

Review Article

Intervening on the Side Effects of Hormone-Dependent Cancer Treatment: The Role of Strength Training

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While prostate and breast cancers are both highly prevalent and treatable using hormone suppression therapy, a constellation of side effects ensue, which mimic typical aging effects but at an accelerated pace. Because strength training is considered to be an intervention of choice for addressing the musculoskeletal and metabolic consequences of normal aging in older adults, it may be an effective intervention to attenuate or reverse the side effects of hormone-dependent cancer treatment. This paper provides an overview of the independent effects of strength training on common musculoskeletal and metabolic side effects of hormone-dependent therapy used for prostate and breast cancers. Strength training appears to be an effective complementary therapy for some of the adverse effects of prostate and breast treatment. Future research needs to address potential mechanisms to explain recent findings and to explore the role of strength training in addressing specific risk factors resulting from cancer treatment.

1. Introduction

Cancer is the leading cause of death worldwide, accounting for 7.4 million deaths (~13% of all fatalities) in 2004 and is projected to rise to more than 12 million deaths by the year 2030 [1]. Prostate cancer (PCa) in men (28% of all cancer sites) and breast cancer (BCa) in women (28%) are the most prevalent types of cancer in the US [2]. They are the second leading causes of cancer-related deaths for men and women in the US, respectively [2], while BCa is the leading cause of cancer death in women across the globe [1].

The prevalence of all cancers increases with age [2], with those ≥ 65 years of age accounting for >60% of all cancers [3]. Because this age group is also more likely to have other comorbid conditions, such as osteoporosis, arthritis, and cardiovascular disease than younger age groups [3], treatment options become more complicated. Moreover, these patients tend to avoid physical activity, leading to some of the same adverse consequences as those previously experienced by cardiac patients who failed to engage in physical activity [4]. As is the case for cardiac patients, this course of action can result in losses of functional capacity

and quality of life (QoL) measures for cancer patients. In contrast, regular exercise can reduce cancer-related fatigue and other adverse symptoms of the disease, as well as substantially improve the QoL in cancer patients [4, 5]. Because five-year survival rates in localized PCa and BCa remain high [2], QoL related issues are of great concern. Although regular exercise has long been recommended for cancer patients, investigators have only recently focused on some of the specific musculoskeletal and metabolic adverse consequences (side effects) of cancer treatment, particularly those of hormone ablation medications.

There appears to be an interesting parallel between the many side effects of both PCa and BCa treatment and the changes that occur with typical aging [6–9], but at an accelerated pace. Given the role of strength training (ST) as a countermeasure for the age-related changes in body composition and physical function [10], this review will focus on the effects of ST on the side effects elicited from medications used in the two most common hormone-dependent cancers, that is, PCa and BCa. It will not include combined exercise training programs (e.g., those using both aerobic and resistance exercise) unless combined training

programs are the only source of information available on the side effect being discussed.

2. Treatments for PCa and BCa

There is a wide variety of treatment options for both PCa and BCa, depending on a patient's medical history, diagnosis, age, and current state of health. Although primary treatment for PCa may include radical prostatectomy, radiation, and other therapies, a common adjuvant treatment is the suppression of endogenous testosterone through the use of hormonal agents [11]. Likewise, while surgery is the primary therapy for BCa treatment, hormone suppression therapy serves as an important adjuvant therapy [12]. Chemotherapy is also used as a systemic treatment for BCa, either before surgery (neoadjuvant) or after (adjuvant) as needed. However, a common consequence of chemotherapy is ovarian failure [13, 14] and the onset of premature menopause.

Because most PCAs are androgen dependent, androgen deprivation therapy (ADT) is a commonly used treatment for PCa [11] and results in what is sometimes referred to as a chemical castration. Although this treatment slows the growth of existing tumors, thereby potentially saving lives, the associated suppression of testosterone also leads to numerous adverse side effects, including an increase in the number of comorbidities, which ultimately have a negative impact on QoL.

Analogous to the treatment of PCa, hormonal therapy for the treatment of BCa is to inhibit the effects of estrogen. This can be accomplished using selective estrogen-receptor modulators, such as tamoxifen [15], or aromatase inhibitors, another example of an antiestrogen treatment [12]. Both treatments reduce growth in estrogen-responsive tumors. Historically, tamoxifen has been a mainstay in BCa treatment and can be administered to both premenopausal and postmenopausal women [15] while aromatase inhibitors are typically reserved for postmenopausal women [12].

3. Side Effects of PCa and BCa Therapy and Strength Training

3.1. Does Hormone Therapy Mimic Aging Effects?

Sex hormone levels decline gradually with age in men and abruptly, with menopause in women. Previously, the cessation of endogenous production of androgens and estrogens during PCa and BCa treatment has been equated with increases in hormone-dependent age-related changes [6, 9]. While it is evident that treatment of hormone-dependent cancers via ablation or modulation of the sex hormones is effective in shrinking tumor masses and extending long-term survival rates, such treatments also bring about declines in muscle mass [16–20], strength [21, 22], and bone mineral density (BMD) [17, 22–27] and increases in fat mass [16, 17, 19–21, 28, 29], insulin resistance [30–33], and fatigue [17, 34–36]. Collectively, these effects negatively influence physical function [18, 22, 37–39] and QoL [21, 34, 36, 40, 41].

ST has been advocated as the intervention of choice for addressing many age-related declines [7, 8]. In this regard, many researchers have demonstrated that ST can reverse age-associated losses in muscle mass [42, 43], strength [44], muscle power [42, 45], bone loss [46], insulin sensitivity [47, 48], and increases in regional fat deposition [49], as well as the deterioration of muscle functional abilities, leading to declines in activities of daily living [50, 51]. Losses in muscle mass are also associated with declines in resting metabolic rate, which can lead to obesity. In this context, our group has shown increases in resting metabolic rate with ST [52, 53]. These results from healthy individuals support the hypothesis that ST can reverse or delay the musculoskeletal and metabolic consequences of hormone-dependent cancer treatment. Below is an overview of the evidence from studies that have tested this hypothesis.

3.2. Muscle Mass and Strength. Significant loss of muscle mass is observed within the first year of ADT in PCa patients [16, 17, 19, 20], and the longer the treatment period, the greater the loss in muscle mass [18]. When compared with healthy controls and PCa patients not undergoing ADT, ADT treatment revealed substantial reductions in muscle mass as well as strength [21, 22]. Ultimately, the loss of muscle mass and strength may be adversely linked to survival because higher levels of muscular strength are associated with lower cancer mortality risk in men, independent of other risk factors [54]. Declines in strength and mass may also occur in BCa patients during treatment, but the cause of this effect is unclear. In one study involving BCa patients undergoing localized treatment alone versus localized treatment and chemotherapy, there was a slight decline (<0.5 kg) in fat-free mass over 12 months in the dual treatment group while the localized treatment only group increased fat-free mass [28]. However, this difference was no longer present when results were adjusted for other factors that may have influenced fat-free mass, such as age, race, radiation therapy, baseline body mass index, and baseline fat-free mass. In another study, the effects of chemotherapy and tamoxifen on fat-free mass depended on what method was used to assess fat-free mass [55]. Other investigators have also observed no treatment effect on fat-free mass [56, 57] or strength [58] in BCa patients. Thus, declines in muscle mass and strength appear to be a concern primarily for PCa patients on ADT, given the anabolic role of androgens on muscle mass [59].

In two separate randomized trials, Segal et al. [60, 61] observed strength gains with ST in patients with PCa undergoing ADT. Another study showed that ST improved strength but without changes in whole body fat-free mass in PCa patients on ADT, though a significant increase in quadriceps thickness was reported [62]. Hansen et al. [63] examined the muscle hypertrophic response in PCa patients with and without ADT. Using eccentric resistance exercise, the men not on ADT experienced significant regional hypertrophy whereas the men on ADT did not. No significant differences between groups were observed, but the low statistical power from the small sample size may have contributed to this result. In contrast, we recently detected significant increases

in thigh muscle volume, directly assessed by computed tomography and whole body fat-free mass with ST in African Americans with PCa on long-term ADT (Hanson et al., unpublished data). BCa patients undergoing treatment are also able to increase their strength levels with ST [41, 57, 58, 64]. However, many of the existing exercise and cancer studies use a mixture of aerobic and ST protocols, which precludes the independent effects of ST. Nevertheless, it is likely that the strength increases reported in these studies are due to ST, given that aerobic exercise training does not typically result in significant strength increases.

3.3. Muscle Power. Muscle power is the product of the force and speed of muscular contractions. It is a strong predictor of the ability to perform the activities of daily living necessary for maintaining a high QoL in older adults [65], to an even greater extent than muscle strength [66, 67]. For this reason, power has the potential to be an important QoL indicator for patients with cancer. While muscle power declines with advancing age [68], the effects of cancer therapy on muscle power have not yet been reported in PCa or BCa patients.

The authors [42] and others [45, 69] have reported significant improvements in peak muscle power with ST in older healthy adults. Since movement speed is unlikely to improve with hormone therapy or decline with ST, it is likely that ST would improve power in cancer patients on hormone therapy, as it does for healthy people, given the reported ST-induced strength increases in these patients. To the best of our knowledge, this has not been studied. However, similar to our unpublished muscle volume data, we observed significant improvements in muscle power at various relative loads with ST (Hanson et al., unpublished data).

3.4. Bone Mineral Density. The hormone therapies used for PCa [17, 22, 27] and BCa [15, 58, 70, 71] are both associated with a loss in BMD. However, the specific type of BCa treatment affects BMD differently, as patients on aromatase inhibitors led to declines in BMD while those on tamoxifen experienced significant increases [23–25]. Moreover, bone loss associated with aromatase inhibitor treatment in women with BCa is twofold higher than that of healthy, age-matched postmenopausal women [26]. Chemotherapy treatment for BCa also reduces BMD, probably as a result of ovarian failure, and occurs in ~71% of patients [13, 14, 58]. Patients who retained ovarian function did not show any loss in BMD [14]. With the possible exception of fatigue, BMD loss and fracture risk appear to be the single largest consequence of BCa treatment.

We could find only one study each for PCa and BCa reporting the effects of ST on bone mass [58, 62]. ST for 20 weeks did not result in any changes in BMD in PCa patients [62]. In a randomized clinical trial of BCa patients, six months of home-based aerobic training versus resistance training versus usual care, demonstrated BMD declines of -0.76% , -4.92% , and -6.23% , respectively, with only a significant difference between the aerobic training and usual care groups [58]. However, the ST program was performed

using Thera-Bands and light resistance. Recently, Newton et al. [72] proposed a study that could potentially be the best controlled and most thorough physiological investigation on ST effects in patients on ADT. In particular, they propose to address the impact of ST on bone density as an indicator of fracture risk. They will also determine the effects of impact-loading exercise on bone mass. The rationale for this latter aspect of their study is that high and frequent impact forces on long bones are thought to stimulate bone formation.

Despite the lack of direct evidence of significant improvements in BMD in cancer patients, ST can increase BMD in healthy older adults [46, 73–75]. Although not all studies report improvements, those that have compared ST results to controls support the hypothesis that ST is effective for preventing or delaying the loss of BMD over time in older adults. Therefore, it is logical that a similar effect could be present in cancer patients if sufficient intensities are used, despite limited evidence to the contrary [58]. While increases in BMD directly reduce fracture risk, it has been argued that the ST-induced gains ($<5\%$) are not sufficient to overcome the estimated 20% gain in BMD that may be necessary to actually prevent a fracture during falls [76]. Instead, ST may indirectly reduce fracture risk by improving walking mechanics, balance, and strength, some of which have been observed in PCa patients during treatment [62], leading to a reduced risk of falling.

3.5. Fat Mass. Unlike fat-free mass, treatment of both PCa [16–20, 61, 77] and BCa [28, 29, 55] is consistently associated with a significant increase in fat deposition. The increase in fat mass can lead to obesity, diabetes, and metabolic syndrome. Although not directly assessed in previous cancer studies, it is quite likely that PCa and BCa therapies increase fat infiltration in muscle, leading to the accumulation of intermuscular fat [78]. This too has important health implications because elevated levels of intermuscular fat have been linked to insulin resistance and to the development of type 2 diabetes [79]. In addition, fat infiltration is associated with reduced strength [80], poorer leg function [81], and greater incidence of mobility limitations in older adults [82]. While weight gain is widely reported with BCa treatment, it is not well established if the gain is specifically due to tamoxifen. In a cohort of women who experienced weight gain of 1.7 kg and increased body fat 2.1%, there were no differences in weight and percent body fat increases between those being treated with tamoxifen and those who were not [29].

Segal et al. [61] found that ST may play a preventative role against the increase in body fat associated with PCa treatment. The patients who performed ST had no change in fat mass while those in the control group experienced significant increases in fat mass. Along these same lines, Galvão et al. [62] reported no change in body fat with ST and ADT, but had no control group for comparison. Similar findings of no significant reductions in body fat have been reported in BCa [57]. Mixed training protocols (ST and aerobic exercise training) can result in a significant loss of fat mass in some [56] but not all [83] studies in BCa patients during treatment.

3.6. Insulin Resistance. Insulin resistance refers to a reduction in the effectiveness of glucose uptake. This defect is linked to a whole spectrum of disorders, including obesity, cardiovascular disease, and the metabolic syndrome. Basaria et al. [30] observed a substantially higher prevalence of insulin resistance in PCa patients on ADT than in two other control groups, one in normal healthy controls and the other in a group having a similar disease state, but not on ADT. These results were independent of age and obesity. Similar declines in insulin sensitivity were found after a 12-week prospective study at the onset of ADT [32]. In addition, two independent reviews have corroborated this conclusion showing a strong link between ADT administration and insulin resistance [77, 84] and that this association becomes evident within the first few months of treatment. The authors emphasize the need for men receiving ADT to develop healthy lifestyle practices, such as regular exercise, particularly ST [84]. Furthermore, Basaria [77] found that ADT use for 12 months revealed a higher prevalence of diabetes, metabolic syndrome, and death from cardiovascular disease compared to controls. Similar to PCa patients, BCa patients on hormone therapy also have elevated insulin, glucose, and HbA1c levels [33]. Moreover, low doses of hormone therapy result in a loss of insulin sensitivity in women at a high risk for BCa [31]. Women being treated for BCa also had higher C-reactive protein levels and incidence rates of metabolic syndrome [33, 85].

To the best of our knowledge, however, the independent effect of ST has not been studied in cancer patients undergoing treatment for hormone-dependent cancers. The best evidence available is that BCa patients who underwent supervised ST and home-based aerobic exercise had significant decreases in fasting insulin levels with no change in the control group [83]. There was only a trend for between-group differences and no change in fasting glucose levels were found. Patients on ADT undergoing a mixed training protocol had no adjusted group differences after 12 weeks of training for insulin or glucose [86]. In healthy individuals, ST reduces insulin resistance and is as effective as aerobic training in both healthy older adults [48] and diabetics [47]. ST improves the insulin responses during oral glucose tolerance testing and hyperinsulinemic-euglycemic clamps in older men [87, 88] and postmenopausal women [89]. The similarity of findings between ST effects in healthy older adults and those undergoing cancer treatments for other risk factors supports the hypothesis that ST would also produce improvements in insulin resistance in cancer survivors. The data available do not entirely support this, but the independent effects of ST have yet to be evaluated.

3.7. Fatigue and Physical Activity Levels. Fatigue may be the most prevalent and distressing side effect during and after cancer treatment [4, 5], as high numbers of patients report suffering from chronic fatigue during this time [17, 34–36, 55, 90]. It is likely that both aging and hormone therapy contribute to fatigue by eliciting physiological events (such as anemia, declines in strength and fat-free mass, and increased

fat mass) that promote loss in fatigue resistance and the ability or willingness to engage in physical activity. Both PCa and BCa patients have reduced physical activity levels after the onset of treatment [17, 91]. Lower levels of physical activity, in part, result in overall reductions in fitness levels, leading to declines in physical function and ultimately to loss in QoL.

Compliance to regular exercise may break the vicious cycle of fatigue followed by avoidance of physical activity [4, 5]. Segal et al. [60, 61] found that fatigue negatively impacts on activities of daily living and QoL measures but both were improved as a result of ST in men with PCa. They also observed improvements in muscle endurance with the ST group compared to a control group [60]. This finding has been corroborated by others [62], supporting the hypothesis that ST improves fatigue resistance in patients undergoing ADT. Reductions in fatigue with ST have also been observed in patients being treated for BCa [57], but these reductions were not significantly different from those of a control group. As described for other factors previously, the independent effects of ST are not entirely clear because many studies used both aerobic and ST [36, 92, 93]. There is little doubt, however, that regular exercise reduces fatigue in BCa patients undergoing therapy.

3.8. Physical Function. The loss of physical function during ADT treatment is a common side effect [18, 22, 37] and is likely the result of decreased muscle mass and physical activity levels coupled with increases in fat mass and fatigue. Investigators who study functional abilities in men with PCa often administer a standardized battery of tests that simulate activities of daily living. This form of testing is seldom reported in women with BCa, rather the declines in function often focus on shoulder dysfunction and lymphedema following surgery rather than hormone treatments [39] or assess function via questionnaire. Reduced shoulder function in BCa is associated with poorer physical condition, minimal physical activity, increased body mass index, and poorer physical QoL [38], similar to the loss of function and QoL associated with PCa.

ST in men on ADT led to reported improvements of 7 to 27% in simulated activities of daily living [62]. Others have also reported improved activities of daily living in men with PCa but have used either combined exercise programs or resistance in which only the lengthening phase of the exercise is loaded (eccentric) [63, 86]. Studies on the effects of ST on upper body function are limited in BCa patients, possibly because ST was previously contraindicated due to concerns of lymphedema. However, recent studies have specifically addressed this concern. While no data are available on physical function, adverse events and worsening of lymphedema symptoms did not occur with ST [57, 64, 94]. The fact that women with BCa can safely participate in this type of exercise without adverse consequences provides a rationale for future studies to examine the role of ST on upper body function given the connection between limited function and QoL [38].

3.9. Quality of Life. Quality of life is arguably the most egregious side effect resulting from cancer treatment and is intertwined with strength, body composition, fatigue, and physical function. The changes observed with cancer treatment to the above traits are likely to influence QoL. Thus, it is not surprising that men and women undergoing hormone therapy for PCa and BCa report reduced QoL indicators [21, 34, 36, 40, 41]. The questionnaires used to assess QoL varied between studies, although several trends appear to be evident. For example, lower QoL scores were observed for the physical function but not the mental health in both PCa and BCa patients [21, 40, 41]. Other studies that used QoL questionnaires specific to each cancer type demonstrated reduced overall scores with treatment [34, 36]. Improved QoL scores with ST are observed in some studies in PCa and BCa patient populations [41, 60, 61], though not in others [57, 63]. Moreover, Ohira et al. [41] reported that several musculoskeletal improvements with ST were correlated with higher QoL indicators.

4. Conclusions and Future Directions

Some of the effects of hormone-related treatments for persons with PCa and BCa are similar to the typical effects of normal aging but occur at an accelerated pace. These include a long list of musculoskeletal, metabolic, body composition, and functional outcomes. ST appears to have a positive influence on many, but not all of these characteristics. In particular, ST is effective in reversing the loss of strength and function and may be able to slow fat gains and bone losses common to both types of cancer treatments. Due to the widespread use of mixed training protocols, there are some side effects that are reduced from training, but the independent effects of ST cannot be distinguished from effects of other training modalities, such as aerobic exercise. With five-year survival rates for BCa and PCa approaching 100% [2], maintaining high QoL in cancer patients is of paramount importance. In this regard, ST may contribute toward achieving this goal by serving as an effective adjunct therapy and countermeasure to the adverse effects of PCa and BCa treatment.

Over the past decade, the role of exercise has expanded from a means of improving QoL in cancer patients toward addressing specific risk factors resulting from cancer treatment, as well other lifestyle choices that limit function and influence QoL. Future research should address the issue of whether ST can (1) reverse ADT-induced muscle atrophy through direct assessments of muscle area in PCa patients, (2) enhance direct measures of whole body physical function in BCa patients, (3) improve muscle power and bone mineral densities in both populations, and (4) establish a relationship between favorable functional outcomes (activities of daily living, fatigue, QoL) and specific ST-induced adaptations (strength, power, body composition). This additional information will help guide clinicians in exercise prescription designed specifically to reduce comorbidities and particular side effects to enhance QoL in men and women undergoing hormone treatment for PCa and BCa, respectively.

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