EDITORIAL

Working hard or hardly working? A brief commentary of latest research on exercise and prostate cancer

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Worldwide, prostate cancer (PCa) is the second most common malignancy and the fifth leading cause of death in men. In 2020, it was estimated that there were 1.4 million incident PCa and over 375,000 PCa deaths [1]. Although screening and treatment have improved PCa survival rates, as many PCa patients are older, patients diagnosed at any stage are susceptible to declines in physical and mental health. This is compounded among patients receiving treatment due to treatment-induced toxicities.

For years, researchers focused on identifying the effects of physical exercise in patients with cancer. In patients with PCa, aerobic exercise and resistance exercise improve quality of life (QOL) and preserve physical health. To date, most research has shown benefits when exercise regimens are professionally supervised, moderate to high intensity and at least twice per week, although previous studies have broad variations in efficacy [2]. Key questions remain. Do alternative and home-based exercise regimens provide similar benefits for PCa patients as supervised exercise? At what disease stages are the greatest impacts seen? Through what mechanisms does exercise impact tumor biology? What biomarkers are affected by exercise that are relevant to PCa patients? Fortunately, several recent papers have begun to address these issues.

For this collection, we summarized nine manuscripts reporting the effect of exercise on PCa published in *Prostate Cancer and Prostatic Diseases* from February 2021 to May 2022 listed from pre-clinical to clinical studies by disease stage.

1. "Exercise training as a modulator of epigenetic events in prostate tumors" [3]. The authors studied the effects of exercise on the PCa epigenome using a well-established rat PCa model. Comparing trained vs. sedentary rats, exercise resulted in differential expression of 75 microRNAs, decreased expression of DNA methyltransferases and increased global DNA methylation, but had no effect on histone acetylation. Given the increasing recognition of the importance of epigenetics, these results provide additional insight to the mechanisms by which exercise could impact PCa.
2. "Exercise in advanced prostate cancer elevates myokine levels and suppresses in-vitro cell growth" [4]. The authors examined if aerobic and resistance exercise induces positive systemic adaptations in men with metastatic castration-resistant PCa (mCRPC). In a randomized trial of supervised vs. self-directed exercise, after 6 months of supervised training, men had higher serum myokine levels and when their serum was applied to DU145 PCa cells in vitro, it decreased growth vs. men randomized to self-directed exercise. While these data suggest that exercise training promoted systemic adaptations that theoretically could slow PCa progression, further research is needed to determine if myokines inhibit tumor growth and the mechanisms behind this.
3. "Effects of yoga in men with prostate cancer on quality of life and immune response: a pilot randomized controlled trial" [5]. In a small, randomized trial ($n = 29$), 6 weeks of yoga prior to radical prostatectomy improved QOL. In addition, the yoga group had improved anti-tumor immune responses, shown by increased circulating $CD4^+$ and $CD8^+$ T-lymphocytes and decreased regulatory T-cells and myeloid-derived suppressor cells, vs. the standard-of-care group. Although practicing yoga before surgery was feasible, further studies are needed to determine the impact of yoga on PCa progression and recurrence.
4. "Physical activity decreases the risk of cancer reclassification in patients on active surveillance: a multicenter retrospective study" [2]. In a retrospective review of 85 men on active surveillance, higher levels of self-reported physical activity were associated with a lower risk of reclassification. These data support the potential value of exercise to reduce reclassification in men on active surveillance, but questions remain including, is there a certain threshold of exercise needed to see benefits and whether results apply equally across races given the cohort was all white men?
5. "Feasibility of home-based exercise training in men with metastatic castration-resistant prostate cancer" [6]. In a single-arm, multi-site pilot study, a home-based exercise intervention for 12 weeks in men with mCRPC receiving androgen receptor signaling inhibitors resulted in greater endurance, muscle mass, and improved aerobic capacity. Given the small study size, future studies are needed to confirm these results as well as assess the time course over which these changes are seen.
6. "Comprehensive Lifestyle Improvement Program for Prostate Cancer (CLIPP) is associated with improvement in weight and components of metabolic syndrome in men exposed to androgen deprivation therapy for prostate cancer" [7]. Men on androgen deprivation therapy (ADT) lost weight and improved their blood pressure following a 24-week comprehensive lifestyle modification intervention that included physical exercise. This supports prior observations that exercise is associated with improved QOL in men on ADT for PCa [8].
7. "A randomized controlled trial comparing changes in fitness with or without supervised exercise in patients initiated on enzalutamide and androgen deprivation therapy for non-metastatic castration-sensitive prostate cancer (EXTEND)" [9]. Supervised aerobic and resistance training can be used prior to initiating enzalutamide and ADT to prevent side effects in men with non-metastatic castration-sensitive PCa. An unexpected and consequential finding was the stark

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decline in cardiorespiratory fitness in the control group: 12 weeks of enzalutamide and ADT was equivalent to 10 years of normal aging.

8. "Psychological distress in men with prostate cancer undertaking androgen deprivation therapy: modifying effects of exercise from a year-long randomized controlled trial" [10]. Compared to other PCa treatments, ADT seems to place patients at greater risk of psychological distress. Whether this can be reduced with exercise is unknown. In a randomized trial, a year of supervised exercise training led to reductions in psychological distress in men with PCa on ADT and greater reductions in men with higher levels of psychological distress.
9. "Supervised exercise therapy compared with no exercise therapy to reverse debilitating effects of androgen deprivation therapy in patients with prostate cancer: a systematic review and meta-analysis" [11]. This meta-analysis (18 RCTs) included patients with PCa undergoing ADT regardless of stage and compared supervised exercise therapy to no exercise therapy. Supervised exercise therapy improved "disease-specific QOL" and "physical performance" measured by walking performance, but increased the risk of fractures. Whether exercise impacts cancer control, however, remains unanswered.

Exercise seems to be beneficial at all PCa stages, but particularly for patients treated with ADT. Three studies suggest exercise improves overall QOL and physical performance, and reduces psychological distress in these patients [2, 5, 7, 10]. Unsurprisingly, most research focuses on patients treated with ADT, as they are known to lose bone and muscle mass, gain weight, feel fatigued and develop insulin resistance [12]. Thus, becoming more active is thought to be helpful particularly for these patients.

Research also suggests that exercise interventions across disease course are feasible. Although most studies examined a combination of aerobic and resistance training, one study looked at the effects of yoga and observed similar outcomes [5]. This is intriguing, since this could be a low-impact activity that could be easily adapted for men with advanced PCa. However, further research is needed to determine differences by intervention type and their effectiveness over time.

However, many questions remain. What are the mechanisms underlying the benefits of exercise in men with PCa? The above studies propose mechanisms including enhancing anti-tumor immunity, inducing epigenetic alterations, and possibly modulating circulating myokines; however, these results remain correlational. Does exercise have other associations in PCa beyond QOL and fitness, such as progression or recurrence? While men on active surveillance had lower rates of reclassification with higher self-reported exercise, RCTs on cancer control are lacking. We hope future studies will answer these important questions to continue optimizing care for PCa patients.

Gloria Cecilia Galván[1], Sanjay Das[1,2,3], James P. Daniels[1], Nadine A. Friedrich[1] and Stephen J. Freedland[1,3]✉

[1]Department of Surgery, Division of Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA. [2]Department of Urology, University of California—Los Angeles, Los Angeles, CA, USA. [3]Department of Surgery, Urology Section, Veterans Affairs Health Care System, Durham, NC, USA. ✉email: stephen.freedland@cshs.org

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GCG did the literature search, planning and wrote the manuscript. SD JPD and NAF wrote the manuscript. SJF revised content, wrote the manuscript and approved the final version.

COMPETING INTERESTS

SJF is a consultant to Bayer, Sanofi, Astellas, Astra Zeneca, Pfizer, Myovant, Janssen, and Merck. The other authors declare that they have no conflict of interest.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Stephen J. Freedland.