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Exercise in Prevention and Management of Cancer

*Robert U. Newton, PhD**
Daniel A. Galvão, PhD

Address
**Vario Health Institute, Edith Cowan University, Joondalup, WA, 6027, Australia.*
E-mail: r.newton@ecu.edu.au

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

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.

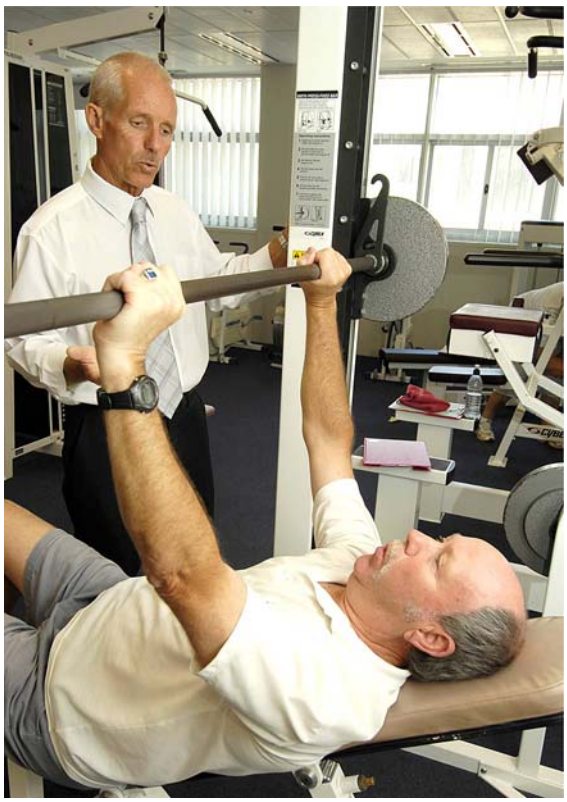

Fig. 2. Resistance training or "anabolic" exercise appears very effective for preserving muscle and bone content, reducing fat gain, and improving functional capacity. Mental health, in particular depression, is also improved.

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

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

Do moderately intense aerobic exercise 30 minutes a day, 5 days a week
Or
Do vigorously intense aerobic exercise 20 minutes a day, 3 days a week
And
Do anabolic exercise consisting of eight to ten exercises, eight to twelve repetitions of each exercise twice a week

Table 2. For healthy adults over 65 years or adults 50–64 years of age with chronic conditions, the recommendation is as follows [10••]

Do moderately intense aerobic exercise 30 minutes a day, 5 days a week
Or
Do vigorously intense aerobic exercise 20 minutes a day, 3 days a week
And
Do anabolic exercise consisting of eight to ten exercises, 10–15 repetitions of each exercise twice to three times per week
And
If you are at risk of falling, perform balance exercises
And
Have a physical activity plan

Table 3. For most cancer patients and survivors specific exercise recommendations are as follows [11••]

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)
And
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
And
Do flexibility exercises for major muscle groups, two to four sets of each exercise two to three times per week

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.

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. Giovannuci *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

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

Increased	Decreased
Muscle mass	Nausea
Muscle strength and power	Body fat
Cardiorespiratory fitness	Fatigue
Maximum walk distance	Symptom experience
Immune system capacity	Lymphocytes and monocytes
Physical functional ability	Duration of hospitalization
Flexibility	Heart rate
Quality of life	Resting systolic blood pressure
Hemoglobin	Psychological and emotional stress
	Depression and anxiety

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

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

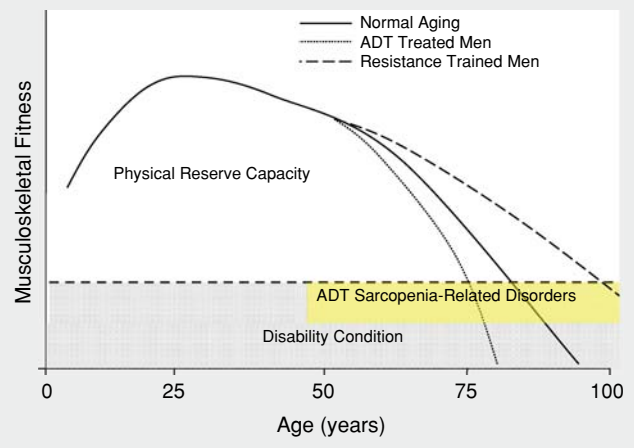

Fig. 3. Theoretical model of musculoskeletal fitness reduction during aging and ADT. Potential role of resistance exercise providing an increase in musculoskeletal fitness and physical reserve capacity in ADT treated men [31].

body (2.4%) and upper limb (1.3%) BMD following 36 weeks of ADT [30]. Greenspan *et al.* [36] 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

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.

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