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## **Improving Physical and Mental Health in Patients with Prostate Cancer Undergoing Androgen Deprivation Therapy: Strategies to Promote and Improve Physical Activity Quality and Quantity**

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## **Abstract**

**Objective:** Prostate cancer continues to be one of the highest incident cancers among men. Reducing serum testosterone with androgen deprivation therapy (ADT) is a common effective treatment. While well demonstrated for cancer suppression, there are numerous adverse effects caused by ADT that can contribute to short- and long-term prognosis. Increased levels of physical activity (PA) during treatment may reduce these side effects, however uptake of PA is low. The purpose of this review is to identify and evaluate current literature on strategies to promote and increase the levels of PA in patients with prostate cancer undergoing ADT.

**Data sources:** Electronic databases including CINAHL, MEDLINE, PsychINFO, Scopus, and grey literature were searched using Google scholar up until April 2020.

**Conclusion:** At present the most appropriate modes and dosages of PA for specific ADT toxicities is not known. It is established that some PA in the form of exercise, whether aerobic or resistance, is better than being sedentary for improvements in physical health, but beyond this prescription specifics have not been established. Further research is required to understand the impact of PA on the mental and physical health of prostate cancer men undergoing ADT.

**Implications for Nursing Practice:** Being physically active and avoiding sedentary behaviour is important for men with prostate cancer undergoing ADT, especially the implementation of strength training. Physical activity in the form of exercise can assist in reducing the adverse physical side effects in the short- and long-term, with limited understanding of the effects on mental health. Physical activity improves mental health outcomes across populations, which may also translate to men with prostate cancer, although further research is required. An important strategy to improve PA within the prostate cancer population is to provide an early referral to an exercise professional such as an Accredited Exercise Physiologist/Clinical Exercise Physiologist or Physical Therapist/Physiotherapist and is supported by research as best practice for people affected by cancer undergoing active treatment.

**Key words:** Prostate cancer, mental health, physical activity, exercise, strength training

## Introduction

Worldwide, prostate cancer is the second leading malignancy (after lung cancer) in men with 1,276,106 new cases diagnosed in 2018 [1], and a higher prevalence seen in developed countries [2]. Increased risk of prostate cancer and mortality is linked with increasing age, with the average age at diagnosis of 66 years [1]. There is currently no evidence of how to prevent prostate cancer, though some research suggests that it is possible to lower the risk by changing behavioural factors such as increasing levels of physical activity (PA) and in particular avoid being sedentary [3]. Although epidemiological studies have shown that increased levels of PA may prevent prostate cancer and improve survival after diagnosis [4], low levels of PA and sedentary behaviour is widespread across the globe, which includes men with prostate cancer [5-7]. Many gaps remain in the knowledge to better serve cancer survivors, as well as best practice for exercise and health care professionals [8] to improve the clinical outcomes for patients diagnosed with prostate cancer.

The sex hormone, testosterone, is essential for prostate cancer cell growth in hormone responsive cancers. The aim of androgen deprivation therapy (ADT) treatment is to reduce systemic testosterone levels or prevent testosterone binding to the androgen receptor. Resistance based exercise has not been shown to increase levels of testosterone in patients undergoing ADT [9]. Chemical castration slows the progression of prostate cancer and can prolong life and palliate symptoms [10]. Castration can be achieved pharmacologically using luteinizing-hormone-releasing hormone (LHRH) agonists, LHRH antagonists, anti-androgens or oestrogens, or surgically with bilateral subcapsular orchidectomy, see **Table 1**. Common side-effects for ADT include: psychological effects: mood disturbance, cognitive impairment, difficulties with self-image and masculinities; physical effects such as hot flushes, osteoporosis, fatigue, sexual dysfunction, and changes in muscle mass; and adiposity.

Aerobic and resistance exercise may impact cancer signalling pathways, potentially reducing tumour growth [11], muscle wasting and the physical side effects of ADT [12 13]. The maintenance of skeletal muscle is essential to ensure function and movement, strength and breathing, glucose and insulin management potentially via hormonal balance mechanisms [14] as well as various anti-tumour cytokine and immunological mechanisms [15 16]. Sarcopenia (muscle wasting) is orchestrated by a network of specific signalling pathways [17] that cause an imbalance in muscle protein synthesis and degradation [18]. The loss of lean body mass seen in men receiving ADT is often associated with increased fat mass, which is referred to as sarcopenic obesity [19]. An appropriate combination of aerobic and resistance exercise could regulate this signalling pathway, causing a slowing of, or even reversing, muscle atrophy and potentially preventing or minimising fat

gain. Impacting this system by the early introduction of resistance exercise could most importantly minimise the loss of muscle function in patients with prostate cancer, particularly for older men on ADT who experience greater levels of muscle mass and function loss and more debilitating treatment related side effects. Although the evidence to support improvements in lean muscle mass is limited [20], the maintenance or slowing of cachexia and increased muscle performance could be enhanced by improving neural pathways and neuromuscular function with resistance based exercise [21 22] resulting in improvements in physical strength and quality of life.

The mechanisms of prostate carcinogenesis consist of both behavioural and environmental factors [23]. After years of controversial research studies [24 25], it has recently been established that sedentary behaviour, overweight or obesity (which are not always mutually inclusive) can increase risk of aggressive advanced prostate cancer [26 27]. Being overweight or obese may cause changes in several mechanisms including altered endocrine status, increased sympathetic nervous system activity, increased intra-abdominal pressure, increased inflammation and oxidative stress, all of which have been linked to benign hyperplasia prostate cancer [28-32]. Because prostate cancer treatment can also impact different mechanisms such as reduced testosterone and androgens, insulin resistance, unfavourable adipokine secretion caused by inflammation, being obese and the side effects of prostate cancer treatment can increase the risk of the development of higher-grade prostate cancer [33-35].

Androgen deprivation therapy increases the risk of metabolic diseases including cardiovascular, type 2 diabetes, hypertension and obesity impacting the physical and mental health of men with prostate cancer. Due to the hypogonadal state caused by ADT, men undergo physical and psychological side effects including atrophy of muscle and bone tissues decreasing physical and metabolic function [13], and psychological distress related to changes in masculinity [14]. Patients receiving ADT have an increased risk of depression [10], which is also linked to clinical and demographic factors such as older age, comorbidities and a concurrent history of depression [11]. Unfortunately, the older the patient the worse the increased loss of physical function and psychological distress, because of the already present age-related muscle and bone loss [13].

Emerging evidence shows that PA improves physical functioning for men previously treated with ADT [36]. Physical activity in the form of aerobic and progressive resistance exercise has been shown to improve cardiorespiratory fitness, strength and slow muscle wasting [11] and it has been reported that highly targeted exercise can slow bone loss [12]. The effect of increased levels of both forms of PA is associated with additional positive physiological, functional and psychological adaptations across a number of healthy, ageing and chronic diseased populations [13]. These

benefits are likely to be translated to patients with prostate cancer as stronger evidence develops [14 15].

Aerobic and progressive resistance exercise have recently been endorsed by the American College of Sports Medicine (ACSM), Exercise and Sports Science Australia (ESSA) and the Clinical Oncology Society of Australia (COSA) for patients with all cancers [37-39], to reduce or alleviate adverse side effects of cancer treatments, enhance treatment effectiveness, reduce risk of cancer specific mortality and recurrence as well as ameliorate other chronic diseases exacerbated by cancer and its treatment. They recommend both aerobic (150 minutes per week) and resistance based (two or more sessions per week) exercise as a generic dosage of exercise in relatively healthy individuals. However, currently there are limited randomised controlled trials providing strong indication of the optimal mode and intensity required to improve the physical and mental health of men with prostate cancer. General guidelines are based on research that has found that increased levels of PA can reduce rates of cancer recurrence and improve survival, but the specific effects of different types of PA modalities (such as aerobic and resistance exercise) on physical and mental health in prostate cancer are currently not well understood [39-41]. Some evidence reports that that both resistance and aerobic exercise may illicit the greatest effect and that resistance training improves strength and maintains muscle mass, despite the catabolic drive of ADT treatment for prostate cancer [42 43]. Exercise treatment or strategies, including the optimal mode and dosage of PA, how to get patients to commence and adhere to an exercise program to improve levels of PA and how to pragmatically implement these programs into the health system are not known, but are urgently needed to establish optimal treatment pathways for men with prostate cancer undergoing ADT. Given the importance and potential of PA and exercise to improve outcomes for men on ADT for prostate cancer we will discuss the strategies to promote and improve PA levels and to inform clinical service delivery to help improve physical and mental health outcomes in men affected by prostate cancer receiving ADT. We will do this by discussing clinical management, barriers to PA for patients and health professionals, general cancer evidence-based PA guidelines currently available and potential PA strategies to improve mental health outcomes for men with prostate cancer undergoing ADT.

**Table 1.** Androgen deprivation therapy (ADT) for prostate cancer [44]

<p><b>Surgical castration using bilateral orchiectomy</b></p>	<ul style="list-style-type: none"> <li>• Performed under local anaesthesia</li> <li>• less than 12 hours to achieve decline in testosterone level and induce a hypogonadal status</li> <li>• does not allow for intermittent treatment.</li> <li>• No testosterone flare</li> </ul>
<p><b>Oestrogens</b></p>	<ul style="list-style-type: none"> <li>• Mechanisms of action in management of prostate cancer include: <ul style="list-style-type: none"> <li>○ down regulation of LHRH secretion</li> <li>○ androgen inactivation</li> <li>○ direct suppression of Leydig cell function.</li> </ul> </li> <li>• Good response rates associated with oestrogen use in castrate-refractory prostate cancer.</li> <li>• Precluded as standard first-line treatment due to cardiotoxicity.</li> </ul>
<p><b>Luteinizing hormone-releasing hormone (LHRH) agonists</b></p>	<ul style="list-style-type: none"> <li>• Synthetic analogues of LHRH.</li> <li>• Chronic exposure to LHRH agonists results in the downregulation of LHRH-receptors, suppressing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion and therefore testosterone production. The castration level is usually obtained within 2-4 weeks.</li> <li>• A ‘testosterone surge’ or ‘flare up’ phenomenon may occur after the first dose and might lead to detrimental effects such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and fatal cardiovascular events due to hypercoagulation status.</li> </ul>
<p><b>Luteinizing hormone-releasing hormone (LHRH) antagonists</b></p>	<ul style="list-style-type: none"> <li>• LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland leading to rapid decrease in LH, FSH and testosterone levels without any flare.</li> <li>• Use limited by lack of long-acting formulation.</li> </ul>
<p><b>Anti-androgens</b></p>	<ul style="list-style-type: none"> <li>• Compete with androgens at the receptor level</li> <li>• Oral compounds classified as: <ul style="list-style-type: none"> <li>○ steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ non-steroidal or pure, e.g. nilutimide, flutamide and bicalutamide.</li> </ul>
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## Clinical management

Health promotion is a key component of cancer survivorship care. Regular follow-up visits with survivors of cancer provide a prime opportunity for healthcare providers to encourage important health behaviours, like PA, for the maintenance of health-related quality of life (HRQOL), physical and psychological functioning in older adulthood. Further, targeted exercise to manage disease and treatment related side effects is increasingly being implemented in best-practice care of people affected by cancer [39]. Integrated care is becoming increasingly accepted to overcome fragmentation of patient management to provide a consistent approach across the multidisciplinary team, with the specialist nurse at the hub of cancer care [45]. Physical activity as well as prescribed aerobic and resistance exercise are important components of the management of cancer, other comorbid conditions, and maintenance of physical and psychological functioning [46-48] and particularly relevant for men receiving ADT.

## Barriers to physical activity in prostate cancer patients

There are few studies examining the barriers to PA and exercise after prostate cancer treatment. Links can be made from research on barriers to commencing PA in the age group and with men who have other health concerns [49], or other cancer treatments [50]. Psychosocial stress and distress are common amongst all cancer patients [51]. While prostate cancer patients were found to have lower distress scores than other cancers, fatigue, pain, depression, and anxiety are all barriers to undertaking PA. Carlson et al [51] found that men with prostate cancer were much less likely to seek psychosocial care than any other type of cancer. In a study of 193 prostate cancer survivors, being busy, or lacking willpower as well as access to fitness facilities or exercise equipment were barriers to commencing or continuing PA [52]. Throughout treatment, these men reduced their barriers to PA by 36%, increasing their PA time by an average of 43 minutes over 12 months of a home based PA intervention [53]. Urinary function and bowel bother post prostate cancer treatment are also frequently seen as barriers to commencing PA. At 12 and 52 months post radical prostatectomy (RP) (often the first line treatment with subsequent ADT) or external beam radiation (EBR) urinary bother was found to be a concern in 8% and 4% post RP and 2% post ERB. Bowel bother occurred in 2% post PR and 11% post EBR at 52 months [54].

Worldwide, different PA participation barriers are reported by prostate cancer patients, depending on the country, for example in Australia most health care professionals (Doctors and Nurses) do not discuss the importance of PA and exercise with their patients [55]. Two thirds of the population are sedentary [56], and this is reflected within the prostate cancer population. Education and behaviour change strategies are needed to improve referrals and the level of uptake of PA within the population. A referral to a clinical psychologist (as part of the multidisciplinary team) may be considered to help with treatment and PA adherence and the psychological barriers experienced by men receiving ADT.

There are challenges within health systems because exercise as medicine has a financial cost (albeit not as great as the cost of diseases which could be prevented by PA) which is not adequately supported by medical/Medicare systems and not uniformly available across countries such as Australia. The UK offer free exercise programming through the national health service (NHS), this opportunity removes the barrier of not having access to a program to improve PA. A review by Fox et al. [57] from the UK suggested that better coordination of multidisciplinary teams could facilitate improved levels of PA. Enabling a more comprehensive approach and well timed interventions and access to highly individualised support, including group exercise classes, are important facilitators to improve health outcomes for men with prostate cancer undergoing ADT [57]. Similarly, within Australia, men with prostate cancer can receive up to five consultations per calendar year with an Accredited Exercise Physiologist as part of their chronic disease management plan during which health and fitness assessment is completed as well as prescription of a tailored exercise program [39]. Health care professionals and men on ADT are reportedly in favour of PA and exercise programs as part of their cancer care, but the need for financial support is reportedly a major barrier to the provision of best practice [58].

### **Barriers to discussing physical activity by healthcare professionals**

Very little has been written on the barriers that healthcare professionals encounter to discussing PA in men who are undergoing treatment for prostate cancer. One study explored the barriers to referral to physiotherapy for management of post prostatectomy incontinence [59]. The findings identified that social or professional role and beliefs of the healthcare professional's capabilities, often stopped a health care professional from discussing management of incontinence with patients, thereby preventing timely referrals. Lack of resources and funding were also reported to be a barrier, where health care services were stretched and at full capacity, especially in the public sector, lacking resources and time to have the conversation about the importance of PA.

Santa Mina et al. [60] explored enablers and barriers of the delivery of a cancer exercise program among healthcare professionals. Barriers experienced were lack of funding and lack of physician support. Most healthcare professionals reportedly acknowledge the value of PA and agree that discussing PA with the cancer patient is part of their role, however, the majority of the recommendations when given do not align with the current guidelines [61]. In Australia, despite our national health system, Medicare, providing support for cancer patients to receive consultations with an Accredited Exercise Physiologist, the pathway is rarely engaged by healthcare professionals [39]. The evidence for the safety and efficacy of targeted exercise prescriptions for prostate cancer management is compelling and increasingly being integrated into best practice, but barriers (cost, access and behaviour change) for patients remain [37]. Optimising education about the benefits of PA for patients and healthcare professionals, as well as improvements in logistical strategies for the referral processes, would improve the uptake of PA and exercise programs for men undergoing ADT.

### **Evidence-based guidelines and strategies to promote PA**

The ACSM, ESSA and COSA encourage Oncologists and Nurses to refer men affected by prostate cancer to Qualified Exercise Professionals such as Accredited Exercise Physiologists / Clinical Exercise Physiologists and Physical Therapists / Physiotherapists with experience in cancer care for the right advice on what PA and exercise is appropriate for the individual patient before, during and after treatment. Generally, both aerobic and resistance exercise should be considered as part of the multi model approach to care for men with prostate cancer to reduce the detrimental effects of ADT, however the balance of mode and the actual dosage needs to be tailored to the individual patient [39 62], with special considerations feeding into the clinical rationale for each patient. Most importantly, prolonged sedentary behaviour irrespective of PA levels [63] may be linked to aggressive prostate cancer through mechanisms associated with obesity [27 64]. A holistic approach towards men with prostate cancer and potentially their families and carers are needed to improve the multitude of undesirable outcomes which can be experienced by patients [62]. Interventions most likely will encompass strategies for improved strength, mental health and significant fat loss requiring a clinical psychologist, nutritionist or dietitian on the multidisciplinary care team.

### **Physical activity and Mental Health**

Physical activity in the form of exercise has in general demonstrated to be associated with better mental health; however, the results are variable in terms of the extent to which amount of

exercise and other demographic variables may influence these effects [65]. Androgen deprivation therapy is associated with higher 3-year cumulative incidences of depression with a 23% increased risk ratio [66]. It was also shown in a large study of elderly men with prostate cancer that ADT increased the risk of depression [67]. There appears to be an increased risk of both depression and cognitive impairment for men receiving ADT, and it seems that even today the optimal treatment for either is unclear. Considering approximately half of men diagnosed with prostate cancer will receive ADT within the first year of diagnosis [68], it leaves a large cohort of men at clinical risk of depression and cognitive decline with no proven treatment options. Not only are men dealing with the impact of treatment to their mental health, there are also numerous other changes in their overall health that are associated. These include as mentioned above, decreases in cardiovascular health, decreases in strength, increases in fat composition and decreases in bone density, along with decreases in libido, erections, and changes in insulin sensitivity [69]. Physical activity and exercise have been shown with good evidence to improve physical health (cardiovascular and muscle strength) in men undergoing ADT and it is especially important for men to participate in exercise if they are on long term ADT treatments [70]. Targeted exercise prescription may be required to improve mental health outcomes with the inclusion of both aerobic and resistance exercise integrated at the same time as commencing ADT. Although experts suggest that this would be advantageous for these men, the evidence is limited on the impact of exercise on mental health outcomes [71]. Exercise when beginning ADT may be preferable to reduce treatment toxicities because it aids in preventing decline rather than relying on it later as a rehabilitative intent to reverse treatment side effects, which if prolonged negatively affects mental health [22 72].

Situational psychological changes may have a greater impact on the psychological wellbeing of men with prostate cancer than biological changes and the complexity of adding ADT may further disrupt balance for these men. This imbalance can contribute to further complications in men's relationships due to the exacerbation of changes to body image, cognitive decline, decreased libido and erections [73]. Partner psychological distress due to these changes have been reported to be as high or even higher than the patients themselves [45 74]. Treatment options for men with prostate cancer to reduce the physical and mental health burden of the side effects of ADT treatment should also be considered for their partners. It should include a range of professions working together to individually prescribe what is needed on a case by case basis, including psychological therapy. The inclusion of PA programs and/or targeted exercise to minimise treatment side effects would be optimal for patients undergoing ADT. Future research should look at a multi-disciplinary team approach to ensure that behaviour change and education strategies are successful for both men affected by prostate cancer and their partners. Furthermore, impending studies are required to

identify optimal treatments for both the physical and mental health needs of men with prostate cancer receiving ADT. At present the most appropriate modes and dosages of exercise for specific ADT toxicities is not known. It is well established that some exercise, whether aerobic or resistance, is better than being sedentary, the evidence for resistance training to improve strength in prostate cancer patients undergoing ADT is building, but beyond this prescription specifics have not been established. We must also ultimately demonstrate a survival benefit for exercise in a randomised control trial to convince patients, clinicians, and governments that participation and financial support for quality and effective exercise programs should be an essential component of best practice care of men with prostate cancer undergoing ADT.

### **Nursing implications**

The Prostate Cancer Specialist Nurse provides a hub of survivorship care across the entire cancer care continuum embedded within the wider multidisciplinary team [75], with clear role distinction and overlaps with other disciplines. For example, the Urological Surgeon will only be involved with the treatment of radical surgery itself, but the specialist nurse can further assist treatment decisions through information and support. Whereas, often, the specialist nurse will take the lead on managing the after effects of treatment and symptom management and providing timely referrals to Health Psychologists, Sex Therapists, and Qualified Exercise Professionals such as Accredited Exercise Physiologists / Clinical Exercise Physiologists and Physical Therapists / Physiotherapists with experience in cancer care. Therefore, it is essential that nurses advocate and support for all patients to be physically active and trigger timely referrals to appropriately trained professionals. Specialist Nurses provide clinical leadership which can help to facilitate and develop clinical pathways for timely referral for tailored exercise programmes for men affected by prostate cancer [62]. Future cancer pathways must support the implementation of exercise guidelines and should serve as a model of enhanced care delivery to increase the health and well-being of people with cancer.

### **Key Points**

- Androgen deprivation therapy (ADT) increases risk of adverse metabolic and musculoskeletal effects impacting physical and mental health of men with prostate cancer
- Promoting participation in a combination of aerobic and resistance exercise benefits the physical health of men with prostate cancer undergoing ADT

- Training for muscle size and strength with the use of resistance exercise is key to maintain and improve functional capacity in men undergoing ADT
- Increases in physical activity may improve the mental health of men undergoing ADT, however more research is needed
- An early referral to an exercise professional may improve treatment outcomes and the physical health of men with prostate cancer undergoing ADT

## **Conclusion**

Future research is needed to understand current PA and exercise behaviours in men with prostate cancer undergoing ADT, especially an understanding of the impact of exercise on patients' mental health. Targeted PA in the form of exercise has been shown to improve quality of life, fitness, fatigue, and muscular strength in men with prostate cancer and should be considered as part of the treatment plan for men undergoing ADT. Conclusions from this review are that promoting the importance of resistance training for men undergoing ADT which will improve physical and potentially mental health. Also promoting participation in PA could reduce the severity of toxicities experienced during treatment, even though the optimal intensity and dosage of prescription to improve these outcomes is currently unknown. Best practice for people affected by cancer undergoing active treatment should include person-centred timely referrals to wider members of the multidisciplinary clinical team.

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