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Review

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Exercise therapy across the prostate cancer continuum

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Abstract

Exercise has been increasingly investigated as an adjunct therapy for cancer patients. The purpose of this paper is to comprehensively review the literature regarding exercise as a therapeutic adjunct for prostate cancer (PC). Several studies in patients with PC have shown quality of life improvements associated with exercise. Although no study has established the effect of exercise as a monotherapy for PC, the molecular mechanisms responsible for the potential association between exercise and PC are being elucidated. Given the low-risk, high-reward nature of these studies, further investigations are needed to better define the function of exercise along the PC continuum.

Keywords: prostatic neoplasms, exercise, disease progression, lifestyle

Introduction

The wide array of treatment options available to men with primary prostate cancer (PC) includes invasive techniques such as surgery, radiation therapy and cryotherapy and less invasive treatments such as hormonal therapy and expectant management (that is, active surveillance). Unfortunately, these therapies are often associated with unique and varying degrees of debilitating physiological and psychological side effects that can negatively impact a patient's quality of life (QOL).^{1, 2, 3} Morbidity notwithstanding, the efficacy of primary PC therapy is limited as one in three men will develop a PC recurrence despite aggressive local therapy.^{4, 5}

For men with recurrent PC, androgen deprivation therapy (ADT) has been shown to dramatically reduce tumor burden; however, it has been associated with reduced libido, lean muscle mass and bone density.^{6, 7, 8} Furthermore, recent data have linked ADT to an increased risk of cardiovascular morbidity and mortality, including new onset diabetes, coronary artery disease and sudden cardiac death.^{9, 10, 11, 12}

When ADT fails, patients with hormone-refractory PC have fewer treatment options and a poorer prognosis as the mainstay of therapy is cytotoxic chemotherapy that confers a mere 2-month survival advantage.¹³

In recent years, increased attention has focused on exercise as a supportive adjunct therapy following a cancer diagnosis. There is clear and indisputable evidence that exercise improves psychological and physiological outcomes and is associated with significant reductions in cardiovascular and all-cause mortality in non-cancer individuals.¹⁴ What is unclear is the function that exercise may have in preventing and/or slowing PC pathogenesis. The purpose of this paper is to comprehensively review the extant evidence investigating the function of exercise along the PC continuum.

Exercise and prostate cancer prevention

Over the last several decades, 32 studies have investigated the association between exercise and the primary risk of being diagnosed with PC. More than half the studies in this area show an inverse relationship between physical activity and PC,^{15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30} other studies show no association^{31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42} and four studies even found exercise increased PC risk.^{43, 44, 45, 46} Perhaps this uncertainty in the literature can be attributed to the epidemiological nature of the research designs utilized in these studies, which relied upon survey or patient self-reporting to elicit physical activity and/or exercise exposure. In addition, many of these studies made no distinctions about the type of physical activity that respondents were performing and few validated physical activity exposure with objective measurements of fitness (that is, cardiorespiratory fitness testing). Although these epidemiological data provide some promising evidence that exercise may confer a reduction in PC risk, studies that quantify physical activity using objective measures are needed to better determine the true association between exercise and PC risk.

Exercise and prostate cancer therapy

A limited number of studies examining the effects of exercise in men with known PC have been conducted. In the following sections we will summarize the available literature regarding exercise in the setting of conventional PC therapies, including active surveillance, surgical treatment and nonsurgical treatment. Studies investigating exercise as part of a comprehensive lifestyle intervention suggest a therapeutic potential for exercise in low-risk PC. In addition, exercise may reduce the risk of both short- and long-term morbidities associated with conventional PC therapy. Finally, improvements in clinically important outcomes such as symptom control and QOL have been demonstrated in those patients with PC who exercise.

Active surveillance

No study to date has investigated the independent effects of exercise in men adhering to an active surveillance protocol; however, several investigations from the Ornish group did examine the effect of a program of comprehensive lifestyle changes consisting of moderate aerobic exercise (walking 30 min 6 days per week) as well as a vegan diet and stress management training in men undergoing active surveillance for low-risk PC.^{47, 48, 49}

Ornish *et al.*⁴⁷ randomized 93 men with low-grade PC (Gleason sum <7) undergoing a watchful waiting protocol to a program of comprehensive lifestyle changes or a control group that received usual care. The program adherence rate was 95% in the experimental group and after 1 year these men had a statistically significant decrease in prostate-specific antigen (PSA) as compared to men in the control group. In addition, serum obtained from men after 1 year in the experimental group significantly inhibited *in vitro* LNCaP cell growth as compared to serum from men in the control group. At both 1⁴⁷ and 2 years⁴⁸ after randomization, fewer patients in the comprehensive lifestyle modification program had undergone conventional PC therapy (that is, prostatectomy, radiation therapy, ADT) as compared to the control group.

Ornish *et al.*⁴⁹ also examined the changes in prostate gene expression in a cohort of 30 men with low-risk PC who elected to undergo active surveillance. These men participated in an intensive lifestyle and nutrition program similar to the aforementioned study that included recommendations for moderate

exercise. After 3 months men reported exercising >3.6 h per week (s.d.=1.5). Each participant underwent a control prostate needle biopsy at baseline and an experimental biopsy after 3 months of adhering to the lifestyle intervention. Gene expression profiles were obtained from the 30 participants comparing RNA obtained from the paired control and 3-month post-intervention biopsy specimens. Microarrays identified 48 upregulated and 453 downregulated transcripts after intervention. Notably, pathway analyses detected modifications of several pathways critical for tumorigenesis, including protein metabolism and modification, intracellular protein traffic and protein phosphorylation.⁴⁹

The above evidence suggests that exercise as part of a lifestyle modification program may have a beneficial effect for men with low-grade PC as evidenced by the decline in serum PSA, the *in vitro* inhibition of PC cell growth and the reduction in clinical events in the group adhering to the program as compared to the group receiving usual care. Furthermore, the hypothesis-generating alterations seen in gene expression provide a foundation to investigate molecular mechanisms responsible for the postulated association. Although these results are promising, it is important to remember that they cannot be attributed to exercise alone as exercise was not studied as a single intervention in these men. Larger trials of men undergoing active surveillance and adhering to only an exercise training intervention would eliminate the confounding influence of other therapies and provide the information necessary to clarify the effects of exercise on PC tumor biology.

Surgical treatment

Prostatectomy, whether performed through an open, laparoscopic or robotic-assisted approach, is associated with both short- and long-term morbidity and mortality. In a series of 11 010 prostatectomy patients examining short-term morbidity and mortality, Alibhai *et al.*⁵⁰ found at least one complication (cardiovascular, respiratory, vascular, wound and/or genitourinary) within 30 days of surgery in 19.9% of patients. Men who had more comorbidities at the time of surgery, including cardiovascular disease (CVD), diabetes, obesity and chronic obstructive pulmonary disease, had an increased risk for every category of complications as well as 30-day mortality, independent of age. For men who have an established history of engaging in regular exercise, they may potentially have a reduction in short-term morbidity and mortality associated with prostatectomy as regular exercise has been repeatedly shown to reduce the risk for developing the aforementioned comorbidities.¹⁴

Even for individuals who have not been chronically engaging in regular exercise, there is evidence to suggest that intensive exercise training interventions in the acute setting before surgery may be beneficial. In a cohort of patients undergoing surgical resection of malignant lung lesions, Jones *et al.*⁵¹ found an improvement in cardiorespiratory fitness (mean VO_{2Peak} increased by 2.4 ml kg⁻¹ per min) after only 4–6 weeks of presurgical structured exercise training. Several studies investigating cardiac surgery patients have demonstrated that surgical complications are inversely associated with exercise capacity.^{52, 53} Similar to cardiac surgery, prostatectomy is a significant surgical procedure and therefore attempting to improve exercise capacity in the acute setting before prostatectomy could potentially have a similar benefit of reducing surgical complications as seen in cardiac patients.

In addition to possibly reducing short-term morbidity and mortality associated with prostatectomy, exercise may have a function in reducing a significant long-term morbidity seen with prostatectomy, erectile dysfunction (ED), which has an estimated frequency between 14 and 80% despite bilateral nerve-sparing techniques.⁵⁴ ED has been shown to be intimately related to atherogenesis and increased CVD risk. For example, in the Massachusetts Male Aging Study (MMAS),⁵⁵ a community-based random cohort study of health and aging in 1709 men aged 40–69 years, Feldman *et al.* reported that ED increased in association with CVD risk factors such as obesity, hypertension and tobacco use. Using the MMAS, Derby *et al.*⁵⁶ reported that obesity and physical inactivity were inversely associated to the risk of ED.

Exercise may theoretically help to reduce post-prostatectomy ED by modulating the molecular mechanisms responsible for penile erection, specifically nitric oxide (NO). NO activates guanylyl cyclase in penile smooth muscle cells causing GTP to convert to cyclic GMP with activation of protein kinase G and accelerated efflux of calcium and potassium from smooth muscle cells, resulting in vascular dilation and increased penile blood flow.⁵⁶ Improved NO bioavailability not only allows increased penile blood inflow but also has been shown to influence myocardial function and peripheral blood flow in vascular endothelium helping to reduce CVD risk. The central importance of NO to both ED and CVD has led investigators in our group to begin to investigate the utility of exercise for concomitantly improving ED and CVD risk factors in men with PC.

Nonsurgical treatment

Two randomized-controlled clinical trials have been conducted to investigate the effect of exercise on symptom control, QOL and fitness in men undergoing concomitant ADT or radiation therapy. Segal *et al.*⁵⁷ studied the effects of resistance exercise training on muscle strength and QOL in men with PC. Specifically, 155 men diagnosed with PC who were undergoing ADT were randomized to an exercise group or a control group. Those in the exercise group participated in supervised upper and lower body resistance exercise training three times per week for 15 weeks, whereas the control group did not participate in such activity. They found that participants in the exercising group were more likely to have increased upper and lower body strength, increased QOL measures and decreased fatigue as compared to men in the control group.⁵⁷

In a similar study, 66 patients with PC receiving radiation therapy were randomized to an exercise intervention group or a control group. In this study, the exercise intervention was home-based aerobic exercise therapy three times weekly for 16 weeks. The men participating in the exercise intervention had significantly higher aerobic fitness (as measured by increased walking distance) than their nonexercising counterparts.⁵⁸

These results support that exercise has beneficial effects on muscle strength, aerobic fitness and QOL for patients with PC receiving ADT or radiation therapy as exercise may counter some of the morbid side effects of these treatments. Although the significance of symptom control and improved patient QOL as valuable clinical end points are undisputed, major unanswered questions in this field have yet to be determined. More evidence in the form of preclinical, correlative or randomized-controlled clinical trials is required to establish whether exercise modulates PC growth and metastases (following diagnosis), if and how exercise interacts with conventional PC therapy and ultimately how this affects PC-specific mortality and overall mortality. Identifying the biological mechanisms orchestrating these questions is also of paramount importance. Such corollary studies are critical to fully understand the application of exercise in the treatment of PC.

Proposed molecular mechanisms

Exercise is a pleiotropic intervention that influences numerous molecular pathways implicated in PC pathogenesis. Specifically, aerobic exercise lowers serum levels of several metabolic and sex steroid hormones hypothesized to stimulate PC, including insulin-like growth factor-1 (IGF-1), fasting insulin, leptin and testosterone.^{59, 60, 61, 62, 63} Chronic exercise is a potent stimulator of endogenous antioxidant protection pathways.^{64, 65, 66, 67} Exercise may also improve innate immune function and surveillance.^{68, 69, 70} In addition, the reductions in systemic inflammation and pro-inflammatory factors seen with exercise have been postulated to decreased cancer risk.⁷¹ Investigators in our group are beginning to explore alterations in angiogenesis as a potential molecular mechanism to explain the effect of exercise on PC pathogenesis. It is not yet clear what specific molecular mechanisms are involved in the associations seen between exercise and PC; however, a definitive understanding of the mechanisms responsible would allow us to exploit the influence of exercise to maximize its preventative and therapeutic potentials.

No randomized trials of exercise alone have been conducted in humans to examine the effect of exercise on PC biology. However, observational studies have been performed to provide some initial insight into the molecular mechanisms through which exercise may affect PC biology. For example, Leung *et al.*^{61, 62} found that exercise may inhibit PC cells by altering components of the IGF axis that increase cellular p53 protein content. The protein p53 is a regulator of DNA that protects the genome by activating cell-cycle arrest, triggering DNA repair and/or initiating apoptosis when mutations occur in the genome. Serum from men who participated in a regular exercise program for more than 10 years had reduced IGF-I and increased IGFBP-1 compared to men who did not exercise regularly, and both of these alterations increased p53 protein content.^{61, 62} Furthermore, serum from men who exercised reduced the growth rate and induced apoptosis in LNCaP cells *in vitro* significantly more than serum from a control group of men who did not exercise.^{59, 61, 62}

In addition to modulation through metabolic pathways, there are other molecular avenues, such as antioxidants and immune function, through which exercise could possibly exert an effect on PC biology.

Specifically, chronic exercise has been shown to modify endogenous antioxidant protection pathways by decreasing lipid peroxidation and reducing reactive oxygen species (ROS).^{64, 65, 66, 67} One possible underlying mechanism responsible for the age-associated increase in PC incidence is oxidative damage from ROS, such as superoxide, hydroxyl radical and hydrogen peroxide;^{72, 73} therefore, exercise could have a negative effect on PC by reducing these free radicals. Exercise has also been shown to improve innate immune function and surveillance,^{68, 69, 70} and previous studies have demonstrated the importance of innate immune function on PC pathogenesis.^{74, 75, 76, 77, 78}

These studies provide valuable information about the molecular framework through which exercise could exert effects on PC biology. What is unknown is how these molecular actions work in concert to affect PC biology and overall patient outcomes in the milieu of each stage along the PC continuum. The key to more clearly understanding this relationship is investigating the effect of exercise on PC growth and progression *in vivo*.

Surprisingly, even in animal models, very few studies have been conducted to clarify the relationship between exercise and PC biology. Zheng *et al.*⁷⁹ conducted the first published *in vivo* study to investigate the effect of voluntary exercise on the growth of prostate PC-3 tumors in a mouse model. Specifically, they found that voluntary running wheel exercise, beginning 1 week before tumor implantation, suppressed the growth of subcutaneously implanted PC-3 tumors (a hormone-refractory cell line). They implicated decreased mitosis and increased apoptosis as the mechanistic basis underlying this growth inhibition.⁷⁹

Potter *et al.*⁸⁰ conducted a similar preclinical study to explore the effect of exercise (that is, voluntary wheel running) on growth rate of subcutaneously implanted LAPC-4 tumor cells (a hormone-sensitive cell line) in a mouse model. They hypothesized that exercise would lead to decreased PC tumor growth rate and therefore prolonged survival; however, their results surprisingly showed that those mice with access to the exercise wheel had a faster rate of PC xenograft growth and shorter survival. Upon histological examination, they found 70% less necrosis and 154% greater microvessel density (endothelial structures) in the tumors of the exercise group.⁸⁰ On the basis of these data, the proposed molecular mechanism modulating increased tumor growth in the exercising mice was improved tumor vascularization (angiogenesis) initiated by exercise increasing perfusion to peripheral structures. Further investigation is required to determine if the increased perfusion seen in the PC tumors in exercising mice was unique to subcutaneous implantation.

Collectively, the biological actions that exercise exerts on the body favor an environment of decreased malignant cell growth, proliferation and survival. *In vitro* studies have identified and defined the alterations that exercise induces in individual molecular pathways important to PC biology. The limited number of *in vivo* studies done in the mouse model is beginning to help elucidate how these alterations work in concert to culminate in an overall effect on PC. The next and most important step will be to implement prospective human *in vivo* studies, perhaps in those men engaged in a watchful waiting protocol, to ultimately establish the independent effect of exercise on human PC growth, disease progression and patient survival.

Our recommendations

Given the limited data regarding the function of exercise as a modulator of human PC biology, it is clear that more studies are needed. With the current dearth of evidence, what can we recommend to our patients? In agreement with the American Cancer Society⁸¹ and the Prostate Cancer Foundation,⁸² we recommend that all patients with PC adopt a regular exercise program consisting of at least 20 min of continuous aerobic exercise (for example, walking, cycling) on at least 5 days per week at a moderate intensity. This program should also be supplemented with a resistance (strength) training program performed 2–3 times per week involving all major muscle groups (at least two sets per muscle group of 8–12 repetitions at moderate intensity). Exercise has been shown to be safe for men with PC and it is associated with significant improvements in fatigue, cardiorespiratory fitness and QOL in cancer patients. In addition, non-PC causes of death, namely CVD, currently exceed disease-specific mortality for patients with PC.⁸³

Conclusion

Although potential advantages have been most clearly established in epidemiological studies attributing a benefit with regard to exercise and PC prevention, there is evidence along other points of the PC continuum for QOL improvements associated with exercise—particularly for those undergoing ADT or radiation therapy. In addition, *in vitro* and recently emerging *in vivo* data have begun to delineate the molecular mechanisms by which exercise may modulate PC biology and therefore disease progression.

The general health benefits of exercise have long been established, and the evidence summarized in this review suggests exercise may confer additional benefits to patients with PC and therefore likely have a function in PC prevention and management. Ultimately, to confirm the associations that are beginning to be revealed between exercise and PC, randomized-controlled clinical trials including exercise training interventions are required across the entire PC spectrum.

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