Exercise in Prevention and Management of Cancer

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Opinion statement
Regular and vigorous physical exercise has been scientifically established as providing strong preventative medicine against cancer with the potential to reduce incidence by 40%. The effect is strongest for breast and colorectal cancer; however, evidence is accumulating for the protective influence on prostate cancer, although predominantly for more advanced disease and in older men. Following cancer diagnosis, exercise prescription can have very positive benefits for improving surgical outcomes, reducing symptom experience, managing side effects of radiation and chemotherapy, improving psychological health, maintaining physical function, and reducing fat gain and muscle and bone loss. There is now irrefutable evidence from large prospective studies that regular exercise postdiagnosis will actually increase survivorship by 50%–60% with the strongest evidence currently for breast and colorectal cancers. In our work with prostate cancer patients, we have found that exercise can limit or even reverse some of the androgen deprivation therapy (ADT) adverse effects by increasing muscle mass, functional performance, and cardiorespiratory fitness without elevating testosterone levels. Hormone therapies for breast and prostate cancer can result in alarmingly increased risk of cardiovascular disease, obesity, type 2 diabetes, osteoporosis, and sarcopenia. Increasingly, patients are questioning the benefit of some cancer treatments as the risk of morbidity and mortality from other chronic diseases begins to outweigh the initial cancer diagnosis. Over three decades of research in exercise science and many hundreds of RCTs demonstrate the efficacy of appropriate physical activity for preventing and managing these secondary diseases. Based on this evidence it is now clear to us that exercise is a critical adjuvant therapy in the management of many cancers and will greatly enhance the therapeutic effects of traditional radiation and pharmaceutical treatments by increasing tolerance, reducing side effects, and lowering risk of chronic diseases, even those not aggravated by cancer treatment. While patients and their clinicians deal with their cancer, other chronic disease mechanisms continue unabated. Anxiety, depression, poor nutritional choices, and a counterproductive rest strategy will accelerate these processes, while a well-designed exercise program adhered to by the patient and supported by the medical and exercise professionals will effectively control and even reverse these diseases and disabilities. In the wide range of cancer populations that we work with, both young and old and with curative and palliative intent, our overwhelming experience is that exercise is first well tolerated, and benefits the patient
psychologically and physically. While some of our patients are on individual, home-based programs, we find that small group exercise sessions with close supervision by Exercise Physiologists (EP) provides a more motivating setting and the social interaction is critical for adherence and retention as well as greater psychological benefits such as reduced anxiety and depression and enhanced social connectedness. While managing many hundreds of cancer patients over the last 6 years, our clinic has not experienced any instances of the exercise hindering patient recovery or treatment purpose, nor have any significant injuries occurred. However, it is critical that the exercise prescription and management be tailored to the individual patient and that they are monitored by appropriately trained and professionally accredited exercise specialists. For those patients at low exercise risk and without significant musculoskeletal issues, community-based physical activity is of excellent benefit where the emphasis should be on adherence, affordability, convenience, and enjoyment.

Introduction

Physical exercise is essential to maintaining human health and is now recognized by the American College of Sports Medicine and the American Heart Association as medicine (see http://www.exerciseismedicine.org) for both the prevention and management of chronic disease, injury, and other illnesses. Booth et al. [1] present extensive evidence that the modern sedentary lifestyle adopted by the majority of the population in most developed nations is incompatible with the human genome, and this results in the wide array of chronic diseases which now account for most of the World’s health burden [2]. With regard to cancer, regular physical activity has a protective effect with the strongest evidence for breast [3] and colorectal cancer [4] but less convincing data for prostate cancer [5].

Postcancer diagnosis, exercise is now considered an important adjuvant therapy to reduce symptom experience, ameliorate side effects of radiation and pharmaceutical therapies, improve psychological, wellness and increase survivorship. Of particular importance is the prevention and management of other often more life threatening chronic diseases such as cardiovascular disease and type 2 diabetes which are increasingly being observed as outcomes of cancer therapy [6, 7]. Further, reduced fitness and muscle and bone mass, and increased body fat are frequently observed in people with cancer in part resulting from reduced physical activity, poor nutrition, and depression. The majority of our research has been in men with prostate cancer receiving androgen deprivation therapy (ADT) and so we will present some of these findings; however, much of this work applies to all cancers.

Defining exercise

- The field of exercise science is now quite mature with a very large volume of research literature ranging from elite sports performance, maintenance of health, to management of disease and disability. In terms of physiological effects there are several parallels between exercise and drug therapy. Concepts of mode, dosage, and duration apply, and as with drug prescription, the effects on the human body vary markedly with different exercise regimes. Before continuing with this review we will define some key terms.
- Broadly exercise mode can be divided into two categories. Aerobic or cardiorespiratory exercise (Fig. 1) involves large muscle groups performing continuous or intermittent activity over an extended period of time. Most prominent effects are on the cardiovascular and respiratory systems increasing their capacity and improving blood lipid profile. Anabolic or resistance exercise (Fig. 2) involves performing sets of repeated movements against a resistance during which neuromuscular fatigue occurs within 6–12 repetitions. Most prominent effects are on the neural and muscular systems but marked changes also occur to the endocrine and skeletal systems. In the noncancer older
population, anabolic exercise has been endorsed as a potent countermeasure to sarcopenia and its implementation in clinical and home settings are relatively simple and inexpensive [8]. Additionally, this exercise mode has reliably been shown to induce other health benefits by promoting increases in the ability to perform daily tasks and increased physical reserve capacity. For both exercise modes, altering intensity, rest periods, and volume of work results in varying influences on all of the body systems. As a result it is often difficult to interpret the research literature with regard to exercise, physical activity, and cancer because these distinctions are not made. In terms of overall health, our initial recommendation is the American College of Sports Medicine and the American Heart Association combined position stand released in 2007 (Tables 1 and 2) [9, 10]. This applies to healthy people trying to reduce their risk of developing cancer.

Fig. 1. Aerobic exercise encompasses any activity that uses large muscle groups over 20 minutes or more duration. Modes can include rowing, cycling, running, walking, and swimming. Both continuous and intermittent exercise can be performed and each has different effects acutely and chronically on the human physiology.

Fig. 2. Resistance training or “anabolic” exercise appears very effective for preserving muscle and bone content, reducing fat gain, and improving functional capacity. Mental health, in particular depression, is also improved.
as well as cancer patients and survivors. However, presurgery, immediately postsurgery, during radiation and chemotherapy, and palliative care require much more specific and well-monitored exercise prescription best performed by a qualified health practitioner. A detailed descriptive review of prospective exercise studies identifying both cardiorespiratory and resistance exercise programs has been published elsewhere [11••]. We have also proposed overall exercise prescription guidelines to be used by cancer patients and survivors (Table 3) [11••].

- Many cancer patients experience muscle and bone tissue loss as a result of general cachexia and/or the effects of chemotherapy or hormone therapy and/or reduced physical activity. Anabolic exercise has the greatest potential to reverse these conditions. Hormone therapy for breast and prostate cancer patients can lead to fat gain and metabolic syndrome and here aerobic exercise is particularly effective. Thus, depending on cancer type, treatment side effects, and co-morbid conditions, the exercise prescription may vary considerably. In our Cancer Survivor program we always include a combination of both aerobic and anabolic exercise with the emphasis being adjusted according to the individual patient.

Table 1. For healthy adults under 65 years of age, the recommendation is as follows [9]

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Do moderately intense aerobic exercise 30 minutes a day, 5 days a week</td>
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<tr>
<td>Or</td>
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<tr>
<td>Do vigorously intense aerobic exercise 20 minutes a day, 3 days a week</td>
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<tr>
<td>And</td>
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<tr>
<td>Do anabolic exercise consisting of eight to ten exercises, eight to twelve repetitions of each exercise twice a week</td>
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Table 2. For healthy adults over 65 years or adults 50–64 years of age with chronic conditions, the recommendation is as follows [10••]

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Do moderately intense aerobic exercise 30 minutes a day, 5 days a week</td>
</tr>
<tr>
<td>Or</td>
</tr>
<tr>
<td>Do vigorously intense aerobic exercise 20 minutes a day, 3 days a week</td>
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<tr>
<td>And</td>
</tr>
<tr>
<td>Do anabolic exercise consisting of eight to ten exercises, 10–15 repetitions of each exercise twice to three times per week</td>
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<td>And</td>
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<td>If you are at risk of falling, perform balance exercises</td>
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<td>And</td>
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<td>Have a physical activity plan</td>
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Table 3. For most cancer patients and survivors specific exercise recommendations are as follows [11••]

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tr>
<td>Do continuous or intermittent aerobic exercise for 20–60 minutes undertaken three to five times per week at 55% to 90% maximal heart rate (estimated as 220-age)</td>
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<td>And</td>
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<tr>
<td>Do anabolic exercise 6–12 repetitions (50%–85% of 1RM) and one to four sets of each exercise for major muscle groups one to three times per week</td>
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<tr>
<td>And</td>
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<tr>
<td>Do flexibility exercises for major muscle groups, two to four sets of each exercise two to three times per week</td>
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Exercise and cancer risk

- Physical inactivity has been associated with a wide range of cancer types, and while the mechanisms are not precisely known, interactions between exercise, obesity, immune, and endocrine function can either facilitate or suppress cancer development. The strongest epidemiological evidence is for colorectal and breast cancers.

Colorectal cancer

- Physical inactivity accounts for around 13%–14% of colon cancer [12] incidence; however, the mechanism of effect is not well understood. Possible actions of exercise include decreased gastrointestinal transit-time, improved immune function and insulin levels, insulin-like growth factors, and reduced obesity [12]. Whether it be occupational or recreational physical activity a Cochrane type review of the available literature [13] suggests a 20% reduction in risk of developing colorectal cancer in both men and women. In terms of the amount of exercise it appears that more is better, with one study [14] suggesting a 30% reduction in risk between the highest and lowest quartile of habitual exercise.

Breast cancer

- Friedenreich and Cust [15] published an extensive review of the available literature reporting physical activity patterns and risk of breast cancer. They found evidence for a risk reduction associated with increased physical activity in 47 (76%) of 62 studies examined. The average risk decrease was 25%–30% and there was a dose-response effect in 28 of 33 studies. It appears that more vigorous activity is better and should be pursued throughout life, although high levels of physical activity in later life were quite protective for older women [15].

Prostate cancer

- Evidence in support of the benefit of physical activity reducing risk of prostate cancer is not as strong; however, several studies suggest a significant reduction for more advanced forms and in older men. Giovannucci et al. [16] found no relationship between level of physical activity and prostate cancer incidence. However, on further analysis the authors reported a statistically significant reduction in risk of 54% for metastatic prostate cancer but only for the category of vigorous activity. In a subsequent study [5] reporting data from the 14-year follow-up to this cohort a very similar pattern of relative risk (RR) emerged with no detectable benefit of exercise regardless of how vigorous for the study population overall. However, for men over 65 years and undertaking vigorous exercise there was a significant and meaningful reduction (70%) in risk of advanced and fatal prostate cancer if they achieved at least 3 hours of vigorous activity each week. It does appear a relatively high volume of vigorous exercise is required to reduce risk of prostate cancer and this only applies to advanced forms [17]. In a large (n = 29,110 men) prospective study conducted in Norway [18] frequency and duration of exercise were inversely related to incidence of advanced prostate cancer. Compared to men...
who were sedentary, men in the highest category of physical exercise exhibited a RR of 0.64 for advanced prostate cancer and 0.67 for prostate cancer death. The authors concluded that reduced risk of advanced prostate cancer and prostate cancer death is associated with higher levels of recreational physical exercise.

- The mechanism by which exercise reduces risk of prostate cancer is not known as yet. Speculatively, it may be that the increased binding of testosterone by the muscular system as a result of chronic vigorous exercise result in reduced testosterone availability to the prostate slowing the growth of cancer cells. It is well established that certain types of physical activity, specifically anabolic exercise, results in considerable increases in circulating testosterone even in older men [19]. While this might be interpreted to exacerbate development and growth of prostate cancer, concomitant increases in androgen receptor sites in the trained muscles may offset this potentially deleterious effect.

- Different modes and intensities of exercise produce quite different responses and adaptations by the endocrine system with alterations in many hormones known to influence prostate cancer cell growth such as insulin-like growth factor 1, leptin, insulin, sex hormone-binding globulin, and testosterone. For example, in one study [20], blood serum taken from men who performed regular aerobic exercise (5 days per week) showed altered insulin-like growth factors that when combined with prostate cancer cells in vitro reduced growth rate and induced apoptosis of the cells. Future research should differentiate aerobic versus anabolic exercise modes in their analysis.

### Role of exercise postdiagnosis

- Ideally, an aggressive exercise program would be initiated by the patient immediately postdiagnosis to prepare them for the ensuing treatments. For example, higher cardiorespiratory fitness [21] improves surgical outcomes and lower body fat decreases risks associated with anesthesia [22]. Given time constraints and the emotional status of the patient this is not practical at present until exercise therapy is better integrated into cancer care. As a result most exercise interventions are initiated either during or after the patient has received treatment. In 2005 we published a review of 26 studies conducted on exercise in cancer patients [11]. The majority of the studies demonstrated meaningful physiological and psychological benefits and this was despite some relatively modest exercise program designs. Predominantly, research had been conducted with breast cancer patients using aerobic rather than anabolic training as the exercise modality and there was a mixture of before and after treatment interventions. A summary of the changes induced by the exercise is presented in Table 4.

- A further observation is that published exercise interventions in cancer patients are quite modest in volume and intensity and in our opinion suboptimal and nonspecific. There is an urgent need for large RCTs examining different modes and dosages of exercise prescription in different cancer populations in order to refine specific program designs.

### Exercise and cancer related fatigue

- Cancer related fatigue is often reported by patients to be one of the most debilitating symptoms of their disease and treatment [23]. Previously the recommendation had been rest; however, more recent research demonstrates that such a strategy exacerbates the fatigue.
condition. In breast cancer patients we have assessed physical activity patterns, strength, and aerobic fitness in women over the course of treatment and observed parallel declines [23]. It appears that reduced physical activity due to clinician recommendation, anxiety, and depression, and an overall feeling of being unwell cause rapid reduction in cardiorespiratory and neuromuscular fitness, and it is this reduced capacity that is the principle cause of fatigue. This explains why several trials in cancer patients have found that regular exercise actually decreases fatigue symptoms [11]. In our clinic, we have found that anabolic exercise is better tolerated in patients suffering fatigue possibly due to the intermittent nature and lower cardiorespiratory demands.

## Exercise and depression

- Depression is a very common co-morbid condition with cancer and impacts severely on their quality of life, recovery, and possibly even survival. In exercise and cancer trials that applied instruments to assess depression, significant decreases have been observed [11]. In otherwise healthy elderly people, high intensity anabolic exercise has actually been found to be more effective than routine medical care with a 61% vs 21% reduction in clinical depression, respectively [24]. The mechanisms for this effect include both physiological and psychological and in our clinic we include anabolic exercise and small group formats to try and maximize these benefits.

## Exercise and cancer survival

- Ultimately the greatest benefit of exercise for cancer patients is an increase in survivorship, which has been demonstrated in a few very large prospective studies to be 50%–60%. The first was an outcome from the Nurse's Health Study by Holmes et al. [25] who surveyed 2987 female nurses who were diagnosed with breast cancer. The adjusted RR of death from breast cancer was 0.5–0.6 when comparing women who performed less than 3 MET-hours per week of exercise with those who performed 9 or more. One MET-hour is equivalent to approximately 1 hour of walking at a normal pace. Holmes et al. [25] concluded that there appeared to be no greater benefit in more exercise than 9 MET-hours per week in terms of breast cancer survival.

### Table 4. Summary of exercise-induced changes in cancer patients reported in 26 research papers reviewed by Galvão and Newton [11]

<table>
<thead>
<tr>
<th>Increased</th>
<th>Decreased</th>
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<tbody>
<tr>
<td>Muscle mass</td>
<td>Nausea</td>
</tr>
<tr>
<td>Muscle strength and power</td>
<td>Body fat</td>
</tr>
<tr>
<td>Cardiorespiratory fitness</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Maximum walk distance</td>
<td>Symptom experience</td>
</tr>
<tr>
<td>Immune system capacity</td>
<td>Lymphocytes and monocytes</td>
</tr>
<tr>
<td>Physical functional ability</td>
<td>Duration of hospitalization</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Heart rate</td>
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<tr>
<td>Quality of life</td>
<td>Resting systolic blood pressure</td>
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<tr>
<td>Hemoglobin</td>
<td>Psychological and emotional stress</td>
</tr>
<tr>
<td></td>
<td>Depression and anxiety</td>
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and that “women with breast cancer who follow the US physical activity recommendations may improve their survival.”

- The next two studies were in colorectal cancer and were editorialized in the Journal of Clinical Oncology under the title “Cancer Survival: Time to Get Moving? Data Accumulate Suggesting a Link Between Physical Activity and Cancer Survival” by Demark-Wahnefried [26••]. Meyerhardt et al. [27, 28] compared colorectal cancer patients engaged in less than three MET-hours per week of physical activity with those performing 18 or more. The adjusted hazard ratio for disease-free survival was 0.51–0.55. Further, the benefit conferred by the physical activity did not appear influenced by sex, body mass index, age, or chemotherapy received. The authors concluded that “physical activity appears to reduce the risk of cancer recurrence and mortality.”

- Mechanisms by which exercise increases cancer survival are numerous and varied ranging from improved immune function to reduced impact of other chronic diseases. Maintenance of a more healthy body fat level appears to improve survival in hormone driven cancers such as that of the breast, and reduced body fat improves early detection of recurrence and secondaries through more accurate visual and palpation identification as well as radiological imaging clarity. Certainly the enhanced psychological health conferred by exercise, in particular reduced depression, contributes to reduced morbidity and mortality.

### Exercise, ADT, and prostate cancer

- Our team has been researching prostate cancer and the impact of exercise to ameliorate the adverse effects of ADT. The following series of studies summarize our work in this field over the past 5 years and should prove informative to the exercise management of all cancers and in particular breast cancer, which has very similar parallels in terms of the side effects of treatment due to the hormonal therapy.

- Several studies have documented marked alterations in body composition in men receiving ADT for prostate cancer. Smith et al. [29] reported a 9.4% increase in whole body fat and a 2.7% reduction in whole body lean mass assessed by dual energy X-ray absorptiometry (DXA) following 48 weeks of ADT. Recently, we have also reported negative changes in regional muscle, fat, and bone following 36 weeks of ADT undertaken by 72 men with prostate cancer [30]. Upper limb, lower limb, trunk, and whole body lean mass decreased by 5.6%, 3.7%, 1.4%, and 2.4%, respectively, while fat mass increased by 20.7%, 18.7%, 12.0%, and 13.8% [30]. Such reduction of lean mass following ADT can reduce musculoskeletal fitness, compromising muscle strength, physical function, and physical reserve capacity (Fig. 3) [31]. Such changes have implications in terms of reducing the age at which the individual falls below the functional capacity threshold, requiring a shift away from independent living and a reduced quality of life. Moreover, the increase in fat mass during ADT can lead to increased levels of total cholesterol and triglycerides [29, 32] and consequently the possible development of metabolic syndrome and cardiovascular complications [33, 7••].

- Apart from a decline in muscle mass and strength, ADT-treated men suffer a reduction in bone mass, and consequently bone strength, that contributes to an increased incidence of fracture and associated disability [34, 35]. Recently, we have reported that hip and spine bone mineral density (BMD) decreased by 1.5% and 3.9% as did whole
Greenspan et al. [30] indicated that men with prostate cancer initiating ADT have a 5- to 10-fold loss of bone mineral density (BMD, g/cm²) compared to healthy controls or men with prostate cancer not on ADT. Importantly, following ADT, there is a significant dose-response relation between fracture risk and the number of LHRHa doses administrated [34]. The reduced structural bone strength is compounded by the reduction in muscle strength and power which has been related to increased falls incidence [37] resulting in two separate side effects of ADT combining to greatly increase fractures due to falls.

- Structured exercise programs could play a major role in improving quality of life as physical and functional adaptations are likely to be derived from such clinical interventions. Segal and colleagues [38] studied 155 men in a multisite trial with localized and nonlocalized prostate cancer undertaking or scheduled to receive different forms of ADT for at least a 12-week exercise training period. Using a randomized controlled design, patients were assigned to either whole body resistance training, which incorporated three upper and 4 lower body exercises, or a nonexercise control group. The exercise group experienced improved symptoms of fatigue and health-related quality of life compared to the nonexercise group. Moreover, submaximal muscle strength increased by 42% and 32% for the chest press and leg press, respectively. The observed changes for fatigue and quality of life are extremely relevant given that they are negatively affected during ADT [39, 40].

- Recently, we examined the effects of a longer (20-week) progressive resistance exercise intervention in a group of men receiving ADT for prostate cancer [41]. Training intensity, volume, and frequency were set at 6–12-RM using 2–4 sets for 10–12 exercises undertaken twice weekly. This study aimed to extend the work of Segal et al. [38] by examining the physical, functional, morphological, and physiological outcomes of the intervention. Dramatic improvements in muscle strength (chest press, 40.5%; seated row, 41.9%; leg press, 96.3%) and muscle endurance (chest press, 114.9%; leg press, 167.1%) resulted as well as improvements in a number of physical performance measurements including the 6-m usual walk, 6-m backwards walk, chair rise, stair climbing, 400-m walk, and balance ranging from 7% to 27%. Despite the suppression of testosterone, changes in muscle strength were comparable to the effects of resistance exercise.

\[ \text{Fig. 3. Theoretical model of musculoskeletal fitness reduction during aging and ADT. Potential role of resistance exercise providing an increase in musculoskeletal fitness and physical reserve capacity in ADT treated men [31].} \]
interventions in healthy older adults not on ADT [42]. Further, changes in muscle endurance and functional capacity indicated that ADT treated men may carry out functional daily activities with less fatigue following resistance exercise regimes and could partially explain the reduced levels of fatigue in resistance trained men previously reported [38]. The results also indicated that muscle thickness increased at the quadriceps site and whole body lean mass measured by DXA was preserved with no change in fat mass. Considering that detrimental alterations in body composition are well-established side effects from ADT, these results provide support for the role of resistance exercise to preserve body habitus and enhance physical function in prostate cancer patients undergoing therapy. We are currently extending those findings in a randomized controlled trial with 50 men on ADT. Preliminary findings indicate that the exercise group is increasing lean mass and cardiorespiratory fitness compared to controls.

- Cardiovascular training at 60%–70% maximum heart rate has also been examined in prostate cancer patients initiating a 4-week external beam radiotherapy program [43]. In this randomized controlled trial, 66 patients were assigned to standard care (control) or an exercise group. While fatigue levels for the control group increased following the radiotherapy regimen, there was no change in the exercise group who also experienced a significant increase in walking endurance of 13%. This study indicates that beneficial effects can be derived from even a modest short-term unsupervised, home-based exercise program.

- Recently we have also examined the effects of resistance training on a range of serum hormones, disease, and inflammatory markers at rest, and following acute bouts of exercise in men on ADT [44]. We found that exercise appears to be safe for these patients without compromising the therapy purpose of testosterone suppression and did not produce any elevation in PSA. In addition, we found that acute exercise induced increases in growth hormone that could potentially underlie improvements observed in physical function and increases in lean mass from our current RCT. Furthermore, we have observed that the immune response to exercise was similar to healthy individuals [44].

- In summary, although lifestyle modifications (predominantly diet, but also physical activity in general, and smoking and alcohol cessation) and agents such as calcium/vitamin D for bone health have been indicated as potential sources available to counter or partially counter the side effects of ADT [45], none are likely to provide the magnitude of effects that are observed with resistance exercise. Larger randomized controlled trials are required to confirm and expand current findings.

**Conclusions**

- Exercise has an important role in prevention and management of cancer. Being physically active throughout life reduces risk of cancer, in particular colorectal and breast and there is emerging evidence of impact on prostate cancer. Postdiagnosis of cancer, appropriate exercise improves symptom experience, ameliorates treatment side effects, enhances psychological well-being, and appears to increase survival through a range of mechanisms. As such, regular exercise should be encouraged in all populations, particularly those at higher risk of cancer. Further, exercise as medicine must be incorporated in the routine clinical care of cancer patients to improve quality of life as well as reduce morbidity and mortality.
References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of major importance


Endocrine and immune responses to resistance training in prostate cancer patients

DA Galvão¹,², K Nosaka², DR Taaffe³, J Peake³, N Spry⁴,⁵, K Suzuki⁶, K Yamaya⁷, MR McGuigan¹,², LJ Kristjanson⁸ and RU Newton¹,²

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This study examined the effect of 20 weeks resistance training on a range of serum hormones and inflammatory markers at rest, and following acute bouts of exercise in prostate cancer patients undergoing androgen deprivation. Ten patients exercised twice weekly at high intensity for several upper and lower-body muscle groups. Neither testosterone nor prostate-specific antigen changed at rest or following an acute bout of exercise. However, serum growth hormone (GH), dehydroepiandrosterone (DHEA), interleukin-6, tumor necrosis factor-α and differential blood leukocyte counts increased (P < 0.05) following acute exercise. Resistance exercise does not appear to compromise testosterone suppression, and acute elevations in serum GH and DHEA may partly underlie improvements observed in physical function.

Keywords: androgen antagonists; testosterone; inflammation; exercise

Introduction

Androgen deprivation therapy (ADT) is widely employed in the management of prostate cancer to improve survival during the early stage of the disease and to gain control of the disease in the more advanced situations.¹,² ADT is achieved by either surgical castration, or more commonly by administering luteinizing hormone-releasing hormone agonist (LHRHa) or antiandrogen medications that block the androgen receptors, or both.² However, ADT is accompanied by a range of adverse effects including reduced muscle strength, lean and bone mass, increased fat mass and fracture risk.³,⁴ These side effects are clinically important, because they are likely to compromise physical function, reduce independence and quality of life.⁵ Regular resistance training is a reliable, safe and effective countermeasure to the age-related loss of skeletal muscle⁶ and bone⁷ in healthy older adults, and may counter or even reverse some of the negative side effects that often accompany ADT.⁸

We and others have recently reported beneficial effects of resistance training on physical function and quality of life in patients on ADT following 12 weeks of moderately intense training⁹ and 20 weeks of heavy training.¹⁰ We noted that muscle strength improved and lean mass was preserved without any harmful effect on prostate cancer disease control, as assessed by the resting level of prostate-specific antigen (PSA),¹⁰ or on the therapeutic castrate resting level of testosterone. The latter finding contrasts with the situation in the non-androgen-suppressed individual, where resistance training can lead to acute testosterone release (changes occurring immediately after an exercise session), which could adversely affect ADT disease control. However, the acute effect of resistance training on testosterone release in prostate cancer patients undergoing ADT is unknown and remains to be determined. Moreover, resistance training may lead to other hormonal changes, such as in circulating levels of growth hormone (GH) and intramuscular insulin-like growth factor-1 (IGF-1), which are well described among healthy older adults.¹¹,¹² In prostate cancer patients, no data are currently available on the acute effects of resistance training on these growth factors and increased circulating levels of GH and IGF-1 in prostate cancer patients may help to improve physical function and quality of life, and to preserve body composition.

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Prostate cancer is also associated with a chronic low-grade inflammation type state, as indicated by elevated circulating levels of the cytokines interleukin (IL)-6, tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and IL-8.\(^{1,2}\) Although elevated levels of IL-6 have been associated with the age-related decline in muscle mass,\(^{1,2}\) IL-6 may not actually contribute to muscle loss. Instead, IL-6 may be elevated in response to ongoing production of TNF-\(\alpha\).\(^{1,2}\) Exercise induces IL-6 production in skeletal muscle, and it has been proposed that IL-6 may underlie some of the beneficial effects of exercise by inhibiting the synthesis of TNF-\(\alpha\) and stimulating the production of other anti-inflammatory cytokines.\(^{1,2}\) Data from cross-sectional studies currently exist to support a relationship between physical inactivity and chronic low-grade inflammation.\(^{1,2}\) However, few longitudinal intervention studies have investigated changes in markers of inflammation in response to exercise training, particularly in patients with prostate cancer.

We initiated a longitudinal study of high-intensity resistance training in men undergoing ADT for prostate cancer with the following aims: (1) to determine if resting concentrations of serum hormones, markers of disease, inflammation and bone turnover are altered following 10 and 20 weeks of high-intensity resistance training and (2) to determine acute changes in these blood variables following a single bout of heavy resistance exercise.

### Methods

#### Subjects

Subject recruitment, inclusion and exclusion criteria, and the effects of the intervention on muscle function, functional performance, balance and body composition have been reported previously.\(^{10}\) Eligible patients had been on ADT for at least 2 months (to avoid the acute phase changes), needed to be no evidence of active disease, and subjects were not to have undertaken any previous resistance training. Before participation, all subjects obtained medical clearance from their physician and completed a health history questionnaire. The study was approved by the University Human Research Ethics Committee, and all subjects provided written informed consent. Eleven men were eligible to participate in the study and they were invited for familiarization sessions. Ten men completed 40 resistance training sessions and two separate acute resistance exercise protocols during the course of 20 weeks. ADT was achieved by LHRHa treatment in nine men and cyproterone acetate in the remaining subject. All subjects received ADT for at least 2 months before the commencement of the study and continued for the duration of the experimental period.

#### Training program

A full description of the training program has been previously reported.\(^{10}\) Briefly, participants were trained twice per week for 20 weeks, in small groups and under direct supervision. The first 10 weeks of the program involved an introductory period of whole body resistance exercise, during which the subjects used hydraulic resistance training machines (Isotronic, Fitness Technology, Adelaide, Australia). These machines are simple and time efficient to use, and are restricted to concentric muscle contractions. In the following 10 weeks, the training program was restricted to the use of isotonic resistance equipment, providing concentric and eccentric muscle contractions for whole body exercises similar to those used in the initial 10-week period (Cybex, Strength Equipment, Medway, Stoughton, MA, USA). Both training phases were designed as weeks 1–2 (two sets of 12 repetition maximum (RM)), weeks 3–4 (three sets of 10-RM), weeks 5–7 (three sets of 8-RM) and weeks 8–10 (four sets of 6-RM). The program was based on the American College of Sports Medicine position stand on progression models in resistance training for healthy adults.\(^{19}\)

#### Acute resistance exercise bout

** Hydraulic acute exercise bout.** Following 10 weeks of hydraulic training, all subjects performed an acute exercise bout using the hydraulic resistance equipment, completing four sets of eight resistance exercises at 6-RM. Rest between sets was 1–1.5 min, with 2–4 min between exercises. The exercises performed were the chest press-seat, row, squat, shoulder press-lat pull, leg press, triceps extension-biceps curl, leg extension-leg curl, upper rower dips and abdominal crunch-back extension.

** Isotonic acute exercise bout.** Following the 10-week period of isotonic training, subjects also performed an acute bout of isotonic exercise, completing four sets of eight exercises at 6-RM. The rest periods were similar to that for the hydraulic exercise bout. The exercises performed were the chest press, leg press, lat pulldown, leg extension, shoulder press, leg curl, seated row and abdominal crunch.

#### Blood sampling

Venous blood samples were drawn from a forearm vein at a fixed time (0830–0010 hours) before the training program commenced, as well as before and immediately after the heavy resistance exercise sessions at weeks 10 and 20. Blood was collected into sterile vacutainers containing K\(_2\)-ethylenediaminetetraacetic acid (EDTA) and serum separation tubes (Becton Dickinson, Franklin Lakes, NJ, USA). The blood collected by K\(_2\)-EDTA tube was used for complete blood cell counts using a Beckman Coulter-Counter Gen-S (France SA, Villepinte, France), and hemoglobin concentration was measured by an automated analyzer (Sysmex XE-AlphaN, Sysmex Corporation, Kobe, Japan). The serum separation tubes were left at room temperature for the blood to clot, and then centrifuged for 10 min at 3000 r.p.m. at 4°C. The serum samples were stored in 0.7 ml aliquots at −80°C until the day of analysis.

#### Prostate cancer markers

PSA in the serum was measured by an Immurise Analyzer (Beckman Coulter Inc., Fullerton, CA, USA) using a test kit (Diagnostic Products Corporation, Los Angeles, CA, USA).
Serum hormone concentrations were determined by RIA for free testosterone (DPC free testosterone kit, Diagnostic Products Corporation), GH (GH Kit, SRL Co., Tokyo, Japan), cortisol (Cortisol Kit, Immunotech, Beckman Coulter Inc., Prague, Czech Republic), and dehydroepiandrosterone sulfate (DHEAS) was measured by an Immturnise Analyzer (Beckman Coulter Inc.) using a commercial kit (Diagnostic Products Corporation). Dehydroepiandrosterone sulfate (DHEAS) was measured by an Immturnise Analyzer (Beckman Coulter Inc.) using a commercial kit (Diagnostic Products Corporation). IGF-1 was measured with an enzyme-linked immunosorbent assay (ELISA) kit (Diagnostic Systems Laboratories Inc., Webster, TX).

Bone markers
The serum markers of bone formation, alkaline phosphatase (ALP) and osteocalcin were measured by a JEOL Clinical Analyzer BM12 (JEOL Ltd., Tokyo, Japan) using an L-Type ALP kit (Wako Pure Chemical Industries Ltd., Osaka, Japan) and by enzyme immunoassay with a BTI Intact Osteocalcin ELIA kit (Biomedical Technologies Inc., Stoughton, MA, USA). Tartrate-resistance acid phosphatase isofrom 5b (TRACP5b), a marker of bone resorption, was measured by ELISA (Suomen Bioanalytiikka Oy, SBA Sciences, Turku, Finland).

Inflammatory markers
Serum C-reactive protein (CRP) was analyzed by ELISA (Max Human C-Reactive Protein ELISA Kit; EC1001-1, Winfield, MO, USA). Serum concentration of IL-6, IL-1 receptor antagonist (IL-1ra), and TNF-α was measured using Quantikine high-sensitivity ELISA kits (R&D Systems, Minneapolis, MN, USA) and IL-8 concentration was measured using OptEIA kits (Becton Dickinson, San Diego, CA, USA).

Other measures
Serum creatine kinase (CK) activity was measured by a ultraviolet method (CPK-L, Nittohboh Medical Co., Tokyo, Japan).

Statistical analyses
Data were analyzed using the SPSS statistical software package (Version 11.0, SPSS Inc, Chicago, IL, USA). One-way repeated measures analysis of variance was used to compare changes over the three time points (baseline, weeks 10 and 20). Where appropriate, the Fisher-protected least significant difference test was employed to locate the source of significant differences. When comparing before and after responses to the acute bouts of exercise, paired t-tests were used. An α = 0.05 was required for significance, and results are presented as the mean ± s.e.

Results
Measures of disease activity: PSA
PSA was not affected by training (Table 1).

Hormonal measures: free testosterone, GH, IGF-1, cortisol, DHEA and DHEAS
The resting concentrations of serum-free testosterone, GH, cortisol, IGF-1, DHEA or DHEAS did not change significantly over the intervention period (Table 1). Following the acute bout of exercise, free testosterone and cortisol did not change. GH tended to increase (P = 0.088) following the hydraulic exercise bout at week 10, and increased significantly in response to the acute bout of isotonic exercise at week 20 (P = 0.009). IGF-1 also tended to increase following both the hydraulic (P = 0.088) and isotonic exercise bouts (P = 0.059). DHEA increased significantly following both acute exercise bouts, whereas there were no changes in DHEAS.

Chronic inflammatory markers: IL-6, IL-8, IL-1ra, TNF-α and CRP
Serum IL-8 concentration increased at rest from week 10 to 20 (P = 0.048), and there was a trend toward an increase between baseline and week 20 (P = 0.065) (Table 2). The resting serum concentrations of IL-6, IL-1ra, TNF-α or CRP did not change during the 20 weeks of training. The acute bout of hydraulic exercise at week 10 had no significant effect on any inflammatory markers, except IL-8, which tended to increase (P = 0.081), whereas the acute bout of isotonic exercise at week 20 resulted in an increase in both IL-6 (P = 0.001) and TNF-α (P = 0.050).

Hematological variables: hemoglobin, white cells, monocytes, neutrophils and lymphocytes
Resting hemoglobin concentration, blood neutrophil and monocyte counts did not change significantly over the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Hydraulic exercise protocol (week 10)</th>
<th>Isotonic exercise protocol (week 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>PSA (ng ml⁻¹)</td>
<td>3.0 ± 2.1</td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>Free testosterone (pg ml⁻¹)</td>
<td>2.1 ± 1.2</td>
<td>2.1 ± 1.2</td>
<td>2.5 ± 1.4</td>
</tr>
<tr>
<td>GH (ng ml⁻¹)</td>
<td>0.72 ± 0.26</td>
<td>0.83 ± 0.27</td>
<td>3.1 ± 1.2</td>
</tr>
<tr>
<td>IGF-1 (ng ml⁻¹)</td>
<td>158.9 ± 19.4</td>
<td>161.4 ± 16.1</td>
<td>181.2 ± 22.6</td>
</tr>
<tr>
<td>Cortisol (ng ml⁻¹)</td>
<td>10.6 ± 1.1</td>
<td>10.3 ± 1.1</td>
<td>8.9 ± 1.5</td>
</tr>
<tr>
<td>DHEA (ng ml⁻¹)</td>
<td>1.6 ± 0.2</td>
<td>1.3 ± 0.3</td>
<td>1.7 ± 0.2*</td>
</tr>
<tr>
<td>DHEAS (ng ml⁻¹)</td>
<td>0.65 ± 0.18</td>
<td>0.61 ± 0.17</td>
<td>0.63 ± 0.17</td>
</tr>
</tbody>
</table>

Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; GH, growth hormone; IGF-1, insulin growth factor-1; PSA, prostate-specific antigen.
*Significant difference, P < 0.05, Pre- and post-exercise protocols (paired sample t-tests).
20-week training period (Table 2). Blood lymphocyte counts increased over time from baseline to week 10 \((P = 0.006)\), whereas total leukocyte counts decreased from week 10 to 20 \((P = 0.038)\). Following the acute hydraulic exercise bout at week 10, total leukocyte \((P = 0.035)\) and neutrophil counts increased significantly \((P = 0.029)\), whereas hemoglobin, monocytes and lymphocytes remained unchanged. The acute isotonic exercise bout at week 20 increased hemoglobin and all leukocyte counts \((P < 0.05)\).

**Bone turnover markers: TRACP5b, ALP and osteocalcin**

The resting serum concentrations of TRACP5b and ALP increased significantly over time from baseline to week 20 \((P < 0.05)\) (Table 2), whereas no changes occurred for osteocalcin.

CK

Resting levels of CK did not change over time but increased following both acute exercise bouts \((P < 0.05)\) (Table 2).

**Discussion**

This is the first study to evaluate the acute and chronic effects of resistance training on serum hormones, markers of disease and inflammation and chronic effects on bone turnover following high-intensity resistance training in prostate cancer patients on ADT. There were three important findings: (1) neither endogenous testosterone production nor disease activity were affected by resistance exercise; (2) significant changes occurred in GH and DHEA concentrations following an acute bout of heavy resistance exercise; (3) the immune response to exercise was similar to healthy individuals.

Resistance training may play an important role in the therapeutic management of prostate cancer patients by countering the adverse consequences of ADT on physical functioning and the musculoskeletal system. However, before such a role for resistance training can be endorsed and recommended for this patient population, clinicians need to be assured that the goals of androgen deprivation treatment are not compromised. We observed no significant effects of training on resting levels of serum hormones and growth factors (free testosterone, GH, IGF-1, cortisol, DHEA and DHEAS) following 20 weeks training. These findings are consistent with responses observed in healthy older adults not undergoing ADT,11,20 and suggest that men undergoing ADT can safely participate in resistance training without adversely increasing their testosterone levels. This is an important outcome, because ADT is aimed at suppressing testosterone synthesis and release. PSA also did not change significantly following the training program, suggesting no detrimental effects on disease progression. These findings support and extend those previously reported by Segal et al.,9 where no changes were observed for testosterone and PSA following 12 weeks training performed at lower intensity and volume.

The acute resistance exercise bout performed at week 10 resulted in an increase in DHEA with no significant changes in PSA or any other serum hormones, while the acute exercise bout performed at week 20 (concentric and eccentric muscle contractions) lead to a significant increase in GH, DHEA and an elevation in IGF-1 with no changes occurring in PSA. Importantly, free testosterone remained suppressed following both acute heavy exercise bouts performed at weeks 10 and 20. This finding indicates that heavy bouts of exercise are unlikely to raise serum testosterone concentration as previously shown in non-ADT-treated older adults.11 The acute increases in GH as well as DHEA following both resistance exercise protocols could partially contribute to the physical and physiological benefits derived from the intervention (for example, strength gains, maintenance of lean mass).10 Others have reported no relationship between prostate cancer markers (for

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Table 2  IL-6, IL-8, IL-1ra, TNF-α, C-reactive protein, CK, TRACP5b, osteocalcin, alkaline phosphatase, hemoglobin, white blood cells, monocytes, neutrophils and lymphocytes pre- and post-hydraulic and isotonic resistance exercise protocols (mean ± s.e.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Hydraulic exercise protocol (week 10)</th>
<th>Isotonic exercise protocol (week 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>IL-6 (pg ml⁻¹)</td>
<td>1.8 ± 0.3</td>
<td>1.5 ± 0.2</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>IL-8 (pg ml⁻¹)</td>
<td>8.2 ± 0.8</td>
<td>7.6 ± 1.1</td>
<td>10.2 ± 1.9</td>
</tr>
<tr>
<td>IL-1ra (pg ml⁻¹)</td>
<td>286.5 ± 39.2</td>
<td>301.8 ± 41.8</td>
<td>344.8 ± 47.8</td>
</tr>
<tr>
<td>TNF-α (pg ml⁻¹)</td>
<td>1.8 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>C-reactive protein (pg ml⁻¹)</td>
<td>0.91 ± 0.31</td>
<td>1.0 ± 0.55</td>
<td>0.71 ± 0.25</td>
</tr>
<tr>
<td>CK (IU⁻¹)</td>
<td>269.3 ± 137.1</td>
<td>150.5 ± 63.0</td>
<td>195.6 ± 62.7a</td>
</tr>
<tr>
<td>TRACP5b (IU⁻¹)</td>
<td>2.7 ± 0.2</td>
<td>3.0 ± 2.2</td>
<td>—</td>
</tr>
<tr>
<td>Osteocalcin (ng ml⁻¹)</td>
<td>2.7 ± 1.5</td>
<td>1.3 ± 0.4</td>
<td>—</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU⁻¹)</td>
<td>112.0 ± 11.7</td>
<td>118.3 ± 13.9</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobin (g l⁻¹)</td>
<td>141.3 ± 4.6</td>
<td>142.3 ± 5.1</td>
<td>142.7 ± 4.7</td>
</tr>
<tr>
<td>White blood cells (10⁹ l⁻¹)</td>
<td>6.4 ± 0.7</td>
<td>6.7 ± 0.7</td>
<td>7.7 ± 0.9a</td>
</tr>
<tr>
<td>Monocytes (10⁹ l⁻¹)</td>
<td>0.56 ± 0.73</td>
<td>0.65 ± 0.09</td>
<td>0.71 ± 0.10</td>
</tr>
<tr>
<td>Neutrophils (10⁹ l⁻¹)</td>
<td>3.9 ± 0.5</td>
<td>4.0 ± 0.5</td>
<td>4.5 ± 0.6a</td>
</tr>
<tr>
<td>Lymphocytes (10⁹ l⁻¹)</td>
<td>1.7 ± 0.2</td>
<td>2.0 ± 0.3d</td>
<td>2.2 ± 0.3</td>
</tr>
</tbody>
</table>

Abbreviations: ANOVA, analysis of variance; CK, creatine kinase; IL-6, interleukin-6; IL-1ra, interleukin-1 receptor antagonist; TNF-α, tumor necrosis-factor-α; TRACP5b, tartrate-resistant acid phosphatase isozyme 5b.

aSignificant difference, \(P < 0.05\), pre- and post-exercise protocols (paired sample t-tests).
bSignificant difference, \(P < 0.05\), weeks 10–20 (ANOVA).
cSignificant difference, \(P < 0.05\), baseline to week 20 (ANOVA).
dSignificant difference, \(P < 0.05\), baseline to week 10 (ANOVA).
example, PSA) and growth factors,21,22 which suggests that the transient increase in GH and IGF-1 may not compromise disease state and progression.

The present study also examined the effects of chronic and acute resistance training on markers of inflammation. We found no significant effect of 20 weeks of resistance training on the systemic concentrations IL-6, IL-1ra and TNF-α at rest. It is difficult to compare absolute concentrations for these cytokines between studies, because different methods have been used to measure cytokine concentrations. Nevertheless, the lack of any significant change in the resting concentration of these cytokines could be due to the fact that the cytokine concentrations were not as high as those reported in other older populations.23,24

It was interesting to note that IL-6 and TNF-α did not change after the acute bout of resistance exercise at week 10, whereas these cytokines increased after the acute bout at week 20. It is likely that the inclusion of eccentric muscle contractions during the second bout of exercise caused more muscle damage, resulting in greater synthesis of IL-6 and TNF-α. CK, which is a common marker of exercise-induced muscle damage,25 increased followed both acute training protocols. The acute changes in IL-6 and TNF-α contrast with other findings following resistance exercise in young healthy individuals. Nieman et al.26 found an increase in plasma IL-6 concentration after 2 h intense resistance training, whereas Brenner et al.27 reported no change in plasma IL-6 or TNF-α concentration following intense circuit training. These differences could be due to variation in exercise protocols and subject characteristics.

Resting serum IL-8 concentration increased from week 10 to 20. Because IL-8 is generally considered to be a proinflammatory cytokine, this result was somewhat surprising – particularly in the absence of changes in IL-6, IL-1ra and TNF-α. The clinical significance of this increase is unclear. IL-8 plays an important role in the proliferation of prostatic epithelial cells in vitro.28 The increase in resting serum IL-8 concentration could therefore be possibly related to changes in disease status. In contrast to other studies,26 serum IL-8 concentration did not change after either bout of acute exercise. It is possible that IL-8 synthesis is impaired following exercise in older compared to young individuals.29

The increase in resting blood lymphocyte counts from baseline to week 10 may represent improved immune surveillance.30 The decrease in total leukocyte counts from week 10 to 20 is consistent with the findings from cross-sectional studies indicating that regular physical activity reduces total leukocyte counts.31,32 The effect of acute exercise on leukocyte, neutrophil, lymphocyte and monocyte counts is consistent with other studies involving resistance exercise,26,31 and indicates a normal immune response to resistance exercise in these patients.

Osteoporosis and the risk of skeletal fractures is increased following ADT.4 A high rate of bone turnover is an indicator of a greater reduction in bone mass.32 In our previous report on these patients, whole body and total hip bone mineral density (BMD) assessed by dual energy X-ray absorptiometry (DXA) were maintained following 20 weeks of training.10 However, 20 weeks is a relatively short period of time to detect changes in BMD as a result of training or treatment. Consequently, it is of interest that we observed that TRACP5b, a biomarker of bone resorption33 and a predictor of trabecular bone fracture,34 as well as ALP increased following training. This could be an indicator of increased bone turnover due to either the exercise intervention or ADT. In addition, with an intervention duration of only 20 weeks, it cannot be determined if this increased activity is leading to bone accrual or depletion. Longer duration studies of at least 12 months and inclusion of an inactive control group are required to elucidate the influence of high-intensity resistance training on bone metabolism in men undertaking ADT.

The strength of this study includes the broad range of biomarkers that were measured, providing data on endocrine function, disease status, inflammation and bone turnover. A stronger experimental design would have been to use a randomized controlled trial, and we recognize this as a limitation to our study. However, it should be recognized that all men recruited for the screening and selection process indicated that they would not have complied with a 20-week control period if they had been allocated to a control group. In addition, a large number of prostate cancer patients (91 subjects) were initially screened for participation, whereas only 11 men met the study inclusion criteria. Consequently, it was not possible to randomly assign some of them to a control group without compromising the power of the study.

In summary, we found that resistance exercise can be safely incorporated as adjuvant therapy for prostate cancer patients on ADT without compromising the purpose of the therapy, which is to suppress testosterone. The present findings, combined with our previously reported findings,10 support resistance exercise as an effective means of reducing treatment-related side effects. Acute increases in GH and DHEA may partly underlie improvements observed in this patient group undergoing resistance training. Further, the immune responses to this exercise mode may improve immunosurveillance in these patients.

Acknowledgements

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Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a comprehensive cross-sectional investigation

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This study examined the effects of androgen suppression therapy (AST) on upper and lower body muscle strength and a range of direct measures of physical performance using a cross-sectional design with 118 men (48 men undertaking AST for prostate cancer and 70 healthy aged-matched controls) from a single tertiary center. Primary end points included muscle strength for the upper- and lower-body; functional performance—repeated chair rise, usual and fast 6-m walk, 6-m backwards walk and 400-m walk time; and dual-energy X-ray absorptiometry assessment—whole body, regional soft tissue composition and bone mineral density (BMD). Men on AST had significantly reduced muscle strength for the upper- and lower-body and impaired functional performance compared to controls ($P < 0.05$). As expected, AST patients had significantly lower whole-body and hip BMD and higher percent of body fat than controls ($P < 0.05$), and tended to have lower whole-body lean mass ($-2.3$ kg, $P = 0.077$). Appendicular skeletal muscle was positively associated with upper-body ($r = 0.400–0.606$, $P < 0.001$) and lower-body ($r = 0.549–0.588$, $P < 0.001$) muscle strength, and strength was related to functional performance. Men undertaking AST were consistently impaired across a broad range of physical and functional musculoskeletal performance assessments compared with their age-matched normal controls. These findings are relevant for those patients considering AST for subclinical disease management, but whose physical reserve is marginal. Strategies to counter these adverse effects of AST need to be initiated so that independent living and quality of life can be maintained.

Keywords: androgen suppression; skeletal muscle; physical function; exercise

Introduction

Prostate cancer is now the commonest cancer after skin cancer in Western men.¹ Increased awareness about men’s health and prostate cancer, combined with the widespread availability of the prostate-specific antigen (PSA) blood test has lead to much earlier diagnosis of prostate cancer. In the last 10–20 years, there has been a substantial increase in use of androgen suppression therapies (ASTs) in men with subclinical prostate cancer for the longer-term benefits of reduced relapse, and possible increased survival.² However, it is becoming clearer that androgen suppression is associated with undesirable side effects³–⁷ and these need to be quantified in a meaningful way to assist informed decision-making, and direct research initiatives to minimize or address the more significant adverse consequences. Although the decline in bone and lean mass (LM) following AST has been consistently documented,⁷–⁹ only scant information exists regarding the impact of testosterone suppression on muscle strength and physical performance. Such adverse alterations in body composition aggravates the age-related loss of muscle mass (termed sarcopenia), which can further compromise muscle strength, physical function and independent living, particularly in older patients who may be approaching thresholds for disability.¹⁰,¹¹ Further, older prostate cancer patients are normally already at a greater risk for other comorbid conditions and physical limitations (for example, cardiovascular disease, diabetes, osteoporosis, skeletal fractures)¹¹,¹² that can dramatically affect their muscle and physical function. However, the
development of effective counter strategies requires a detailed understanding of the consequences of AST on physical adverse effects.

In this cross-sectional study we compared upper- and lower-body muscle strength, and a range of direct physical performance measures in a cohort of older men with localized prostate cancer on AST to age-matched healthy controls. Further, we also examined the impact of AST on whole-body and regional body composition and bone mineral density (BMD).

Methods
Participants
A total of 118 men (48 prostate cancer patients undergoing AST and 70 healthy aged-matched controls) participating in an ongoing exercise intervention study of aerobic and resistance exercise (Australian Clinical Trial Registry—ACTRN12607000263493) served as participants. The eligibility criteria for the prostate cancer patients included: histologically documented prostate cancer, receiving AST in the form of GnRH agonists alone or GnRH agonists plus antiandrogens in the previous 2 months, no bone metastatic disease, absence of any musculoskeletal, cardiovascular or neurological disorder that could inhibit them from exercising, able to walk 400 m and to undertake upper- and lower-limb exercise, and no resistance training in the previous 12 months. The healthy aging cohort included aged-matched men with similar height and body weight. Eligibility criteria for controls included absence of any musculoskeletal, cardiovascular or neurological disorder that could inhibit them from exercising, able to walk 400 m and to undertake upper- and lower-limb exercise, and no resistance training in the previous 12 months. Further, controls did not present for prostate cancer nor were undergoing any form of testosterone suppression. The protocol was approved by the University Human Research Ethics Committee and all participants provided written informed consent.

Dynamic isotonic muscle strength and muscle endurance
Participants underwent one familiarization session that included instruction regarding correct exercise technique and practice on all four isotonic resistance machines (upper body: chest press and seated row, lower body: leg press and leg extension) before muscle strength was determined. Dynamic isotonic muscle strength for the four exercises was measured using 1-repetition maximum (1-RM), as described previously. The 1-RM is the maximal weight an individual can move through a full range of motion by using proper exercise technique and not changing body position other than that of the specific exercise motion. The coefficient of variation in our laboratory for repeated 1-RM measures performed approximately 1 week apart is 2.2–7.5%. Muscle endurance was measured using the maximal number of repetitions performed at 70% of 1-RM for the chest press and leg press exercises. The coefficients of variation for chest press and leg press muscle endurance are 6.3 and 6.8%, respectively.

Physical performance
A battery of tests was used to assess functional performance. Tests were performed in triplicate (except for the 400-m walk) with sufficient recovery time between trials. The fastest time recorded was used in the analyses.

Chair rise to standing. Subjects were seated in a hard-backed chair, with a seat height of 43 cm from the floor, with their arms folded across their chest. They were instructed to rise as fast as possible to a full standing position then return to a full sitting position five times. The coefficient of variation in our laboratory for the repeated chair rise is 5.6%.

6-m walk. Two measures of gait speed were undertaken: usual pace, in which subjects were instructed to walk at a pace similar to which they may use during common daily activities; and a fast pace. Time taken was determined using electronic timing gates (Fitness Technology, South Australia). The coefficients of variation in our laboratory for usual and fast walk are 5.6 and 6.7%, respectively.

6-m backwards walk. As a measure of dynamic balance, subjects walked backwards 6 m placing one foot directly behind the heel of the other with the shoes touching. Time taken was assessed using electronic timing gates. Subjects were spotted by an investigator and if they deviated from the line (lost their balance), they were instructed to move back to the line and continue the test, which increased the time required. The coefficient of variation in our laboratory for the backward walk is 9.4%.

400-m walk. Participants were required to walk 400 m, which consisted of 10 laps out and back over a 20-m course, as fast as they could at a pace they could maintain over the distance. The 400-m walk has been shown to be a valid test to estimate cardio-respiratory fitness and walking endurance in older adults. The coefficient of variation in our laboratory for the 400-m walk is 2.5%.

Body composition and bone mineral density
BMD (g cm−2) of the hip and total body was assessed by dual-energy X-ray absorptiometry (Hologic Discovery A, Waltham, MA, USA). In addition, whole-body LM, fat mass (FM) and percent fat were derived from the whole-body scan. From the whole-body scan, upper limb, lower limb, and trunk LM and FM were derived by manipulating segmental lines according to anatomical landmarks. Upper limb LM (ULLM) and lower limb LM (LLLM) were then summed to derive appendicular skeletal muscle (ASM). The coefficients of variation (duplicate scans with repositioning) for WBLM, ULLM, LLLM and ASM were 0.3, 2.1, 0.8 and 0.3%, respectively.
Other measures
Height and weight were determined by a stadiometer and electronic scale, respectively, and body mass index (BMI, kg m$^{-2}$) was calculated from weight divided by the square of height. Self-rated health was based on a five-point scale of 1, excellent; 2, very good; 3, good; 4, fair and 5, poor. Number of prescription medications and comorbidities, and mild physical activity were assessed using a general health history questionnaire. For men on AST, GnRH agonists and/or antiandrogen medications and prostate cancer were not included as number of prescription medications or comorbidities. For mild physical activity, subjects were asked about their current level of activity and to provide details. Those reporting being physically active listed easy walking, easy bicycling, golf, bowling and gardening as their usual activities.

Statistical analyses
Data were analyzed using the SPSS statistical software package (SPSS Inc., Chicago, IL, USA). Normality of the distribution for the various measures was assessed using the Kolmogorov–Smirnov test. Analyses included standard descriptive statistics, unpaired Student’s t-tests, $\chi^2$-test and Pearson’s correlation test. All tests were two tailed and a P-value of <0.05 was required for significance. Results are given as the mean $\pm$ s.d.

Results
Patient characteristics are shown in Table 1. There was no difference between groups for age, height, weight or BMI, although the AST group had poorer perceived health than controls ($P<0.001$). There was no difference between groups for number of prescription medications taken or number of comorbidities. Both groups showed a similar rate for current mild physical exercise (AST, 85.4% active; controls, 89.9% active).

Muscle function
Men on AST had significantly reduced muscle strength for the seated press, row and leg extension compared to controls (Table 2; $P<0.05$). There were no differences between groups for either leg press strength or muscle endurance ($P>0.05$).

Physical performance
Men on AST performed poorer on the 6-m usual walk, 6-m fast walk, 6-m backwards walk, repeated chair rise and 400-m corridor walk than controls (Table 2; all $P<0.05$). The actual speed in meters per second (m s$^{-1}$) for the 6-m usual and fast walk and the 400-m walk is shown in Figure 1. For all subjects, usual walk speed was correlated ($P<0.001$) with fast walk speed ($r=0.660$), backward walk ($r=0.382$), chair rise ($r=0.430$) and 400-m walk ($r=0.416$). Further, leg extension muscle strength was inversely associated ($P<0.001$) with 6-m usual walk ($r=-0.320$), 6-m fast walk ($r=-0.346$), 6-m backward walk ($r=-0.308$), chair rise ($r=-0.352$) and 400-m walk ($r=-0.391$) with higher quadriceps muscle strength associated with better functional performance.

Body composition and BMD
Men on AST had significantly lower whole-body, upperand lower-limb, and hip BMD and higher percent of body fat than controls (Table 3; $P<0.05$). Further, whole-body FM tended to be higher (+2.2 kg, $P=0.068$) and whole-body LM lower ($-2.3$ kg, $P=0.071$) in AST patients. AST patients had $\sim 1$kg less ASM compared to controls although differences were not statistically significant ($P>0.05$). Further, there was a significant difference between groups for lower limb fat ($P=0.012$) but not for upper limb or trunk FM ($P>0.05$). In AST patients, ASM was positively associated with chest press ($r=0.400$, $P<0.001$), seated row ($r=0.606$, $P<0.001$), leg extension ($r=0.549$, $P<0.001$) and leg press ($r=0.588$, $P<0.001$) muscle strength.

Discussion
There are four important findings from our cross-sectional analysis: (1) prostate cancer patients undergoing AST show reduced performance in a range of

---

**Table 1** Physical characteristics of prostate cancer patients on AST and healthy aged-matched controls (mean $\pm$ s.d.)

<table>
<thead>
<tr>
<th>Variables</th>
<th>AST  ($n=48$)</th>
<th>Controls ($n=70$)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.8 $\pm$ 7.0</td>
<td>69.9 $\pm$ 4.0</td>
<td>0.871</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.9 $\pm$ 8.6</td>
<td>172.6 $\pm$ 6.0</td>
<td>0.573</td>
</tr>
<tr>
<td>Total weight (kg)</td>
<td>80.9 $\pm$ 11.8</td>
<td>80.6 $\pm$ 11.5</td>
<td>0.884</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>27.3 $\pm$ 3.4</td>
<td>27.0 $\pm$ 3.2</td>
<td>0.598</td>
</tr>
<tr>
<td>Number of medications</td>
<td>2.6 $\pm$ 1.9</td>
<td>2.3 $\pm$ 2.3</td>
<td>0.548</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>1.0 $\pm$ 1.2</td>
<td>1.0 $\pm$ 1.0</td>
<td>0.897</td>
</tr>
<tr>
<td>Self-rated health</td>
<td>2.7 $\pm$ 0.7</td>
<td>2.3 $\pm$ 0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Physical activity/inactive</td>
<td>39/07</td>
<td>62/08</td>
<td>0.420</td>
</tr>
</tbody>
</table>

**Table 2** Functional performance, muscle strength and endurance measures in prostate cancer patients on AST and healthy aged-matched controls (mean $\pm$ s.d.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AST ($n=48$)</th>
<th>Controls ($n=70$)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-m usual walk (s)</td>
<td>4.8 $\pm$ 0.6</td>
<td>4.5 $\pm$ 0.6</td>
<td>0.042</td>
</tr>
<tr>
<td>6-m fast walk (s)</td>
<td>3.7 $\pm$ 0.5</td>
<td>3.5 $\pm$ 0.3</td>
<td>0.013</td>
</tr>
<tr>
<td>400-m walk (s)</td>
<td>274.3 $\pm$ 32.7</td>
<td>256.1 $\pm$ 34.0</td>
<td>0.005</td>
</tr>
<tr>
<td>6-m backward walk (s)</td>
<td>23.8 $\pm$ 13.8</td>
<td>19.9 $\pm$ 6.3</td>
<td>0.035</td>
</tr>
<tr>
<td>Chair rise (s)</td>
<td>13.5 $\pm$ 2.8</td>
<td>12.0 $\pm$ 2.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Muscle strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest press (kg)</td>
<td>32.4 $\pm$ 10.5</td>
<td>37.5 $\pm$ 9.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Seated row (kg)</td>
<td>38.7 $\pm$ 6.6</td>
<td>42.4 $\pm$ 8.4</td>
<td>0.014</td>
</tr>
<tr>
<td>Leg press (kg)</td>
<td>91.0 $\pm$ 41.4</td>
<td>86.8 $\pm$ 37.4</td>
<td>0.567</td>
</tr>
<tr>
<td>Leg extension (kg)</td>
<td>36.3 $\pm$ 13.0</td>
<td>44.9 $\pm$ 12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle endurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest press (rep)</td>
<td>11.6 $\pm$ 4.1</td>
<td>11.4 $\pm$ 5.0</td>
<td>0.819</td>
</tr>
<tr>
<td>Leg press (rep)</td>
<td>18.0 $\pm$ 6.7</td>
<td>17.7 $\pm$ 7.5</td>
<td>0.867</td>
</tr>
</tbody>
</table>
total body ASM (kg) 23.7 ± 3.4 24.5 ± 2.9 0.148

Bone mass

<table>
<thead>
<tr>
<th>Variable</th>
<th>AST (n = 48)</th>
<th>Controls (n = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body BMD (g cm⁻²)</td>
<td>1.095 ± 0.110</td>
<td>1.147 ± 0.108</td>
<td>0.013</td>
</tr>
<tr>
<td>Upper limb BMD (g cm⁻²)</td>
<td>0.810 ± 0.068</td>
<td>0.848 ± 0.060</td>
<td>0.002</td>
</tr>
<tr>
<td>Lower limb BMD (g cm⁻²)</td>
<td>1.178 ± 0.126</td>
<td>1.245 ± 0.151</td>
<td>0.015</td>
</tr>
<tr>
<td>Total hip BMD (g cm⁻²)</td>
<td>0.951 ± 0.124</td>
<td>0.999 ± 0.113</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Abbreviations: AST, androgen suppression therapy; ASM, appendicular skeletal muscle; BMD, bone mineral density.

Table 3 Total and regional body composition and bone mass in prostate cancer patients on AST and healthy aged-matched controls (mean ± s.d.).

Figure 1 The actual speed (m s⁻¹) for 6-m usual, 6-m fast and 400-m walk for prostate cancer patients on androgen suppression therapy (AST) and healthy aged-matched controls (mean ± s.e.); *<0.05.

Physical function and androgen suppression

DA Galvão et al

Physical function and androgen suppression therapy can be improved in men on AST compared to healthy aged-matched controls. Although the rapid loss of LM following AST is likely to negatively affect physical function, only limited information exists regarding the impact of AST on muscle function and strength. A previous cross-sectional study suggested that upper- (chest press) but not lower-limb muscle strength (leg press) was reduced following AST.27 Our study extends those findings indicating that quadriceps muscle strength using the leg extension exercise as well as chair rise ability, which incorporates lower limb muscle strength and endurance and also balance, was also improved in men on AST compared to healthy aged-matched controls. The reduction in usual walking speed ability in AST patients compared to controls indicates that mobility is reduced following AST and may possibly lead to further deterioration in physical function by additional inactivity and musculoskeletal wasting.

Aerobic walking capacity (cardiorespiratory fitness) as measured by the 400-m walk has been shown to be a strong predictor of mortality, cardiovascular disease and mobility limitations in older adults.17–19 Moreover, even in individuals with well-known risk factors for cardiovascular disease (for example, hypertension, diabetes, smoking, high total cholesterol), it is clear that those with greater cardiorespiratory fitness are at lower risk for premature death than individuals with lower aerobic fitness (for example, sedentary) but without other risk factors for cardiovascular disease.20 We have observed that cardiorespiratory fitness was significantly reduced in AST patients compared to controls. This is a significant finding as the reduction in cardiorespiratory fitness compounded with increases in FM and abdominal obesity following AST could substantially contribute to the increased incidence of cardiovascular and metabolic complications in men undergoing AST.3,4,25,26

We observed reduced muscle strength in men on AST compared to healthy aged-matched controls. Although the rapid loss of LM following AST is likely to negatively affect physical function, only limited information exists regarding the impact of AST on muscle function and strength. A previous cross-sectional study suggested that upper- (chest press) but not lower-limb muscle strength (leg press) was reduced following AST.27 Our study extends those findings indicating that quadriceps muscle strength using the leg extension exercise as well as chair rise ability, which incorporates lower limb muscle strength and endurance and also balance, was also improved in men on AST compared to healthy aged-matched controls.
reduced in AST patients. Further, we have demonstrated that elbow flexor as well as shoulder extensor muscle strength (seated row) was reduced. This is a significant finding given that the loss of upper- and lower-body muscle strength in AST patients can further compromise physical function and independent living, particularly in older patients who may be approaching thresholds for disability.10,11

The loss of LM and BMD as well as an increase in FM following AST has been well documented.7,8,27–29 Our results confirm these findings and further indicate that ASM is positively associated with upper- and lower-body muscle strength. The reduction in BMD places the individual at a greater risk for fracture following a fall, and the risk of falling is strongly related to muscle strength and balance.30 Our men on AST had poorer strength, dynamic balance (as determined by the 6-m backwards walk test) and BMD, placing them at an increased risk for falls and subsequent fracture. As it has been reported31 that quality of life, morbidity and mortality following hip fracture in older people is particularly poor, this consequence of AST is also of great concern.

The associations we found among muscle mass, strength and physical performance suggest that preserving LM may protect against muscle strength loss and subsequent deterioration in physical function. Currently, there is no established treatment to reverse the loss of LM and physical function during AST. Physical exercise, in particular resistance training, may be an important countermeasure against the reduction of LM and muscle strength that accompanies AST.11 We have previously shown that resistance exercise can be safely undertaken by patients on AST without elevating testosterone32 and can significantly enhance upper and lower body muscle strength and improve physical performance.33 Although long-term studies using exercise are yet to be conducted, exercise may provide an important protective effect against FM gain and exacerbation of sarcopenia that can lead to loss of physical function and the increased risk for AST-associated cardiovascular diseases.34

Our study has several limitations. The cross-sectional nature of the study does not permit us to infer cause and effect. Therefore, prospective studies are required to confirm our findings. Further, we were unable to include data regarding testosterone and PSA as participants were drawn from an ongoing prospective study in which the blood sample data are not yet available; however the patients were undertaking standard AST programs that consistently achieve hypogonadal states. No patients were identified with active disease during or in the 3 months after completion of the study assessment period. Nevertheless, our study has several strengths including the comprehensive battery of functional tests, assessment of upper- and lower-body muscle strength, and measures of regional soft tissue composition. In addition, the healthy aged-matched controls did not differ for height or body weight to AST patients providing a strong comparison between the two groups. Further, all measures were conducted in a single center which reduces variation for the physical measures undertaken.

In summary, we found that men on AST have significantly worse musculoskeletal, physical and performance status compared with normal age-matched controls. These adverse outcomes could impair the ability to perform normal activities of daily living, an outcome of particular relevance to those with already marginal physical reserves such as some older, independent living prostate cancer patients. Our findings therefore have immediate clinical relevance for the informed consent process; elderly patients, with marginal physical reserve, might be less likely to complete AST for subclinical disease management. However, our primary aim was to examine a broad range of measures of musculoskeletal performance to better characterize the impact of AST. Only by understanding a process, can effective strategies be developed to address problems. Currently, the undertaking of resistance exercise by men on AST appears to be the principal strategy to counter these AST-related adverse effects.11,33

Acknowledgements

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References


Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer

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Accepted for publication 22 November 2007

Study Type – Therapy (individual cohort study)
Level of Evidence 2b

OBJECTIVE

To assess the effects of androgen deprivation therapy (ADT) on whole-body and regional muscle, fat and bone mass in men with prostate cancer without metastatic bone disease.

PATIENTS AND METHODS

Seventy-two men aged 44–88 years underwent spine, hip and whole-body dual-energy X-ray absorptiometry scans at baseline and after 36 weeks of ADT. The change in whole-body and regional lean mass (LM), fat mass (FM), and bone mineral content and density (BMD) were determined. In addition, the prostate specific antigen (PSA), serum testosterone and haemoglobin levels were measured, and the level of physical activity and fatigue assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30.

RESULTS

The upper limb, lower limb, trunk and whole-body LM decreased by a mean (SEM) of 5.6 (0.6)%, 3.7 (0.5)%, 1.4 (0.5)% and 2.4 (0.4)% (P < 0.01), respectively, while FM increased by 20.7 (3.3)%, 18.7 (2.7)%, 12.0 (2.5)% and 13.8 (2.3)% (P < 0.001). Hip, spine, whole-body and upper limb BMD decreased by 1.5 (0.5)%, 3.9 (0.4)%, 2.4 (0.3)% and 1.3 (0.3)% (P < 0.001), but not lower limb BMD. Serum testosterone, PSA and haemoglobin levels decreased by 93.3 (0.4)%, 98.2 (0.5)%, and 8.8 (0.9)% (P < 0.001), respectively. In addition, physical activity levels decreased and levels of fatigue increased.

CONCLUSION

After 36 weeks of ADT there was a significant decrease in whole-body and regional LM and bone mass, while whole-body and regional FM increased in older men with prostate cancer. Strategies to counteract changes in soft tissue and bone mass during ADT should be formulated to minimize the risk of sarcopenia, osteoporosis and obesity.

KEYWORDS

lean mass, fat mass, bone mass, androgen deprivation therapy

INTRODUCTION

Androgen deprivation therapy (ADT) is being increasingly used in the management of prostate cancer, in particular as adjuvant treatment and for disease with early PSA relapse. These patients can be expected to live for many years, but ADT is accompanied by several adverse side-effects that include reduced bone mass and increased risk of fracture at multiple sites, reduced lean mass (LM) and muscle strength, and increased fat mass (FM) [1–4]. Given that prostate cancer affects older men, it can be expected that these treatment side-effects would exacerbate the age-related loss of muscle mass, termed sarcopenia, further compromising muscle strength, physical function and independent living [5].

There is only scant information on changes in bone mass and soft tissue after ADT [6–8], and there is no information on changes in the regional distribution of bone, LM and FM (i.e. trunk, upper, UL, and lower limb, LL) during therapy. Abdominal fat has been related to an increased risk of the development of cardiovascular complications; thus, if ADT induces trunk fat accumulation, alternative or adjuvant therapies to counteract this should be devised. Similarly, a reduction in muscle and bone mass, especially at weight-bearing sites, increases the risk of falls and fracture, and subsequent morbidity and mortality.

To devise effective strategies to counter the physiological side-effects of ADT it is necessary to first document the resulting patterns of change to bone mass and body composition. The purpose of the present study was to examine the alterations in the whole-body (WB) and regional bone, LM and FM in men that occurs after receiving ADT for prostate cancer.

PATIENTS AND METHODS

In all, 72 patients with prostate cancer (aged 44–88 years) receiving intermittent ADT had hip, spine and WB scans using dual-energy X-ray absorptiometry (DXA) at baseline and after 36 weeks of treatment. The patients were a
subgroup from one clinical site of those participating (250) in a multicentre trial where we previously reported the effects of intermittent ADT on variables of quality of life [9]. The men were required to have a histological or cytological diagnosis of adenocarcinoma of the prostate and to have an Eastern Cooperative Oncology Group performance status of 0, 1 or 2 at baseline. Previous neoadjuvant hormonal therapy did not preclude study entry, provided that the disease had been confirmed and the PSA level >2 ng/mL, measured on three consecutive 2-month intervals and >2 years previously and was given for ≤6 months. Institutional Ethics Committee approval was obtained and each participant provided written consent. ADT was achieved using a maximum AD programme of flutamide 250 mg three times daily and leuproplide 22.5 mg 3-monthly depot over 36 weeks. The extent of disease was prospectively categorized as: locally advanced with no evidence of metastatic disease but not considered suitable for or declining radical treatment; metastatic, where metastatic disease had been confirmed and the PSA level was >10 ng/mL; recurrent and local after radical prostatectomy or radical radiotherapy, and associated with an increasing PSA level to ≥2 ng/mL, measured on three consecutive occasions at intervals of ≥1 month apart and with no evidence of metastatic disease.

Bone mineral density (BMD, g/cm²) and content (BMC, g) of the total hip, spine and WB was assessed by DXA (Hologic Discovery W, Waltham, MA, USA). In addition, the bone mineral-free LM and FM of the WB, UL, LL, trunk and percentage body fat were derived from the WB scan. The regional analysis was derived by manipulating segmental lines according to specific anatomical landmarks [10,11]. A vertical line extended between the head of the humerus and the glenoid fossa separated the ULs from the trunk, while an oblique line through the femoral neck separated the LLs from the pelvis. ULLM and LLLM represent the sum of left and right extremities; the ULLM and LLLM were then combined to derive appendicular skeletal muscle (ASM) [12,13].

PSA in the serum was measured using an Immurize analyser (Beckman Coulter Inc., Fullerton, CA, USA) using a test kit (Diagnostic Products Corp., Los Angeles, CA, USA).

Serum concentrations of testosterone were determined by radioimmunoassay (DPC free testosterone kit, Diagnostic Products Corp.) and haemoglobin concentration was measured using an automated analyser (Sysmex XE-AlphaN, Sysmex Corporation, Kobe, Japan).

Serum markers of bone formation, alkaline phosphatase and osteocalcin, were measured by radioimmunoassay and by enzyme immunoassay with an Intact Osteocalcin EIA kit (Biomedical Technologies, Inc., MA, USA), respectively. Urine calcium, urine calcium excretion and urine calcium/creatinine ratio were assessed using a chemistry analyser.

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 v 2.0 core questionnaire was used to assess changes in physical activity and levels of fatigue. The QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and an overall health and quality-of-life scale. All scales are scored from 0 to 100; high scores for a functional scale represented high or healthy levels of functioning, as does the overall health or quality of life. High scores for a symptom scale or item represented high levels of symptoms or problems.

The baseline and 36-week values, and the percentage change for WB and regional lean, fat and bone mass are also shown in Table 2. After treatment, WBLM and bone mass significantly (P < 0.001) decreased and FM increased. There were significant (P < 0.01) declines at all regional sites for LM, with the percentage decline in LLLM and ULLM greater than that for trunk LM (P = 0.004). Conversely, FM increased (P < 0.001) at all regional sites with the change in the limbs greater than the trunk (P < 0.001). There was a significant (P < 0.001) reduction in hip and spine BMD of 1.5% and 3.9%, respectively, and a decline in UL BMD of 1.3% (P < 0.001) with no significant change for the LL. The decrease in BMD at the spine was greater than that at the hip site (P = 0.032).

The present results show that 36 weeks of ADT in men with prostate cancer has a deleterious effect on WB and regional tissue composition, by decreasing muscle and bone mass and increasing FM. The change in soft tissue was greater for the limbs than the trunk, and for the older patients might contribute to a decline in their functional performance and loss of independence.

Our findings confirm the changes in WB composition previously reported by Smith et al. [6], where body weight and FM increased by 2.4% and 9.4%, respectively, and LM decreased by 2.7% after 48 weeks of ADT. This same group [8] also reported an increase of 11% in FM and a decrease of ≈4% in LM after 1 year of ADT. The present study extends these findings and indicates that the decline in LM from the upper and lower limbs is greater than changes occurring in the trunk. This

---

**TABLE 1 The distribution of the 72 patients according to performance status, disease extent and descriptive variables**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Descriptive statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>25 (34.7)</td>
</tr>
<tr>
<td>Locally recurrent</td>
<td>41 (57)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>52 (72)</td>
</tr>
<tr>
<td>1</td>
<td>19 (17)</td>
</tr>
<tr>
<td>2</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mean (50, range)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>73.5 (8.3, 44.4–88.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.1 (3.8, 18–38)</td>
</tr>
</tbody>
</table>

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preferential loss from the limbs would be expected, given that the trunk includes a large mass of non-contractile lean tissues. As reduced muscle mass and function are directly associated with impairments and compromised function in older adults [14,15], our findings would suggest that countermeasures need to be implemented to maintain or even reverse the rate of muscle loss in the most affected areas after ADT. Resistance training has been reliably shown to be a safe and effective strategy to improve muscle mass and function in older adults [16], including the very old [17], and might be important in attenuating or reversing this muscle loss in men treated with ADT [18]. For example, we recently reported the preservation of body composition after a resistance-training intervention, and improvements in physical and functional performance, neuromuscular strength and balance, in a group of men undergoing ADT for prostate cancer [19]. In the present study there was also an increase in fat accumulation at all regional sites, with greater changes for the limbs than the trunk. The increase in WB fat is consistent with previous studies [6–8], but there were regional differences in fat distribution with ADT. Increased abdominal FM has been associated with a greater risk of developing coronary artery disease, type 2 diabetes, hyperlipidaemia, and premature death, than accretion of FM in the extremities [20]. Consequently, although the accumulation of fat was relatively less for the trunk, strategies aimed at minimizing fat accretion during ADT should be explored. In addition, the decline in LM would compromise the basal metabolic rate and hence energy requirement, and this would contribute to the increase in FM associated with ADT. Therefore, strategies aimed at preserving LM will also assist in attenuating the increase in FM. Recently, a large observational study indicated the relationship between an increased incidence of diabetes, coronary heart disease, myocardial infarction and sudden cardiac death with ADT [21]. Moreover, a recent report also suggested that patients with prostate cancer and a higher BMI are at greater risk of dying from the disease, reinforcing the importance of maintaining body composition during treatment [22].

In the present study there was also a significant decrease in lumbar spine, hip and WB BMD after therapy. Several studies reported decreases of bone mass after ADT [3,23–25] and recent reviews [4,26] highlighted the importance of addressing bone loss and osteoporosis in this group of patients. In addition, the long-term effects of ADT on bone loss were also reported, with continuous loss of BMD after 12 months of therapy [2]. Interestingly the present analyses showed that although BMD decreased in the UL, there were no such changes in the LL. The loading that the lower extremities are subject to during ambulation and other activities which produce high force transmission through the skeleton might have contributed to preserving bone density compared to the non-weight-bearing upper extremities. The BMD for the spine also decreased more than at the hip. This might be attributed to the greater trabecular bone composition of the spine than in the proximal femur, where earlier bone turnover and therefore loss of BMD in the axial skeleton might occur [27]. Maillefer et al. [24] also reported greater losses in BMD at the lumbar spine than femoral neck in a small group of patients after 18 months of ADT. In addition to the changes in BMD, in the present study there was a marked increase in markers of bone resorption and formation, indicating increased bone turnover.

The present study has some limitations. A stronger experimental design would have been to use a randomized controlled trial. However, the present study was designed to reflect the range of clinical practice in Australia (multicentre trial) [8] and data presented are the results from one hospital site collected during a national study. It can be argued that observed changes in body composition and BMD could be a result of the normal ageing process and not androgen suppression. However, the alterations in body composition and BMD observed are well beyond those expected with normal ageing and probably reflect toxicity from the therapy.

### Table 2: Changes in testosterone, PSA, haemoglobin and bone marker levels, body composition and bone mass, after 36 weeks of ADT for 68 men

<table>
<thead>
<tr>
<th>Mean (SEM) variable</th>
<th>Baseline</th>
<th>36 weeks</th>
<th>% change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone, pg/mL</td>
<td>15.1 (0.8)</td>
<td>0.80 (0.03)</td>
<td>−93.3 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
<td>22.6 (3.1)</td>
<td>0.23 (0.05)</td>
<td>−98.2 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin, g/L</td>
<td>145.2 (1.5)</td>
<td>131.9 (1.5)</td>
<td>−8.8 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bone markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum osteocalcin*, ng/mL</td>
<td>4.7 (0.05)</td>
<td>7.4 (0.7)</td>
<td>341.0 (111.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Alkaline phosphatase†, IU/L</td>
<td>89.0 (6.1)</td>
<td>99.5 (7.1)</td>
<td>13.5 (3.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Urine calcium/creatinine ratio†</td>
<td>240.4 (24.6)</td>
<td>415.3 (39.1)</td>
<td>101.5 (12.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine calcium excretion, mg†</td>
<td>21.2 (2.4)</td>
<td>35.3 (3.6)</td>
<td>94.0 (12.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body composition and bone mass</th>
<th>Lean tissue mass, kg</th>
<th>Fat mass, kg</th>
<th>Body fat, %</th>
<th>BMD, g/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>55.8 (0.8)</td>
<td>54.4 (0.8)</td>
<td>−2.4 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UL</td>
<td>63.0 (0.1)</td>
<td>59.0 (0.1)</td>
<td>−5.6 (0.6)</td>
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</tr>
<tr>
<td>LL</td>
<td>17.1 (0.2)</td>
<td>16.4 (0.2)</td>
<td>−3.7 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trunk</td>
<td>28.8 (0.4)</td>
<td>28.3 (0.4)</td>
<td>−1.4 (0.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>ASM</td>
<td>23.4 (0.3)</td>
<td>22.4 (0.3)</td>
<td>−4.2 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FM</td>
<td>20.8 (0.7)</td>
<td>23.1 (0.7)</td>
<td>13.8 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UL</td>
<td>2.1 (0.1)</td>
<td>2.5 (0.1)</td>
<td>20.7 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LL</td>
<td>5.5 (0.2)</td>
<td>6.4 (0.2)</td>
<td>18.7 (2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trunk</td>
<td>12.13 (0.4)</td>
<td>13.1 (0.4)</td>
<td>12.0 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>25.8 (0.6)</td>
<td>28.5 (0.7)</td>
<td>2.6 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WB</td>
<td>1.164 (0.014)</td>
<td>1.145 (0.014)</td>
<td>−2.4 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UL</td>
<td>1.732 (0.015)</td>
<td>1.708 (0.015)</td>
<td>−1.3 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LL</td>
<td>2.576 (0.038)</td>
<td>2.559 (0.041)</td>
<td>−0.6 (0.4)</td>
<td>0.173</td>
</tr>
<tr>
<td>Total hip‡</td>
<td>1.021 (0.018)</td>
<td>1.001 (0.018)</td>
<td>−1.5 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spine‡</td>
<td>1.123 (0.024)</td>
<td>1.086 (0.023)</td>
<td>−3.9 (0.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

No. of patients: *63; †62; ‡69.
In conclusion, a relatively short period of 36 weeks of ADT had a negative impact on WB and regional tissue composition in men with non-metastatic prostate cancer. These changes were marked, with reductions in LM and increases in FM at all regional sites (UL, LL and trunk). Also, there were decreases in lumbar spine and hip, WB and UL BMD. We propose that strategies to counteract such changes in soft tissue and bone during ADT in older men should be implemented, to minimize the risk of sarcopenia, osteoporosis and obesity, and subsequent disability.

ACKNOWLEDGEMENTS

Research Support from Schering-Plough Pty Ltd and Abbott Australasia Pty Ltd.

CONFLICT OF INTEREST

None declared.

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17 Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High-intensity strength training in nonagenarians. Effects on skeletal muscle. JAMA 1990; 263: 3029–34

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e-mail: Nigel.Spry@health.wa.gov.au

Abbreviations: ADT, androgen deprivation therapy; LM, bone mineral-free lean mass; FM, fat mass; ASM, appendicular skeletal muscle; DXA, dual-energy X-ray absorptiometry; UL, upper limb; LL, lower limb; WB, whole body; BMD(C), bone mineral density (content); BMI, body mass index; EORTC, European Organization for Research and Treatment of Cancer.
REVIEW

Cardiovascular and metabolic complications during androgen deprivation: exercise as a potential countermeasure

DA Galvão, DR Taaffe, N Spry, D Joseph and RU Newton

Apart from the well-established adverse musculoskeletal and sexual health effects of androgen deprivation therapy (ADT), evidence is accumulating of substantial ADT-related cardiovascular and metabolic complications, which may impact quality of life and overall survival. In this brief review we discuss (1) the incidence of cardiovascular and metabolic complications during/following ADT from large cohort studies, (2) the increased risk factors for cardiovascular and metabolic disease from cross-sectional and prospective studies and (3) the use of physical exercise as a countermeasure in this new era of ADT-related toxicity. It is clear that exercise has the potential to provide a myriad of benefits to men undergoing ADT that may result in reduced morbidity and mortality, and subsequently improve quality of life.

Keywords: androgen deprivation; cardiovascular disease; metabolic syndrome; physical exercise; prostate cancer

Introduction

There has been a very substantial increase in the use of temporary androgen deprivation treatment (ADT) in the adjuvant management of prostate cancer to achieve improved prostate-specific antigen relapse-free survival and overall survival. However, these benefits only manifest years later, and then only for a small proportion of those treated. Information about potential treatment toxicity is therefore vital for informed decision making. Well-recognized side effects of ADT include vasomotor flushing, anemia, fatigue, gynecomastia, osteoporosis and skeletal fractures, and toxicity-related musculoskeletal deficits impacting on quality of life. However, additional information from several large scale observational studies has come to light regarding an increased incidence of significant cardiovascular and metabolic complications associated with temporary ADT.

To date, a number of cross-sectional and short-term prospective studies of men treated with ADT have consistently reported an increase in risk factors for cardiovascular and metabolic complications such as increased arterial stiffness and abdominal obesity, hyperglycemia, altered lipoprotein profile, as well as an increased incidence of metabolic syndrome. Such unfavorable metabolic alterations from testosterone suppression could potentially mediate the mechanisms underlying the higher frequency of cardiovascular events observed in prostate cancer patients undergoing this form of treatment. Moreover, this may be compounded by the failure of testosterone to recover in some men following cessation of ADT, hence ADT-related complications that arise may not be temporary.

In non-prostate cancer patients, increased levels of physical activity is well known to reduce risk of type 2 diabetes as demonstrated in large cohort studies where a dose–response relationship between exercise and relative risk of developing diabetes have been reported. Importantly, the protective effect of physical activity seems to be even stronger in individuals at highest risk for type 2 diabetes, defined as those with a high body mass index (BMI), history of hypertension or a family history of diabetes. This could also be the case for prostate cancer patients on ADT where increased fat mass as an adverse effect from therapy is well established. Although studies are yet to be conducted with testosterone-deplete patients examining the effects of exercise on cardiovascular and metabolic complications, there is a strong rationale based on other patient populations, as well as in healthy adults, that exercise may serve to prevent or attenuate ADT-related cardiovascular and metabolic morbidity and mortality.
In this brief review, we discuss (1) the increased incidence of cardiovascular and metabolic disease following ADT, (2) increased risk factors for cardiovascular and metabolic disease (for example, abdominal obesity, high cholesterol) in ADT-treated men from cross-sectional and prospective studies and (3) use of physical exercise as a contemporary patient management strategy in this new era of ADT-related toxicity. Information for this review was obtained by searching PubMed database from 2000 to December 2008 with a combination of the following terms: cardiovascular disease, metabolic syndrome, diabetes, testosterone suppression, cardiovascular training, resistance training, physical activity and prostate cancer. Secondary searching involved scanning the reference lists from the papers identified above and then locating papers, which appeared useful in reviewing the topic.

Incidence of cardiovascular diseases and diabetes during and following ADT

Four recent and large cohort studies have examined the association between ADT and increased incidence of cardiovascular disease and diabetes. Keating et al. reported results from the first large population-based cohort of 73,196 localized prostate cancer patients using the Surveillance, Epidemiology and End Results (SEER) Medicare data examining whether ADT in the form of gonadotropin-releasing hormone (GnRH) agonist or bilateral orchiectomy was associated with coronary heart disease, myocardial infarction, diabetes and sudden cardiac death. In Cox proportional hazards models adjusted for a number of potential confounders, such as age, race, tumor grade, comorbidity score, year of primary diagnosis and primary surgical therapy but not disease-related risk factors such as blood lipids, tobacco use and hypertension, GnRH agonist administration was associated with an increased risk of coronary heart disease, myocardial infarction, sudden cardiac death and diabetes by 16, 11, 16 and 44%, respectively. Moreover, the increased risk for incident diabetes and coronary heart disease was apparent with as little as 1–4 months ADT. Saigal et al. also examined risk of cardiovascular morbidity using the SEER registry. After controlling for a number of factors including patient and tumor characteristics, comorbidity score and pretreatment cardiac disease, men who received ADT had a 20% increased probability of cardiovascular morbidity and this increased risk was observed within the initial 12 months of ADT.

D’Amico et al. reported pooled results from three randomized trials including cohorts from Australia and New Zealand (n = 802), Canada (n = 364) and United States (n = 206), and examined the time to fatal myocardial infarction following three to eight months of ADT (combination of a luteinizing hormone-releasing hormone agonist and a nonsteroidal antiandrogen) in men who were also receiving external beam radiotherapy. Six months of ADT lead to a shorter time to fatal myocardial infarction in men aged 65 years or more compared to men aged 65 years or more not undertaking ADT and to all men less than 65 years. Further, in those aged 65 or more similar time to fatal myocardial infarction was observed between 3 and 6 to 8 months ADT suggesting an increased risk of cardiovascular-related toxicity even after short-term ADT.

Tsaï et al., using data from the Cancer of the Prostate Strategic Urologic Research Endeavor retrospectively examined whether ADT use was associated with death from cardiovascular-related causes in localized prostate cancer patients. A total of 1015 patients were treated with ADT in combination with local therapy (external beam radiation therapy, brachytherapy, cryotherapy or radical prostatectomy) whereas 3877 were not treated with ADT. After a median follow-up time of 3.8 years and median ADT duration of 4.1 months, patients aged 65 or more who underwent both radical prostatectomy and ADT had a 5-year cumulative incidence of cardiovascular death of 5.5% compared to 2% for those undergoing radical prostatectomy but not ADT. Further, men younger than 65 years undergoing the same treatment had a cumulative incidence of 3.6% compared to 1.2% in those not receiving ADT. However, given the retrospective nature of the study, a number of factors that may contribute to cardiovascular death, such as family history, hypercholesterolemia and smoking status were not controlled for in the analyses.

The findings from these four studies extend beyond the well-established adverse effects related to the musculoskeletal system by reporting novel toxicities of ADT on incidence of coronary and metabolic disease and related mortality. This is of considerable concern to patients and clinicians, as survival of the comorbidities exacerbated by ADT becomes a greater threat than the prostate cancer. However, despite the increased incidence of cardiovascular and metabolic disease, two recent reports by Efstathiou and colleagues of men with locally advanced prostate cancer participating in the Radiation Therapy Oncology Group trials have indicated no increased cardiovascular mortality following ADT. In both studies, cardiac risk factors, such as prevalent cardiovascular disease and diabetes, were associated with cardiovascular death; however, with up to 9 years of follow-up there was no increase in cardiovascular mortality in ADT-treated men. Consequently, the results of studies relating ADT treatment to cardiovascular mortality are mixed and this area requires further investigation.

Risk factors for cardiovascular/metabolic complications following ADT

An increasing number of studies have examined the effects of ADT on metabolic profile and risk factors for cardiovascular disease in prostate cancer patients. An overview in chronological order of the cross-sectional and prospective studies is presented in Table 1. A number of studies have consistently reported alterations in body composition with increases in whole body fat and reduction in lean body mass ranging from 6.6 to 13.8% and 2 to 3.6%, respectively, following the initial year of androgen suppression. Further, abdominal fat and abdominal subcutaneous fat assessed by computed tomography (CT) has been shown to increase by 3.9 and 11.1%, respectively, whereas regional trunk fat
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design/duration</th>
<th>n (age; year)</th>
<th>Therapy mode</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. (2001)</td>
<td>Prospective 24 weeks</td>
<td>24 (67)</td>
<td>LHRHa</td>
<td>Body fat ↑ 8.4%, lean mass ↓ 2.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bilateral orchiectomy</td>
<td>Fasting insulin ↑ 63.5%, augmentation index ↑ 20.8%</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>19, PC (72)</td>
<td>LHRHa</td>
<td>Augmentation ↑ 15.3%</td>
</tr>
<tr>
<td>Stoch et al. (2001)</td>
<td>Prospective 48 weeks</td>
<td>40 (66)</td>
<td>LHRHa</td>
<td>Body fat PC &gt; PCN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lean mass PC &lt; PCN</td>
</tr>
<tr>
<td>Smith et al. (2002)</td>
<td>Prospective 48 weeks</td>
<td>22 (67)</td>
<td>LHRHa</td>
<td>% Body fat ↑ 9.4%, abdominal fat ↑ 3.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abdominal sc fat ↑ 11.1%, lean body mass ↓ 2.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hemoglobin ↓ 6.5%, total cholesterol ↑ 9.0%, LDL cholesterol ↑ 7.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Triglycerides ↑ 26.5%</td>
</tr>
<tr>
<td>Chen et al. (2002)</td>
<td>Cross-sectional</td>
<td>62, PC (74)</td>
<td>LHRHa + antiandrogen</td>
<td>% Body fat 13% PC &gt; CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47, CO (72)</td>
<td>LHRHa</td>
<td>Body fat 21% PC &gt; CO</td>
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<tr>
<td></td>
<td>Cross-sectional</td>
<td>51, PC (72)</td>
<td>LHRHa + antiandrogen</td>
<td>Lean mass 2% PC &lt; CO</td>
</tr>
<tr>
<td>Dockery et al. (2002)</td>
<td>Prospective controlled trial 12 weeks</td>
<td>16, PC (71)</td>
<td>LHRHa + antiandrogen</td>
<td>SAC PC &lt; CO</td>
</tr>
<tr>
<td>Basaria et al. (2002)</td>
<td>Cross-sectional</td>
<td>25, CO + PCN (71)</td>
<td>No ADT</td>
<td>% Fat mass PC &gt; PCN, CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20, PC (69)</td>
<td>LHRHa</td>
<td>UB muscle strength PC &lt; PCN, CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20, PC (69)</td>
<td>LHRHa</td>
<td></td>
</tr>
<tr>
<td>Dockery et al. (2003)</td>
<td>Prospective controlled trial 12 weeks</td>
<td>15, CO + PCN (70)</td>
<td>No ADT</td>
<td>SAC ↑ PC, insulin ↑ 66.1% PC</td>
</tr>
<tr>
<td>Smith (2004)</td>
<td>Prospective 48 weeks</td>
<td>79 (71)</td>
<td>LHRHa + antiandrogen</td>
<td>Total cholesterol ↑ 7.3% PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bilateral orchiectomy/LHRHa</td>
<td>HDL cholesterol ↑ 20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% Lean body mass ↓ 3.8%, hemoglobin ↓ 10.5%</td>
</tr>
<tr>
<td>Nishiyama et al. (2005)</td>
<td>Prospective 24 weeks</td>
<td>49 (69)</td>
<td>LHRHa + antiandrogen</td>
<td>Total cholesterol ↑ 6.1%, fasting glucose ↑ 3.5%</td>
</tr>
<tr>
<td>Greenspan et al. (2005)</td>
<td>Prospective controlled trial 52 weeks</td>
<td>30, PCA (69)</td>
<td>LHRHa + antiandrogen</td>
<td>Hemoglobin ↓ 9.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40, PCC (71)</td>
<td>LHRHa + antiandrogen</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2005)</td>
<td>Prospective 52 weeks</td>
<td>65 (66)</td>
<td>LHRHa</td>
<td>% Fat mass ↑ 10.4% PC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% Lean body mass ↓ 3.5% PCA</td>
</tr>
<tr>
<td>Smith et al. (2006)</td>
<td>Prospective 12 weeks</td>
<td>25 (68)</td>
<td>LHRHa + antiandrogen</td>
<td>% Fat mass ↔ PCC, PCN, CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total cholesterol ↔ 2.2%</td>
</tr>
<tr>
<td>Basaria et al. (2006)</td>
<td>Cross-sectional</td>
<td>18, PC (70)</td>
<td>LHRHa</td>
<td>Lean body mass ↔ PCC, PCN, CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17, PCN (66)</td>
<td>No ADT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18, CO (69)</td>
<td>No treatment</td>
<td></td>
</tr>
<tr>
<td>Braga-Basaria et al. (2006)</td>
<td>Cross-sectional</td>
<td>16, PC (69)</td>
<td>LHRHa</td>
<td>BMI PC &gt; PCN, CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14, PCN (65)</td>
<td>No ADT</td>
<td>Fasting glucose PC &gt; PCN, CO</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>14, CO (69)</td>
<td>No treatment</td>
<td>Insulin PC &gt; PCN, CO</td>
</tr>
<tr>
<td>Braga-Basaria et al. (2006)</td>
<td>Cross-sectional</td>
<td>20, PC (69)</td>
<td>LHRHa</td>
<td>BMI PC &gt; PCN, CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18, PCN (66)</td>
<td>No ADT</td>
<td>Non-HDL cholesterol PC &gt; CO</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional</td>
<td>20, CO (69)</td>
<td>No treatment</td>
<td>Abdominal obesity PC &gt; PCN, CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting glucose PC &gt; PCN, CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Triglycerides PC &gt; PCN</td>
</tr>
</tbody>
</table>
### Physical exercise as potential countermeasure

Cardiorespiratory fitness is a strong independent predictor of cardiovascular disease-related mortality and overall mortality in both clinically healthy men and those with established risk factors for coronary heart disease [11,23]. Further, both studies using CT have indicated a preferential increase in subcutaneous fat rather than visceral fat in the abdomen region [11,22]. Not surprisingly, studies have also indicated that men undergoing long-term ADT can develop insulin resistance and hyperglycemia and these metabolic alterations are independent of age and BMI [14]. Alterations in glucose metabolism with reduction in insulin sensitivity and concomitant increases in fasting insulin and glycosylated hemoglobin levels have also been reported following short-term ADT in nondiabetic prostate cancer patients with locally advanced or recurrent disease [9,29]. Other reports have indicated large increases in fasting insulin by 66 and 63% following 12 and 24 weeks of ADT, respectively [10,24]. Changes in glucose metabolism in ADT patients also vary based on diabetic status with greater increases in those with diabetes (48%) compared to nondiabetic patients (7%) following a median ADT treatment duration of 44 weeks [30].

Further, ADT-induced hypogonadal men have shown higher fasting levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol than non-ADT prostate cancer men and age-matched controls [12]. However, contrasting the classical pattern of metabolic syndrome, concomitant increases in both LDL and HDL cholesterol have also been reported [11,22]. In addition, an increase in arterial stiffness, a risk factor for cardiovascular disease, has been reported and may contribute to ADT cardiovascular-related toxicity. Smith et al. [24] reported an increase in the augmentation index, an indicator of arterial stiffness, following 24 weeks of ADT. Dockery et al. [18] also reported a significant reduction in systemic artery compliance between ADT- and non-ADT-treated patients following 12 weeks of treatment indicating an increase in arterial stiffness. Moreover, increased aortic artery stiffness has been reported in cross-sectional comparisons between ADT- and non-ADT-treated prostate patients [31]. However, the effects on systolic and diastolic blood pressures are less clear with modest or negligible effects being reported following the administration of ADT [22,24]. Most of these ADT-induced adverse effects (abdominal obesity, high glucose levels, high serum triglycerides and possible high blood pressure) are characteristics of metabolic syndrome as indicated by the Adult Treatment Panel III report [32]. Details of specific cut-off points for metabolic syndrome risk factors for men are listed in Table 2.

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design/duration</th>
<th>n (age; year)</th>
<th>Therapy mode</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzuki et al. (2007)</td>
<td>Prospective 44 weeks</td>
<td>30 (70)</td>
<td>LHRHa/antiandrogen</td>
<td>Fasting glucose ↑20.3%</td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>Prospective 44 weeks</td>
<td>30 (70)</td>
<td>LHRHa+antiandrogen</td>
<td>Fasting glucose DM↑7.3%</td>
</tr>
<tr>
<td>Galvão et al. (2008)</td>
<td>Prospective 12 weeks single cohort</td>
<td>26 (68)</td>
<td>LHRHa+antiandrogen</td>
<td>Lean mass ↑2.4%, ASM↑4.2%</td>
</tr>
<tr>
<td>Smith et al. (2008)</td>
<td>Prospective 12 weeks single cohort</td>
<td>26 (65)</td>
<td>LHRHa+antiandrogen</td>
<td>Fat mass ↑11.2%, lean mass ↑3.6%</td>
</tr>
<tr>
<td>Smith et al. (2008)</td>
<td>Prospective 12 weeks single cohort</td>
<td>26 (65)</td>
<td>LHRHa+antiandrogen</td>
<td>Adiponectin ↑37.4%, resistin ↓2%</td>
</tr>
</tbody>
</table>

Abbreviations: ADT, androgen deprivation therapy; ASM, appendicular skeletal muscle; BP, blood pressure; CO, non-prostate cancer patients controls; CRP, C-reactive protein; DM, sample of diabetes mellitus patients; DMn, sample of non-diabetes mellitus patients; FPI, fasting plasma insulin; HOMA IR, homeostatic model assessment for insulin resistance; ISI, insulin sensitivity index; LHRHa, luteinising hormone releasing hormone; SAC, systemic arterial compliance. 

* aMedian treatment duration. 

* 2Increase; 

* 2, Decrease; 

* 2, No change.
### Table 2: Details of cut-off points for metabolic syndrome risk factors for men and possible effects of exercise

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Level(^a)</th>
<th>Exercise(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td>&gt; 102 cm</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 150 mg per 100 ml</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (HDL)</td>
<td>&lt; 40 mg per 100 ml</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥ 130/85 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 110 mg per 100 ml</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)To convert plasma glucose from mg per 100 ml to mmol l\(^{-1}\), multiply by 0.0555; to convert serum triglycerides from mg per 100 ml to mmol l\(^{-1}\), multiply by 0.0113; and to convert serum HDL cholesterol from mg per 100 ml to mmol l\(^{-1}\), multiply by 0.0259.

\(^{b}\)Adult Treatment Panel III report.

A summary of the effects of exercise on metabolic syndrome risk factors is shown in Table 2.

Apart from the protective effects of cardiorespiratory fitness on death from all causes, muscle strength has now been shown to be inversely associated with risk of death from all causes including cancer in men. Further, in the recent prospective study by Ruiz et al., the age-adjusted death rate in men with high levels of combined cardiorespiratory fitness and muscle strength was 60% lower than the death rate in the group of unfit men with the lowest levels of muscle strength. Cross-sectional studies have also shown an inverse relationship between muscle strength and incidence of metabolic syndrome in men.

Extensive scientific literature supports resistance training (also known as weight training or strength training where an individual’s muscles contract against a resistance – the resistance could be via a weight-training machine, free weights, bodyweight or elastic bands) as being the most effective exercise method available for enhancing muscle strength, muscle hypertrophy and physical function, and contributes to skeletal health.

Further, in those with established and controlled cardiovascular disease, resistance training is beneficial and has been endorsed by the American Heart Association Council on Clinical Cardiology.

Resistance exercise has considerable potential to counteract the catabolic side effects of ADT by promoting positive effects on the musculoskeletal system. Further, the use of resistance exercise has been reported in the management and prevention of a range of chronic conditions including overweight and mild obesity, diabetes, hypertension and atherosclerotic coronary heart disease. Preliminary work supports the potential beneficial role of resistance exercise in patients diagnosed with prostate cancer undertaking ADT, with improvements in muscle strength, functional performance and psychological outcomes (for example, improvements in quality of life), without compromising androgen suppression and treatment intent.

Moreover, we have reported that patients undergoing 20 weeks of anabolic or resistance training improved their cardiorespiratory capacity by reducing the time to complete a 400-meter corridor walk test by 7.4%. This test for older adults has been shown to be a strong predictor of mortality, cardiovascular disease and mobility limitations in older adults. Further, a recent study using an animal model has found that aerobic exercise has the potential to provide a protective effect against cardiac dysfunction during ADT. Thus, aerobic and resistance exercise may be an effective method to minimize or overcome ADT cardiovascular-related toxicities. Although it has long been known that physical exercise is an essential lifestyle contributor to significantly reduce cardiovascular and metabolic diseases, efficacy for patients receiving ADT has not been established. A theoretical model of exercise as a countermeasure to ADT-induced cardiovascular and metabolic-related toxicities is presented in Figure 1. Combined resistance and aerobic exercise have been shown to reduce both systolic and diastolic blood pressures each by 13 mm Hg in middle-aged men with hypertension and decrease total and LDL cholesterol.

We have recently reported that resistance training as a sole exercise mode in older adults may reduce the risk for adverse cardiovascular events by attenuating cardiac afterload. In this study, older men and women underwent a 20-week program of high-intensity resistance exercise with the primary endpoints being brachial and central blood pressures, and arterial stiffness using pulse wave analysis. Following training, we noted a significant reduction in central systolic and diastolic blood pressures of 6 and 3 mm Hg, respectively, with no adverse effects on arterial stiffness. These changes were also independent of heart rate and body mass and were likely related to a reduction in peripheral vascular resistance.

Exercise prescription recommendations and guidelines that could potentially benefit large number of patients currently on or previously treated with ADT have been suggested. Men on ADT should initiate a program of resistance training incorporating 7–10 exercises,
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Undertaking resistance exercise in small groups will facilitate adherence and compliance, and also reduce the financial cost to the patient, and this can be suggested to patients. In addition, varying components of the program from time to time will assist with motivation. However, it is important for both the specialist and the general practitioner to provide a consistent message regarding exercise and physical activity, and to monitor the patient’s progress.

In the United States, the American College of Sports Medicine (ACSM – www.acsm.org) provides registered professionals with University qualifications in exercise science or related area. Similarly, other countries, such as Australia and United Kingdom possess organizations (Australian Association for Exercise and Sports Science (AAESS) – www.aaess.com.au/ – British Association of Sport and Exercise Sciences (BASES) – www.bases.org.uk/) that provide registered exercise professionals with University qualifications who are able to conduct exercise training with this patient population.

In summary, ADT is associated with a number of adverse effects in men, including cardiovascular and metabolic complications. The general assumption that cessation of ADT will be sufficient for treatment-related morbidity to recover appears to be incorrect as testosterone needs to recover. The result is that the consequences of ADT may be greater than the benefits derived, and may deter men from using this form of therapy. However, a lifestyle activity, exercise, has a powerful beneficial effect that ameliorates certain soft tissue morbidities in the androgen-suppressed state and may potentially counter a number of the risk factors associated with cardiovascular and metabolic diseases. Lifestyle choices, such as exercise, that ameliorate treatment toxicity introduce an interesting covariate to the process of informed decision making. When the benefits of ADT intervention are future based and small, in addition to the risks of morbidity, the patient will need consider their commitment to undertaking lifestyle strategies that ameliorate those toxicities.

Conflict of interest
The authors declare no conflict of interest.

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References


Review of Exercise Intervention Studies in Cancer Patients

Daniel A. Galvão and Robert U. Newton

ABSTRACT

Purpose
To present an overview of exercise interventions in cancer patients during and after treatment and evaluate dose-training response considering type, frequency, volume, and intensity of training along with expected physiological outcomes.

Methods
The review is divided into studies that incorporated cardiovascular training, combination of cardiovascular, resistance, and flexibility training, and resistance training alone during and after cancer management. Criteria for inclusion were based on studies sourced from electronic and nonelectronic databases and that incorporated preintervention and postintervention assessment with statistical analysis of data.

Results
Twenty-six published studies were summarized. The majority of the studies demonstrate physiological and psychological benefits. However, most of these studies suffer limitations because they are not randomized controlled trials and/or use small sample sizes. Predominantly, studies have been conducted with breast cancer patients using cardiovascular training rather than resistance exercise as the exercise modality. Recent evidence supports use of resistance exercise or "anabolic exercise" during cancer management as an exercise mode to counteract side effects of the disease and treatment.

Conclusion
Evidence underlines the preliminary positive physiological and psychological benefits from exercise when undertaken during or after traditional cancer treatment. As such, other cancer groups, in addition to those with breast cancer, should also be included in clinical trials to address more specifically dose-response training for this population. Contemporary resistance training designs that provide strong anabolic effects for muscle and bone may have an impact on counteracting some of the side effects of cancer management assisting patients to improve physical function and quality of life.

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INTRODUCTION

A progressive increase of cancer burden, with an estimated 15 million new cases and 10 million new deaths, is expected by the year of 2020. In this context, prostate cancer is the sixth most common cancer in the world, representing 14.3% of cancers among men in developed countries with more than 80% of the cases occurring in men older than 65 years. Breast cancer appears as the third most common cancer in the world, and it is ranked as the fifth most prevalent cause of death from cancer overall, being the leading cause of cancer mortality in women. Treatments for cancer include surgery as well as systemic and radiation therapy and have successfully shown reductions in mortality rates. However, for cancer patients, the increased levels of fatigue during treatment remains a concern as it affects the majority of patients during radiotherapy.
and/or chemotherapy periods compromising their physical function and quality of life. Dimeo has proposed that the lack of physical activity during treatment may affect the increased levels of fatigue observed during and after cancer management. As such, several studies examining the role of exercise with cancer patients have included the increased levels of physical activity during and after cancer treatment with positive effects on decreasing rates of fatigue, enhancing physical performance, and improving quality of life. However, the majority of the exercise interventions undertaken with this population have focused on cardiovascular training. With few studies using the combination of aerobic and resistance exercises or resistance exercise alone. Therefore, little is known as to the effect of resistance training being a primary exercise choice to counteract some of the physiological conditions accompanied by cancer disease and the traditional treatments. Considering that most of the experimental exercise studies have incorporated breast cancer patients and other types of cancer but not prostate cancer, there is a particular lack of information on how prostate cancer patients undertaking traditional treatment would respond to an exercise program. Yet, given the documented effects of androgen deprivation therapy (ADT), these patients should benefit particularly from resistance exercise. To date, only one published report has examined the effects of a short-term resistance exercise program on patients diagnosed with prostate cancer undertaking ADT. Interestingly, they reported quite promising results. In view of the extensive scientific literature supporting resistance training as being the most effective method available for improving muscle strength and increasing lean tissue mass in different populations ranging from athletes to frail older adults, resistance exercise may also have a great potential to counteract the side effects of prostate cancer during ADT by increasing muscle function, lean tissue mass, and bone mineral density with subsequent reduction in levels of fatigue.

There are specific training variables involving resistance exercise prescription that include number of sets and repetitions (volume), intensity of training (load), duration of rest between sets and exercises, frequency of training, and repetition velocity. Currently, there is no information with regard to such training variables and possible variations with cancer patients undertaking resistance training programs. Interestingly, some of these variables have been examined in untrained older adults and favorable responses in strength and function result from a variety of training regimens, even those that involve relatively low intensities, frequencies, and volume. Considering the detrained state and high levels of fatigue of many cancer patients, it may be expected that even a training program consisting of lower intensity, volume, and frequency could significantly promote positive physiological and psychological adaptations increasing quality of life in this population.

The purpose of this article is to present a descriptive overview and chronological perspective of developments of the experimental exercise intervention studies undertaken during and after cancer management. The second aim of this review attempts to establish a dose response of training for this population considering type of exercise, frequency of training, volume of training, intensity of training and expected physiological outcome measures. In addition, we also highlight specific points that should be examined in the future with the goal of obtaining more information on exercise prescription for this population. This review reports 26 published studies appearing in the Medline (electronic version of Index Medicus) database, published by June of 2004 and searched by the terms: exercise; cardiovascular training; resistance training; rehabilitation; and cancer. For many cancer patients, it may be expected that even a training program consisting of lower intensity, volume, and frequency could significantly promote positive physiological and psychological adaptations increasing quality of life in this population.

A summary of the published studies examining the effect of exercise on cancer patients undertaking treatment is shown in Table 1. Of the 18 experimental exercise interventions under cancer treatment, 14 had used some type of cardiovascular training while the other two studies applied a mixed training program using cardiovascular, resistance, and flexibility exercises while the other two studies applied a structured resistance training program. The main outcome measures from these studies include: levels of fatigue, quality of life, emotional-related distress, immunological parameters, aerobic capacity, and muscle strength.

### Cardiovascular Training

The first study by Winningham et al. examined the effect of a 10-week aerobic program performed three times per week on nausea responses of patients with breast cancer undertaking chemotherapy. Subjects were randomly assigned to a supervised aerobic exercise group three times per week, a placebo group that performed low-intensity supervised flexibility training once weekly, or a control noneexercise group. Nausea responses to training were assessed by a self-report system inventory (Symptom Checklist-90-R; Pearson Assessments, Eagan, MN). The exercise group improved significantly more on symptoms of nausea compared with control and placebo groups (P < .05). Considering that nausea is a consistent symptom experienced by...
Table 1. Experimental Design Exercise Studies During Cancer Treatment

<table>
<thead>
<tr>
<th>Study (Reference Number)</th>
<th>Duration</th>
<th>Frequency (weeks)</th>
<th>No. of Patients</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Type of Cancer</th>
<th>Exercise Program</th>
<th>Intensity</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham et al, 198649</td>
<td>5</td>
<td>3-5/week</td>
<td>40 M, W</td>
<td>14-44</td>
<td>Leukemia</td>
<td>Resistance training</td>
<td>Unspecified</td>
<td>↓ Nitrogen balance</td>
<td>← Creatinine excretion</td>
</tr>
<tr>
<td>Winningham et al, 198850</td>
<td>12</td>
<td>3/week</td>
<td>42 W</td>
<td>45-48</td>
<td>Breast</td>
<td>Cardiovascular cycling</td>
<td>IT 20-30 minutes</td>
<td>60-85% MHR</td>
<td>↑ Nausea</td>
</tr>
<tr>
<td>Winningham et al, 198951</td>
<td>12</td>
<td>3/week</td>
<td>24 W</td>
<td>45</td>
<td>Breast</td>
<td>Cardiovascular cycling</td>
<td>IT 20-30 minutes</td>
<td>60-85% MHR</td>
<td>↑ Lean tissue mass</td>
</tr>
<tr>
<td>Macvicar et al, 1989</td>
<td>10</td>
<td>3/week</td>
<td>45 W</td>
<td>43-46</td>
<td>Breast</td>
<td>Cardiovascular cycling</td>
<td>IT</td>
<td>60-85% MHR</td>
<td>↓ 42% V̇O₂max</td>
</tr>
<tr>
<td>Mook et al, 199723</td>
<td>6</td>
<td>4-5/week</td>
<td>46 W</td>
<td>35-64</td>
<td>Breast</td>
<td>Cardiovascular walking</td>
<td>20-30 minutes</td>
<td>Self-paced</td>
<td>4% 12-MWT</td>
</tr>
<tr>
<td>Dimeo et al, 199729</td>
<td>~2</td>
<td>Daily</td>
<td>70 M, W</td>
<td>39-40</td>
<td>Breast</td>
<td>Cardiovascular cycling</td>
<td>IT 30 minutes</td>
<td>50% HRR</td>
<td>↑ 14% MP, ↓ Thro</td>
</tr>
<tr>
<td>Dimeo et al, 199822</td>
<td>6</td>
<td>5/week</td>
<td>5 M, W</td>
<td>18-55</td>
<td>Breast, Hodgkin’s lymph, Non-Hodgkin’s lymph, bronchial, breast, medulloblastoma</td>
<td>Progressive treadmill walking 30-35 minutes</td>
<td>3 mmol/L (LC)</td>
<td>↓ 100% LC</td>
<td></td>
</tr>
<tr>
<td>Dimeo et al, 199935</td>
<td>* Daily</td>
<td>59 M, W</td>
<td>40 B</td>
<td>6-24</td>
<td>Breast</td>
<td>Cardiovascular cycling</td>
<td>IT 30 minutes</td>
<td>50% HRR</td>
<td>↓ Psychologic distress</td>
</tr>
<tr>
<td>Schwartz et al, 200125</td>
<td>8</td>
<td>4/week</td>
<td>27 W</td>
<td>35-57</td>
<td>Breast</td>
<td>Cardiovascular walking</td>
<td>35 minutes</td>
<td>Self-paced</td>
<td>10.4% 12-MWT</td>
</tr>
<tr>
<td>Na et al, 200023</td>
<td>2</td>
<td>5/week</td>
<td>35 *</td>
<td>28-75</td>
<td>Stomach</td>
<td>Cardiovascular arms and cycling ergometers</td>
<td>30 minutes</td>
<td>60% MHR</td>
<td>↑ 26% NKCA</td>
</tr>
<tr>
<td>Schwartz et al, 200131</td>
<td>8</td>
<td>3-4/week</td>
<td>72 W</td>
<td>27-69</td>
<td>Breast</td>
<td>Cardiovascular walking</td>
<td>12 minutes</td>
<td>Self-paced</td>
<td>15% 12-MWT</td>
</tr>
<tr>
<td>Mook et al, 200131</td>
<td>6-24</td>
<td>5-6/week</td>
<td>52 W</td>
<td>28-75</td>
<td>Breast</td>
<td>Cardiovascular walking</td>
<td>10-30 minutes</td>
<td>Self-paced</td>
<td>6% 12-MWT</td>
</tr>
<tr>
<td>Segal et al, 200145</td>
<td>26</td>
<td>5/week</td>
<td>123 W</td>
<td>51.4</td>
<td>Breast</td>
<td>Cardiovascular walking, home vs. non-home based</td>
<td>50-60% V̇O₂max</td>
<td>↓ Physical functioning</td>
<td></td>
</tr>
<tr>
<td>Kolden et al, 200224</td>
<td>16</td>
<td>3week</td>
<td>40 W</td>
<td>45-76</td>
<td>Breast</td>
<td>Cardiovascular walking, cycling, stepping, resistance training, flexibility</td>
<td>Unspecified</td>
<td>↑ 11% Flexibility</td>
<td></td>
</tr>
<tr>
<td>Segal et al, 200327</td>
<td>12</td>
<td>3/week</td>
<td>155 M</td>
<td>68.2</td>
<td>Prostate</td>
<td>Resistance training, 2 sets, 12 repetitions</td>
<td>60-70% 1-RM</td>
<td>↑ 42% UB</td>
<td></td>
</tr>
<tr>
<td>Dimeo et al, 200326</td>
<td>~2</td>
<td>Daily</td>
<td>66 M, W</td>
<td>20-73</td>
<td>Leukemia</td>
<td>Cardiovascular walking</td>
<td>70% MHR</td>
<td>← Walking speed</td>
<td></td>
</tr>
<tr>
<td>Courneya et al, 200337</td>
<td>16</td>
<td>3-5/week</td>
<td>102 M, W</td>
<td>61.1</td>
<td>Colorectal</td>
<td>Cardiovascular walking, flexibility</td>
<td>65-75% MHR</td>
<td>← Quality of life</td>
<td></td>
</tr>
<tr>
<td>Adame et al, 200328</td>
<td>6</td>
<td>4/week</td>
<td>23 M, W</td>
<td>18-63</td>
<td>Leukemia, breast, colon, ovary, tests, cervix, Hodgkin’s lymph, non-Hodgkin’s lymph</td>
<td>Resistance training, 3 sets, 5-8 repetitions; cardiovascular cycling</td>
<td>60-100% MHR</td>
<td>↓ 32.5% WB</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: M, men; W, women; ↔, no change; ↑, increase; ↓, decrease; *, not described; PSA, prostate-specific antigen; LC, lactate concentration; V̇O₂max, maximum concentration of oxygen consumption; lymp., lymphoma; IT, interval training; TD, training distance; MHR, maximum heart rate; MP, maximal performance (MET); HEM, hemoglobin; AC, arm circumference; UB, upper body strength; LB, lower body strength; WB, whole body strength; RSBP, resting systolic blood pressure; NKCA, natural killer-cell cytotoxic activity; HRR, heart rate reserve Neutro, duration of neutropenia; Thro, duration of thrombopenia; Hosp, duration of hospitalization.
cancer patients during treatment, these preliminary data showed that cardiovascular training can safely be incorporated during breast cancer traditional treatment and may decrease symptoms of nausea. Winningham et al. presented data related to a subgroup of their earlier report, which examined the effect of a 10- to 12-week aerobic training program on body composition responses of breast cancer subjects undertaking chemotherapy. Subjects were randomly allocated to an exercise group that trained three times per week for 20 to 30 minutes with intensity set at 60% to 80% of maximal heart rate or a control group that did not receive the exercise treatment. Although elementary techniques for body composition determination, such as skinfold measurement, were in used in this intervention, the results were an increase in lean tissue mass for the training group compared with the control group. Considering the specificity of the training program in this study (aerobic exercise only), the relative increase in lean tissue mass may be attributed to the decreased fat tissue.

The effect of a 10-week aerobic interval training program was also investigated by MacVicar et al. Forty-five women with breast cancer receiving chemotherapy were randomly assigned to an aerobic exercise group (cycling training), a flexibility training group, or a control group. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum heart rate reserve. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum heart rate reserve. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum heart rate reserve. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum heart rate reserve. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum heart rate reserve. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum heart rate reserve. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum heart rate reserve. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum heart rate reserve. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differ-

A progressive walking treadmill program up to 30 to 35 minutes with intensity set to elicit a blood lactate level of 3 mmol/L in capillary blood was prescribed. At the end of the intervention, walking distance, walking maximal performance, heart rate, and lactate concentration were improved (P < .05) demonstrating once more the positive physiological responses accrued with cardiovascular training. In addition, the authors also noted a clear decrease in levels of fatigue at post-test. Subsequently, in 1999, the same group of investigators also examined a daily exercise protocol consisting of a supine bike program followed by an interval training pattern for 30 minutes in cancer patients receiving high doses of chemotherapy. Outcome measures included psychological distress and levels of fatigue. It was demonstrated at the end of the intervention that subjects undertaking the exercise program significantly decreased psychological distress with no changes in fatigue levels.

Schwartz et al. reported results from a 8-week exercise intervention in 27 women with breast cancer undertaking chemotherapy. The exercise program included a home-based walking program with self-paced intensity measured by an accelerometer. Subjects who underwent the exercise program demonstrated greater response in the physical performance assessment (12-minute walk test), as well as decreasing levels of fatigue compared with subjects who did not adopt the training program (P < .05).

The short-term effect of cardiovascular training on natural killer-cell cytotoxic activity (NKCA) in patients with stomach cancer were reported by Na et al. Subjects were assigned to an exercise group that performed 30 minutes of supervised cardiovascular training using arm and cycle ergometer or a nonexercise control group. Blood samples were collected at baseline, day 7, and day 14. At post-test, a significantly greater increase in NKCA was noted for the exercise group (27.9%) compared with the control group (13.3%; P < .05). Although the training period was short in duration, it is interesting to note that both groups had similar values for NKCA at the midpoint of intervention, with the differences between groups occurring during the second half of the training period.

Schwartz et al. also investigated the relationship of fatigue and exercise through a home-based aerobic exercise program consisting of a 12-minute walk in women undergoing chemotherapy treatment for breast cancer. Functional abilities were assessed through a 12-minute walk test and fatigue levels by a self-reported instrument. The exercise program increased functional ability by 15% whereas the nonexercisers decreased performance by 16%. In addition, decreased levels of fatigue (P < .01) for the exercise group were observed after the intervention. It is interesting to note that the exercise program was unsupervised with none of the sessions being accompanied by an exercise physiologist. Considering that training program variables were not well controlled during training, the results are...
somewhat attractive and one would expect even greater adaptations for an exercise program that incorporates a more controlled setting resulting in an enormous impact on the outcome measures with this population.

The effect of a similar home-based walking exercise intervention on patients with breast cancer undertaking either radiotherapy or chemotherapy was also examined by Mock et al.\textsuperscript{19} The exercise program consisted of a progressive walking (10 to 30 minutes) program 5 to 6 days per week with an unspecified training intensity. Similar to Schwartz et al.\textsuperscript{40} and their previous report,\textsuperscript{11} physical function was assessed by the 12-Minute Walk Test. In addition, fatigue and emotional distress were measured by the Piper Scale and Profile of Mood States (POMS), respectively. Consistent with their previous findings,\textsuperscript{11} the exercise intervention lead to a significant improvement in physical performance by increasing walking distance. Additionally, fatigue and emotional distress were enhanced at post-test, indicating once more that positive psychological outcomes may be achieved with a simple home-based walking exercise program.

Segal et al.\textsuperscript{33} conducted a randomized controlled trial examining the effect of a supervised and unsupervised walking program on patients with breast cancer undertaking treatment (radiotherapy, hormonal therapy, or chemotherapy) over 26 weeks. Aerobic capacity, body weight, and generic and disease-specific health-related quality of life were assessed (MOS SF-36) at baseline and post-test. Results demonstrated that physical function measured by the MOS SF-36 decreased in the control group while it increased in both training groups ($P < .05$). At post-test, no differences among groups were detected for quality of life, aerobic capacity, or body weight. However, when groups were stratified by type of adjuvant therapy, in this case not receiving chemotherapy, differences in improvement were observed between the supervised and control group for aerobic capacity ($P < .01$). It is relevant to point out that the small changes in aerobic capacity (3.5%) may be related to the nonspecific aerobic capacity test protocol (stepping ergometer) utilized by the authors to assess chronic response of a walking program.

The effect of 2 weeks of cardiovascular training on a mixed cancer population undergoing conventional or high-dose chemotherapy during hospitalization was examined by Dimeo et al.\textsuperscript{14} The training program consisted of a daily walking treadmill interval training program with intensity set at 70% of the maximum heart rate. Submaximal stress test results demonstrated that physical performance remained unaltered during treatment with significant reductions in hemoglobin levels at hospital discharge ($P < .05$). Although physical performance did not change at post-test, results demonstrated that cardiovascular training may assist on preserving performance status during intensive chemotherapy.

Finally, Courneya et al.\textsuperscript{15} conducted a randomized controlled trial examining the effect of a home-based exercise program on quality of life and cardiovascular capacity of colorectal cancer patients undertaking adjuvant therapy. The exercise group was instructed to perform cardiovascular and flexibility activities three to five times per week over 16 weeks whereas the control group was advised to not participate in any exercise activity during the study period. No significant differences were observed between groups for quality of life and cardiovascular capacity at the end of the intervention. The failure to detect differences between groups is primarily explained by the fact that 51.6% of the control group did not comply with the study and exercised during the study period. The nature of the exercise itself (home-based program) was pointed out by the authors as being one possible reason of the high contamination during the intervention with little effectiveness.

### Cardiovascular, Resistance, and Flexibility Training

Kolden et al.\textsuperscript{12} examined the effect of an exercise training intervention including cardiovascular, resistance, and flexibility training over 16 weeks in patients with breast cancer undertaking some type of adjuvant therapy (radiotherapy, chemotherapy, or hormonal therapy). Subjects were tested for resting blood pressure, body composition, aerobic capacity, flexibility, and strength. In addition, numerous psychological outcomes were also examined using the Beck Depression Inventory, State-Trait Anxiety Inventory, Positive and Negative Affect Schedule, Hamilton Scale for Depression, Quality of Life, and Global Assessment Scale. At the end of the intervention, there was an observed effect for time for upper and lower body strength, cardiovascular capacity (estimated VO$_{2\text{max}}$), flexibility, and resting systolic blood pressure ($P < .05$). Additionally, subjects experienced positive psychological adaptations with training improving some of the quality-of-life measures.

Recently, Adamsen et al.\textsuperscript{16} examined the effect of a high-intensity supervised exercise program on a mixed cancer population over 6 weeks. The training program included interval training with intensity set at 60% to 100% of the maximal heart rate, resistance exercises performed at 85% to 95% of 1 repetition maximum (RM) for five to eight repetitions, and relaxation training. The results demonstrated an increase of 32.5% in maximal strength ($P < .0001$) and 16% improvement in VO$_{2\text{max}}$ ($P < .001$). Several measures of quality of life were also improved; however, no statistically significant values were noted. It is relevant to highlight that this is the first study that incorporates a higher intensity training design; however, the absence of a control group and the short duration of the intervention limited the interpretation of the data.

### Resistance Training

The earliest published study examining the effects of resistance exercise was a short-term intervention involving patients with acute leukemia undertaken by Cunningham et al.\textsuperscript{37} Subjects were randomly assigned to two exercise
The training program consisted of several upper and lower body exercises including the chest press, biceps curl, triceps extension, straight leg raises, knee extension, hip extension, hip abduction, shoulder retractors, and sit-ups performed with 15 repetitions at an unspecified intensity. Outcome measures included skinfold measures, arm circumference, nitrogen balance, and creatinine excretion. Results indicated that groups did not change arm circumference and skinfold measures over the course of the intervention. Although there were no differences among groups for nitrogen balance during the course of the study, the authors suggested that the exercise program favored both training groups with the control group decreasing levels of creatinine excretion from pretest to post-test (P < .05).

Recently, Segal et al. reported the results from a 12-week whole body resistance training intervention in patients with prostate cancer undergoing ADT. The resistance training program consisted of two sets of 8 to 12 repetitions at 60% to 70% of 1 RM for six upper body and three lower body exercises performed three times per week. Outcome measures included fatigue, disease-specific quality-of-life assessment, and muscle strength and body composition. Results showed positive effects of resistance training on decreasing fatigue levels, health-related quality of life, and muscle strength with no changes in body composition by the subjects embarking on the exercise program. The fact that body composition was unaffected by the training program may be related in part to the elementary body composition methods used to assess changes in muscle and fat tissue. In addition, it is well known that strength gains during the first stages of resistance training are predominantly caused by neural factors with gains in muscle size becoming dominant as training continues.70-72 Consequently, the shorter duration of ral factors with gains in muscle size becoming dominant as stages of resistance training are predominantly caused by neu-

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Experimental studies examining the effect of exercise on patients with cancer after treatment are presented in Table 2. Four studies had used cardiovascular exercise programs whereas the other four implemented a mixed training program using cardiovascular, resistance, and flexibility exercises. Levels of fatigue, muscle strength, cardiovascular function, immunological parameters, symptoms of emotional-related distress, and quality of life were the major outcome measures from these studies.

**Cardiovascular Training**

Sharkey et al. conducted the first experimental exercise study examining the chronic response of a 12-week cardiovascular training program on children and young adults with mixed cancer diagnosis who had completed chemotherapy for at least 1 year. Outcome measures included cardiovascular and pulmonary physiological responses. Although none of the physiological parameters changed with training, exercise tolerance assessed by exercise time was increased significantly (P < .05).

The effect of cardiovascular training on NKCA, monocytes, and personality was examined in a group of breast cancer survivors by Peters et al. Their training program consisted of 30 to 40 minutes of cycling at approximately 60% of maximum heart rate performed five times per week during the first 5 weeks of training with a subsequent reduction of training frequency for the following 6 months completing a total 7-month training period. Although NKCA cell numbers were unaltered over the course of the intervention, an increase in the cytotoxic activity was noted at post-test. While the total number of leukocytes was unchanged after the training program, significant changes in leucocyte subpopulations were detected with an increased number of granulocytes and a decreased number of lymphocytes and monocytes (P < .05). The authors suggested that cardiovascular training would possibly alter the number of specific receptors in the surface membrane on monocytes. Moreover, satisfaction of life increased in the first 5 weeks of training with a subsequent decrease during the other 6 months of the intervention.

Dimeo et al. examined the effects of a cardiovascular training program on maximal performance and hemoglobin levels of cancer patients directly after hospital discharge. The exercise program consisted of 6 weeks of treadmill walking every weekday with intensity set to elicit a blood lactate level of 3 mmol/L in capillary blood. Results indicated that subjects that underwent the exercise program showed a significant increase in maximal performance and hemoglobin concentration compared with controls (P < .05).

The effects of 10 weeks of cardiovascular exercises on women who had undergone breast cancer treatment were examined by Segar et al. Subjects were randomly allocated to an exercise group, exercise plus behavior modification group, or a control group in an experimental crossover design. Symptoms of depression, state of anxiety, and self-esteem were assessed by the Beck Depression Inventory, the State...
Anxiety Inventory, and the Rosenberg Self-Esteem Inventory, respectively. At post-test, it was observed that the exercise group had significantly less depression and state of anxiety compared with controls with no differences between exercise and exercise plus behavior modification groups. After the crossover, the controls also showed optimistic changes by decreasing depression and state of anxiety showing positive psychological response accrued with cardiovascular training.

**Cardiovascular, Resistance, and Flexibility Training**

The effects of an exercise program on breast cancer survivors who had undergone surgery, radiation, and chemotherapy were examined by Nieman et al. Subjects were randomly assigned to an exercise or control group. In addition to physical performance measures that included symptoms-limited exercise testing on the treadmill, 6-minute walk test and lower body strength, immunological training response was also assessed by measuring NKCA and concentrations of circulating immune cells. The training program included 30 minutes of walking at 75% of heart rate maximum and seven different resistance exercises performed for 12 repetitions at an unspecified intensity. Results indicated significant improvement for the exercise group on 6-minute walk distance test compared with controls ($P < .05$). However, differences between groups were neither observed for lower body strength nor for NKCA. It should be noted that the small sample size ($n = 6$ per group) limited the ability to detect significant difference between groups.

Durak et al. conducted an exercise intervention in a mixed cancer patient population over 10 weeks. The exercise program was performed twice weekly and consisted of cardiovascular training at their own perceived exertion, resistance training machines using unspecified intensity, and flexibility exercises. Outcome measures included quality of life (Modified Rotterdam Quality of Life Survey), endurance capacity, and a four- to six-repetition maximum strength test. Results demonstrated an average increase of 43% for both upper and lower body strength combined and a 41.4% increase in MET level from the first to the last session of the exercise program. In addition, the quality of life assessment indicated a significant improvement in participants’ ability to perform daily functions. The same group of investigators also examined the effect of a 20-week cardiovascular and resistance training program on survivors of prostate cancer, carcinoma, and leukemia. The exercise protocol was described with little detail in the

### Table 2. Experimental Design Exercise Studies After Cancer Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Frequency (weeks)</th>
<th>No. of Patients</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Type of Cancer</th>
<th>Exercise Program</th>
<th>Intensity</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al, 2000</td>
<td>28</td>
<td>2-5/week</td>
<td>24</td>
<td>W</td>
<td>49</td>
<td>Breast</td>
<td>Cardiovascular cycling</td>
<td>~ 60% MHR</td>
<td>↓ Leukocytes</td>
</tr>
<tr>
<td>Nieman et al, 1995</td>
<td>8</td>
<td>3/week</td>
<td>12</td>
<td>W</td>
<td>61</td>
<td>Breast</td>
<td>Cardiovascular resistance training</td>
<td>75% MHR</td>
<td>↓ 2.1% Lymphocytes</td>
</tr>
<tr>
<td>Dimeo et al, 1997</td>
<td>6</td>
<td>1/week</td>
<td>36</td>
<td>W</td>
<td>39–42</td>
<td>Non-Hodgkin’s lymphoma, breast, sarcoma, seminoma, lung</td>
<td>Cardiovascular walking 30 minutes</td>
<td>3 mmol/L (LC)</td>
<td>↓ 32% MP</td>
</tr>
<tr>
<td>Segar et al, 1999</td>
<td>10</td>
<td>0/week</td>
<td>24</td>
<td>W</td>
<td>30–65</td>
<td>Breast</td>
<td>Cardiovascular resistance training</td>
<td>30–40 minutes</td>
<td>10% ET, ↓</td>
</tr>
<tr>
<td>Durak et al, 1998</td>
<td>10</td>
<td>2/week</td>
<td>20</td>
<td>M, W</td>
<td>50</td>
<td>Carcinoma, lymphoma, leukemia</td>
<td>Cardiovascular resistance training, flexibility</td>
<td>Own RPE</td>
<td>43% WB, 41.4% ↑ MP</td>
</tr>
<tr>
<td>Durak et al, 1999</td>
<td>20</td>
<td>2/week</td>
<td>25</td>
<td>M, W</td>
<td>44–71</td>
<td>Prostate carcinoma, leukemia</td>
<td>Cardiovascular resistance training</td>
<td>Unspecified</td>
<td>↓ Quality of life</td>
</tr>
<tr>
<td>Porock et al, 2000</td>
<td>4</td>
<td>*</td>
<td>9</td>
<td>M, W</td>
<td>51–77</td>
<td>Bowel, breast, oral, pancreas, melanoma</td>
<td>Cardiovascular resistance training</td>
<td>Unspecified</td>
<td>↓ Depression</td>
</tr>
</tbody>
</table>

Abbreviations: M, men; W, women; ↔, no change; ↑, increase; ↓, decrease; ↑, increased at week 5 and decreased at posttest; *, not described; LC, lactate concentration; MHR, maximum heart rate; MP, maximal performance (MET); HEM, hemoglobin; LB, lower body strength; WB, whole body strength; NKCA, natural killer-cell cytotoxic activity; ET, exercise tolerance; AT, anaerobic threshold; peak OX, peak oxygen uptake; peak HR, peak heart rate.
original manuscript; therefore it is unclear what intensity and volume were applied during the exercise intervention for both cardiovascular and resistance exercises. In addition, neither strength maximum nor cardiovascular capacity tests were implemented at pretest and post-test; therefore it was extremely difficult to analyze the authors’ presented data. At post-test, subjects completed a quality-of-life survey with the same questionnaire being reassessed in a 2-year follow-up period. It was reported that the training protocol induced an increase of 38% and 52% for overall strength in the prostate cancer and carcinoma/leukemia groups, respectively. No significant change was noted for aerobic capacity. It is interesting to point out the high level of adherence to the exercise program from both groups with subjects from the prostate cancer group having 100% compliance to the training program whereas the carcinoma/leukemia group recorded 65% of adherence over the 2-year period.

Finally, Porock et al.25 investigated the effect of a short-term home-based exercise intervention in a mixed population of cancer patients. The training program appears to include both cardiovascular and resistance exercises but lacked an exact description of training program variables (intensity, frequency, and volume). Outcome measures included fatigue, anxiety, depression, symptoms of distress, and quality of life. Results indicated positive adaptations for depression and anxiety with no change in fatigue levels. It should be noted that the short-term duration of the intervention and the small sample size (n = 9) limited the ability to detect significant changes with training.

### DISCUSSION

The primary aim of this article was to present an overview of published studies undertaken with any cancer population during and after treatment. Unfortunately, most of these studies suffer limitations because they are not randomized controlled trials, use small sample sizes, and/or report insufficient scientific methodological criteria. Despite this, it appears that there is a reasonable amount of data in the literature that underline preliminary positive physiological and psychological benefits from exercise when undertaking during or after traditional cancer treatment. It is interesting to point out that the early published report on cancer and exercise by Cunningham et al.17 used resistance exercises as the training modality that was based on the original work by Delorme,73,74 who introduced the model of progressive workload with resistance exercises. Subsequently, the majority of studies examining the effect of exercise on cancer patients undertaking treatment completed from the late 1980s to 2003 implemented the cardiovascular training modality10,11,13,15,17–19,23,33–36,38,40 with only two interventions using the combination of resistance, flexibility, and cardiovascular training.12,16 Therefore, particular attention should be taken of the recent report from Segal et al.20 who reported positive effects of resistance exercises alone on rates of fatigue, health-related quality of life, and muscle strength in patients with prostate cancer undertaking ADT. Although these results support positive psychological and physical outcomes, it remains to be examined how specific physiological parameters such as muscle tissue mass and bone mineral density would respond with resistance exercises in this population, especially in long-term trials. Recently, Smith et al.47 reported an increase of 11% of fat mass and a decrease of 3.8% of lean-free bone tissue mass from a year-long prospective assessment of the effects of ADT on body composition responses evaluated by dual energy x-ray absorptiometry. Further, the concern related to the negative effects of ADT on accelerating bone loss has been extensively reported in the literature.46,75–83 As an alternative, resistance exercise studies in older adults have consistently shown it to be a safe and effective strategy to counteract sarcopenia50,54–57,59,84,85 and preserve or induce gains in bone mineral density.84,86–88 Recently, Villareal et al.86 reported positive effects of a 9-month resistance training program on bone mineral density in older women undertaking hormonal replacement. A meta-analysis undertaken by Wolff et al.89 also proposes that resistance training preserves or reverses bone loss of up to 1% per year in both femoral neck and lumbar spine sites for pre- and postmenopausal women. Taking into consideration the long-term benefits of this exercise modality on bone response, resistance training may have an important role on reducing the effect of bone loss rate in men with prostate cancer undertaking ADT. Moreover, considering that, traditionally, ADT varies from 2 to 3 years but can also take up to 20 years,90 the role of resistance exercise may be even more relevant by improving psychological and physiological parameters and, therefore, improving quality of life.

In the context of maintaining or increasing lean tissue content in healthy elderly and various patient populations in which muscle and bone loss are problematic, resistance exercise might be more appropriately termed “anabolic exercise.” It is not surprising, therefore, that the many cardiovascular exercise interventions with cancer patients have produced mixed results as such exercise does not provide a strong anabolic effect for muscle and bone and may not elicit the changes in endocrine status that are desirable in these patients.

It is interesting to note that, among the different cancer types, breast cancer has been the most common cancer type examined during exercise trials. Of the 18 studies undertaken during treatment, nine had used exclusively breast cancer subjects11,12,18,19,21,33–35,38,40 with three studies including breast cancer plus a mix of cancer populations10,17,23 and few other experiments using leukemia, stomach cancer, prostate, colorectal, and a mix population of cancer types.13,15,16,20,37 A similar figure can be observed with the experimental trials undertaken after cancer treatment where three studies were
conducted with breast cancer patients,\textsuperscript{27,28,31,32} three in a mixed cancer population including breast cancer,\textsuperscript{24,25,29} and two in a mixed cancer population not including breast cancer.\textsuperscript{26,30} Therefore, future studies aiming to examine the role of exercises in cancer populations should also include other cancer types than breast to reveal possible physiological and psychological benefits from exercise among other cancer groups.

As a secondary purpose of this review, we attempted to establish a training dose-response with this population based on the existing literature. The importance of scientific exercise principles has been extensively reported.\textsuperscript{39,61,62,91} It is well known that manipulation of the training program variables of frequency of training, intensity of training, specificity of training, and rest period between sets and exercise sessions produces clearly differentiated effects on specific physiological adaptations for both cardiovascular and resistance exercise. Nevertheless, long-term trials comparing different training models are rare even in healthy adult populations as reported by the American College of Sports Medicine position stand on the recommended quantity and quality of exercise prescription in healthy adults.\textsuperscript{39} Therefore, most of the studies presented in this review that aim to elucidate training response for cancer patients during and after treatment, were short in duration\textsuperscript{10,13,14,16,18,20,24,25,29,31,32,34-38,40} with some interventions still not controlling elementary training variables.\textsuperscript{12,25,29,30,92} The short-term nature of these interventions would likely limit the ability to detect specific physiological responses with training. Moreover, considering that exercise has been endorsed as a crucial component of a healthy lifestyle and is viewed as a lifelong behavior that may prevent and control various disease conditions,\textsuperscript{93-96} further studies undertaken for longer periods are needed. Additionally, the specific training dose for this population and how it would differentiate from many of the cancer types, treatment modalities, and stages of treatment remains an open area for prospective trials. Despite the work by Segal et al\textsuperscript{33} and Cunningham et al,\textsuperscript{37} which compared a home-based versus supervised exercise and five times versus three times weekly resistance exercises, respectively, none of these studies had actually used more than one training protocol, attempting to compare differences in training response due to various intensities, frequencies, volume, and type of training. Consequently, a requirement for future studies on this topic should include randomized controlled trials comparing how various types of cancer undergoing different treatments and stages of the disease would respond to different training stimuli.

Finally, the majority of the studies involving resistance training did not draw on the wealth of scientific research that has been published in regard to resistance training for muscle hypertrophy and strength gain. In all cases excepted one,\textsuperscript{16} the intensity of exercise in particular was inferior to the 6 to 10 RM load that has been deemed optimal for muscle growth and strength enhancement.\textsuperscript{61,62} One of the better designed resistance training interventions addressed in this review was by Cunningham et al\textsuperscript{37} and yet their model was based on research completed around 1950.\textsuperscript{73,74} Moreover, the only study that incorporated a better-quality training intensity limited the program to 6 weeks and performed no more than three resistance exercises.\textsuperscript{16} Although much more research is required in this important area, some guidelines and possible physiological outcomes are provided in Table 3. Future research into exercise interventions with cancer patients should involve contemporary resistance training program designs incorporating adequate intensity, periodization, selection of functional exercises involving large muscle groups, and manipulation of rest period and recovery strategies to maximize the anabolic effect on muscle and bone as well as positive endocrine responses.

**Table 3. Guidelines and Possible Physiological Outcomes from Exercise in Cancer Patients**

<table>
<thead>
<tr>
<th>Exercise Modality</th>
<th>Intensity</th>
<th>Frequency (/week)</th>
<th>Volume</th>
<th>Dosage</th>
<th>Cancer Relevant Expected Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular exercises</td>
<td>55-90% MHR 40-85% MHRR</td>
<td>3-5</td>
<td>20-60 minutes</td>
<td>Continuous or intermittent</td>
<td>↑ Cardiopulmonary function, ↑ Insulin sensitivity, ↓ HDL, ↓ LDL, ↓ Fat mass, ↓ Fatigue</td>
</tr>
<tr>
<td>Anabolic/resistance</td>
<td>50-80% 1-RM 6-12 RM</td>
<td>1-3</td>
<td>1-4 sets per muscle group</td>
<td>↑ Muscle mass, ↑ Muscle strength, ↑ Muscle power, ↑ Muscle endurance</td>
<td>BMD, ↑ FP, ↓ Fatigue, Resting metabolic rate, ↓ Fat mass</td>
</tr>
<tr>
<td>Flexibility exercises</td>
<td>?</td>
<td>2-3</td>
<td>2-4 sets per muscle group</td>
<td>10-30 seconds</td>
<td>↑ ↓ Range of motion</td>
</tr>
</tbody>
</table>

Abbreviations: ↑, increase; ↓, decrease; ↔, no change; MHR, maximum heart rate; MHRR, maximum heart rate reserve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMD, bone mineral density; FP, functional performance; RM, repetition maximum.

\textsuperscript{1}Data not available with cancer population, recommendation based from studies undertaken with noncancer population.\textsuperscript{2}

**Conflicts of Interest**

Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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REVIEW

Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer

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Side effects accompanying androgen deprivation therapy (ADT), including sarcopenia, loss of bone mass and reduction in muscle strength, can compromise physical function, particularly in older patients. Exercise, specifically resistance training, may be an effective and cost-efficient strategy to limit or even reverse some of these adverse effects during and following therapy. In this review, we discuss common morphological and physiological ADT-related side effects or ‘Androgen Deprivation and Sarcopenia-Related Disorders’ and the existing clinical trials incorporating physical exercise in prostate cancer patients receiving active therapy. Further, training concepts and guidelines are provided for prescribing resistance exercise programs for this population.

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Keywords: androgen antagonists; skeletal muscle; exercise

Introduction

Worldwide prostate cancer is the second most common cancer in men representing 19% of cancers among men in developed countries.¹ With the aging of the population in developed and developing countries, the incidence of all cancers, which are normally higher in those aged >65 years, is predicted to substantially rise, particularly for colon and prostate cancer, which are well established aging-related cancers.² Advancing age increases not only the vulnerability to cancer but also the risk for other comorbid conditions (for example, cardiovascular disease, diabetes, osteoporosis, arthritis and sarcopenia)³ that can compromise physical function and independent living and ultimately result in death.

The introduction of the prostate-specific antigen (PSA) blood test into routine clinical practice in Australia and the USA in the 1990s has led to earlier diagnosis of disease.⁴,⁵ Men are often minimally symptomatic or completely asymptomatic and can be expected to survive substantially longer than their historical counterparts.⁵,⁶ Full characterization of toxicity is now seen to be an important priority for research.⁶-⁸ For example, sarcopenia, which is the age-related loss of muscle mass and strength, can be largely exacerbated in this cancer group owing to the catabolic side effects of some forms of treatment such as androgen deprivation therapy (ADT).⁹

In the non-cancer older population, resistance exercise has been endorsed as a potent countermeasure to sarcopenia and its implementation in clinical and home settings are relatively simple and inexpensive.¹⁰ Additionally, this exercise mode has reliably shown to induce other health benefits by promoting increases in the ability to perform daily tasks and increased physical reserve capacity.¹¹ Recently, the role of structured exercise as a possible adjuvant therapy during cancer treatment has gained recognition, with most intervention trials incorporating cardiovascular activities.⁹,¹² Research into the effects of resistance exercise in prostate cancer patients and survivors are limited with only two studies reported.¹³,¹⁴ Although research in this area is still emerging, preliminary findings indicate the beneficial effect of resistance exercise on the musculoskeletal system, reducing levels of fatigue and enhancing quality of life among cancer patients and survivors.⁹,¹²,¹⁵

In this review, we discuss (1) common ADT treatment-related side effects relevant to the musculoskeletal system, chronic disease and functional ability; (2) the beneficial effects derived from existing resistance exercise trials in this patient group and (3) guidelines for implementing this exercise mode as a potential treatment strategy.

Treatment of prostate cancer

Prostate cancer is the most frequent cancer in older men (those 65 years and older) with 80% of cases occurring in this age group. ADT is a widely employed means of treating this cancer, and is achieved by either surgical
castration or more commonly by administering LHRHa (luteinizing hormone-releasing hormone agonist) and/or antiandrogen medications that block the androgen receptors. Traditionally, ADT has been administrated in the latter stage of prostate cancer (for example presence of metastases). However, owing to earlier detection of prostate cancer through better screening (for example PSA), patients are undertaking ADT in the early stages of the disease and therefore being exposed to this therapy for longer periods of time. Additionally, ADT is now used as adjuvant therapy to radical prostatectomy and radiotherapy. Concerns related to the detrimental effects of ADT on muscle, fat and bone mass have arisen as it can exacerbate the risk of sarcopenia, osteoporosis and obesity, and therefore induce other health related complications. This array of side effects related to ADT affecting the musculoskeletal system and physiological function or ‘Androgen Deprivation and Sarcopenia-Related Disorders’ is presented in Table 1. ADT has also been shown to contribute to emotional disturbances, fatigue and memory difficulties, with these cognitive ADT-related disorders referred to as ‘Androgen Deprivation Syndrome’ (Table 1).

**Side effects from ADT**

**Androgen deprivation and sarcopenia-related disorders**

*Body composition.* Several studies have documented marked alterations in body composition in men receiving ADT for prostate cancer. Smith et al. reported a 9.4% increase in whole body fat and a 2.7% reduction in whole body lean mass assessed by dual energy X-ray absorptiometry (DXA) following 48 weeks of ADT. Recently, Greenspan et al. observed comparable changes in whole body fat (10.4%) and lean mass (−3.5%) during the initial 12 months of ADT. Cross-sectional studies comparing ADT- versus non-ADT-treated prostate cancer patients and healthy matched individuals have also indicated lower whole body lean mass, higher percent and whole body fat mass in ADT-treated men. Importantly, reduction of lean mass following ADT can reduce musculoskeletal fitness, compromising muscle strength, physical function and physical reserve capacity. Such changes have implications in terms of reducing the age at which the individual falls below the functional capacity threshold, requiring a shift away from independent living and a reduced quality of life. Moreover, the increase in fat mass during ADT can lead to increased levels of total cholesterol and triglycerides and consequently the possible development of cardiovascular complications.  

**Bone mass and skeletal fracture.** Apart from a decline in muscle mass and strength, ADT-treated men suffer a reduction in bone mass, and consequently bone strength, that contributes to an increased incidence of fracture and associated disability. The ADT-related bone losses are significant and exceed those of women experiencing early menopause. Recently, Greenspan et al. indicated that men with prostate cancer initiating ADT have a 5- to 10-fold loss of bone mineral density (g/cm²) compared to healthy controls or men with prostate cancer not on ADT. Importantly, following ADT, there is a significant dose-response relation between fracture risk and the number of LHRHa doses administrated. The reduced structural bone strength is compounded by the reduction in muscle mass and strength (Figure 1).  

**Table 1** Side effects from androgen deprivation therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Androgen deprivation and sarcopenia-related disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al.</td>
<td>Decrease whole-body lean mass</td>
</tr>
<tr>
<td>Greenspan et al.</td>
<td>Increase whole-body fat mass</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>Decrease bone mass</td>
</tr>
<tr>
<td>Basaria et al.</td>
<td>Increase fracture risk</td>
</tr>
<tr>
<td>Basaria et al.</td>
<td>Decrease muscle strength</td>
</tr>
<tr>
<td>Greenspan et al.</td>
<td>Increase insulin resistance</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>Negative lipoprotein profile</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>Androgen deprivation syndrome</td>
</tr>
<tr>
<td>Shahinian et al.</td>
<td>Increase depression</td>
</tr>
<tr>
<td>Spry et al.</td>
<td>Decrease cognitive function</td>
</tr>
<tr>
<td>Spray et al.</td>
<td>Increase fatigue</td>
</tr>
<tr>
<td>Spray et al.</td>
<td>Other side effects from androgen deprivation</td>
</tr>
<tr>
<td>Spray et al.</td>
<td>Decrease health-related quality of life</td>
</tr>
<tr>
<td>Spray et al.</td>
<td>Hot flashes</td>
</tr>
<tr>
<td>Spray et al.</td>
<td>Decrease libido</td>
</tr>
</tbody>
</table>
strength and power, which has been related to increased falls incidence, resulting in two separate side effects of ADT combining to greatly increase fractures due to falls.

**Insulin resistance and lipoprotein profile.** Recently, Basaria et al. suggested that men with prostate cancer undergoing long-term ADT can develop insulin resistance and hyperglycemia and these metabolic alterations are independent of age and body mass index. In this cross-sectional study, ADT-treated men had significantly higher fasting levels of glucose, insulin and leptin when compared to healthy aged-matched controls and prostate cancer patients not on ADT. Moreover, significant negative correlations were reported between total and free testosterone levels with fasting glucose, insulin and leptin. Further, data from the same research group also indicated that long-term ADT-induced hypogonadal men have higher fasting levels of total cholesterol, low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol than non-ADT prostate cancer men and aged-matched controls. Other studies have also indicated the long-term negative alterations in lipoprotein profile in men treated with ADT with increases in serum total cholesterol (9%) and triglycerides (26.5%) following 48 weeks of therapy.

**Androgen deprivation syndrome and quality of life**

**Quality of life, depression and cognitive function.** Testosterone suppression for prostate cancer has been shown to negatively affect health-related quality of life. As such, reduced physical function and general health have also been reported in men on ADT compared to non-ADT treated men and healthy matched controls. For example, Spry et al. reported results from a large longitudinal, multicenter study examining the dynamic change in quality of life and testosterone in men initiating an intermittent maximal androgen blockade program. ADT lead to a significant reduction in health-related quality of life during the initial 9 months of therapy with substantial changes occurring by 3 months. Further, during the recovery phase (off-ADT), improvements in quality of life occurred in a more gradual manner and were of smaller magnitude than the changes observed during the ADT phase.

Bioavailable testosterone has been positively associated with cognitive function in older men. Further, the hypogonadal condition has been associated with an increased incidence of depressive illness. Despite the limited number of controlled studies examining the effects of testosterone suppression on depressive and cognitive function during ADT, a recent large population-based study reported an increased incidence of depressive and cognitive disorders in ADT-treated men, although the effects were diminished after adjustment for potential confounders.

**Exercise interventions in prostate cancer patients**

**Resistance exercise**

A summary of the exercise interventions examining the effect of resistance or cardiovascular training in cancer patients undergoing treatment is shown in Table 2. To date, only two studies have examined the effects of resistance training in prostate cancer patients receiving ADT. Segal et al. studied 155 men in a multisite trial with localized and non-localized prostate cancer undertaking or scheduled to receive different forms of ADT for at least a 12-week exercise training period. Using a randomized controlled design, patients were assigned to either whole body resistance training, which incorporated three upper and four lower body exercises (n = 82) or a non-exercise control group (n = 73). Training intensity was set at 60–70% of one repetition maximum (1-RM; the maximal weight that can be lifted once only) for two sets of 12 repetitions three times per week. Progression was incorporated by increasing load (~2.5 kg) when subjects were able to pass the 12-repetition mark. The exercise group experienced improved symptoms of fatigue and health-related quality of life compared to the non-exercise group. Moreover, submaximal muscle strength increased by 42 and 32% for the chest press and leg press, respectively. The observed changes for fatigue and quality of life are extremely relevant given that they are negatively affected during ADT. Importantly, information from this study provides support that even a low volume training program at a moderate intensity undertaken for a relatively short time period can confer substantial benefits to this group of cancer patients on therapy.

Recently, we examined the effects of a longer (20-week) progressive resistance exercise intervention in a group of men receiving ADT for prostate cancer. Training intensity, volume and frequency were set at 12- to 6-RM using two to four sets for 10–12 exercises undertaken twice weekly. This study aimed to extend the work of Segal et al. by examining the physical, functional, morphological and physiological outcomes of the intervention. Dramatic improvements in muscle strength (chest press, 40.5%; seated row, 41.9%; leg press, 96.3%) and muscle endurance (chest press, 114.9%; leg press, 167.1%) resulted as well as improvements in a number of physical performance measurements including the 6-m usual walk, 6-m backwards walk, chair rise, stair climbing, 400-m walk and balance ranging from 7 to 27%. Despite the suppression of testosterone, changes in muscle strength were comparable to the effects of resistance exercise interventions in healthy older adults not on ADT. Further, changes in muscle endurance and functional capacity indicated that ADT-treated men may carry out functional daily activities with less fatigue following resistance exercise regimes and could partially explain the reduced levels of fatigue in resistance trained men reported by Segal et al. The results also indicated that muscle thickness increased at the quadriceps site and whole-body lean mass by DXA was preserved with no change in fat mass. Considering that detrimental alterations in body composition are well established side effects from ADT, these results provide support for the role of resistance exercise to preserve body habitus and enhance physical function in prostate cancer patients undergoing therapy.

**Cardiovascular exercise**

Although a number of studies have utilized cardiovascular exercise programs in other cancer groups, only...
### Table 2
Experimental design exercise studies in prostate cancer patients undergoing therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design/duration</th>
<th>n (age)</th>
<th>Therapy mode/time</th>
<th>Exercise program</th>
<th>Intensity/volume/frequency</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segal et al.</td>
<td>Randomized controlled trial (multi-site) 12 weeks</td>
<td>n = 155 (68 years)</td>
<td>Receiving or scheduled to receive ADT for at least 12 weeks</td>
<td>Resistance training (clinic-based)</td>
<td>12-RM, 2 sets 3 x week</td>
<td>Fatigue*</td>
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<td>Quality of life*</td>
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<td>Testosterone*</td>
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<td>PSA*</td>
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<tr>
<td>Windsor et al.</td>
<td>Randomized controlled trial (single-site) 4 weeks</td>
<td>n = 66 (69 years)</td>
<td>External beam radiotherapy 50 grays in 20 fractions over 4 weeks</td>
<td>Cardiovascular walking (home-based)</td>
<td>60–70% MHR 30 min 3 x week</td>
<td>Fatigue*</td>
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<td>Fatigue*</td>
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<td></td>
<td></td>
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<td>Walking distance*</td>
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<tr>
<td>Galvão et al.</td>
<td>Non-randomized controlled trial (single-site) 20 weeks</td>
<td>n = 10 (70 years)</td>
<td>Minimum 8 weeks on ADT prior to entering the study and scheduled to receive ADT for at least 20 weeks</td>
<td>Resistance training (clinic-based)</td>
<td>12- to 6-RM, 2–4 sets 2 x week</td>
<td>Muscle strength</td>
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<td>Muscle endurance</td>
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<td>Functional performance</td>
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<td>Body composition</td>
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<td>Muscle thickness</td>
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<td>Balance</td>
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<td>PSA</td>
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<td></td>
<td>GH</td>
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</tbody>
</table>

**, no change; ↑, increase; ↓, decrease; ADT, androgen deprivation therapy; PSA, prostate-specific antigen; GH, growth hormone; MHR, maximum heart rate; *, exercise intervention group; †, control group.

**Possible role of exercise during on- and off-treatment phases**

Exercise during on- and off-treatment phases may help to enhance physical function, particularly during off-ADT phases, when physical function is likely to be diminished. During treatment, exercise may help to reduce the side effects of ADT and facilitate the transition back to normal functioning. Exercise during off-treatment phases may also help to maintain physical function and enhance physical reserve capacity when ADT is stopped.

**Exercise studies and effects on testosterone and PSA**

Exercise studies in prostate cancer patients have shown that resistance training can help maintain PSA levels without compromising basal levels of PSA. Cardiovascular walking has also been shown to be effective in reducing PSA levels. These findings collectively suggest that non-androgen-mediated mechanisms, such as muscle growth mediators, may be responsible for the observed changes in PSA.

**Possible role of exercise during off-treatment phases**

Exercise during off-treatment phases may help to enhance physical function, particularly during off-ADT phases, when physical function is likely to be diminished. During treatment, exercise may help to reduce the side effects of ADT and facilitate the transition back to normal functioning.
undergoing periods of testosterone suppression is a potentially important strategy that should be considered in future clinical trials.

**Guidelines for resistance exercise prescription**

Designing a resistance-training regimen involves the manipulation of a range of variables, such as the number of sets and repetitions, intensity of training (load lifted), duration of rest between sets and exercises, frequency of training and repetition velocity. Each of these training variables have been previously identified\(^ {10}\) and are listed in Table 3. Importantly, most of these training variables have been examined in healthy older adults and favorable responses in muscle strength and physical performance result from a range of training programs, including those using moderate exercise intensity, frequencies and volume of work.\(^ {11,42,43}\) However, it is also well known that acute and chronic manipulation of these variables results in distinct adaptations of the neuromuscular and skeletal systems. Practical examples of structured resistance programs based on previous studies\(^ {13,14}\) undertaken with ADT-treated men are shown in Table 4. Particularly for this cancer group experiencing a reduction in lean mass and physical function, the exercise goal is to progressively overload the muscles, so that increases in muscle strength and physical capacity can be achieved. As in the older non-cancer population, exercises should be dynamic in nature using both concentric (lifting and pushing/pulling phase) and eccentric (controlled lowering/returning phase) muscle contractions.\(^ {10}\) Major functional lower body muscle groups, such as knee flexors and extensors, hip extensors, dorsiflexors and plantarflexors, should be targeted to maintain or enhance functional mobility and balance and therefore decrease the risk of falls and fractures. Suggested guidelines\(^ {9}\) for resistance exercise programs in cancer patients are shown in Table 5.

A vast array of equipment is available, so that resistance can be applied to the target muscle groups in a safe manner for the user. Most use the gravitational weight force but there are also a number of machines that use elastic, surface friction, hydraulic, aerodynamic drag or pneumatic resistance. Further, free weights or dumbbells and barbells can also be used, although some exercises will require a training partner or trainer to provide assistance during the activity. Body weight, elastic bands specifically designed for exercise and homemade resistance devices can be particularly effective for implementing an inexpensive, home-based resistance training program.

In addition, clinicians could inform patients that exercise does not aggravate the cancer, even low amounts are better than nothing and more activity may provide additional benefits. In cases of significant

![Image](image_url)

**Table 3** Resistance training program variables

<table>
<thead>
<tr>
<th>Training components</th>
<th>Description</th>
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<tbody>
<tr>
<td>Repetition</td>
<td>One completed movement of exercise</td>
</tr>
<tr>
<td>Set</td>
<td>Series of repetitions performed without stopping (for example eight repetitions/set)</td>
</tr>
<tr>
<td>Intensity</td>
<td>Amount of weight lifted that can be determined by the percentage of 1-RM or a specific number of RM</td>
</tr>
<tr>
<td>RM</td>
<td>The maximal number of repetitions that can be performed at a given exercise intensity (for example 8-RM)</td>
</tr>
<tr>
<td>1-RM</td>
<td>The maximal weight that can be lifted once with acceptable form</td>
</tr>
<tr>
<td>Velocity</td>
<td>Repetition movement speed (for example 2–3 s concentric and 2–3 s eccentric)</td>
</tr>
<tr>
<td>Rest between sets</td>
<td>Recovery period undertaken between sets for a particular exercise (for example 1–2 min)</td>
</tr>
<tr>
<td>Frequency</td>
<td>Days per week</td>
</tr>
<tr>
<td>Duration</td>
<td>Length of an individual session (for example 40 min)</td>
</tr>
</tbody>
</table>

Abbreviation: RM, repetitions maximum.

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**Table 4** Resistance exercise by specific region from studies undertaken with prostate cancer patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Upper body</th>
<th>Lower body</th>
<th>Trunk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segal et al.(^ {13})</td>
<td>Chest press, lat pull down, shoulder press biceps curl, triceps extension</td>
<td>Leg extension, leg curl, calf raises</td>
<td>Modified curl-ups</td>
</tr>
<tr>
<td>Galvão et al.(^ {14})</td>
<td>Chest press, lat pull down, seated row, shoulder press, biceps curl, triceps extension</td>
<td>Leg extension, leg curl, squat, leg press</td>
<td>Abdominal crunch, back extension</td>
</tr>
</tbody>
</table>

**Table 5** Guidelines for resistance exercise in cancer patients

<table>
<thead>
<tr>
<th>Exercise modality</th>
<th>Intensity</th>
<th>Frequency</th>
<th>Volume/dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabolic/resistance exercises</td>
<td>50–80% 1-RM 6–12-RM</td>
<td>1–3 × per week</td>
<td>1–4 sets per muscle group</td>
</tr>
</tbody>
</table>

Abbreviation: RM, repetition maximum.

Reprinted with permission from the American Society of Clinical Oncology (Redrawn from Galvão and Newton).\(^ {9}\)
comorbidity, a referral to an exercise clinic would be appropriate given that unsupervised or inappropriate supervision may lead to injury. Consequently, the clinician needs to locate appropriate health professionals, such as exercise physiologists, trained to deal with individuals with chronic and complex conditions and refer their patients (see below). Suggesting that patients undertake resistance exercise in small groups will facilitate adherence and compliance, and also reduce the financial cost to the patient. In addition, varying components of the program from time to time will assist with motivation. However, it is important for both the specialist and the general practitioner to provide a consistent message regarding exercise and physical activity, and to monitor the patient’s progress.

It should be recognized that progressive resistance training can result in some minor delayed onset muscle soreness during the initial phases of training or when training components are modified (e.g. resistance and/or number of sets increased) but should quickly resolve and patients can be informed that this may occur. Warm-up and cool-down activities of stretching and low-intensity level activities such as walking/cycling should be incorporated into each training session to prepare the individual for exercise and to return the individual to their resting level before leaving the training facility.

Although it is possible for the practicing oncologist to develop a small-scale exercise facility for patients, it may be more efficient to refer patients to clinical exercise physiologists or to exercise centers with qualified staff in this field. The American College of Sports Medicine (ACSM – www.acsm.org) provides registered professionals with University qualifications in exercise science or related area. Similarly, other countries, such as Australia and United Kingdom possess organizations (Australian Association for Exercise and Sports Science, AAESS – www.aaes.com.au/ – British Association of Sport and Exercise Sciences, BASES – www.bases.org.uk/) that provide registered exercise professionals with University qualifications who are able to conduct exercise training with this patient population.

Implications for oncologists and future directions

Although lifestyle modifications (predominantly diet, but also physical activity in general, smoking and alcohol cessation) and agents such as calcium/vitamin D for bone health have been indicated as potential sources available to counter or partially counter the side effects of ADT,17 none are likely to provide the magnitude of effects that are observed with resistance exercise. Although considerably more work is required in the area of exercise and prostate cancer recovery, preliminary results indicate that resistance exercises can be an important adjuvant therapy to counteract the catabolic side effects from ADT in older men with prostate cancer. Larger randomized controlled trials are required to confirm and expand current findings, as are studies to investigate the role of progressive resistance training before ADT as well as those incorporating this training mode during radiation therapy to combat treatment-related side effects.

References

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Can exercise ameliorate the increased risk of cardiovascular disease and diabetes associated with ADT?

Daniel A Galvão, Robert U Newton*, Dennis R Taaffe and Nigel Spry

Androgen deprivation therapy (ADT) in the form of gonadotropin-releasing hormone (GnRH) agonists is being increasingly used in the management of prostate cancer, particularly as adjuvant treatment and for patients with early PSA relapse. ADT is, however, associated with a number of adverse effects, including reduced bone mass, increased risk of fracture at multiple sites, reduced lean mass and muscle strength, and increased fat mass: these effects compromise physical function, independence, and quality of life.1

Apart from these well-established adverse effects of ADT, accumulating evidence indicates that ADT is also associated with substantial cardiovascular and metabolic complications, which can affect patients’ quality of life and overall survival. Four studies published within the last 2 years provide strikingly similar findings of these increased cardiovascular and metabolic risks associated with ADT, and highlight the need for strategies to counter treatment-induced morbidity and mortality.2–5 In a large, population-based cohort of men aged ≥66 years with localized prostate cancer, Keating et al.2 examined whether ADT in the form of a GnRH agonist or bilateral orchiectomy was associated with an increased incidence of cardiovascular disease and diabetes. Using Surveillance, Epidemiology and End Results (SEER) Medicare data, 73,196 men were observed for up to 10 years. Cox proportional hazards models, adjusted for a number of potential confounders, showed that GnRH agonist administration was associated with an increased risk of coronary heart disease (CHD; 16%), myocardial infarction (MI; 11%), sudden cardiac death (16%) and diabetes (44%). Moreover, the increased risk of incident CHD and diabetes was apparent with as little as 1–4 months of ADT.

In the study by D’Amico and colleagues,4 the authors pooled results from three randomized trials, which included cohorts from Australia and New Zealand, Canada, and the US. The time to fatal MI following 3–8 months of ADT, in men who were also receiving external beam radiotherapy, was examined: the study showed that 6 months of ADT led to a shorter time to fatal MI in men aged ≥65 years compared with men aged <65 years, or men who did not receive ADT. Furthermore, in those men aged ≥65 years, a similar time to fatal MI was observed for 3 months and 6–8 months of ADT, again indicating an increased risk of cardiovascular-related toxicity even after short-term ADT. Lastly, Tsai and colleagues,5 using data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, retrospectively examined whether ADT use was associated with death from cardiovascular-related causes in 4,892 men who underwent radical prostatectomy, external beam radiotherapy, brachytherapy or cryotherapy. After a median ADT duration of 4.1 months and a follow-up time of 3.8 years, patients aged ≥65 years who underwent both radical prostatectomy and ADT had a 5-year cumulative incidence of cardiovascular death of 5.5%, compared with 2% for those who underwent radical prostatectomy alone.

These four large studies clearly indicate novel cardiovascular and metabolic toxicities associated with ADT that are beyond the well-known and established adverse effects related to the musculoskeletal system.2–5 These findings are of considerable concern to patients and clinicians, as surviving the comorbidities associated with ADT can become more difficult than surviving the prostate cancer. Consequently, patients might decline to use ADT when it might be effective, and clinicians might be more hesitant to prescribe ADT. Before ADT is initiated, identifying patients at the greatest risk of these adverse effects, by assessing body composition, serum lipoproteins, fasting insulin, physical activity, cardiorespiratory fitness, and arterial stiffness, might be useful.
Keating et al.² suggest that the risk of developing cardiovascular and metabolic disease as a result of ADT must outweigh the risk posed to health by prostate cancer. A more beneficial approach, however, might be to prescribe adjuvant therapy to reduce the risks associated with ADT.

We believe that aerobic and resistance exercise might be an effective method to minimize or overcome these risks. In people without prostate cancer, increased levels of physical activity are well known to reduce the risk of type 2 diabetes in a dose-dependent fashion.⁶ Importantly, the protective effect of physical activity seems to be even stronger in individuals at the highest risk of developing type 2 diabetes.⁶ This effect might also be seen in patients with prostate cancer who receive ADT, where increased fat mass is a well-established adverse effect. Aerobic exercise (e.g. walking, running and cycling activities) has also been proven to improve insulin sensitivity in patients with type 2 diabetes,⁷ and is recognized as being able to reduce risk factors for cardiovascular disease in sedentary individuals by improving cardiorespiratory capacity and reducing blood pressure and body fat. In addition, aerobic exercise has been endorsed as a nonpharmacological strategy to improve lipoprotein metabolism, which is another major risk factor for cardiovascular complications. An extensive number of long-term prospective studies have indicated a protective effect of physical activity and aerobic capacity on death from any cause, including those of cardiovascular disease.⁸ Moreover, even in individuals with well-known risk factors for cardiovascular disease (e.g. hypertension, diabetes, smoking and high total cholesterol), high cardiorespiratory capacity clearly lowers the risk of premature death when compared with individuals with lower aerobic fitness and no other risk factors for cardiovascular disease.⁹ Our own work has established that exercise during ADT increases physical function, reduces fatigue and improves quality of life. For example, in a 20-week resistance exercise program, large improvements in muscle strength (chest press, 40.5%); seated row, 41.9%; leg press, 96.3%) and muscle endurance (chest press, 114.9%; leg press, 167.1%) were observed, as well as improvements of 7–27% in a number of physical performance measurements including 6 m usual walk, 6 m backwards walk, chair rise, stair climbing, 400 m walk and balance. Despite the suppression of testosterone, changes in muscle strength and aerobic capacity during the 400 m walk were comparable to the effects of resistance exercise interventions in healthy, elderly adults not receiving ADT. The results also indicated that muscle thickness increased at the quadriceps site, and whole-body lean mass was preserved. Furthermore, levels of PSA and testosterone remained unchanged, indicating that resistance exercise can be safely tolerated in this group of men receiving ADT.¹⁰

A critical need exists for the development of interventions that prevent the cardiovascular and metabolic toxicities associated with ADT. An official report from the American Cancer Society on Nutrition and Physical Activity indicates inclusion of resistance exercise to combat the occurrence of adverse effects (e.g. sarcopenic obesity and osteopenia) among some cancer patients who receive systemic therapy. Different exercise modes, including aerobic and resistance training, when undertaken during therapy, are safe and feasible for patients with cancer, and can lead to a range of positive physiological and psychological benefits. While not definitively confirmed, these same protective effects should be realized in patients receiving ADT, and thus reduce the risk reported in this new era of ADT.²–⁵ In our opinion, exercise is the front-runner for overcoming the newly discovered ADT-associated risks.

References

Acknowledgments
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Competing interests
The authors declared no competing interests.