.8 (26.8)	67.4 (48.9)	33.3 (24.0)
Mean number of comorbid conditions (SD)	1.4 (1.2)	1.6 (1.4)	1.9 (1.3)	1.6 (1.5)	1.6 (1.3)
Radical prostatectomy, <i>n</i> (%)	24 (13.8)	22 (22.0)	19 (24.7)	5 (19.2)	70 (18.6)
Employment status, <i>n</i> (%)					
Full time	57 (32.8)	17 (17.0)	13 (16.9)	3 (11.5)	90 (23.9)
Part time	25 (14.4)	20 (20.0)	13 (16.9)	1 (3.8)	59 (15.6)
Retired	73 (41.9)	53 (53.0)	49 (63.6)	19 (73.1)	194 (51.5)
Disability/sick leave	9 (5.2)	4 (4.0)	1 (1.3)	1 (3.8)	15 (4.0)
Other	8 (4.6)	5 (5.0)	1 (1.3)	1 (3.8)	15 (4.0)
Missing	2 (1.1)	1 (1.0)	0 (0.0)	1 (3.8)	4 (1.1)
RT type, <i>n</i> (%)					
Brachytherapy	136 (78.2)	9 (9.0)	0 (0.0)	0 (0.0)	145 (38.5)
EBRT	37 (21.3)	63 (63.0)	53 (68.8)	25 (96.2)	178 (47.2)
Brachytherapy + EBRT	1 (0.6)	28 (28.0)	24 (31.2)	1 (3.8)	54 (14.3)

RT, radiotherapy; EBRT, external beam radiotherapy; ADT, androgen deprivation therapy.

PCa [42,43]. Items are divided into two subscales measuring depression (seven items) and anxiety (seven items). The total score range for each subscale is 0 to 21. Interpretation of anxiety and depression symptoms is based on the raw score of each subscale: normal (0–7); mild (8–10); moderate (11–14); and severe (15–21). In the current study, ‘caseness’ refers to HADS subscale scores in the range of 8 to 21. Scores within this range are considered to be suggestive of clinically significant levels of depression or anxiety.

The International Physical Activity Questionnaire (IPAQ) was used to measure PA levels of men with PCa. This 31-item psychometrically sound measure consists of four domains including domestic, work, transport and leisure time, assessing the frequency, intensity and duration of PA over the last 7 days [44,45]. It is the only PA measure for which normative data from an Australian sample are available [46] and was considered most suitable for use in the present study. The literature suggests that measurement of PA conducted voluntarily in leisure time may provide a more accurate measure of PA for health benefit [47–49]. For consistency with previous research [37,38], the present study used the leisure-time PA domain score to evaluate whether participants were meeting NPAGA. Each activity on the IPAQ is assigned a metabolic equivalent (MET) value, which is the energy expended compared with sitting at rest [50]. Three levels of PA are proposed (low: <600 MET-min per week; moderate: 600–1500 MET-min per week; and high: >1500 MET-min per week). It has been suggested that 150 min of moderate-intensity activity per week could be regarded as equivalent to 500 MET-min per week [50]. Therefore, participants categorised as low PA according to the IPAQ were considered not to be meeting NPAGA.

The Functional Assessment of Cancer Therapy—Prostate (FACT-P) is a 39-item multi-dimensional, self-report QoL instrument specifically designed for use with PCa patients. Developed as a disease-specific adjunct to the FACT measurement system, the 12-item prostate cancer subscale (PCS) measures symptoms specific to PCa [51] and has adequate psychometric properties [51,52]. For the purposes of this study, the 12-item PCS was used as a measure of QoL specific to PCa.

Data analysis

One-way analysis of variance (ANOVA) was used to examine differences in levels of depression, anxiety and QoL by treatment category (RT only; RT+6 months ADT; RT+2.5 years ADT; RT+ADT indefinitely), RT type (EBRT; brachytherapy; EBRT+brachytherapy) and employment status (full time; part time; retired; disability/sick leave; other). Pearson correlations were calculated to examine the relationships between independent variables (age, time since diagnosis and comorbid conditions) and outcome variables (depression, anxiety and QoL). Independent *t*-tests were used to assess differences between patients who met NPAGA and those who did not on levels of depression, anxiety and QoL.

Two logistic regression analyses were used to predict cases of anxiety and depression. Variables significantly associated at a univariate level with depression and anxiety were selected and entered into a multivariate logistic regression. On the basis of univariate analyses, the following variables were included in regressions: treatment category; RT type; employment status; meeting NPAGA (yes or no); age; time since diagnosis; and number of comorbid conditions. To examine QoL, a multiple regression analysis was conducted. The same predictor variables were included as for the logistic regressions, with the addition of a dichotomous variable indicating whether patients had received a radical prostatectomy (yes or no). Finally, a forward step-wise multiple regression analysis was conducted with the same set of variables to determine whether a more parsimonious model could be developed that was equally, if not more, predictive.

Results

Depression, anxiety and quality of life

Descriptive statistics for QoL and for caseness by treatment category are presented in Table 2. A summary of bivariate analyses is presented in Table 3. The ANOVA results revealed significant differences by treatment categories for depression ($F(3, 373)=6.20, p<.001$), but not anxiety ($F(3, 372)=1.96, p=.12$). The Scheffé

post hoc criterion indicated that those on RT+ADT indefinitely had significantly higher mean scores on the HADS depression subscale than those treated with RT only and RT+2.5 years ADT (all $ps < .01$).

A significant difference by treatment categories was also observed for QoL ($F(3, 371) = 10.75, p < .001$). The Scheffé post hoc criterion showed that the RT+ADT indefinitely treatment group scored significantly lower on the FACT-P than those in the RT only ($p < .001$) and RT+6 months ADT ($p < .01$) groups. Likewise, those treated with RT+2.5 years ADT scored significantly lower on the FACT-P than those treated with RT only ($p < .01$). Mean QoL scores declined with increasing length of time on ADT, and generally, mean scores of

depression and anxiety appeared to increase with length of time on ADT, with the exception of the RT+2.5 years ADT group (Table 2).

Significant positive relationships were observed between comorbid conditions and both depression ($r(374) = 0.31, p < .01$) and anxiety ($r(373) = 0.17, p < .01$). A significant negative relationship was detected between comorbid conditions and QoL ($r(372) = -0.33, p < .001$). No relationship was found between age and depression ($r(375) = 0.03, p = .59$); however, significant negative correlations were observed between age and anxiety ($r(374) = -0.12, p < .05$) and age and QoL ($r(372) = -0.15, p < .01$). Time since diagnosis was positively correlated with depression ($r(375) = 0.12, p < .05$) and negatively

Table 2. HADS and FACT-P subscale scores and case percentages by treatment category

Measure	n	Treatment category	Median	Range	Mean (SD)	Non-case, n (%)	Mild case, n (%)	Moderate case, n (%)	Severe case, n (%)	Total cases, n (%)
Depression	174	RT only	2.0	0.0–21.0	3.3 (3.4)	155 (89.1)	12 (6.9)	4 (2.3)	3 (1.7)	19 (10.9)
	100	RT + 6 months ADT	4.0	0.0–19.0	4.2 (3.7)	86 (86.0)	10 (10.0)	1 (1.0)	3 (3.0)	14 (14.0)
	77	RT + 2.5 years ADT	3.0	0.0–11.0	3.5 (2.5)	70 (90.9)	6 (7.8)	1 (1.3)	0 (0.0)	7 (9.1)
	26	RT + ADT indefinitely	5.0	1.0–15.0	6.2 (4.1)	17 (65.4)	3 (11.5)	5 (19.2)	1 (3.8)	9 (34.6)
	377	Total sample	3.0	0.0–21.0	3.8 (3.4)	328 (87.0)	31 (8.2)	11 (2.9)	7 (1.9)	49 (13.0)
Anxiety	173	RT only	4.0	0.0–18.0	4.7 (3.6)	138 (79.8)	21 (12.1)	13 (7.5)	1 (0.5)	35 (20.2)
	100	RT + 6 months ADT	4.0	0.0–18.0	5.1 (3.8)	79 (79.0)	12 (12.0)	7 (7.0)	2 (2.0)	21 (21.0)
	77	RT + 2.5 years ADT	3.0	0.0–15.0	3.9 (3.4)	67 (87.0)	6 (7.8)	3 (3.9)	1 (1.3)	10 (13.0)
	26	RT + ADT indefinitely	4.0	0.0–14.0	5.5 (4.1)	18 (69.2)	4 (15.4)	4 (15.4)	0 (0.0)	8 (30.8)
	376	Total sample	4.0	0.0–18.0	4.7 (3.7)	302 (80.1)	43 (11.4)	27 (7.2)	4 (1.1)	74 (19.6)
FACT-P	173	RT only	35.6	11.0–48.0	35.6 (7.3)	–	–	–	–	–
	100	RT + 6 months ADT	34.0	15.0–48.0	34.0 (6.8)	–	–	–	–	–
	76	RT + 2.5 years ADT	32.0	16.0–44.0	31.9 (6.4)	–	–	–	–	–
	26	RT + ADT indefinitely	28.0	8.0–48.0	28.1 (10.1)	–	–	–	–	–
	375	Total sample	35.0	8.0–48.0	33.9 (7.5)	–	–	–	–	–

HADS, Hospital Anxiety and Depression Scale; FACT-P, Functional Assessment of Cancer Therapy—Prostate; RT, radiotherapy; ADT, androgen deprivation therapy.

Table 3. Summary of bivariate analyses

Variable	HADS (Depression)			HADS (Anxiety)			FACT-P (QoL)		
	M	SD	p	M	SD	p	M	SD	p
Employment status			<.001			<.01			<.001
Full time	3.1	2.8		4.9	3.6		35.9	6.9	
Part time	3.5	3.8		6.6	3.7		34.8	7.3	
Retired	3.8	3.0		4.3	3.4		33.4	7.3	
Disability/sick leave	7.4	5.9		8.6	5.1		26.0	6.6	
Other	4.6	5.5		4.7	3.8		33.7	9.6	
Treatment category			<.001			.12			<.001
RT only	3.3	3.4		4.7	3.6		35.6	7.3	
RT + 6 months ADT	4.2	3.7		5.1	3.8		34.0	6.8	
RT + 2.5 years ADT	3.4	2.5		3.9	3.4		32.0	6.4	
RT + ADT indefinitely	6.2	4.1		5.5	4.1		28.1	10.1	
RT type			<.01			.36			<.001
Brachytherapy	2.9	3.0		4.4	3.8		36.9	6.9	
EBRT	4.4	3.7		4.9	3.5		32.4	7.3	
Brachytherapy + EBRT	3.9	3.4		4.6	3.7		31.0	7.1	
Radical prostatectomy			.31			.11			.06
Yes	4.1	3.8		5.3	4.0		32.4	7.2	
No	3.7	3.3		4.5	3.6		34.3	7.5	
Meeting NPAGA			<.001			<.05			<.001
Yes	3.5	3.1		4.6	3.6		34.5	7.3	
No	6.9	5.7		6.3	4.7		27.2	9.5	

HADS, Hospital Anxiety and Depression Scale; FACT-P, Functional Assessment of Cancer Therapy—Prostate; RT, radiotherapy; ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; NPAGA, National Physical Activity Guidelines of Australia.

Prostate cancer and androgen deprivation therapy

correlated with QoL ($r(372) = -0.12$, $p < .05$), but no relationship was observed with anxiety ($r(374) = 0.02$, $p = .78$).

The relationship between physical activity and depression, anxiety and quality of life

A total of 320 cases were available for analysis using PA as the outcome measure. Of these 320 participants, 149 (41.9%) met the NPAGA. Mean depression and anxiety scores were significantly higher for those not meeting NPAGA than for those who did, with $t(318) = 4.84$, $p < .001$ and $t(317) = 2.32$, $p < .05$, respectively (Table 3). Mean QoL scores were significantly higher for those meeting NPAGA than for those not meeting NPAGA, $t(316) = -5.08$, $p < .001$.

Predictors of depression, anxiety and quality of life

After removing cases with missing data, 319 and 318 cases were available for logistic regression analysis of depression and anxiety, respectively. The logistic regression model for depression with all predictors against a constant-only model was significant ($\chi^2(7) = 50.27$, $p < .001$). The model accurately predicted 98.2% of non-cases and 26.8% of cases, with an overall success rate of 89.0%. The odds of a depression score indicative of

caseness significantly increased as the number of comorbid conditions increased (Table 4). Not meeting NPAGA and younger age were also significant predictors of caseness for depression.

The logistic regression model for anxiety with all predictors against a constant-only model was also significant ($\chi^2(7) = 22.91$, $p < .01$). The model accurately predicted 98.4% of non-cases and 3.0% of cases, with an overall success rate of 78.3%. The odds of an anxiety score indicative of caseness significantly increased with younger age and increasing number of comorbid conditions (Table 4).

The results of multiple regression analyses using both the forced enter and step-wise methods to predict FACT-P total scores are presented in Table 5. By using the forced enter method, a significant model emerged, indicating that five of the eight variables explained a significant proportion of the variance in QoL scores ($R^2 = 0.22$; $F(8, 309) = 11.91$, $p < .001$). These variables were comorbid conditions ($b = -1.58$, $t(309) = -5.48$, $p < .001$), treatment category ($b = -1.46$, $t(309) = -3.37$, $p < .01$), meeting NPAGA ($b = 6.30$, $t(309) = 4.54$, $p < .001$), RT type ($b = -1.36$, $t(309) = -2.20$, $p < .05$) and radical prostatectomy ($b = 3.20$, $t(309) = 2.69$, $p < .01$). However, using the step-wise method, only three variables emerged as significant predictors of QoL, accounting

Table 4. Logistic regressions to predict cases indicative of clinical depression and anxiety

Variable	Category	Depression				Anxiety			
		Intercept	Odds ratio	(95% confidence interval)	p value	Intercept	Odds ratio	(95% confidence interval)	p value
Treatment category	RT only		1				1		
	RT + 6 months ADT	0.32	1.38	(0.58, 3.28)	.47	0.13	1.14	(0.58, 2.26)	.75
	RT + 2.5 years ADT	-1.37	0.25	(0.05, 1.24)	.09	-0.49	0.62	(0.24, 1.56)	.31
	RT + ADT indefinitely	1.17	3.21	(0.78, 13.26)	.11	0.66	1.93	(0.56, 6.66)	.30
Meeting NPAGA	No		1				1		
	Yes	-1.13	0.33	(0.12, 0.92)	<.05	-0.12	0.89	(0.34, 2.32)	.81
No. of comorbid conditions		0.62	1.86	(1.44, 2.40)	<.01	0.32	1.37	(1.12, 1.69)	.01
Age (years)		-0.06	0.94	(0.89, 1.00)	<.05	-0.07	0.93	(0.90, 0.97)	≤.001
Time since diagnosis (months)		0.01	1.01	(0.99, 1.03)	.21	0.01	1.01	(0.99, 1.02)	.50

NPAGA, National Physical Activity Guidelines of Australia; RT, radiotherapy; ADT, androgen deprivation therapy.

Table 5. Summary of enter and step-wise multiple regression analyses for variables predicting total FACT-P scores ($N = 317$)

Variable	Forced enter model				Step-wise model			
	B	SE B	β	R^2	B	SE B	B	R^2
				0.22				0.20
No. of comorbid conditions	-1.58	0.29	-0.28***		-1.60	0.29	-0.28***	
Treatment category	-1.46	0.43	-0.19**		-1.67	0.40	-0.22***	
Meeting NPAGA	6.30	1.39	0.23***		5.73	1.37	0.21***	
Radical prostatectomy	3.20	1.19	0.17**					
Working status	-0.12	0.85	-0.01					
RT type	-1.36	0.62	-0.13*					
Age (years)	-0.11	0.06	-0.11					
Time since diagnosis (months)	0.00	0.02	-0.00					

FACT-P, Functional Assessment of Cancer Therapy—Prostate; NPAGA, National Physical Activity Guidelines of Australia; RT, radiotherapy.

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$.

for 20.3% of the variance in FACT-P total scores ($R^2=0.20$; $F(3, 314)=27.91$, $p<.001$). Number of comorbid conditions predicted the greatest variance in QoL, accounting for 10.9% of the variance in FACT-P total scores; treatment category accounted for 5.8%; and meeting NPAGA accounted for 4.4%.

Discussion

The first aim of the study was to examine the effects of ADT on depression, anxiety and QoL. The results indicate that a relatively small proportion of patients reported HADS scores indicative of clinically significant anxiety (19.6%) or depression (13.0%). These findings are comparable to those reported in an earlier study [43] observing levels of anxiety and depression in patients with PCa similar to those of age-adjusted normative comparison groups. Findings of the present study suggest that increasing length of time on ADT was associated with poorer QoL. The PCS component of the FACT-P used to measure QoL in this study assesses physical symptoms specific to PCa such as urinary incontinence and erectile dysfunction. These results are consistent with previous research suggesting that continuous use of ADT impacts on QoL in the physical and sexual function and related domains of vitality, energy and fatigue [5,12,13,21,53–57].

The results of previous studies have suggested that long-term ADT use does not exacerbate the emotional functioning aspect of QoL [53,55,56], with one study noting improvements in every general QoL domain after 2 years of treatment [54]. This is consistent with the results from the present study where those treated with ADT for 2 ½ years reported less symptoms of depression and anxiety than those treated with ADT for 6 months or indefinitely. This also corresponds with the argument that over time patients with chronic conditions adapt to their symptoms from a psychological perspective [58]. Although patients treated with ADT for an indefinite period reported the highest scores on depression and anxiety, patients in this treatment category are treated with palliative intent, and therefore, these psychological conditions may be confounded by existential concerns associated with dying and death [59].

The second aim of this study was to examine the relationship between meeting NPAGA and the presence and level of psychological sequelae and physical side effects associated with ADT. Results indicate that those meeting NPAGA had significantly lower levels of depression and anxiety and improved QoL compared with those not meeting NPAGA. These findings are consistent with previous research reporting improvements in several aspects of QoL in patients meeting PA guidelines receiving ADT for PCa [35], and in ovarian cancer [36], non-Hodgkin's lymphoma [37] and colorectal cancer survivors [38]. However, psychological constructs were not assessed in these studies. Therefore, the current findings suggesting an association between meeting NPAGA and reduced symptoms of depression and anxiety in this patient group are novel.

The final aim of this study was to determine the predictors of depression, anxiety and QoL in patients with PCa. Initially, all variables found to have significant

bivariate relationships with outcome variables were included in logistic regression models to determine if they were predictors of depression and anxiety. However, employment status and RT type did not contribute significantly to the logistic regression model and were therefore excluded from the final analyses. The results of the present study indicate that the likelihood of clinically significant anxiety and depression increased with the number of comorbid conditions. This is consistent with previous research [13,43,60] and highlights the importance of controlling for this factor when using general non-disease-specific measures, such as the HADS, to measure well-being. Meeting NPAGA was a significant predictor of caseness for depression but not anxiety. This is congruent with the results of a review of 37 studies in which the dose–response relationship of PA with depressive and anxiety disorders was investigated. In this review, Dunn and colleagues [61] concluded that both moderate and vigorous PA reduced symptoms of depression. Few studies, however, have found an association between PA and a decrease in anxiety symptoms. Younger age also predicted the likelihood of clinically significant anxiety and depression in the present study. This finding is consistent with numerous studies that have documented an association between younger age and increased vulnerability to depression and psychological distress in the context of cancer [62–66]. The logistic regression analyses revealed that time since diagnosis and treatment category were unrelated to caseness for depression and anxiety after controlling for age, meeting NPAGA and comorbid conditions. Consistent with bivariate and logistic regression analyses for depression and anxiety, the multiple regression model used to examine predictors of QoL revealed that comorbid conditions and increasing length of time on ADT predicted worse QoL, whereas meeting NPAGA predicted improved QoL.

Limitations and future research

A widely recognised problem of self-report PA measures is overestimation of intensity and time spent in PA, and there is a lack of valid and accurate PA measures available [67–69]. Furthermore, the benefits of both aerobic and resistance exercise for maintenance of physical and psychological health in patients with PCa is widely documented [70]. However, the IPAQ does not evaluate these exercise components separately. Further research examining the association between meeting NPAGA and the presence and level of psychological sequelae and physical side effects associated with ADT in patients with PCa is therefore required to determine the level of PA sufficient to yield improvements in QoL and psychosocial well-being in this population.

The logistic regression models for predicting anxiety and depression caseness were accurate for non-cases, but poor for cases. This suggests that other important predictor variables were not included in the current study. For example, the relationship between severity of physical symptoms and depression, anxiety and QoL may be an important factor for future research. Finally, given the limitations associated with cross-sectional research designs,

longitudinal studies to examine change in depression, anxiety and QoL prior to, during and post-treatment and with long-term ADT use may also be important directions for future research.

Conclusions

This study appears to be the first to examine the association between meeting NPAGA and the presence and level of psychological morbidity in PCa patients undergoing ADT. The potential utility of PA for men undergoing ADT was reinforced, and findings suggest that 150 min of moderate-intensity PA weekly may improve QoL and psychosocial well-being in this patient population. Results indicate that long-term ADT use may significantly impact on QoL, particularly in relation to physical function. Increasing awareness of the impact of ADT on QoL and psychosocial well-being will enable clinicians and patients to make informed treatment

decisions. The findings of the present study also highlight the necessity for treating physicians to consider the cumulative impact of comorbid conditions on depression, anxiety and QoL in patients with PCa.

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Conflict of interest

Abbott Pharmaceuticals and Cabrini contributed funds towards this research; however, there are no conflict of interest issues. These organisations were not involved with any aspects of the research other than sponsorship. The authors have full control of all primary data, and the journal may review data if requested.

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9.3. Summary and Conclusions

The paper presented in this chapter provided a unique contribution to the research literature on depression, anxiety and QoL in men treated with ADT for PCa, in that these constructs were compared across treatment categories and varying lengths of time on ADT. Furthermore, the current study appeared to be the first to examine the association between meeting NPAGA and the presence and level of psychological morbidity in men with PCa receiving ADT. In the next chapter, the types of cognitive difficulties experienced by this population are identified and cognitive function across treatment categories is compared. The relationship between cognitive function and PA is also explored in this patient group.

Chapter 10. Factors Associated with Cognitive Function in Men with Prostate Cancer Receiving Androgen Deprivation Therapy

10.1. Rationale and Aims for Paper Four

The results of the systematic review presented in Chapter 6 suggest that the impact of PA on cognitive function in men with PCa receiving ADT has not been examined. Given the results of previous research indicating that ADT has an adverse effect on cognitive function in this patient group, identifying interventions that may improve this outcome is essential. Therefore, the focus of the paper presented this chapter was to describe the cognitive difficulties experienced by this patient group and determine the utility of PA as an intervention to improve cognitive function.

The research questions addressed in the current chapter were:

1. What types of cognitive difficulties are experienced by men with PCa?
2. What are the levels of cognitive functioning in patients with PCa by treatment category (RT only; RT + 6 months ADT; RT + 2.5 years ADT; and RT + ADT indefinitely)?
3. Does cognitive functioning differ based on socio-demographic and medical factors?
4. What is the relationship between cognitive functioning and PA, depression, anxiety and QoL?
5. Based on bivariate analyses and prior research, which of the following factors were predictors of cognitive functioning: Treatment centre; education;

employment status; treatment category; RT type; depression; anxiety; QoL; comorbid conditions; Age; and PA?

Following is a manuscript which was submitted to the *International Journal of Urology* in April 2013 and is currently under review by the journal's editorial board. The format of this paper was in accordance with the style specified by the editorial board.

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter 10

Declaration by candidate

In the case of Chapter 10, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Research design, ethics applications, data collection, data analysis, writing draft paper and communication with participants.	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Ms Jane Fletcher	Guidance with research design, ethics application, data analysis, critical review of draft paper; duty of care for participants.	
A/Prof Jeremy Millar	Medical advice, data collection, critical review of draft paper.	
Dr Joanne Brooker	Guidance with data analysis, critical review of draft paper.	
Ms Robin Smith	Guidance with ethics application, data collection, critical review of draft paper; duty of care for participants.	
A/Prof Mark Frydenberg	Medical advice, critical review of draft paper.	
Dr Sue Burney	Guidance with research design, ethics application, data analysis, critical review of draft paper; duty of care for participants.	

Candidate's
Signature



Date

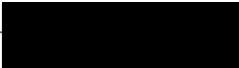
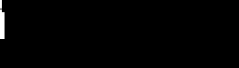
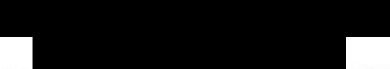
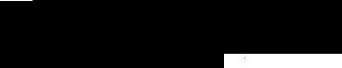


21/11/2012

Declaration by co-authors

The undersigned hereby certify that:

- (1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
- (2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
- (4) there are no other authors of the publication according to these criteria;
- (5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
- (6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) **School of Psychology and Psychiatry, Clayton Campus, Monash University**

Signature 1	Ms Jane Fletcher:		Date 26/11/12
Signature 2	A/Prof Jeremy Millar:		16-11-12
Signature 3	Dr Joanne Brooker:		28-11-12
Signature 4	Ms Robin Smith:		16/11/12
Signature 5	A/Prof Mark Frydenberg:		18/10/12
Signature 6	Dr Sue Burney:		21/11/2012

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**FACTORS ASSOCIATED WITH COGNITIVE FUNCTION IN MEN WITH
PROSTATE CANCER RECEIVING ANDROGEN DEPRIVATION
THERAPY**

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10.2. ABSTRACT

Objective: Objective one was to identify the types of cognitive difficulties reported by patients with prostate cancer (PCa) and compare cognitive function across treatment types: radiotherapy (RT) only; RT + 6 months ADT; RT + 2 ½ years ADT and RT + ADT indefinitely. Objective two was to establish the relationship between physical activity (PA) levels and cognitive function in patients with PCa. A further objective was to determine factors associated with cognitive function in patients with PCa. **Methods:** English speaking patients aged between 40 and 80 years, who received RT for PCa between 9 and 30 months prior to study initiation, were mailed a questionnaire. Measures included: the Functional Assessment of Cancer Therapy - Cognitive (FACT-Cog); the International Physical Activity Questionnaire (IPAQ); the Hospital Anxiety and Depression Scale (HADS); the Functional Assessment of Cancer Therapy – Prostate (FACT-P); and socio-demographic items. **Results:** A higher proportion of participants who received androgen deprivation therapy (ADT) reported cognitive complaints than those who received RT only. Length of time on ADT appeared to affect cognitive ability, with patients treated with ADT indefinitely reporting the poorest cognitive function. Multiple regression analyses revealed that depression was the strongest predictor of cognitive impairment. Anxiety, QoL, age, comorbid conditions, PA and treatment centre were also predictors of poor cognitive function. **Conclusions:** It appears that the use of ADT in the management of patients with PCa has a measurable impact on cognitive function. These findings support the utility of PA interventions for men with PCa undergoing ADT.

Keywords: Physical activity; Oncology; Prostate cancer; Quality of life; Cognitive function

10.3. INTRODUCTION

Prostate cancer (PCa) was the most commonly diagnosed cancer worldwide in 2010, with this disease estimated to represent 28% of all new cancer cases in the male population (Jemal, Siegel, Xu, & Ward, 2010). Approximately 20,000 men living in Australia are diagnosed with the disease every year (Prostate Cancer Foundation of Australia, 2012). Contributing to the rise in prevalence is the ageing population and increased use of screening tests, while continual advancement in treatment options is prolonging survival (Kirby & Patel, 2008). Numerous treatment options are available for PCa including radical prostatectomy, external beam radiotherapy (EBRT), brachytherapy and androgen deprivation therapy (ADT) (Kirby & Patel, 2008).

ADT is a hormone treatment which can reduce prostate and tumour volume, testosterone levels and prostate specific antigen (PSA) levels by suppressing testicular androgen production (Sharifi, Gulley, & Dahut, 2005). Previously, ADT was incorporated into the treatment of patients with metastatic disease to palliate symptoms and delay disease progression. However, it is now common practice to integrate ADT into the treatment of localised disease (Bria et al., 2009; Scherr, Swindle, & Scardino, 2003; Shahinian, Kuo, Freeman, Orihuela, & Goodwin, 2005). The increasing use of ADT has led to closer examination of the potential adverse effects associated with this treatment to assist in treatment decisions and improve understanding of the impact of this therapy on quality of life (QoL) (Sadetsky et al., 2011). The possible physiological side effects of ADT are widely documented and include detrimental effects on muscle, fat and bone mass with increased risk of osteoporosis, diabetes, obesity and cardiovascular related mortality (Galvao, Taaffe, Spry, & Newton, 2007; Keating, O'Malley, & Smith, 2006; Lage, Barber, & Markus,

2007; Taylor, Canfield, & Du, 2009). Aside from the physical consequences of ADT, there has been increasing recognition of adverse psychological outcomes such as depression, anxiety and cognitive dysfunction (Shahinian, Kuo, Freeman, & Goodwin, 2006; Taylor, et al., 2009).

The research evidence suggests that testosterone is related positively to cognitive functioning and consequently, the significant and abrupt reduction of testosterone levels in men receiving ADT may contribute to cognitive difficulties (Jenkins, Bloomfield, Shilling, & Edginton, 2005). In numerous studies, the relationship between testosterone levels and cognitive function has been examined with results suggesting that higher testosterone levels have a beneficial effect on spatial ability and visual/verbal memory (Barrett-Connor, Goodman-Gruen, & Patay, 1999; Cherrier et al., 2001; Moffat et al., 2002; O'Connor, Archer, Hair, & Wu, 2001). Furthermore, the research evidence suggests that the degree of change in cognitive performance is related to the magnitude of testosterone decline (Salminen, Portin, Koskinen, Helenius, & Nurmi, 2004).

Previous research has attempted to isolate the effect of ADT on cognitive functioning in men with PCa. However, inconsistencies in the research literature are apparent. For example, in several studies a lack of association between ADT and cognitive dysfunction has been reported (Cherrier, Rose, & Higano, 2003; Mohile et al., 2010). Of particular relevance to the present study, patients with PCa in Joly and colleagues' (2006) research failed to report more cognitive problems on the Functional Assessment of Cancer Therapy – Cognitive (FACT-Cog) than control participants. Conversely, in numerous studies deficits in cognitive functioning have been reported in patients with PCa receiving ADT in several domains of performance

including, spatial memory and spatial ability (Cherrier, Aubin, & Higano, 2009; Jenkins, et al., 2005); executive function (Green et al., 2002); and information processing (Green et al., 2004). In addition, Jim and colleagues (2010) found that patients with PCa receiving ADT had lower scores and higher rates of impairment on five of seven individual tests of cognitive functioning compared to age- and education-matched healthy control participants.

Although in numerous studies it has been suggested that cognitive skills relating to spatial abilities and memory may be affected by declining testosterone levels with ADT treatment, there appears to be a lack of consensus as to which specific cognitive domains are affected. Nevertheless, it is clear that testosterone may play some role in mediating cognitive ability, and therefore is of relevance when considering the possible side effects of ADT for patients with PCa, particularly if it is prescribed long-term (Jenkins, et al., 2005). Furthermore, with the broad range of negative side effects associated with ADT treatment previously discussed, loss of cognitive function may have significant implications for QoL in patients with PCa. It has therefore been suggested that patients be monitored for cognitive changes while on ADT as part of a comprehensive assessment of treatment-related toxicity (Jim, et al., 2010). In conjunction with this, patients receiving ADT for PCa may benefit from interventions that promote cognitive stimulation.

Physical activity (PA) has been proposed as a behavioural intervention to improve health and wellbeing for patients with cancer (Conn, Hafdahl, Porock, McDaniel, & Nielsen, 2006). Numerous PA intervention studies involving patients with PCa receiving ADT have demonstrated beneficial effects on a variety of biopsychosocial outcomes including physical function, fatigue, depression and QoL

(Galvão et al., 2006; Galvao, Taaffe, Spry, Joseph, & Newton, 2009; Galvão, Taaffe, Spry, Joseph, & Newton, 2010; Segal et al., 2003; Segal et al., 2009). However, after an extensive review of the literature in this area it appears that associations between PA levels and cognitive function in men with PCa have not been examined. It is also evident that there has been no research into whether PA may ameliorate cognitive declines related to ADT treatment. Several review papers, however, support the utility of PA in preventing cognitive decline, suggesting that PA stimulates important metabolic changes that affect cognition directly by altering structural and functional plasticity (Denkinger, Nikolaus, Denkinger, & Lukas, 2012; Given et al., 2004; Kraft, 2012). In relation to the protective role that PA may play following cancer treatment, Fardell et al (2012) used animal models to demonstrate that rats engaging in PA post chemotherapy had improved cognition relative to non-exercising rats. Therefore, these authors concluded that PA may be a useful intervention for counteracting the cognitive impairments induced by chemotherapy.

The purpose of the current study was to examine the types of cognitive difficulties reported by patients with PCa and compare differences in cognitive function across the treatment types of radiotherapy (RT) only; RT + 6 months ADT; RT + 2 ½ years ADT and RT + ADT indefinitely. Another aim was to establish the relationship between PA levels and cognitive function in patients with PCa. A further aim was to determine factors associated with cognitive function in patients with PCa.

10.4. METHOD

Approval for the research was gained from the ethics committees at the participating institutions.

10.4.1. Participants and Procedure

To be eligible to participate in the study, patients with PCa had to be aged between 40 and 80 years at the time of RT completion, be English speaking and have received RT between 9 and 30 months ago. Previous research suggests a plateau in RT treatment effects after 12 months, with the effects diminishing after 36 months, hence providing the rationale for the latter selection criterion (Gore, Kwan, Lee, Reiter, & Litwin, 2009). Data were collected between October 2010 and August 2011. In total, 377 patients consented to participate in the study and returned the questionnaire, yielding an overall response rate of 59%. Participants were categorised into one of four groups based on the treatment they had received at the time of survey completion. In total, 168 (46.3%) participants had undergone RT only; 94 (25.9%) RT + 6 months ADT; 77 (21.2%) RT + 2 ½ years ADT; and 24 (6.6%) RT + ADT indefinitely. Demographic and medical details of participants, who answered all items related to cognitive function, are displayed in Table 10.1.

Table 10.1.

Participant Socio-demographic and Medical Details for the Sample by Treatment Group.

Study Characteristic	RT Only	RT + ≤ 6mths ADT	RT + 6mths - 2.5yrs ADT	RT + ≥ 2.5yrs ADT	Total Sample
<i>n</i>	168 (46.3)	94 (25.9)	77 (21.2)	24 (6.6)	363 (100.0)
Mean age, years (SD)	65.3 (0.6)	68.5 (0.7)	70.2 (0.9)	71.7 (1.9)	67.6 (7.5)
Mean time since diagnosis, months (SD)	26.9 (1.1)	34.2 (1.7)	32.8 (3.1)	68.7 (10.7)	33.2 (24.4)
Mean PSA (SD)	5.6 (0.3)	10.1 (1.0)	21.0 (2.1)	86.5 (30.2)	15.3 (42.2)
Marital status, <i>n</i> (%)					
Married/Defacto/Partner	145 (86.3)	80 (85.1)	61 (79.2)	23 (95.8)	309 (85.1)
Divorced/Separated	11 (6.5)	8 (8.5)	7 (9.1)	1 (4.2)	27 (7.4)
Single	5 (3.0)	4 (4.3)	4 (5.2)	0 (0.0)	13 (3.6)
Widowed	7 (4.2)	2 (2.1)	5 (6.5)	0 (0.0)	14 (3.9)
Educational level, <i>n</i> (%)					
Primary or secondary school	83 (49.4)	45 (47.9)	41 (53.2)	12 (50.0)	181 (49.9)
Tertiary	65 (38.7)	40 (42.6)	30 (39.0)	8 (33.3)	143 (39.4)
TAFE/apprenticeship	14 (8.3)	7 (7.4)	5 (6.5)	1 (4.2)	27 (7.4)
Postgraduate	4 (2.4)	2 (2.1)	1 (1.3)	1 (4.2)	8 (2.2)
Missing	2 (1.2)	0 (0.0)	0 (0.0)	2 (8.3)	4 (1.1)
Employment status, <i>n</i> (%)					
Full-time	56 (33.3)	17 (18.1)	13 (16.9)	2 (8.2)	88 (24.2)
Part-time	25 (14.9)	20 (21.3)	13 (16.9)	1 (4.2)	59 (16.3)
Retired	72 (42.9)	47 (50.0)	49 (63.6)	18 (75.0)	186 (51.2)
Disability/sick leave	7 (4.2)	4 (4.3)	1 (1.3)	1 (4.2)	13 (3.6)
Other	7 (4.2)	5 (5.2)	1 (1.3)	1 (4.2)	14 (3.9)
Missing	1 (0.5)	1 (1.1)	0 (0.0)	1 (4.2)	3 (0.8)
Number of co-morbidities, <i>n</i> (%)					
0	36 (21.4)	21 (22.3)	11 (14.3)	8 (33.3)	76 (20.9)
1-2	108 (64.3)	50 (53.2)	47 (61.0)	10 (41.7)	215 (59.2)
>3	24 (14.3)	23 (24.5)	18 (23.4)	6 (25.0)	71 (19.6)
Missing	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.3)
Clinical risk category, <i>n</i> (%)					
Low	73 (43.5)	3 (3.2)	0 (0.0)	0 (0.0)	76 (20.9)
Intermediate	85 (50.0)	79 (84.0)	2 (2.6)	3 (12.5)	168 (46.3)
High	11 (6.5)	12 (12.8)	75 (97.4)	21 (87.5)	119 (32.8)
Stage category, <i>n</i> (%)					
T1	23 (13.7)	3 (3.2)	1 (1.3)	1 (4.2)	28 (7.7)
T2	134 (79.8)	70 (74.5)	44 (57.1)	4 (16.7)	252 (69.4)
T3 or 4	10 (6.0)	20 (21.2)	30 (39.0)	19 (79.2)	79 (21.8)
Missing	1 (0.5)	1 (1.1)	2 (2.6)	0 (0.0)	4 (1.1)
Gleason score, <i>n</i> (%)					
< 7	69 (41.1)	12 (12.8)	3 (3.9)	0 (0.0)	84 (23.1)
7	94 (56.0)	78 (83.0)	27 (35.1)	10 (41.7)	209 (57.6)
> 7	5 (3.0)	4 (4.3)	47 (61.0)	14 (58.3)	70 (19.3)
RT Type, <i>n</i> (%)					
Brachytherapy	133 (79.2)	9 (9.6)	0 (0.0)	0 (0.0)	142 (39.1)
EBRT	34 (20.2)	59 (62.8)	53 (68.8)	23 (95.8)	169 (46.6)
Brachytherapy + EBRT	1 (0.6)	26 (27.7)	24 (31.2)	1 (4.2)	52 (14.3)
Previous cancer diagnosis, <i>n</i> (%)	11 (6.5)	10 (10.6)	6 (7.8)	0 (0.0)	27 (7.4)
Radical prostatectomy, <i>n</i> (%)	21 (12.5)	21 (22.3)	19 (24.7)	4 (16.7)	65 (17.9)
Currently receiving ADT, <i>n</i> (%)	0 (0.0)	4 (4.3)	59 (76.6)	23 (95.8)	86 (23.7)

PSA = prostate specific antigen; RT = radiotherapy; EBRT = external beam radiotherapy; ADT = androgen deprivation therapy; TAFE = Technical and Further Education.

10.4.2. Measures

Cognitive function was measured using the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog), Version 3 (Wagner, Sweet, Butt, Lai, & Cella, 2009). This 37-item measure is designed to assess cognitive complaints in patients with cancer. The FACT-Cog includes both negatively and positively worded items and yields four subscale scores: 1) Perceived Cognitive Impairments (CogPCI); 2) Impact of Perceived Impairments on QoL (CogQOL); 3) Comments from Others (CogOTH); and 4) Perceived Cognitive Abilities (CogPCA). Participants rate the frequency with which each statement occurred in the past seven days on a five-point Likert scale (0 = 'never' to 4 = 'several times a day'). Higher scores reflect fewer cognitive problems and better QoL. Wagner (2008) reported moderate to strong internal consistency of the FACT-Cog version 3 with Cronbach's alpha ranging from 0.67 (CogPCA) to 0.95 (CogPCI). The FACT-Cog assesses a range of cognitive complaints, thereby providing more detailed information about the types of cognitive difficulties patients are experiencing (Jacobs, Jacobsen, Booth-Jones, Wagner, & Anasetti, 2007).

Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS, (Snaith & Zigmond, 1994)). The HADS is a 14-item measure assessing depression and anxiety symptoms over the past seven days and is suitable for use with patients who have a physical illness (Herrmann, 1997) or PCa (Mehnert, Lehmann, Graefen, Huland, & Koch, 2010; Nelson, Mulhall, & Roth, 2011). Items are divided into two subscales measuring depression (7 items) and anxiety (7 items). Each item has four response options rated on a Likert scale of 0 to 3. The total score range for each subscale is 0 to 21. Interpretation of anxiety and depression symptoms is based on the raw score of each subscale: normal (0-7); mild

(8-10); moderate (11-14); and severe (15-21). Previous research with the HADS has demonstrated adequate to excellent internal consistency with Cronbach's alpha of 0.93 for the anxiety and 0.85-0.90 for the depression subscale (Spinhoven et al., 1997).

The International Physical Activity Questionnaire (IPAQ) was used to measure PA levels of patients with PCa. The 31 item measure asks about the frequency, intensity and duration of PA over the last seven days, across four PA domains including work, transport, domestic and leisure-time. Adequate reliability and validity of the instrument across 12 countries has been reported (Craig et al., 2003). The IPAQ is the only PA measure for which normative data from an Australian sample are available (Craig, et al., 2003) and therefore was considered most suitable for use in the present study. The literature implies that measurement of PA conducted voluntarily in leisure-time may provide a more accurate measure of PA for health benefit (Armstrong, Bauman, & Davies, 2000; Lynch, Cerin, Owen, & Aitken, 2007; Merom, Phongsavan, Chey, Bauman, & Australian Bureau of, 2006; Tremblay et al., 2011; Vallance, Courneya, Jones, & Reiman, 2005). For consistency with previous research, in the present study the leisure-time PA subscale of the IPAQ was used as a measure of PA level.

The Functional Assessment of Cancer Therapy - Prostate (FACT-P) is a 39 item multi-dimensional, self-report QoL instrument specifically designed for use with PCa patients. Developed as a disease-specific adjunct to the FACT measurement system, a 12-item prostate cancer subscale (PCS) with items pertaining to symptoms specific to PCa was developed and tested in three independent samples (Cella, Nichol, Eton, Nelson, & Mulani, 2009). Previous reports of the internal consistency of the PCS have ranged from 0.65 to 0.69 (Cella, et al., 2009; Esper et

al., 1997). For the purposes of this study, the 12-item PCS was used as a measure of QoL specific to PCa. Each item is rated on a 0 to 4 Likert scale, and then combined to produce a subscale score representative of PCa specific QoL. Higher scores indicate better QoL.

10.4.3. Data Analysis

Data were analysed using IBM SPSS Statistics 18 (2010). A significance level of $p < .05$ was used for all statistical tests. Selected variables were examined for outliers, skewness and kurtosis. All FACT-Cog subscale scores violated normality and therefore non-parametric statistical tests were used for bivariate analyses.

To specify the number and type of cognitive complaints, FACT-Cog scores were dichotomized by classifying responses as a complaint (2 or greater) or non-complaint (0 or 1). This method of analysis is consistent with Jacobs et al. (2007). Chi-square tests were used to analyse relationships between treatment type (RT only; RT + ADT) and cognitive complaints.

Mann-Whitney and Kruskal-Wallis tests were used to examine differences in FACT-Cog subscale scores by centre (urban; rural), employment status (employed; not employed), radical prostatectomy (yes; no), meeting National Physical Activity Guidelines of Australia (NPAGA) (yes; no), education (primary or secondary; technical and further education (TAFE)/apprenticeship; tertiary; postgraduate), treatment category (RT only; RT + 6 months ADT; RT + 2 ½ years ADT; RT + ADT indefinitely), RT type (EBRT; brachytherapy; EBRT + brachytherapy). Spearman's rho correlations were calculated to assess the relationships between independent variables (depression, anxiety, QoL, leisure-time PA, age; comorbid conditions) and outcome variables related to cognitive function.

To examine factors associated with cognitive function, a multiple regression analysis (Enter method) was conducted. On advice from the developers of the FACT-Cog, the CogPCI subscale score was used as the outcome measure of cognitive function in regression analyses (email correspondence with Wagner, L. dated 26/6/2012). As the dependent variable was negatively skewed, a reflected square root transformation was applied (Tabachnick & Fidell, 2007). Variables significantly associated at a univariate level with CogPCI scores were selected and entered into the regression model. Accordingly, the following variables were included in the regression analysis: Treatment centre; education; employment status; treatment category; RT type; depression; anxiety; quality of life; comorbid conditions; age; and leisure-time PA.

10.5. RESULTS

10.5.1. Cognitive Complaints

Table 10.2 presents the most commonly reported cognitive complaints according to treatment category. Overall, the most common cognitive complaints were endorsed by 22.5% to 38.7% of participants. Table 2 indicates that across all items, a higher proportion of participants who received ADT reported cognitive complaints than those who received RT only. Chi-square analyses revealed that a significantly greater proportion of participants who received ADT reported cognitive complaints as described by items 36 ($\chi^2 (1, N = 377) = 6.52, p < .05$); 33 ($\chi^2 (1, N = 367) = 6.37, p < .05$); 27 ($\chi^2 (1, N = 368) = 3.84, p \leq .05$); and 26 ($\chi^2 (1, N = 368) = 5.29, p < .05$).

Table 10.2.

Chi-square Analyses of Most Common Complaints Endorsed on the FACT-Cog by Treatment Type.

Item #	Item	FACT-Cog Domain - Subscale	ADT		χ^2	p
			Yes	No		
-	n (%)	-	203 (53.8)	174 (46.2)	-	-
13	I have forgotten names of people soon after being introduced	M - CogPCI	87 (43.3)	59 (33.9)	3.45	.06
31	My memory is as good as it has always been (reverse coded)	FC - CogPCA	71 (35.7)	50 (29.8)	1.44	.23
30	My mind is as sharp as it has always been (reverse coded)	FC - CogPCA	64 (32.2)	43 (25.4)	2.00	.16
36	These problems have interfered with the quality of my life	CogQOL	59 (29.1)	31 (17.8)	6.52	< .05
5	I have had trouble remembering where I put things, like my keys or wallet	M - CogPCI	48 (23.9)	41 (23.6)	0.01	.94
33	I am able to keep track of what I am doing, even if I am interrupted (reverse coded)	MI - CogPCA	58 (29.1)	30 (17.9)	6.37	< .05
18	I have been able to remember things, like where I left my keys or wallet (reverse coded)	M - CogPCA	47 (23.5)	39 (22.4)	0.06	.80
27	I have had to use written lists more often than usual so I would not forget things	M - CogPCI	55 (27.6)	32 (18.9)	3.84	< .05
7	I have had trouble recalling the name of an object while talking to someone	VF - CogPCI	51 (25.4)	35 (20.1)	1.46	.23
26	I have been able to bring to mind words that I wanted to use while talking to someone (reverse coded)	VF - CogPCA	55 (27.8)	30 (17.6)	5.29	< .05
32	I am able to shift back and forth between two activities that require thinking (reverse coded)	MI - CogPCA	53 (26.6)	32 (19.0)	2.95	.09

FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive; ADT = Androgen Deprivation Therapy; M = Memory; FC = Functional Change; MI = Multi-tasking/Interruption; VF = Verbal Fluency; CogPCI = Perceived Cognitive Impairment; CogPCA = Perceived Cognitive Abilities; CogQOL = Impact on Quality of Life.

10.5.2. Factors Associated with Cognitive Function

A summary of the univariate analyses is presented in Table 10.3. Mann-Whitney tests revealed that those attending for treatment at the rural centre had significantly lower CogPCI ($Z = -2.43, p < .05$) and CogPCA scores ($Z = -2.34, p < .05$) than those attending the urban centre. Likewise, participants who were not employed at the time of survey completion had significantly lower scores on CogPCI ($Z = -3.27, p < .01$) and CogPCA indices ($Z = -2.35, p < .05$), along with the CogOTH subscale ($Z = -2.44, p < .05$), than participants who were currently working. Those who had a radical prostatectomy scored significantly lower on the CogQOL subscale than those who did not ($Z = -2.25, p < .05$).

Kruskal-Wallis tests showed significant differences in CogPCA scores based on education level ($H = 19.43, p < .001$), with a post hoc Mann-Whitney test revealing that participants with primary/secondary school or TAFE/apprenticeship level of education had significantly lower CogPCA scores than participants with tertiary or postgraduate qualifications ($Z = -3.72, p < .001$). CogQOL and CogPCA subscale scores significantly differed across treatment categories, with $H = 11.32, p < .05$ and $H = 8.17, p < .05$, respectively. Post hoc Mann Whitney tests showed that participants treated with ADT had significantly lower scores on CogQOL ($Z = -2.49, p < .05$), CogPCA ($Z = -2.49, p < .05$) and CogPCI ($Z = -2.62, p < .01$) subscales than those treated with RT only. Furthermore, those treated with ADT indefinitely scored significantly lower on CogQOL ($Z = -2.80, p < .01$) and CogPCA ($Z = -2.20, p < .05$) subscales than participants in all other treatment groups. CogPCI, CogQOL and CogPCA scores also significantly differed according to RT type ($H = 9.57, p < .01$; $H = 15.20, p < .01$; and $H = 7.13, p < .05$, respectively). Post hoc Mann Whitney tests indicated that participants treated with EBRT only scored significantly lower on all

FACT-Cog subscales than those treated with brachytherapy only or EBRT + brachytherapy (CogPCI: $Z = -2.11, p < .05$; CogQOL: $Z = -2.53, p < .05$; CogOTH: $Z = -2.22, p < .05$; CogPCA: $Z = -2.44, p < .05$).

Table 10.3

Summary of Univariate Analyses.

Variable	FACT-Cog PCI subscale score		FACT-Cog QoL subscale score		FACT-Cog Oth subscale score		FACT-Cog PCA subscale score	
	Median (min, max)	<i>p</i>	Median (min, max)	<i>p</i>	Median (min, max)	<i>p</i>	Median (min, max)	<i>p</i>
Treatment centre		< .05		.65		.05		< .05
Urban centre	63.0 (2.0, 72.0)		15.0 (0.0, 16.0)		16.0 (0.0, 16.0)		23.0 (0.0, 28.0)	
Rural centre	61.0 (16.0, 72.0)		14.5 (0.0, 16.0)		16.0 (4.0, 16.0)		21.0 (0.0, 28.0)	
Education		.28		.16		.15		< .001
Primary or secondary	62.0 (2.0, 72.0)		15.0 (0.0, 16.0)		16.0 (0.0, 16.0)		22.0 (0.0, 28.0)	
TAFE/apprenticeship	61.0 (18.0, 72.0)		14.0 (0.0, 16.0)		16.0 (8.0, 16.0)		19.0 (0.0, 28.0)	
Tertiary	64.0 (12.0, 72.0)		15.0 (0.0, 16.0)		16.0 (6.0, 16.0)		24.0 (0.0, 28.0)	
Postgraduate	66.0 (59.0, 70.0)		16.0 (10.0, 16.0)		16.0 (13.0, 16.0)		25.0 (21.0, 28.0)	
Employment status		< .01		.09		< .05		< .05
Employed	65.0 (12.0, 72.0)		15.0 (2.0, 16.0)		16.0 (4.0, 16.0)		24.0 (0.0, 28.0)	
Not Employed	62.0 (2.0, 72.0)		15.0 (0.0, 16.0)		16.0 (0.0, 16.0)		22.0 (0.0, 28.0)	
Treatment category		.07		< .05		.35		< .05
RT only	64.0 (2.0, 72.0)		15.0 (0.0, 16.0)		16.0 (0.0, 16.0)		24.0 (0.0, 28.0)	
RT + 6mths ADT	62.0 (12.0, 72.0)		15.0 (0.0, 16.0)		16.0 (4.0, 16.0)		22.0 (0.0, 28.0)	
RT + 2.5yrs ADT	63.0 (18.0, 72.0)		15.0 (3.0, 16.0)		16.0 (6.0, 16.0)		22.0 (0.0, 28.0)	
RT + ADT indefinitely	61.5 (21.0, 72.0)		12.0 (0.0, 16.0)		16.0 (4.0, 16.0)		18.0 (1.2, 28.0)	
RT type		< .01		< .01		.06		< .05
Brachytherapy	65.0 (2.0, 72.0)		16.0 (0.0, 16.0)		16.0 (0.0, 16.0)		24.0 (0.0, 28.0)	
EBRT	62.0 (16.0, 72.0)		14.0 (0.0, 16.0)		16.0 (4.0, 16.0)		21.0 (0.0, 28.0)	
Brachytherapy + EBRT	62.0 (12.0, 72.0)		14.0 (2.0, 16.0)		16.0 (9.0, 16.0)		22.0 (0.0, 28.0)	
Radical prostatectomy		.57		< .05		.45		.78
Yes	63.0 (18.0, 72.0)		14.0 (0.0, 16.0)		16.0 (4.0, 16.0)		23.0 (0.0, 28.0)	
No	63.0 (2.0, 72.0)		15.0 (0.0, 16.0)		16.0 (0.0, 16.0)		22.0 (0.0, 28.0)	

FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive; PCI = Perceived Cognitive Impairments; QoL = Impact of Perceived Cognitive Impairments on Quality of Life; Oth = Comments from Others; PCA = Perceived Cognitive Abilities; RT = Radiotherapy; ADT = Androgen Deprivation Therapy; EBRT = External Beam Radiotherapy; NPAGA = National Physical Activity Guidelines of Australia.

Correlations between FACT-Cog subscale scores and the key study variables are displayed in Table 10.4. Significant negative relationships were observed between all four cognitive function outcome variables and depression (CogPCI: $r(377) = -0.49, p < .001$; CogQOL: $r(374) = -0.60, p < .001$; CogOTH: $r(374) = -0.36, p < .001$; CogPCA: $r(369) = -0.36, p < .001$) and anxiety scores (CogPCI: $r(376) = -0.45, p < .001$; CogQOL: $r(373) = -0.55, p < .001$; CogOTH: $r(373) = -0.33, p < .001$; CogPCA: $r(368) = -0.30, p < .001$). Likewise, significant positive relationships were detected between FACT-P subscale scores and all FACT-Cog subscale scores (CogPCI: $r(375) = 0.46, p < .001$; CogQOL: $r(372) = 0.58, p < .001$; CogOTH: $r(372) = 0.29, p < .001$; CogPCA: $r(367) = 0.36, p < .001$). Significant positive correlations were observed between leisure-time PA and CogQOL ($r(353) = 0.16, p < .01$), CogOTH ($r(353) = 0.16, p < .01$), and CogPCA ($r(348) = 0.11, p < .05$) scores. However, no relationship was observed between leisure-time PA and CogPCI scores. The number of comorbid conditions was negatively correlated with all FACT-Cog subscale scores (CogPCI: $r(376) = -0.30, p < .001$; CogQOL: $r(373) = -0.18, p < .001$; CogOTH: $r(373) = -0.20, p < .001$; CogPCA: $r(368) = -0.15, p < .01$). No relationship was observed between age and CogQOL scores. Significant negative relationships, however, were observed between age and all other FACT-Cog scores (CogPCI: $r(377) = -0.18, p < .001$; CogOTH: $r(374) = -0.13, p < .01$; CogPCA: $r(369) = -0.19, p < .001$).

Table 10.4

Correlation Matrix of Examined Variables with FACT-Cog Subscale Scores.

	1	2	3	4	5	6	7	8	9	10
1 FACT-CogPCI subscale score										
2 FACT-CogQoL subscale score	0.52**									
3 FACT-CogOth subscale score	0.63**	0.42**								
4 FACT-CogPCA subscale score	0.54**	0.38**	0.41**							
5 HADS depression subscale score	-0.49**	-0.60**	-0.36**	-0.36**						
6 HADS anxiety subscale score	-0.45**	-0.55**	-0.33**	-0.30**	0.63**					
7 FACT-P subscale score	0.46**	0.58**	0.29**	0.36**	-0.51**	-0.35**				
8 IPAQ leisure subscale score	0.06 ^{n/s}	0.16**	0.16**	0.11*	-0.23**	-0.11*	0.18**			
9 Comorbid conditions	-0.30**	-0.18**	-0.20**	-0.15**	-0.24**	0.13*	-0.33**	-0.14**		
10 Age	-0.18**	-0.05 ^{n/s}	-0.13**	-0.19**	0.90 ^{n/s}	-0.10*	-0.17**	-0.04 ^{n/s}	0.15**	

* $p < .05$, ** $p < .01$, n/s = non-significant

FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive; PCI = Perceived Cognitive Impairments; QoL = Quality of Life; Oth = Comments from Others; PCA = Perceived Cognitive Abilities; HADS = Hospital Anxiety and Depression Scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; IPAQ = International Physical Activity Questionnaire

10.5.3. Factors Associated with Cognitive Function

In Table 10.5 the results of multiple regression analyses using the forced enter method to predict transformed CogPCI scores are presented. A significant model emerged, with 7 of the 11 variables explaining a significant proportion of the variance in CogPCI scores ($R^2 = 0.42$; $F(11, 341) = 22.04$, $p < .001$). These variables were depression ($b = 0.10$, $t(340) = 3.54$, $p < .001$); QoL ($b = -0.05$, $t(340) = -4.74$, $p < .001$); anxiety ($b = 0.10$, $t(340) = 0.23$, $p < .001$); comorbid conditions ($b = 0.13$, $t(340) = 2.32$, $p < .05$); leisure-time PA ($b = 0.00$, $t(340) = 2.41$, $p < .05$); age ($b = 0.02$, $t(340) = 2.31$, $p < .05$) and treatment centre ($b = 0.47$, $t(340) = 2.74$, $p < .05$). Depression predicted the most variance in cognitive function, accounting for 26.7%. QoL accounted for 7.0% and anxiety accounted for 2.6%. Age, treatment centre, leisure-time PA, and comorbid conditions accounted for 1.6%, 1.0%, 1.1% and 0.9% of the variance in cognitive function, respectively.

Table 10.5

Summary of Multiple Regression Analyses for Variables Predicting FACT-CogPCI Scores (N = 352).

Variable	<i>B</i>	<i>SE B</i>	β	R^2
				0.42
HADS depression total score	0.10	0.03	0.22***	
FACT-P total score	-0.05	0.01	-0.25***	
HADS anxiety total score	0.10	0.03	0.23***	
Age (yrs)	0.02	0.01	0.11*	
Treatment centre	0.47	0.17	0.12**	
IPAQ leisure subscale score	0.00	0.00	0.10*	
Comorbid conditions	0.13	0.05	0.10*	
Employment Status	-0.08	0.15	-0.03	
Treatment category	-0.05	0.08	-0.03	
Education	0.08	0.10	0.03	
RT type	0.16	0.10	0.07	

* $p < .05$, ** $p < .01$, *** $p < .001$

FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive; PCI = Perceived Cognitive Impairments; HADS = Hospital Anxiety and Depression Scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; RT = radiotherapy; IPAQ = International Physical Activity Questionnaire.

10.6. DISCUSSION

The first aim of this study was to identify the types of cognitive difficulties reported by patients with PCa and compare differences in cognitive function by treatment type. The most common cognitive complaints were endorsed by 22.5% to 38.7% of participants. The most common complaints related to memory, functional change, multi-tasking / interruption and verbal fluency. The percentage of patients with PCa endorsing cognitive complaints in the present study was comparable to

findings by Jacobs et al (2007), with the most common complaints endorsed by 34% to 47% of hematopoietic stem cell transplant (HSCT) patients.

A higher percentage of participants who received ADT reported cognitive complaints compared to those who received RT only, suggesting that patients with PCa who received ADT experienced more cognitive difficulties than those treated with RT. This is consistent with previous research observing reduced cognitive functioning in ADT patients compared with healthy controls, particularly in spatial ability, working memory, attention and executive function (Cherrier, et al., 2009; Green, et al., 2002; Jenkins, et al., 2005). Although in the present study the spatial ability domains of cognitive function were not able to be assessed, findings suggest that items relating to memory function were most commonly endorsed and this is consistent with previous research (Cherrier, et al., 2009; Jenkins, et al., 2005). Conversely, using the same measure of cognitive function as in the present study, Joly et al (2006) found that patients treated with ADT did not report more cognitive problems on the FACT-Cog than healthy controls. However, it appears that in previous research cognitive function of PCa patients receiving RT only were not compared to patients treated with ADT and therefore this aspect of the present study is novel.

A second aim of this study was to identify the factors associated with cognitive functioning and establish if there was a relationship between PA levels and cognitive function in patients with PCa. Participants with lower levels of education reported lower perceptions of their cognitive abilities than patients with a higher level of education. Evidence suggests that level of education influences cognitive functioning with the results of previous studies indicating that low educational attainment predicts cognitive decline (Evans et al., 1993; Harder et al., 2002).

Patients from the rural centre involved in the current study reported lower cognitive functioning than patients from the urban centres. This finding is not surprising, as the Australian Government Department of Health and Ageing (2009) has reported that people in rural and remote localities tend to have lower levels of education and generally lower socio-economic status than those in metropolitan areas. This discrepancy is the result of limited opportunities for further education in rural areas. Participants who were employed had better cognitive function than participants who were not currently working. This is consistent with previous research reporting positive relationships between cognitive function and employment status in patients with physical illness (Harder, et al., 2002; Rothenhäusler, Ehrentraut, Stoll, Schelling, & Kapfhammer, 2001). The research evidence suggests that maintaining intellectual engagement through participation in everyday activities buffers against cognitive decline (Hultsch, Hertzog, Small, & Dixon, 1999).

As hypothesised, patients treated with ADT self-reported poorer cognitive function than those treated with RT only. Results indicated no differences in cognitive function of participants treated with 6 months or 2 ½ years of ADT. However, those treated with ADT indefinitely reported the poorest cognitive function of all ADT treatment groups. Patients treated with ADT for an indefinite period are generally treated with palliative intent and therefore cognitive function may be confounded by psychological conditions such as depression, anxiety and existential concerns associated with dying and death (Bolmsjo, 2000).

Symptoms of depression and anxiety and poorer QoL were associated with reduced cognitive function. The inverse association between depression and reduced cognitive performance has been widely reported, with effects on information processing speed, executive function, attention and inhibition, working memory, and

visuospatial memory (Steffens, Otey, & Alexopoulos, 2006; Vinkers, Gussekloo, Stek, Westendorp, & van der Mast, 2004). Furthermore, growing evidence suggests that depression may represent an independent risk factor predisposing individuals to dementing disorders (Steffens, et al., 2006). Similarly, research has shown that individuals with high anxiety exert more effort to maintain the same level of performance on cognitive tests than non-anxious control participants (Ansari & Derakshan, 2011). However, the relationship between anxiety, poor QoL and cognitive dysfunction has previously been explained by adjustment for comorbid depression (Biringer et al., 2005), suggesting that symptoms of depression may be key contributors to cognitive difficulties.

A positive relationship was observed between leisure-time PA and cognitive function, however, correlations were weak. Therefore, these results should be interpreted with caution and suggest that there are other variables associated with cognitive function that were not measured in the current study. Nevertheless, there is substantial evidence supporting the effectiveness of regular PA for improvements in cognitive function (Cotman & Berchtold, 2002; Cotman & Engesser-Cesar, 2002; Denking, et al., 2012; Kraft, 2012; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). Previous research conducted by Cotman and Berchtold (2002) using animal models showed that PA increases brain-derived neurotrophic factor, a molecule increasing neuronal survival, enhancing learning and protecting against cognitive decline. Likewise, in PA intervention studies involving neuroimaging techniques with human participants, structural changes in the brain have been observed with increases in grey matter volume in the frontal and temporal cortices (Kraft, 2012).

Increasing age and comorbid conditions were correlated with cognitive impairment in the present study. However, again, correlations were weak. The

relationship between ageing and cognitive decline is well established (Bishop, Lu, & Yankner, 2010; Hultsch, et al., 1999). Deterioration of the structural framework of the brain may generate changes such as decreased brain volume; weakening of serotonin, acetylcholine and dopamine receptor binding and signalling; cortical thinning and loss of myelin integrity; accumulation of neurofibrillary tangles; and alterations in hormone and brain metabolite concentrations (Bishop, et al., 2010). Collectively, these changes induce cognitive difficulties associated with ageing such as forgetfulness and deterioration of the capacity to maintain focus and solve problems. Likewise, many comorbid conditions impact on cognitive function. For example, diabetes has been linked to decreased brain volume, lower levels of neuronal growth factors, and higher incidence of dementia (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; McIntyre et al., 2010). The literature suggests that in elderly populations, those engaging in higher levels of PA are less likely to experience cognitive decline (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). Overwhelming evidence for the effectiveness of regular PA in the prevention and attenuation of several chronic diseases exists, including cardiovascular disease, diabetes, obesity, cancer, depression, osteoporosis and hypertension (Armstrong, et al., 2000; Warburton, Nicol, & Bredin, 2006). PA is therefore a commonly recommended intervention to improve existing comorbid conditions.

A final aim of the current study was to determine the factors associated with cognitive function in patients with PCa. The multiple regression model used to examine factors associated with cognitive function revealed that depression was the strongest predictor of cognitive impairment. Anxiety and poor QoL were also predictors of cognitive dysfunction. However, as previously discussed this may be associated with comorbid depression with significant correlations between these

three variables observed. Increasing age and number of comorbid conditions, lower levels of PA and treatment centre were also predictors of cognitive impairment, although these variables accounted for a small proportion of the variance in cognitive function.

10.6.1. Limitations and Future Research

Given the cross-sectional design of the present study, it was not possible to measure baseline or change in cognitive function prior to, during and post-treatment. Consequently, longitudinal research designs will be important in future research. While a self-report cognitive evaluation may be a useful approach for screening a large sample of patients, the caveats of self-report measures are widely acknowledged and the FACT-Cog version 3 is still undergoing validation. Although the FACT-Cog assesses a broad range of cognitive complaints and provides evidence for the types of cognitive difficulties patients are experiencing, inherent problems with the measure were identified. A number of participants commented on difficulties answering the CogPCA subscale with confusion around the switch to positive wording of questions and being unrelated to the 5-point Likert scale responses. Four participants changed the response scale with a score of zero meaning “always” as opposed to “never”. Fourteen participants were excluded due to inconsistent responses on the CogPCA subscale in comparison to other items on the FACT-Cog, suggesting the wording of the CogPCA subscale was misunderstood. Furthermore, the negatively worded items (CogPCI subscale) and positively worded items (CogPCA subscale) are independent factors and consequently a total score for cognitive function cannot be generated as combining all items undermines the psychometric properties of the instrument. Further work is required to improve the validity of self-report measures of cognitive function. Given the lack of consensus

regarding the domains of cognitive function affected by ADT, further research is required using a battery of observational and self-report neuropsychological tests. With several studies reporting an association between testosterone levels and spatial abilities, future research examining the cognitive function of patients receiving ADT should attempt to measure this domain.

10.6.2. Conclusions

Findings of the present study indicated that declining cognitive function is related to increasing duration of ADT treatment. Factors associated with cognitive dysfunction were identified, with results implying that symptoms of depression may be a key contributor to cognitive difficulties. Given that depression is recognised as a potential side effect of ADT (Pirl, Siegel, Goode, & Smith, 2002; Rosenblatt & Mellow, 1995; Shahinian, et al., 2006), interventions to attenuate the possibility of comorbid depression are critical in this patient group. Clinical trials have demonstrated the utility of PA in counteracting the side effects of ADT and in particular for improving QoL and psychosocial wellbeing. However, the current study appears to be the first to examine the relationship between cognitive function and PA in a sample of patients with PCa. The results of this study have identified a positive relationship between PA and cognitive function. With the overwhelming research evidence supporting the value of regular PA in strengthening the systems that support plasticity and protect against neurodegeneration, PA may be considered a vital supplementary treatment for patients with PCa receiving ADT.

10.7. References

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10.8. Summary and Conclusions

This chapter took the form of the final empirical paper in the thesis. The findings presented indicated that increasing duration of ADT is associated with cognitive decline. Furthermore, the results suggest that symptoms of depression are a key contributor to cognitive difficulties in this patient group. A positive relationship between PA and cognitive function was also identified. Given these results, PA could be considered a vital behavioural intervention to improve cognitive function, depression, anxiety and consequently, QoL in this population. In the next and concluding chapter, the findings of the current study are integrated and synthesised. The limitations and implications of the results are discussed and directions for future research provided.

Chapter 11. Integrated Discussion

11.1. Rationale for the Study

As outlined in Chapters 2 and 3, a diagnosis of PCa and the associated treatments can have a substantial impact on QoL and psychosocial wellbeing. In Chapter 4 the psychological impact of ADT was described. In Chapter 5, PA as a potential behavioural intervention to improve psychosocial wellbeing in men with PCa was described as well as the results of previous PA intervention studies that have demonstrated improvements in physical function and QoL in this patient group. However, as emphasised in the systematic review presented in Chapter 6, there are very few studies in which the impact of PA on psychological constructs including depression, anxiety and cognitive function has been examined in patients with PCa receiving ADT. Furthermore, there are very few studies into whether these outcomes would be improved by meeting the NPAGA.

Given these gaps in the existing research literature, the overarching aims of the present study were to: (1) describe the PA behaviour of patients with PCa; (2) evaluate the impact of ADT on depression, anxiety, cognitive function and QoL in men with PCa; and (3) examine the relationship between meeting NPAGA and the presence and severity of the physical and psychological side effects of ADT. In this final chapter, the specific aims of the research are restated, and the key findings of the cross-sectional survey are summarised and integrated. The implications of the findings, limitations and strengths of the research, and directions for future research are also discussed.

11.2. Research Aims and Summary of Results

Several major aims were addressed by undertaking the current study, with three empirical papers and one review paper submitted for publication. The aim of the first of these empirical papers was to estimate the proportion of patients with PCa meeting NPAGA, determine socio-demographic and medical factors associated with meeting these guidelines, and establish factors predicting the likelihood that patients with PCa would meet NPAGA. The second aim was to evaluate the effects of ADT on depression, anxiety and QoL, examine the relationship between meeting NPAGA and the presence and severity of psychological sequelae associated with ADT, and to establish predictors of depression, anxiety and QoL in this patient group. The final aim was to identify the types of cognitive difficulties reported by patients with PCa according to treatment type, establish the relationship between PA levels and cognitive function, and determine predictors of cognitive function in patients with PCa.

As reported in Chapter 8, less than half of participants in the present study met NPAGA (41.9%). However, a larger proportion of participants who had completed tertiary level of education met NPAGA (50.7%) compared to those with primary/secondary school (38.5%) or TAFE/apprenticeship (23.1%) qualifications. Relationships between leisure-time PA and comorbid conditions, depression, anxiety and QoL were also observed. The proportion of participants meeting NPAGA or leisure-time PA levels did not differ based on the following socio-demographic and medical variables: Employment status; marital status; treatment group; RT type; radical prostatectomy; currently receiving ADT; previous cancer diagnosis; treatment centre; age; or time since diagnosis.

Participants receiving ADT were significantly less active according to the total PA score of the IPAQ compared to participants receiving RT only. No significant differences between treatment groups across the individual domains of leisure, domestic, transport and work-related PA were observed. However, patients receiving ADT appeared to be less physically active across all PA domains apart from work-related PA. Participants were least active in the transport and leisure PA domains, implying that PA is primarily undertaken involuntarily as part of work or domestic chores. Finally, the likelihood that patients with PCa met NPAGA was associated with less educational achievement and symptoms of depression. Treatment group, comorbid conditions, age, anxiety and QoL were not significant predictors of meeting NPAGA.

As described in Chapter 9, a relatively small proportion of participants reported HADS scores indicative of clinically significant anxiety (19.6%) or depression (13.0%). Increasing length of time on ADT was associated with poorer QoL. This pattern of results, however, was not consistent for depression and anxiety, as those treated with ADT for 2 ½ years reported less symptoms of depression and anxiety than those treated with 6 months of ADT or indefinitely. Participants meeting NPAGA had significantly lower levels of depression and anxiety and improved QoL compared to those not meeting NPAGA. The likelihood of clinically significant anxiety and depression increased with the number of comorbid conditions and younger age, while meeting NPAGA was a significant predictor of caseness for depression but not anxiety. Comorbid conditions and increasing length of time on ADT predicted poorer QoL, while meeting NPAGA predicted better QoL.

As discussed in Chapter 10, the most common cognitive complaints in this patient group were about memory, functional change, multi-tasking/interruption, and

verbal fluency. A higher proportion of participants who received ADT reported cognitive complaints compared to those who received RT only. No difference in cognitive function was reported between participants treated with 6 months or 2 ½ years of ADT. However, those treated with ADT indefinitely reported the poorest cognitive function of all ADT treatment groups. Participants with lower levels of education, or from rural localities, or who were not currently working reported poorer cognitive function. Likewise, increasing age and comorbid conditions were related to cognitive impairment. Symptoms of depression and anxiety and poorer QoL were associated with reduced cognitive functioning, while engagement in leisure-time PA was related to improved cognitive ability. Finally, depression was the strongest predictor of cognitive impairment in this patient group accounting for 26.7% of the variance in cognitive function. Anxiety and poor QoL were also predictors of cognitive dysfunction. Increasing age and number of comorbid conditions, lower levels of PA and rural locality were also predictors of poorer cognition. However, these variables accounted for a small proportion of the variance in cognitive function (4.6%).

11.3. Synthesis of Results

The finding that less than half of participants in the present study met NPAGA (41.9%) is comparable to the results of a similar study by Keogh et al. (2010), where 45% of men with PCa undergoing ADT met the American Cancer Society PA guidelines. This is in accord with the results of two studies using other tumour streams. In Lynch et al. (2007), 53% of colorectal cancer survivors met PA guidelines and in Sprod et al. (2012) 46% of older cancer patients engaged in regular PA.

Findings of the present study documented relationships between leisure-time PA and comorbid conditions, depression, anxiety and QoL, with a larger proportion of participants with tertiary level of education meeting NPAGA compared to those with primary/secondary school or TAFE/apprenticeship qualifications. This is consistent with the results of previous research suggesting that lower levels of education (Armstrong, et al., 2000; King et al., 2000); comorbid conditions (Craike, Livingston, & Botti, 2011; Penedo, Schneiderman, Dahn, & Gonzalez, 2004; Sprod, et al., 2012); and symptoms of depression (Dunn, et al., 2001; Sieverdes, et al., 2012) are associated with decreased PA participation. However, no relationship was found between age and PA level in the present study and this finding was unexpected, given that previous research indicates a decline in PA levels with increasing age (Craike, et al., 2011; Penedo, et al., 2004; Sprod, et al., 2012). A possible explanation for this unexpected finding is that the limited range in PA levels and age represented in the current sample restricted the opportunity to observe such a relationship between these variables. The self-report format of PA may have lead participants to over-estimate their PA levels causing a ceiling effect and with a mean age of 67.6 years, an over-representation of older participants was apparent in the present study sample.

Given the research evidence suggesting that severe treatment side effects are linked with reduced PA participation (Sprod, et al., 2012) and the adverse effects associated with ADT intensifying the impact of other forms of PCa treatment on QoL and psychosocial wellbeing (Fowler, et al., 2002; Sharifi, et al., 2005), it is not surprising that participants receiving ADT in the present study were less physically active than those receiving RT only. However, the physical and psychological benefits of PA for men receiving ADT for PCa have been previously demonstrated

(Galvão, et al., 2010; Segal, et al., 2003), emphasising the need to promote engagement in regular PA in this patient group. Furthermore, the results of the present study imply that PA is primarily undertaken involuntarily as part of work or domestic chores, despite evidence that domestic- and work-related PA may not provide a health benefit (Armstrong, et al., 2000). Therefore, PA recommendations for patients with PCa should include discussion about the types of activity considered sufficient to incur improvements in QoL and psychosocial wellbeing.

Findings of the present study suggested that the likelihood of meeting NPAGA diminished with increases in depressive symptoms and lower levels of education. This is consistent with findings from Sieverdes et al. (2012) that men accumulating approximately 150 minutes of moderate-intensity leisure-time PA per week had significantly lower odds of depressive symptoms. It was surprising that treatment category (RT only; or RT + ADT), age, or comorbid conditions were not predictors of meeting NPAGA in the present study. However, again, this may reflect an inability to observe such a relationship in the current sample due to the restrictions imposed by the inclusion criteria of the study, in particular age range.

The small proportion of participants reporting clinically significant levels of anxiety (19.6%) or depression (13.0%) in the present study is consistent with the results of previous research (Crawford, Henry, Crombie, & Taylor, 2001; Mehnert, et al., 2010). Furthermore, the findings of the present study suggesting that increasing length of time on ADT is associated with poorer QoL, is comparable to the results of prior research indicating that continuous use of ADT impacts on QoL in the domains of physical and sexual function (Fowler, et al., 2002; Herr & O'Sullivan, 2000; Sharifi, et al., 2005; Smith, et al., 2009). However, the results suggested that participants treated with ADT for 2 ½ years reported less symptoms of depression

and anxiety than those treated with 6 months or indefinite ADT. Although this pattern of results was unexpected, it is consistent with previous studies indicating that long-term ADT administration does not exacerbate the emotional functioning aspect of QoL (Alibhai, Gogov, & Allibhai, 2006; Green, Pakenham, Headley, & Gardiner, 2002) and improvements in QoL observed after two years of ADT (Lubeck, Grossfeld, & Carroll, 2001). Likewise, this finding is in accord with the argument that patients with chronic conditions adapt to their symptoms over time (Sprangers & Schwartz, 1999).

The finding that participants meeting NPAGA had lower levels of depression and anxiety and improved QoL compared to those not meeting NPAGA is consistent with the results of numerous intervention studies demonstrating the benefits of PA engagement for men with PCa receiving ADT (Culos-Reed, et al., 2007; Culos-Reed, et al., 2010; Galvão, et al., 2010; Segal, et al., 2003). In a similar cross-sectional study by Keogh et al. (2010) men receiving ADT for PCa who were meeting PA recommendations had significantly higher QoL than those not meeting PA guidelines. Likewise, studies with ovarian cancer (Stevinson, et al., 2009), colorectal cancer (Lynch, et al., 2007), and non-Hodgkin's Lymphoma survivors (Vallance, et al., 2005) have found that those engaging in 150 minutes of moderate-intensity PA weekly reported better QoL than those describing lower levels of PA participation. However, there are no prior studies in which the association between engagement in regular PA and the presence and level of psychological side effects of ADT has been investigated in men with PCa. Therefore, the inclusion of the psychological constructs depression, anxiety and cognitive function in the present study are novel and contribute important new findings to the existing literature.

The present study finding that the likelihood of clinically significant anxiety and depression increased with comorbid conditions and younger age is consistent with the results of previous research. Comorbid conditions (Brooker, et al., 2012; Mehnert, et al., 2010; Smith, et al., 2009) and younger age (Kissane et al., 2004; National Breast Cancer Centre (NBCC) and National Cancer Control Initiative (NCCI), 2003; Schag et al., 1993) have been found to increase vulnerability to depression and psychological distress in the context of cancer. Furthermore, results of the present study indicate that meeting NPAGA was a significant predictor of depression but not anxiety. This result is consistent with Dunn et al's (2001) review of 37 studies suggesting that both moderate and vigorous PA reduces symptoms of depression. However, no association between PA and decreased anxiety has been documented.

In the current study men with PCa who received ADT reported more cognitive difficulties than those treated with RT only. This finding is comparable with previous research in which reduced cognitive function was reported in this patient group in contrast to healthy controls (Cherrier, et al., 2009; Jenkins, et al., 2005). Furthermore, the most common cognitive complaints related to memory dysfunction in the present study and this is also consistent with findings from prior research (Cherrier, et al., 2009; Jenkins, et al., 2005). However, given the self-report nature of the current study, it was not possible to assess the spatial ability domain of cognition. With an association documented between testosterone levels and spatial abilities (Barrett-Connor, Goodman-Gruen, et al., 1999; Cherrier, et al., 2001), previous research has observed dysfunction in the spatial domain of cognitive function in men receiving ADT for PCa (Cherrier, et al., 2009; Jenkins, et al., 2005). The impact of ADT on spatial ability should therefore be a focus for future research.

Contrary to expectations, no differences in cognitive function of participants treated with 6 months or 2 ½ years ADT were observed. However, this result could be explained by the contention that patients adapt to the symptoms of their condition over time, making previously bothersome side effects of treatment less noticeable (Sprangers & Schwartz, 1999). Results suggesting that those treated with ADT indefinitely had the poorest cognitive function of all treatment groups was not surprising and may be related to the palliative intent of treatment (Bolmsjo, 2000). Patients treated with palliative intent may be physically unwell and confronted with existential issues related to dying and death which may confound assessment of cognitive function.

Socio-demographic and medical factors found to be associated with cognitive impairment in the present study were consistent with previous research. Lower educational attainment has been found to predict cognitive decline (Evans et al., 1993; Harder et al., 2002). Furthermore, those patients from rural and remote localities have limited opportunities for further education (Australian Government Department of Health and Ageing, 2009), accounting for the fact that participants with lower levels of education or from rural localities reported poorer cognitive function. Furthermore, prior research has reported positive relationships between cognitive function and employment in patients with a physical illness (Harder, et al., 2002; Rothenhäusler, Ehrentaut, Stoll, Schelling, & Kapfhammer, 2001), supporting results of the present study that those not currently employed reported poorer cognitive ability. The relationship between ageing and cognitive decline is well established (Bishop, Lu, & Yankner, 2010; Hultsch, Hertzog, Small, & Dixon, 1999) and likewise, number of comorbid conditions have been found to impact on cognitive function (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006). Therefore, the

relationships between ageing, increasing comorbid conditions and cognitive impairment observed in the present study were expected and consistent with the existing literature.

The positive relationship between leisure-time PA and cognitive function and lower PA levels predicting cognitive impairment in the present study is consistent with the substantial evidence in the literature supporting the effectiveness of regular PA for improving cognition (Cotman & Berchtold, 2002; Cotman & Engesser-Cesar, 2002; Denking, et al., 2012; Kraft, 2012; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). The relationship between anxiety, poor QoL and cognitive dysfunction in the present study has been explained in previous research by adjustment for comorbid depression (Biringer et al., 2005), suggesting that symptoms of depression may be a key contributor to cognitive difficulties. The finding that depression was the strongest predictor of cognitive impairment in the current study supports this contention and suggests that behavioural interventions targeting depression in this patient group will also have benefits for cognitive function. Therefore, further support is provided for PA as an intervention to improve cognitive ability in this population with evidence that moderate and vigorous PA reduces symptoms of depression (Dunn, et al., 2001).

11.4. Implications of the Results for Theory and Practice

The findings of this research contributes important knowledge about the frequency, intensity and duration of PA required (i.e., 150 minutes of moderate-intensity PA per week) to improve QoL and psychosocial wellbeing in patients receiving ADT for PCa. Furthermore, the results of the present study support the utility of behavioural interventions targeted at meeting NPAGA for inclusion in PCa

rehabilitation programs. Such programs could possibly contribute to a reduction in the burden of PCa on public health in terms of disability and cost, and improve the QoL of such patients. However, findings of the present study suggesting that the majority of patients with PCa are not achieving optimal PA levels is cause for concern and emphasises the need for health professionals and government initiatives to promote the benefits of PA in this patient group. Furthermore, providing clear and structured recommendations regarding the frequency, intensity, duration and types of PA suitable for this population may increase the likelihood of PA participation.

The results of the present study may also assist health professionals in the identification of patients most vulnerable to reduced QoL and the development of interventions to assist these individuals. For example, the results indicate that patients receiving long-term ADT are most vulnerable to deterioration in QoL and psychosocial wellbeing. In addition, socio-demographic variables such as education, locality, employment status and age may represent significant risk factors for depression, anxiety, cognitive dysfunction and poor QoL. Furthermore, the results of the present study highlight the necessity for treating clinicians to consider the cumulative impact of comorbid conditions on QoL and psychosocial wellbeing. Increasing awareness of the adverse effects of ADT in terms of psychological morbidity and the additional impact of socio-demographic and medical factors will enable clinicians to make informed treatment decisions. Accordingly, patients with evident risk factors and/or troubling symptoms may be encouraged to seek assistance through their health care team early on in the treatment process.

The results of the present study may also be useful to physicians when discussing the likely impact of treatment for PCa on QoL and emotional wellbeing with patients. For example, it may be reassuring for patients to know that, for the

current sample, scores for depression and anxiety were low and comparable to those in the general population. However, it is important for healthcare professionals to counsel patients with PCa on ADT and stimulate awareness that although the risk of adverse psychological symptoms is low, if these do manifest, the impact on QoL can be severe. For example, while urinary incontinence and erectile dysfunction may be discussed in relation to treatment side effects, the impact of these adverse events on QoL and psychosocial wellbeing may be ignored. Discussion, consideration and knowledge of how physical side effects may influence perceptions of masculinity and emotional wellbeing may better prepare men for treatment and encourage them to seek help if needed.

A number of government and professional organisations have recommended that patients with cancer be screened routinely for the presence of depression, anxiety and psychological distress (Jacobsen & Moffitt, 2007) to improve the psychosocial wellbeing of cancer patients and their ability to reduce the burden of the disease. Unfortunately, depression and anxiety often go undetected and therefore many patients with cancer do not receive treatment for this often significant problem (National Breast Cancer Centre (NBCC) and National Cancer Control Initiative (NCCI), 2003). Findings of the present study combined with the results of previous research suggest that routine screening for distress, anxiety and depression is a necessity and may alleviate other associated problems including poor adherence to treatment recommendations (Kennard et al., 2004); reduced satisfaction with care and QoL (Von Essen, Larsson, Oberg, & Sjoden, 2002); relationship difficulties; and reduced survival rates (Jacobsen & Moffitt, 2007). Identification of psychological morbidity through the provision of routine assessment using validated screening

tools for depression and anxiety symptoms will enable effective management of these symptoms through pharmacologic and psychological interventions.

With regard to theoretical implications, the findings of the present study provide support for the biopsychosocial model of health, adding to the literature documenting a link between psychological factors and physical, social and emotional wellbeing in patients with a chronic illness. The results have exemplified the interaction between physical, psychological and social wellbeing domains proposed in this model. One example that illustrates this interaction in the current study was that a number of physical symptoms measured by the FACT-P PCS subscale were associated with reduced psychological and social wellbeing.

11.5. Limitations of the Current Research

As mentioned in Chapter 7, data were collected using the SF-12 but these had to be excluded because it was discovered that an incorrect version of the SF-12 was included in the study questionnaire. The version that was used was obtained from a website called ‘painxchange’ produced by Lifeblood and sponsored by CSL Biotherapies. Upon closer examination, however, this measure appeared to contain a mixture of items from versions one and two of the SF-12 and consequently, standard scoring procedures could not be used. The Doctoral candidate contacted Lifeblood, CSL Biotherapies and two other organisations associated with the development of the measure, Medical Outcomes Trust and Quality Metric Incorporated. However, no scoring protocol could be obtained and it appears that this particular version of the SF-12 has not been used in previous research. Since correspondence with the research department at Lifeblood (email correspondence with Koniaras, C. dated

16/5/2011) the ‘painxchange’ website and incorrect version of the SF-12 has been removed from the public domain.

A further limitation of the present study was the cross-sectional design that prevented drawing causal relationships between the variables examined and an inability to determine change in depression, anxiety, QoL, cognitive function and PA levels prior to, during and post-treatment. Therefore, an investigation of these variables within a prospective design is required to determine these relationships. The use of self-report instruments to measure PA levels and cognitive function also imposed limitations in the present study. Over-reporting is a widely recognised problem in self-report PA measures and unfortunately there is also a lack of valid and accurate PA measures available (Prince et al., 2008; Rzewnicki, Vanden Auweele, & De Bourdeaudhuij, 2003). For example, Grimm et al. (2012) found the IPAQ significantly overestimated time spent in almost all PA intensities. Further, more research is required to improve the validity of self-report measures of cognitive function, with the FACT-Cog version 3 still undergoing validation. Another limitation was the apparent confusion among participants in the present study in responding to the CogPCA subscale. A number of participants commented on difficulties answering the CogPCA subscale with confusion around the switch to positive wording of questions and these items being unrelated to the 5-point Likert scale responses. Four participants changed the response scale with a score of zero meaning “always” as opposed to “never”. Fourteen participants were excluded due to inconsistent responses on the CogPCA subscale in comparison to other items on the FACT-Cog, suggesting the wording of the CogPCA subscale was misunderstood.

A final limitation, given the 59% response rate achieved in the present study, is that non-responders may have differed significantly from responders on important

study variables, such as demographic factors, psychological wellbeing and QoL. However, due to privacy issues and an inability to access medical records of non-responders, it was not possible to determine demographic or other differences between participants and non-participants. Consequently, there may be some unknown sample-related bias in the results.

11.6. Strengths of the Research

The large sample size was a strength of the present study ($n = 377$), increasing power, allowing generalisability of findings and enabling the use of multivariate statistical analysis (Tabachnick & Fidell, 2007). A further strength is that, participants were recruited from three different treatment centres, allowing comparison of QoL outcomes across treatment locations. Compared to the large body of research in which the physical symptoms of patients were clinically assessed, the self-report format of the present study enabled patients to document their perception of the impact of treatment on QoL and psychosocial wellbeing.

A further strength of the present study was the range of outcome variables examined. As highlighted in Chapter 6, only one prior study has included depression (Culos-Reed, et al., 2010) and one cognitive function (Galvão, et al., 2010) to evaluate the impact of PA in patients with PCa receiving ADT. Although there have been numerous studies in which a relationship between ADT administration in men with PCa and cognitive dysfunction has been documented (Cherrier, et al., 2009; H. J. Green, et al., 2002; Jenkins, et al., 2005; Jim, et al., 2010), only one previous study has inadvertently assessed the utility of PA as an intervention to improve cognitive function in this patient group (Galvão, et al., 2010). The present study appears to be the first to include a specific measure of cognitive function and identify a positive

relationship between PA and cognition in men receiving ADT for PCa.

Consequently, support for PA as a supplementary behavioural intervention to improve cognitive function in this population is provided. No previous studies have investigated anxiety in this patient group and measurement of QoL appears to have focused primarily on physical symptoms and function rather than emotional wellbeing. Therefore the results of the current study have contributed new information to the existing literature. Furthermore, examining the impact of meeting NPAGA on depression, anxiety, QoL and cognitive function in this population is unique and provides important information about the frequency, intensity and duration of PA required to detect improvement in these outcomes.

Another strength of the present study is that participants had undergone RT between 9 and 30 months prior to data collection. This inclusion criterion allowed comparison of three participant clusters: (1) those currently receiving ADT (RT + 2 ½ years ADT); (2) those who had never received ADT (RT only); and (3) those who had previously received ADT but long enough ago that the effect would mostly have worn off (RT + 6 months ADT). For men in the ‘high risk’ group who had received 2 ½ years of ADT, starting 6 months prior to RT, the period 9 to 30 months following RT provided a snapshot of these participants while on ADT treatment. Given the limitations imposed by cross-sectional study designs, this inclusion criterion provided the best alternative to longitudinal analysis within a study measuring outcomes at one specific point in time.

11.7. Directions for Future Research and Concluding Remarks

The problems identified with the measurement of PA in the present study highlight the need for further research using objective measures of PA. Clinical trials

combining objective assessments including direct observation, pedometers or accelerometers with self-report PA measures should, for example, enhance the accuracy of PA measurement (Vanhees, et al., 2005). In fact, the doctoral candidate intends to initiate a prospective clinical trial with the support of Abbott Pharmaceuticals to examine the impact of a PA program, designed in accordance with the NPAGA, in men receiving ADT for PCa. Using such a research design will determine whether meeting NPAGA is sufficient to yield improvements in QoL and psychosocial wellbeing in this patient group. However, validation studies are also required to determine the energy expenditure of PA in domestic and occupational settings (Armstrong, et al., 2000; Haskell, et al., 2007). The development of more structured and well-defined PA guidelines is necessary to provide both men with PCa and the general public with accurate information about the type and context of activity to provide a health benefit.

Future research implementing PA interventions in men receiving ADT for PCa should include cognitive function outcome measures. Ideally, such studies should include a battery of observational and self-report neuropsychological tests. It appears that one such study is currently underway with a recently published study protocol (Lee, Kilgour, & Lau, 2012).

Another direction for future research is to implement longitudinal study designs to examine change in depression, anxiety, QoL and cognitive function prior to, during and post-treatment and with long-term ADT use. Results of the present study indicate that these psychosocial outcomes may differ according to duration of ADT administration. Identifying key time points across the ADT continuum where patients are at an increased risk of poor QoL and psychosocial outcomes will inform health professionals about when patients are likely to need more support in their

treatment journey. Furthermore, it would establish when administration of a PA intervention would be most beneficial to the patient.

Despite the advances in diagnostic and treatment options, individuals diagnosed with PCa face the likelihood of living with a chronic illness. Both the disease and associated treatments have numerous physical side effects, having a consequent impact on QoL and psychosocial wellbeing. Therefore, the rationale for the current research was to add to the existing knowledge of QoL and psychological morbidity experienced by this population. The results from this study may be useful in the treatment decision-making process for patients and their treating team. Furthermore, the results may assist healthcare professionals in identifying individuals at greatest risk of poor QoL and psychosocial wellbeing during and post-treatment. Therefore physicians may be provided with the opportunity to individualise treatment discussions with patients and set their expectations around the likely impact of treatment on QoL and psychosocial wellbeing. Finally, the results support the utility of PA in rehabilitation programs for men undergoing ADT and suggest that 150 minutes of moderate-intensity PA weekly may improve QoL and psychological outcomes in this patient population. The findings provide a benchmark for the development of PA interventions targeting the improvement of psychosocial outcomes in men receiving ADT for PCa.

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List of Appendices

Appendix A	Ethics Approval
Appendix B	Study Questionnaire
Appendix C	Invitation Letter
Appendix D	Participant Information Statement
Appendix E	Consent Form
Appendix F	Reminder Letter
Appendix G	Phone Call Script for Participants with a High HADS Score

Appendix A: Ethics Approval



MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date: 23 August 2010

Project Number: CF10/2180 - 2010001238

Project Title: The protective role of physical activity against psychological distress in men undergoing Androgen Deprivation Therapy (ADT) for prostate cancer

Chief Investigator: Dr Sue Burney

Approved: From: 23 August 2010 to 23 August 2015

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research.
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash University letterhead and the Monash University complaints clause must contain your project number.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.



Professor Ben Canny
Chair, MUHREC

Cc: Ms Jane Fletcher; Assoc Prof Jeremy Millar; Assoc Prof Mark Frydenberg; Ms Robin Smith; Ms Catherine Walsh; Ms Kelly Chipperfield

Postal – Monash University, Vic 3800, Australia
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ABN 12 377 614 012 CRICOS Provider #00008C



ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 87/10

Project Title: The protective role of physical activity against psychological distress in men undergoing Androgen Deprivation Therapy (ADT) for prostate cancer

Principal Researcher: Dr Sue Burney

Project proposal: 87/10

Participant Information Statement version 3 dated: 10-May-2010

Consent Form version 3 dated: 10-May-2010

*was considered by the Ethics Committee on **29-Apr-2010** and **APPROVED** on **17-May-2010***

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project (*forms to be provided*);

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

SIGNED

Chair, _____ (or delegate)

Please quote Project No and Title in all correspondence

**R. FREW
SECRETARY
ETHICS COMMITTEE**



TheAlfred

Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

**Project 87/10 The protective role of physical activity against
psychological distress in men undergoing Androgen Deprivation Therapy
(ADT) for prostate cancer**

Principal Researcher: **Dr Sue Burney**

**Amendment: Letter of clarification to men who were not treated with
androgen deprivation therapy**

have been approved in accordance with your amendment application dated
28-Oct-2010 on the understanding that you observe the National Statement on
Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this
particular research project are made aware of what has actually been approved
and any caveats specified in correspondence with the Ethics Committee. Any
further change to the application which is likely to have a significant impact on
the ethical considerations of this project will require approval from the Ethics
Committee.



Chair, Ethics Committee (or delegate)

Date: 28-Oct-2010

R. FREW

SECRETARY

ETHICS COMMITTEE

*All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with
the National Statement on Ethical Conduct in Human Research (2007).*

*The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in
accordance with the National Statement on Ethical Conduct in Human Research (2007).*



**Cabrini
Institute**

Education
and Research

21 May 2010

Dr Sue Burney
Psycho-oncology Department
Cabrini Institute
183 Wattleree Road
MALVERN VIC 3144

Dear Sue

03-12-04-10

The protective role of physical activity against psychological distress in men undergoing Androgen Deprivation Therapy (ADT) for prostate cancer.

Thank you for addressing and submitting the minor amendments as requested by the Cabrini Human Research Ethics Committee at its meeting on 12 April 2010.

The study is now approved and approval covers protocol version 1 of 25 March 2010; patient information and consent form version 3 of 10 May 2010; study questionnaire version 1 of 25 March 2010; template cover letter version 1 of 25 March 2010; template reminder letter version 1 of 25 March 2010; phone call script version 1 of 25 March 2010; and the evaluation of research protocol version 1 of 25 March 2010.

If the study does not commence before the anniversary of approval, approval will lapse. Approval is ongoing for the life of the project, subject to satisfactory compliance and reporting.

In accordance with the NHMRC's *National Statement on Ethical Conduct in Human Research* of March 2007, section 5.5 on monitoring, you are obliged to:

- provide the CHREC with annual reports on the anniversary of this approval;
- provide the CHREC with a final report on study completion,
- be available for audits/site visits/interviews as requested.

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CABRINI HEALTH
ABN 33 370 684 005

A Facility of the
Missionary Sisters of the
Sacred Heart of Jesus

In addition, you are obliged to inform the CHREC of:

- any change to the protocol, participant information or consent form;
- any adverse events that occur during the process of this trial;
- any changes to the research team;
- study completion;
- any change in the financial arrangements regarding the study.

We attach a list of CHREC members present when the project was approved.

We wish you well with your project.

Yours sincerely



Anne Spence
Manager
Cabrini Human Research Ethics Committee



Human Research Ethics Committee Certificate of Approval

This is to certify that

Project No: 2010-09

Project Title: The protective role of physical activity against psychological distress in men undergoing Androgen Deprivation Therapy (ADT) for prostate cancer

Principal Researcher: Dr Sue Burney

has been given approval by the Human Research Ethics Committee from:

Approval date: 28 September 2010 **Expiry date:** 30 December 2012

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval. A copy of the approved ethics application and supporting documents must be kept on your files for audit purposes.

The Principal Researcher is required to notify the Human Research Ethics Committee in relation to the following.

- Any significant changes to the project and the reason for that change, including an indication of ethical implications (Amendment Form on LRH Research website)
- Adverse Event Reports regarding participants;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Commencement date of the project (form on LRH Research website); and
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report every 12 months for the duration of the project (form are available on the LRH Research website);
- A Request for Extension of the project prior to the expiry date, if applicable; and,
- A detailed Final Report at the conclusion of the project (form are available on the LRH Research website).

The Human Research Ethics Committee may conduct an audit at any time.

All research subject to the Latrobe Regional Hospital Human Research Ethics Committee review must be conducted in accordance with the *National Statement on Ethical Conduct in Human Research (2007)*.

The Latrobe Regional Hospital Human Research Ethics Committee is constituted in accordance with the *National Statement on Ethical Conduct in Human Research (2007)*.

SPECIAL CONDITIONS

Nil



Chief Executive

Please quote Project No and Title in all correspondence

Appendix B: Study Questionnaire

We'd like to ask you a few questions about you...

1. What is your age? _____(in years)
2. Which of the following best describes you? (Please tick)
 - ☐ Australian
 - ☐ New Zealander
 - ☐ English / U.K.
 - ☐ Asian
 - ☐ Italian
 - ☐ Russian
 - ☐ Greek
 - ☐ Other (Please state) _____
3. Are you? (Please tick)
 - ☐ Married / defacto
 - ☐ Single
 - ☐ Widowed
 - ☐ Divorced / separated
 - ☐ In a relationship but not living together
 - ☐ Other (Please state) _____
4. What is the highest education level you have completed? (Please tick)
 - ☐ Primary school
 - ☐ Secondary School
 - ☐ Tertiary
 - ☐ Other (Please state) _____
5. Were you working before you were diagnosed with cancer? (Please tick)
 - ☐ Yes, full time
 - ☐ No, I perform home duties
 - ☐ Yes, part time
 - ☐ No, I am unable to work due to illness or injury
 - ☐ No, I am looking for work
 - ☐ No, I have retired
 - ☐ Other (Please state) _____
6. Are you currently working? (Please tick)
 - ☐ Yes, full time
 - ☐ No, I perform home duties
 - ☐ Yes, part time
 - ☐ No, I am unable to work due to illness or injury
 - ☐ No, I am looking for work
 - ☐ No, I have retired
 - ☐ Other (Please state) _____

7. Have you ever had any of the following medical conditions?

	(Please tick one box for each item)	Yes	No
i.	Diabetes	<input type="checkbox"/>	<input type="checkbox"/>
ii.	Heart attack, chest pain	<input type="checkbox"/>	<input type="checkbox"/>
iii.	Stroke	<input type="checkbox"/>	<input type="checkbox"/>
iv.	Amputation	<input type="checkbox"/>	<input type="checkbox"/>
v.	Circulation problems in your legs or feet	<input type="checkbox"/>	<input type="checkbox"/>
vi.	Asthma, emphysema, breathing problems	<input type="checkbox"/>	<input type="checkbox"/>
vii.	Stomach ulcer, irritable bowel	<input type="checkbox"/>	<input type="checkbox"/>
viii.	Kidney disease	<input type="checkbox"/>	<input type="checkbox"/>
ix.	Major depression	<input type="checkbox"/>	<input type="checkbox"/>
x.	Seizures	<input type="checkbox"/>	<input type="checkbox"/>
xi.	Alcoholism or alcohol problems	<input type="checkbox"/>	<input type="checkbox"/>
xii.	Drug problems	<input type="checkbox"/>	<input type="checkbox"/>
xiii.	Current or past cigarette smoker	<input type="checkbox"/>	<input type="checkbox"/>

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐

Yes

☐

No



Skip to PART 2: TRANSPORTATION

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐

No vigorous job-related physical activity



Skip to question 4

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐

No moderate job-related physical activity ➡ ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐

No job-related walking ➡ ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**

_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐

No traveling in a motor vehicle ➔ **Skip to question 10**

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**

_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐

No bicycling from place to place ➔ **Skip to question 12**

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**

_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐

No walking from place to place



***Skip to PART 3:
HOUSEWORK, HOUSE
MAINTENANCE, AND CARING
FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**

_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐

No vigorous activity in garden or yard



Skip to question 16

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐

No moderate activity in garden or yard



Skip to question 18

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐

No moderate activity inside home



***Skip to PART 4:
RECREATION, SPORT AND
LEISURE-TIME PHYSICAL
ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**

_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐

No walking in leisure time → **Skip to question 22**

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**

_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐

No vigorous activity in leisure time → **Skip to question 24**

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐

No moderate activity in leisure time



***Skip to PART 5:
TIME SPENT
SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**

_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**

_____ **minutes per day**

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Clinicians are aware that emotions play an important role in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **tick the box** which comes closest to how you have been feeling in the **last 7 days**.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

1. I feel tense or "wound up"

- ☐ Most of the time
- ☐ A lot of the time
- ☐ From time to time, occasionally
- ☐ Not at all

2. I still enjoy the things I used to enjoy

- ☐ Definitely as much
- ☐ Not quite as much
- ☐ Only a little
- ☐ Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen

- ☐ Very definitely and quite badly
- ☐ Yes, but not too badly
- ☐ A little, but it doesn't worry me
- ☐ Not at all

4. I can laugh and see the funny side of things

- ☐ As much as I always could
- ☐ Not quite so much now
- ☐ Definitely not so much now
- ☐ Not at all

5. Worrying thoughts go through my mind

- ☐ A great deal of the time
- ☐ A lot of the time
- ☐ Not too often
- ☐ Very little

6. I feel cheerful

- ☐ Never
- ☐ Not often
- ☐ Sometimes
- ☐ Most of the time

7. I can sit at ease and feel relaxed

- ☐ Definitely
- ☐ Usually
- ☐ Not often
- ☐ Not at all

8. I feel as if I am slowed down

- ☐ Nearly all the time
- ☐ Very often
- ☐ Sometimes
- ☐ Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach

- ☐ Not at all
- ☐ Occasionally
- ☐ Quite often
- ☐ Very often

10. I have lost interest in my appearance

- ☐ Definitely
- ☐ I don't take as much care as I should
- ☐ I may not take quite as much care
- ☐ I take just as much care as ever

11. I feel restless as if I have to be on the move

- ☐ Very much indeed
- ☐ Quite a lot
- ☐ Not very much
- ☐ Not at all

12. I look forward with enjoyment to things

- ☐ As much as I ever did
- ☐ Rather less than I used to
- ☐ Definitely less than I used to
- ☐ Hardly at all

13. I get sudden feelings of panic

- ☐ Very often indeed
- ☐ Quite often
- ☐ Not very often
- ☐ Not at all

14. I can enjoy a good book or radio or television program

- ☐ Often
- ☐ Sometimes
- ☐ Not often
- ☐ Very seldom

SF-12 HEALTH SURVEY

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. In general would you say your health is:

☐ Excellent

☐ Very good

☐ Good

☐ Fair

☐ Poor

The following items are about activities you might do during a typical day.

Does your health now limit you in these activities? If so, how much?

2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf

☐ Yes, limited a lot

☐ Yes, limited a little

☐ No, not limited at all

3. Climbing several flights of stairs

☐ Yes, limited a lot

☐ Yes, limited a little

☐ No, not limited at all

During the past month, have you had any of the following problems with your work or other regular activities as a result of your physical health?

4. Accomplished less than you would like

☐ Yes

☐ No

5. Were limited in the kind of work or other activities

☐ Yes

☐ No

During the past month, have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

6. Accomplished less than you would like

☐ Yes

☐ No

7. Didn't do work or other activities as carefully as usual

☐ Yes

☐ No

8. During the past month, how much did pain interfere with your normal work (including both outside the home and housework)?

☐ Not at all

☐ A little bit

☐ Moderately

☐ Quite a bit

☐ Extremely

These questions are about how you feel and how things have been with you during the past month. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past month:

9. Have you felt calm and peaceful?

☐ All of the time

☐ Most of the time

☐ A good bit of the time

☐ A little of the time

☐ None of the time

10. Did you have a lot of energy?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ A little of the time
- ☐ None of the time

11. Have you felt downhearted and blue?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ A little of the time
- ☐ None of the time

12. During the **past month**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

FACT- P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

ADDITIONAL CONCERNS

	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I am losing weight	0	1	2	3	4
2. I have a good appetite	0	1	2	3	4
3. I have aches and pains that bother me	0	1	2	3	4
4. I have certain parts of my body where I experience pain	0	1	2	3	4
5. My pain keeps me from doing things I want to do	0	1	2	3	4
6. I am satisfied with my present comfort level	0	1	2	3	4
7. I am able to feel like a man	0	1	2	3	4
8. I have trouble moving my bowels	0	1	2	3	4
9. I have difficulty urinating	0	1	2	3	4
10. I urinate more frequently than usual	0	1	2	3	4
11. My problems with urinating limit my activities	0	1	2	3	4
12. I am able to have and maintain an erection	0	1	2	3	4

Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.

13. I am satisfied with my sex life	0	1	2	3	4
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FACT- Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

PERCEIVED COGNITIVE IMPAIRMENTS

	Never	About Once a Week	Two to three times a week	Nearly everyday	Several times a day
1. I have had trouble forming thoughts	0	1	2	3	4
2. My thinking has been slow	0	1	2	3	4
3. I have had trouble concentrating	0	1	2	3	4
4. I have had trouble finding my way to a familiar place	0	1	2	3	4
5. I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
6. I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
7. I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
8. I have had trouble finding the right word(s) to express myself	0	1	2	3	4
9. I have used the wrong word when I referred to an object	0	1	2	3	4
10. I have had trouble saying what I mean in conversations with others	0	1	2	3	4
11. I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
12. I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
13. I have forgotten names of people soon after being introduced	0	1	2	3	4

14. My reactions in everyday situations have been slow	0	1	2	3	4
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	Never	About Once a Week	Two to three times a week	Nearly everyday	Several times a day
15. I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
16. My thinking has been slower than usual	0	1	2	3	4
17. I have had to work harder than usual to express myself clearly	0	1	2	3	4
18. I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
19. I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
20. I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

COMMENTS FROM OTHERS

	Never	About Once a Week	Two to three times a week	Nearly everyday	Several times a day
21. Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
22. Other people have told me I seemed to have trouble speaking clearly	0	1	2	3	4
23. Other people have told me I seemed to have trouble thinking clearly	0	1	2	3	4

24. Other people have told me I seemed confused	0	1	2	3	4
---	---	---	---	---	---

Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

PERCEIVED COGNITIVE ABILITIES

	Never	About Once a Week	Two to three times a week	Nearly everyday	Several times a day
25. I have been able to concentrate	0	1	2	3	4
26. I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
27. I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
28. I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
29. I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
30. My mind is as sharp as it has always been	0	1	2	3	4
31. My memory is as good as it has always been	0	1	2	3	4
32. I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
33. I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

IMPACT ON QUALITY OF LIFE

	Not at all	A little bit	Some-what	Quite a bit	Very much
34. I have been upset about these problems	0	1	2	3	4
35. These problems have interfered with my ability to work	0	1	2	3	4
36. These problems have interfered with the quality of my life	0	1	2	3	4
37. These problems have interfered with my ability to do things I enjoy	0	1	2	3	4

If you have any further questions please contact Dr Sue Burney (Principal Investigator)

or

Thank you for your participation in this important research

Appendix C: Invitation Letter

William Buckland Radiation Oncology
www.wbrc.org.au



TheAlfred

«AddressBlock»

55 Commercial Road
Melbourne VIC 3004

Mailing Address:
PO Box 315
PRAHRAN VIC 3181
Telephone 03 9076 2000
www.alfred.org.au

«GreetingLine»

RE: Prostate cancer and exercise research

I hope this letter finds you well. I am writing to invite you to take part in a research project for men treated for prostate cancer, looking at the effect of exercise.

We are collaborating with the study conducted through Monash University. This study involves surveying people with prostate cancer who had – or are having – treatment organised through The Alfred, Cabrini or Latrobe Regional Hospital. The research looks at physical activity levels, quality of life and psycho-social wellbeing. We hope the study will provide a greater understanding of the issues faced by men undergoing treatment for prostate cancer and whether physical activity improves psycho-social outcomes.

There is some information enclosed with all the details. The package contains: a Participant Information Statement (for you to keep), Consent Form (for you to return) and the study questionnaire (for you to complete and return if you choose to participate). There is also a prepaid return envelope to return the information to the Monash University Researchers. If you do not wish to participate in the study please return the Consent Form provided indicating that you do not wish to participate by ticking the appropriate box. This will ensure that you receive no further contact from the research team.

I realise that it can be difficult to find spare time with the demands of other life commitments, but we would really appreciate you taking the time to complete the questionnaire, since it will help us help others by giving us a better understanding of the effects of prostate cancer treatment.

If you would like to discuss any specific concerns regarding this study with a member of staff at the William Buckland Radiotherapy Centre (WBRC) or if you require any clarification or additional information, please contact me as per the details below.

Thanks for your help, and kind regards,



A/Prof Jeremy Millar MB ChB FRANZCR FACHPMed
Director of Radiation Oncology
Alfred Health, William Buckland Radiotherapy Centre (WBRC)
Phone: (03) 9076 2167
Fax: (03) 9076 2916



The Alfred
Part of Alfred Health
ABN 27318956319

Appendix D: Participant Information Statement



Participant Information Statement

For Men with Prostate Cancer Receiving Treatment at The Alfred, Cabrini or Latrobe Regional Hospital

Full Project Title: *The protective role of physical activity against psychological distress in men undergoing treatment for prostate cancer.*

This information sheet is for you to keep

Where is this research being conducted and by whom?

This research is being conducted by:

- Dr Sue Burney, Chief Investigator, Head Cabrini Monash Psycho-oncology Research Unit
- A/Prof Jeremy Millar, Director of Radiation Oncology, William Buckland Radiotherapy Centre (WBRC), Alfred Health
- Ms Jane Fletcher, Cabrini Monash Psycho-oncology Research Unit
- Ms Kelly Chipperfield, Student Investigator, Monash University
- A/Prof Mark Frydenberg, Chairman, Department of Urology, Monash Medical Centre and Cabrini Health
- Ms Robin Smith, William Buckland Radiotherapy Centre (WBRC)
- Ms Cath Walsh, Physiotherapist, Alfred Health

1. Introduction

You are invited to take part in this research project. This is because you are currently undergoing or have completed treatment for prostate cancer at Cabrini, The Alfred or Latrobe Regional Hospital. The aim of the research project is to determine the relationship between regular physical activity, quality of life and psychosocial wellbeing and if physical activity may help to protect against the negative side effects of treatment among people with prostate cancer. This Participant Information Sheet tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend, healthcare worker or Dr Sue Burney, Principal Investigator.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible medical care whether you take part or not.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to participate in the research processes that are described;
- Consent to the use of your personal and health information as described.

2. What is the purpose of this research project?

Prostate cancer is an age-related cancer commonly occurring in men aged over 65 years and consequently, the prevalence is predicted to rise due to the ageing population. A common form of treatment for prostate cancer is hormonal therapy, also known as Androgen Deprivation Therapy (ADT). Although it is an effective form of treatment, ADT can lead to a range of other health complications such as osteoporosis, obesity, diabetes and cardiovascular disease. There has also been increasing recognition of negative side effects such as depression, anxiety, fatigue and cognitive difficulties which can have a significant impact on quality of life and wellbeing among people with prostate cancer receiving ADT treatment.

A number of studies have demonstrated the beneficial effects of physical activity on quality of life and wellbeing in people with prostate cancer undergoing ADT treatment. It has been proposed that physical activity may be one of the few ways in which to enhance quality of life and wellbeing among people with prostate cancer and therefore, it may be a useful addition to current coping and rehabilitation programs. The purpose of this research project is to determine the relationship between regular physical activity, quality of life and wellbeing and examine how physical activity may protect against the negative side effects of ADT among people with prostate cancer.

One of the other aims of this study is to compare the effects of different forms of treatment for prostate cancer on quality of life. Therefore even if you have not received ADT treatment you are still eligible to participate.

Over 600 people with prostate cancer receiving treatment from Cabrini, The Alfred or Latrobe Regional Hospitals will be asked to participate in the study. The results of this research will be used by the researcher Ms Kelly Chipperfield to obtain a Doctor of Clinical Psychology degree.

3. What does participation in this research project involve?

As part of your participation in this research, you will be asked to complete a questionnaire package consisting of several short surveys, which is expected to take you approximately 60 minutes to complete. The short surveys included are as follows:

1. Demographics Questionnaire – this component of the questionnaire consists of seven items and requires you to provide us with details such as age,

ethnicity, marital status, level of education, employment status and medical conditions.

2. The International Physical Activity Questionnaire (IPAQ) – The IPAQ consists of 31 items which ask you about the frequency, intensity and duration of your physical activity participation over the last 7 days in four different domains.
3. The Hospital Anxiety and Depression Scale (HADS) – The HADS consists of 14 items which ask you about your emotional state over the last 7 days.
4. The Short-Form 36-Item Health Survey (SF-36) – The SF-36 consists of 36 items which ask you about your general health and wellbeing over the past month.
5. The Functional Assessment of Cancer Therapy-Prostate (FACT-P) – The FACT-P consists of 13 items which asks about symptoms specific to patients with prostate cancer.
6. The Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) – The FACT-Cog consists of 50 items which asks about any cognitive complaints experienced by patients with cancer.

You will not be paid for your participation in this research. If you wish to participate, you will need to complete the enclosed Consent Form and return it along with your completed questionnaire in the reply-paid envelope provided. As part of participation in this research, the research team will need to access your medical records to obtain personal and health information relevant to the project. Returning a signed Consent Form and completed questionnaire will be viewed as evidence of your consent for the research team to access your medical records. Only members of the research team (listed above) will have access to your medical records.

4. What are the possible benefits?

There will be no clear benefit to you from your participation in this research. However, the information you provide will be used to improve support services offered to people with cancer to improve quality of life and psycho-social wellbeing.

5. What are the possible risks?

We do not expect that you will experience any undue harm or distress as a result of completing the questionnaire. However, if you become upset or distressed as a result of your participation in the research, the research team is able to arrange for counselling or other appropriate support.

You may prefer to suspend or end your participation in the research if you become distressed. If you find it difficult to answer some of the questions or you feel confronted,

embarrassed or uncomfortable by participating in this project, ***you are free to withdraw from the research at any time.***

One of the surveys included in the questionnaire package, The Hospital Anxiety and Depression Scale (HADS), measures symptoms of depression and anxiety. Participants found to have elevated scores on the HADS will be phoned by the principal researcher and advised to contact their GP, medical specialist or one of the services listed below. However, please do not hesitate to contact your general practitioner, or one of the services listed below which offer free anonymous counselling services if you feel concerned or distressed at any point during or after your involvement in this study.

Lifeline 13 11 14 www.lifeline.org.au	Australia-wide 24-hour counselling
Cancer Council Helpline 13 11 20 www.cancervic.org.au	Monday – Friday 8:30am – 8pm
Beyondblue 1300 22 46 36 www.beyondblue.org.au	Australia-wide 24-hour counselling
Mensline Australia 1300 78 99 78 www.menslineaus.org.au	Australia-wide 24-hour counselling
Crisis Support Services 1300 659 467 www.crisissupport.org.au	Australia-wide 24-hour counselling

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage and you are under no obligation to answer any questions that you feel are too personal or intrusive. If after completing the questionnaire and returning it you decide that you would not like to have the information you have provided included in the research, you may contact the research team and request that your data be destroyed and excluded from the research.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine medical treatment or your relationship with those treating you. As this project is looking at the beneficial effects of physical activity among people with prostate cancer, you may have a desire to increase your activity level. It is recommended that you consult your medical practitioner before undertaking additional exercise.

7. What if I withdraw from this research project?

If you decide to withdraw, please notify a member of the research team before you withdraw. This will ensure that the research team is aware of your withdrawal and does

not inconvenience you with further contact. You will not experience any change in your medical care should you choose to withdraw from the study.

8. How will I be informed of the results of this research project?

It is anticipated that the results of the research will be available by 30th June 2012. A brief summary of the results will also be published on the Cabrini Monash Psycho-oncology Research Unit's website at:

www.cabrini.com.au/cabriniinstitute/academicdepartment_pscho-oncology_research_unit.asp.

If you would like notification of the results of this study, please notify me (my contact details are at the end of this document) or tick the appropriate box following the statement at the end of the Consent Form so the results can be automatically sent to you.

9. What will happen to information about me?

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law. Information about you may be obtained from your health records held at this, and other, health services for the purposes of this research. Your confidentiality will be protected in the following ways: Limiting access to data to research personnel, security procedures for data handling including password access to information and no identifiable information included on any publications or reports. The research data will be collated and analysed in a report to the participating hospitals and research findings may be published in edited journals, through conference presentations and media releases. Only group data will be reported or published from the questionnaire responses and you will not be identified in any of these. Storage of the data collected will adhere to Cabrini Health, Alfred Health and Monash University regulations. All of your data will be kept at Monash University in a locked filing cabinet for seven years after which time it will be destroyed.

10. How can I access my information?

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

11. Is this research project approved?

The ethical aspects of this research project have been approved by the Cabrini Human Research Ethics Committee, The Alfred Human Research Ethics Committee, the Latrobe Regional Hospital Human Research Ethics Committee and the Monash University Standing Committee on Ethics in Research Involving Humans.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

CONTACT

If you would like to find out more about this research, please contact:

- Dr Sue Burney, Chief Investigator, on telephone [REDACTED] or email [REDACTED]

You may call/email at any time and can leave a message with your contact details so that we can contact you to respond to your enquiry.

If you have any other concerns regarding any aspect of this project, please contact:	If you have a complaint concerning the manner in which this research (Project # 87/10) is being conducted, please contact:
<p>Dr Sue Burney Phone Number: [REDACTED] or [REDACTED] Email: [REDACTED]</p>	<p>Rowan Frew (Ethics Manager) The Alfred Research and Ethics Unit Ethics Office - Second Floor, East Block Telephone: 03 9076 3848 Facsimile: 03 9076 8841 Email: r.frew@alfred.org.au</p> <p>Or</p> <p>Anne Spence (Ethics Manager) Cabrini Human Research Ethics Committee 183 Wattletree Road, Malvern VIC 3144 Telephone: 03 9508 1376 Facsimile: 03 9508 1368 Email: hrec@cabrini.com.au</p> <p>Or</p> <p>Patient Liaison Officer Latrobe Regional Hospital Telephone: (03) 5173 8003 Email: inquiry@lrh.com.au</p>

Thank you,

Dr Sue Burney
Principal Research Investigator

Appendix E: Consent Form



CONSENT FORM

Please return in the pre-paid envelope provided

PROJECT TITLE: *The protective role of physical activity against psychological distress in men undergoing treatment for prostate cancer.*

▪ **Research Investigators:**

- | | | |
|--------------------|-------------------------|--------------------------|
| ▪ Dr Sue Burney | ▪ A/Prof Jeremy Millar | ▪ A/Prof Mark Frydenberg |
| ▪ Ms Jane Fletcher | ▪ Ms Kelly Chipperfield | ▪ Ms Robin Smith |
| | | ▪ Ms Catherine Walsh |

If you wish to take part in this research project please read and sign the bottom of this form and return it to the in the reply paid envelope.

If you do not wish to participate in this project, please read and sign the bottom of this form and return it in the reply paid envelope.

I have read the *Participant Information Statement* and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Monash University concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

In agreeing to take part in this research I acknowledge that:

- (a) My participation is voluntary and I can choose to participate in part, or all, of the project.
- (b) I can withdraw at any stage of the project without prejudice.
- (c) Having read the *Participant Information Statement*, I agree to the general methods and demands of the project.
- (d) All information I provide is private and confidential.
- (e) Any data that the researchers extract from my completed questionnaire for use in reports or published findings will not, under any circumstances, contain names or identifying information.
- (f) Data from my questionnaire will be kept in secure storage and will only be accessible to the research team. Data will be destroyed after a 7-year period.

I have read both the *Participant Information Statement* and *Consent Form* and I choose to:

☐ PARTICIPATE

☐ NOT PARTICIPATE

Participant's name (printed)

Signature

Date

I wish to receive written notification of the results of this study

☐
Yes

☐
No

Appendix F: Reminder Letter

William Buckland Radiation Oncology
www.wbrc.org.au



TheAlfred

«AddressBlock»

55 Commercial Road
Melbourne VIC 3004

Mailing Address:
PO Box 315
PRAHRAN VIC 3181
Telephone 03 9076 2000
www.alfred.org.au

«GreetingLine»

RE: Prostate cancer and exercise research

A few weeks ago you may recall receiving a questionnaire package inviting you to participate in a research project for men treated for prostate cancer, looking at the effect of exercise. There is still time to respond; after this we will not contact you again regarding this research. If you have time, we would appreciate a response by the 31st August 2011.

This study involves surveying people with prostate cancer who had – or are having – treatment organised through The Alfred, Cabrini or Latrobe Regional Hospital. The research looks at physical activity levels, quality of life and psycho-social wellbeing. We hope the study will provide a greater understanding of the issues faced by people with prostate cancer undergoing treatment and whether physical activity improves psycho-social outcomes.

We realise that it can be difficult to find spare time with the demands of other life commitments, but we would really appreciate you taking the time to complete the questionnaire, since it will help us help others by giving us a better understanding of the effects of prostate cancer treatment.

We apologise for bothering you if you have returned the questionnaire in the interim. If you have discarded it and now would like to reconsider, please contact Ms Kelly Chipperfield (0408 920 618) as she is happy to send you another. If you would like to discuss any specific concerns regarding this study or if you require any clarification/additional information, please contact A/Prof Jeremy Millar as per the details below.

Thank you for your help and kind regards,



A/Prof Jeremy Millar MB ChB FRANZCR FACHPMed
Director of Radiation Oncology
Alfred Health, William Buckland Radiotherapy Centre (WBRC)
Phone: (03) 9076 2167
Fax: (03) 9076 2916



«Participant»

The Alfred
Part of Alfred Health
ABN 27318956319

Appendix G: Phone Call Script for Participants with a High HADS Score

Hello, I am Dr Sue Burney, Principal Investigator for the project entitled “The protective role of physical activity against psychological distress in men undergoing Androgen Deprivation Therapy (ADT) for prostate cancer” at The Alfred/Cabrini/Latrobe Regional Hospitals. If you recall you completed a questionnaire for this project some weeks ago. In accordance with my responsibility as Principal Investigator, I need to inform you that your score on one of the measures you completed in that questionnaire indicates that you may be suffering from depression and/or anxiety.

As I am concerned about your well-being, I encourage you to discuss this result with your GP or your medical oncologist and ask him or her if you would benefit from seeing a psychologist who has experience dealing with cancer patients. Another alternative is contact one of the free support services listed on the Participant Information Sheet. Do you still have that sheet? If not, I will go through these services with you now.

Lifeline 13 11 14 www.lifeline.org.au	Australia-wide 24-hour support
Crisis Support Services 1300 659 467 www.crisissupport.org.au	Australia-wide 24-hour support
Cancer Council Helpline 13 11 20 www.cancervic.org.au service	Monday – Friday 8:30am – 6pm Cancer information and support

Of course, it is entirely your choice as to whether you would like to take up any of the options I have told you about today as you are under no obligation to do so. However, if you decide to use the services of a psychologist in private practice, I encourage you to discuss this with your GP, as you may be eligible to access these services under the Better Access to Mental Health Care initiative, which provides Medicare benefits for some services. You need to know that you must be referred by your GP and not your treating specialist to receive the benefits from this scheme. Once your GP has assessed your current state of health, and agrees you would receive benefit from a consultation with a psychologist he/she will be able to refer you to a registered practitioner who is eligible to receive the Medicare rebate.

I am happy to answer any of your questions now if you have any.

Thank you once again for your involvement in this important project. Good bye.