

Effectiveness of Exercise Therapy for Patients with Prostate Cancer Focusing on High-Intensity Interval Training: A Narrative Review

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ABSTRACT

Prostate cancer (PC) is the most frequently diagnosed cancer in men, and the population of survivors continues to increase. Although PC has a slower progression rate and a relatively favorable prognosis compared to other cancers, new strategies are needed to enhance outcomes after diagnosis and treatment. The effectiveness of exercise therapy in the prevention and treatment of PC is well documented. The significance of exercise for patients with PC includes prevention of disease progression, maintenance of physical fitness, and enhancement of muscle strength before surgery, as well as during chemotherapy and radiotherapy, all of which contribute to improving prognosis after treatment. High-intensity interval training (HIIT) is a well-established training protocol for long-distance runners that has also been applied to cardiovascular and metabolic diseases as a relatively novel and promising approach. HIIT, which involves high-intensity aerobic exercise, is known to enhance cardiorespiratory fitness, cardiac function, and insulin resistance to a greater extent than moderate-intensity training. Recent studies have demonstrated that HIIT effectively improves cancer cell growth inhibition and decreases prostate-specific antigen levels in both localized PC under active surveillance and metastatic castrate-resistant PC. However, the HIIT protocol should be tailored to each patient's condition and physical fitness level upon implementation. If accumulating evidence confirms the ability of HIIT to enhance physical fitness and suppress PC growth, the benefits to patients with PC would be substantial, and expected to be widespread.

Keywords: High-intensity interval training, prostate cancer, prostate-specific antigen, tumor growth.

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1. INTRODUCTION

Recently, the number of patients with prostate cancer (PC) has increased, making it the most frequently diagnosed cancer in men, with a growing population of survivors [1]. Although PC has a slower progression rate and a relatively favorable prognosis compared with other cancers, treatment approaches substantially impact patient outcomes. For instance, Hamdy et al. examined 1,600 patients with PC detected through prostate-specific antigen (PSA) screening, categorizing them into active surveillance (AS), prostatectomy, and radiotherapy groups. They found that tumor progression and metastasis rates were higher in the AS group than in the prostatectomy and radiotherapy groups, although 10-year PC mortality rates did not differ among the groups

[2]. These findings underscore the need for novel strategies to improve patient prognosis following diagnosis and treatment.

1.1. Exercise for PC

In addition to nutrition, the effectiveness of exercise therapy for the prevention and treatment of PC is well documented. A study by Canadian researchers reported that strenuous physical activity among male residents in their early 50s reduced the risk of PC (relative risk ratio: 0.8) [3]. Kang et al. reported positive results in the Exercise during Active Surveillance for Prostate Cancer (ERASE) trial regarding the effects of high-intensity interval training (HIIT) on cardiometabolic biomarkers in patients with localized PC undergoing AS [4]. Furthermore, a large



systematic review and meta-analysis also found that the amount of physical activity at work and during leisure time was inversely proportional to the risk of PC (relative risk ratio: 0.9) [5]. Another meta-analysis revealed that physical activity following a confirmed PC diagnosis reduced the risk of death from PC (relative risk ratio: 0.69) [6].

The significance of exercise for patients with PC includes prevention of disease progression [5], maintenance of physical fitness, and enhancement of muscle strength before surgery during chemotherapy [7]. Additionally, exercise plays a crucial role in enhancing physical fitness during chemotherapy and radiotherapy [8], as well as improving prognosis after treatment [9], [10]. A large body of literature supports the role of exercise during cancer treatment in enhancing the quality of life and potentially reducing disease progression, leading to favorable outcomes. Continued evaluation of exercise as a low-toxicity intervention that can be tailored to the standard treatment of PC is a high priority and could substantially impact the clinical and public health burden of PC [11]. While early-stage PC patients are expected to have physical fitness and exercise tolerance similar to those of healthy individuals, the prevailing view among patients and clinicians is that exercise is problematic for patients with advanced PC. However, recent studies have demonstrated that tailored resistance and aerobic exercises are well tolerated, safe, and improve physical structure and function [12].

1.2. Potential Mechanisms by Which Exercise Can Reduce PC Progression

Several potential mechanisms have been identified through which exercise may reduce the risk of PC progression [13]. Exercise affects all hormonal systems in the body, including key hormones associated with PC, such as testosterone, growth hormone, insulin, and insulin-like growth factor-1 (IGF-1) [11]. Transactivation by the androgen receptor (AR) and its ligands is one of the most important determinants of PC progression [11], and serum androgen levels can indicate the effectiveness of androgen deprivation therapy (ADT) while serving as an important biomarker for PC progression. Accordingly, the effect of exercise on androgen levels is of interest; however, recent studies have yielded inconclusive results because of the small sample sizes and inadequate methods for measuring low testosterone levels in patients undergoing ADT [14]. Additionally, high levels of inflammatory biomarkers are associated with PC-induced mortality [15]. Exercise is known to lower circulating inflammatory biomarkers, such as interleukin (IL)-6 in older men [16]. Increased exercise activity may induce epigenetic modulation and inhibit tumor cell growth [11]. Epidemiological studies have demonstrated that lower cholesterol levels are linked to a reduced risk and progression of PC [17].

1.3. HIIT for PC

HIIT is a well-established training protocol for long-distance runners and is also applied to cardiovascular and metabolic diseases. This relatively novel and promising approach involves high-intensity aerobic exercise and is known to improve cardiorespiratory fitness (VO_{2max}), cardiac function, and insulin resistance more effectively

than moderate-intensity training (MCT) [18]. HIIT has also been implemented in many patients with cancer in recent years [8], [9], [19]. This narrative review provides an overview of the recent literature on the effects of HIIT on patients with PC, who may particularly benefit from a favorable prognosis compared to patients with other cancers. According to Hamdy et al., the risk of cardiovascular diseases (CVD)-related death under AS in patients with localized PC is approximately three times the risk of death from PC itself [20]. However, it is essential to emphasize that the primary and anticipated effect is the inhibition of tumor progression. Previous studies have classified PC targeted by HIIT into two main groups: localized PC, which is often referred to as early-stage cancer, and metastatic castrate-resistant prostate cancer (mCRPC), which is an advanced cancer. Localized PC is anticipated to tolerate HIIT better than mCRPC because patients with localized PC are generally younger and less frail than those with mCRPC.

1.4. HIIT for Patients with PC under AS

In the ERASE trial, Kang et al. randomized 52 patients with localized PC under AS (low to moderate risk), dividing them into two groups. The effects of HIIT on cardiorespiratory fitness (VO_{2max}) and biological PC progression, as indicated by increased PSA levels, were compared between the HIIT and control groups before and after 12 weeks of intervention [4], [21]. A comparison of VO_{2max} differences demonstrated a substantial increase of 1.6 mL/kg/min in the HIIT group. In comparison with the usual care group, PSA levels decreased substantially more ($-1.1 \mu\text{g/L}$); PSA velocity also decreased considerably; PSA doubling time tended to be 17.8 months longer. Additionally, LNCaP cell growth decreased by -0.13 optical density units (-0.51%) in the HIIT group [4]. Since a PSA velocity of $0.175 \mu\text{g/L/year}$ is used as a criterion for proceeding to radical treatment in the AS setting, the improvements observed with HIIT in this study are clinically meaningful. In summary, these results suggest enhanced fitness and reduced tumor progression [21]. HIIT was performed three times per week, with the protocol consisting of 2 min intervals at 85%–95% of VO_{2max} intensity, followed by 2 min of active recovery at 40% of VO_{2max} intensity. The number of intervals in each session gradually increased from five to eight, while the total exercise duration increased from 28 to 40 min. The usual care group continued with their usual exercise routines. The intervention resulted in 96% adherence, 100% compliance with the protocol, and high motivation [22].

The finding of a marked reduction in PSA levels in this RCT contrasts with previous reports. In other exploratory trials on AS, PSA levels did not change after a year-long home-based exercise intervention [23]. These results suggest that the intensity of the HIIT exercise performed in this study may be necessary for achieving PSA reduction. Additionally, PSA levels may decrease substantially when patients undergoing ADT and/or radiation therapy are included [24], [25]. The ERASE randomized controlled trial (RCT) is the first report demonstrating a substantial effect of exercise alone on LNCaP, PSA levels, and PSA velocity, with further validation anticipated. Lee et al. also

reported the effects of exercise on PSA levels in a meta-analysis [26]. Zhu et al. conducted a systematic review and meta-analysis that included ERASE, comprising six RCTs with 222 patients, and found that the exercise group exhibited a greater reduction in biochemical (serum PSA) progression compared to the MCT group for localized PC. In contrast, the MCT group was superior to the HIIT group in terms of cardiopulmonary function [27].

1.5. HIIT for mCRPC

The mCRPC is a histologically proven adenocarcinoma of the prostate gland with advanced systemic metastasis despite achieving castration levels (<50 ng/dL) of testosterone through prostatectomy or luteinizing hormone-releasing hormone (LHRH) agonist treatment. Kim et al. investigated the effect of one session of 34 min of HIIT on myokines by examining the acute phase of circulation and inhibition of progression to the androgen-independent cell line (DU-145) in PC [28]. Trained patients with advanced PC underwent one session of HIIT (six intervals of 4 min at 70%–85% HR_{max} and active rest of 2 min at 50%–65% HR_{max}). Myokines (serum levels of cysteine, secreted protein acidic and rich in cysteine (SPARC), oncostatin M (OSM), IL-6, IL-15, decorin, irisin, and IGF-1) were measured before, immediately after, and 30 min after the session. Real-time cellular analysis of the human prostate cell line (DU-145) was performed. SPARC, OSM, IL-6, and IL-15 levels increased substantially immediately after treatment and returned to baseline at 30 min. Cell growth and the cell index area under the curve (AUC) were markedly higher when serum collected immediately after and 30 min later was cultured with DU-145; however, these levels substantially decreased from baseline immediately after HIIT and at 30 min after HIIT compared to the control group. In summary, myokine elevation was reversed after 30 min, but the anticancer growth effect was maintained beyond this period [29]. These results indicate that HIIT attenuates tumor growth through multiple mechanisms, not solely through myokine elevation [29].

The Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4) trial is an international multicenter phase III RCT that compared supervised HIIT and resistance training with a control group engaged in self-directed exercise in patients with mCRPC [11]. The primary endpoint was overall survival, while disease progression, and various clinical events served as secondary endpoints; both were followed for 24 months and compared between the two groups [11]. The HIIT protocol is highly tailored and differs from trials in non-cancer patients in that both groups receive psychosocial support. The program is carefully planned on a weekly, monthly, and annual basis. The first year is supervised in an exercise clinic setting, while the second year is self-managed, with a visit every 4 weeks at the beginning of each cycle. Strict periodization is implemented to maximize training stimulus and physiological adaptation. To reduce the risk of injury, overtraining, and staleness, the intensity and volume of exercise are autoregulated in each session by the supervisor, based on fatigue, wellness, energy levels, and

motivation. The first session of HIIT consists of aerobic exercise for six intervals of 60 s at a rating of perceived exertion (PRE) scale of 8/10, with 120 s of recovery during weeks one and three, and 30–40 min of MCT at an RPE of 5/10 in week two. The resistance exercises include four sets of eight repetitions at maximum (RM) across six exercises, with detailed modifications based on the session [11]. However, the results of the trial have not yet been published. A sub-analysis of 25 patients with mCRPC (mean age: 74.7 years) from the INTERVAL-GAP4 trial demonstrated that 6 months of multimodal exercise (HIIT at Borg scale 8/10 for 60 s $\times$ 10) and resistance training markedly increased serum myokine levels and inhibited tumor progression compared with the control group [30]. The OSM and SPARC levels were substantially higher in the exercise group than in the control group. The post-exercise serum of the exercise group demonstrated a substantial decrease in DU-145 cell line growth in the AUC at 72 h. It remains unclear which mode of exercise is more effective, and the cell-to-cell mechanisms of tumor growth are also unknown. HIIT and muscle training can increase the levels of relevant myokines even in advanced cancer with metastasis, suggesting a potential tumor growth-inhibitory effect [30]. This outcome is similar to findings observed in patients with localized PC [4]. These results highlight the potential efficacy of acute- and intermediate-term HIIT for mCRPC; however, further confirmation from additional trials by other groups is warranted.

2. DISCUSSION

Studies on cancer survivors have generally noted that adherence to physical activity tends to be higher when the activity intensity is light [31] or individualized [32]. This suggests that lack of program customization or mismatch in exercise intensity may prevent achieving tumor-suppressive or anti-inflammatory effects. The HIIT protocols of the trials discussed in this review were varied and tailored accordingly, with higher intensities used for patients with localized PC and lower intensities for those with advanced metastatic PC. In particular, because of the physiological, metabolic, and body composition differences among patients with advanced cancer, including those with mCRPC, the ability and safety of patients to participate in moderate-to-high-intensity exercises is influenced or precluded by disease and treatment side effects and must be tailored to each individual. It is essential to determine whether the protocols considered for each condition—not just a single protocol—meet the minimum requirements of exercise intensity, duration, frequency, and sustained efficacy needed to produce a myokine-producing response [33]. However, HIIT is a non-invasive, patient-friendly “medicine” with few side effects, tailored to each individual’s fitness level [34]. If accumulating evidence confirms that HIIT can increase physical fitness and suppress PC growth, the benefits for patients with PC could be substantial and widely impactful.

3. CONCLUSION

HIIT offers various benefits for patients with PC, with the most critical being its potential effectiveness in inhibiting tumor growth. Furthermore, the mechanisms underlying tumor growth inhibition need further clarification. While a limited number of studies have suggested the effectiveness of HIIT, future research should compare other types of exercises and develop their implementation in clinical practice.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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