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Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progression in Men With Localized Prostate Cancer Under Active Surveillance

The ERASE Randomized Clinical Trial

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IMPORTANCE Men with prostate cancer who are undergoing active surveillance are at an increased risk of cardiovascular death and disease progression. Exercise has been shown to improve cardiorespiratory fitness, physical functioning, body composition, fatigue, and quality of life during and after treatment; however, to date only 1 exercise study has been conducted in this clinical setting.

OBJECTIVE To examine the effects of exercise on cardiorespiratory fitness and biochemical progression in men with prostate cancer who were undergoing active surveillance.

DESIGN, SETTING, AND PARTICIPANTS The Exercise During Active Surveillance for Prostate Cancer (ERASE) trial was a single-center, 2-group, phase 2 randomized clinical trial conducted at the University of Alberta, Edmonton, Canada. Eligible patients were recruited from July 24, 2018, to February 5, 2020. Participants were adult men who were diagnosed with localized very low risk to favorable intermediate risk prostate cancer and undergoing active surveillance. They were randomized to either the high-intensity interval training (HIIT) group or usual care group. All statistical analyses were based on the intention-to-treat principle.

INTERVENTIONS The HIIT group was asked to complete 12 weeks of thrice-weekly, supervised aerobic sessions on a treadmill at 85% to 95% of peak oxygen consumption ($\dot{V}O_2$). The usual care group maintained their normal exercise levels.

MAIN OUTCOMES AND MEASURES The primary outcome was peak $\dot{V}O_2$, which was assessed as the highest value of oxygen uptake during a graded exercise test using a modified Bruce protocol. Secondary and exploratory outcomes were indicators of biochemical progression of prostate cancer, including prostate-specific antigen (PSA) level and PSA kinetics, and growth of prostate cancer cell line LNCaP.

RESULTS A total of 52 male patients, with a mean (SD) age of 63.4 (7.1) years, were randomized to either the HIIT (n = 26) or usual care (n = 26) groups. Overall, 46 of 52 participants (88%) completed the postintervention peak $\dot{V}O_2$ assessment, and 49 of 52 participants (94%) provided blood samples. Adherence to HIIT was 96%. The primary outcome of peak $\dot{V}O_2$ increased by 0.9 mL/kg/min in the HIIT group and decreased by 0.5 mL/kg/min in the usual care group (adjusted between-group mean difference (1.6 mL/kg/min; 95% CI, 0.3-2.9; $P = .01$). Compared with the usual care group, the HIIT group experienced decreased PSA level (-1.1 $\mu\text{g/L}$; 95% CI, -2.1 to 0.0; $P = .04$), PSA velocity (-1.3 $\mu\text{g/L/y}$; 95% CI, -2.5 to -0.1; $P = .04$), and LNCaP cell growth (-0.13 optical density unit; 95% CI, -0.25 to -0.02; $P = .02$). No statistically significant differences were found in PSA doubling time or testosterone.

CONCLUSIONS AND RELEVANCE The ERASE trial demonstrated that HIIT increased cardiorespiratory fitness levels and decreased PSA levels, PSA velocity, and prostate cancer cell growth in men with localized prostate cancer who were under active surveillance. Larger trials are warranted to determine whether such improvement translates to better longer-term clinical outcomes in this setting.

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An increasing number of men with low- to intermediate risk prostate cancer receive active surveillance as a primary management strategy.¹ Advantages of active surveillance include avoiding immediate radical treatments without compromising survival^{2,3} and reducing treatment-related medical costs.^{4,5} Men with prostate cancer who are on active surveillance have approximately 3 times higher risk of cardiovascular disease (CVD)-related death than prostate cancer-specific death.² Moreover, approximately 30% of men on active surveillance will ultimately experience disease progression and require radical treatment within 3 years, and 55% will need it within 10 years.² Interventions during active surveillance to boost cardiovascular health, delay disease progression, and precondition these men for possible radical treatments would be desirable.

Research has shown that exercise improves cardiorespiratory fitness, physical functioning, body composition, fatigue, and quality of life during and after radical prostate cancer treatments.⁶ Moreover, aerobic exercise has been found to suppress the progression of prostate tumors and metastasis in animal models⁷ and to enhance the biochemical outcomes of prostate cancer growth in humans.^{8,9} Furthermore, higher levels of physical fitness and functioning during active surveillance may ease adverse effects and lead to better cancer-related outcomes after radical treatments.^{10,11} To our knowledge, however, only 1 clinical trial has examined the feasibility of exercise in men on active surveillance, and no trial has investigated the efficacy of an isolated exercise intervention during active surveillance.¹² In this Exercise During Active Surveillance for Prostate Cancer (ERASE) trial,¹³ we aimed to examine the effects of exercise on cardiorespiratory fitness and biochemical progression in men with prostate cancer who were undergoing active surveillance. We hypothesized that high-intensity interval training (HIIT) would generate substantial improvements in both health-related fitness and biochemical progression of prostate cancer in men on active surveillance compared with patients receiving usual care.

Methods

The ERASE trial was approved by the Health Research Ethics Board of Alberta-Cancer Committee. All eligible patients provided written informed consent for study participation and blood banking before enrollment. The trial protocol is provided in [Supplement 1](#). We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants, Study Design, and Procedure

The detailed methods of the ERASE trial have been reported elsewhere.¹³ Briefly, the ERASE trial was a single-center, 2-group, phase 2 randomized clinical trial conducted at the University of Alberta, Edmonton, Canada. Patient recruitment took place from July 24, 2018, to February 5, 2020. Eligible patients from the Northern Alberta Urology Centre at the Kaye Edmonton Clinic in Edmonton, Alberta, Canada, were informed about the study by their urologists during checkup vis-

Key Points

Question Does a high-intensity interval training program improve cardiorespiratory fitness and delay the biochemical progression of prostate cancer in patients who are undergoing active surveillance?

Findings In this randomized clinical trial of 52 male participants with prostate cancer under active surveillance, 12 weeks of high-intensity interval training significantly improved peak oxygen consumption, decreased prostate-specific antigen levels, and decreased prostate-specific antigen velocity compared with usual care. It also inhibited the growth of prostate cancer cell line LNCaP in this patient population.

Meaning The findings of this study indicate that exercise may be an effective intervention for improving cardiorespiratory fitness and suppressing the progression of prostate cancer for patients undergoing active surveillance.

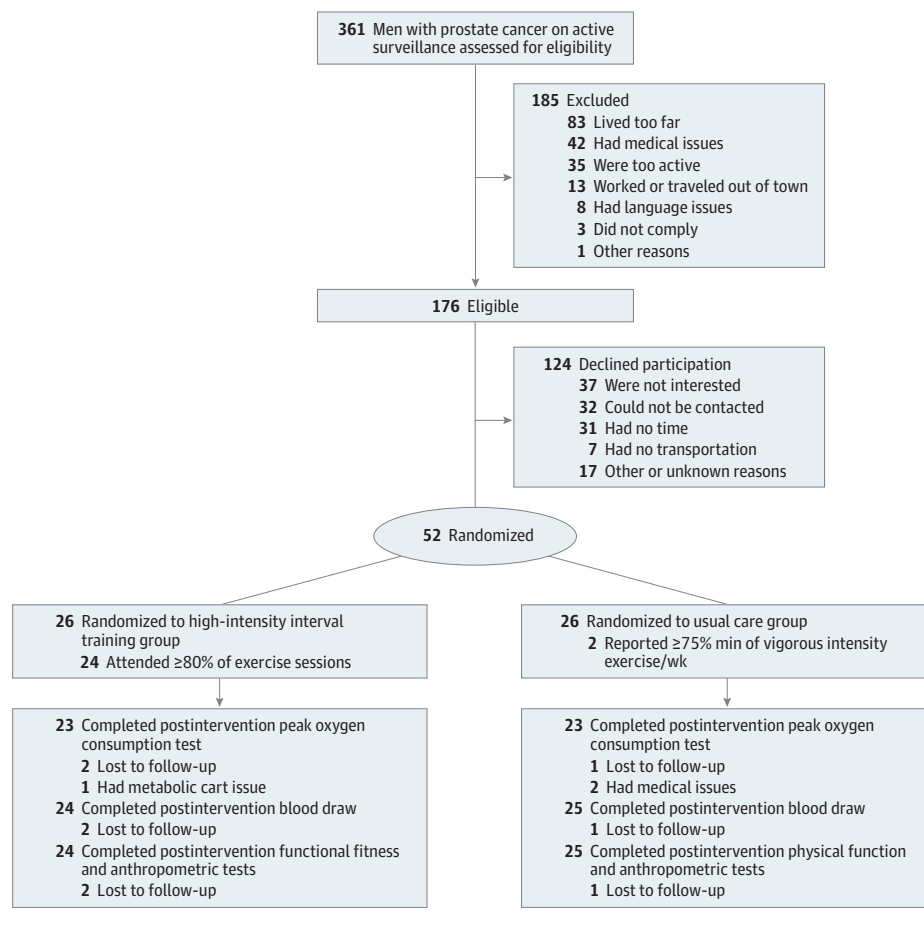
its and were referred to the study coordinator (S.A.W.). These men were eligible if they were (1) 18 years or older, (2) diagnosed with localized very low risk to favorable intermediate risk prostate cancer, (3) undergoing active surveillance with no plans for radical treatment, (4) medically cleared to participate, (5) able to complete the baseline fitness test, (6) not currently engaging in vigorous-intensity exercise, and (7) able to communicate in English. Interested patients were scheduled for baseline assessments. After completion of baseline testing, patients were randomized to either the HIIT group or the usual care group in a 1:1 ratio using a 4 or 6 randomized block design. The randomization sequence was produced by computer-generated block randomization numbers and concealed from study staff who were involved in recruitment and baseline assessment (K.S.C. and D.-W.K.). Participants and interventionists (D.-W.K. and S.A.W.) were not blinded to group assignments. Outcome assessors (D.-W.K. and S.A.W.) were not blinded to group assignments for the health-related fitness assessments, but they were blinded for the biochemical progression outcomes.

The participant flow is illustrated in [Figure 1](#). Overall, 361 men with prostate cancer who were undergoing active surveillance were screened. Of the 176 patients (49%) who were eligible to participate, 52 (30%) were randomized to the HIIT group or the usual care group. Participant accrual was slower than expected because of the limited number of eligible patients at the center. Recruitment stopped short of the target of 66 participants because of budgetary and time constraints. Two patients dropped out of the HIIT group (unwillingness to participate; medical issue), and 1 patient dropped out of the usual care group (could not be contacted).

Intervention

Participants who were randomized to the HIIT group were asked to complete a 12-week, thrice-weekly, supervised exercise program. The exercise program was individualized on the basis of each participant's baseline cardiopulmonary fitness, and the intensity and duration of exercise were increased over time. Each exercise session was performed on a treadmill and consisted of (1) a 5-minute warm-up at 60% of peak oxygen

Figure 1. CONSORT Diagram



consumption ($\dot{V}O_2$), (2) an alternating 2-minute high-intensity interval at 85% to 95% of peak $\dot{V}O_2$ and a 2-minute active recovery at 40% of peak $\dot{V}O_2$, and (3) a 5-minute cooldown at 30% of peak $\dot{V}O_2$. Oxygen consumption was not directly measured during the exercise sessions, but the treadmill speed and grade were selected to match the targeted percentage of peak $\dot{V}O_2$ based on the baseline fitness levels. The number of high-intensity intervals was increased from 5 to 8 in each session, and the total duration of the exercise session was extended from 28 to 40 minutes.

Participants who were randomized to the usual care group were asked not to change their exercise levels during the intervention period. After the postintervention assessments at 12 weeks, the usual care group was offered a 4-week HIIT program at the center and/or referred to a 12-week community-based exercise program.

Outcome Measures

The primary outcome was cardiorespiratory fitness, which was measured as peak $\dot{V}O_2$ and assessed at the baseline and post-intervention periods. Peak $\dot{V}O_2$ is an established surrogate marker for CVD and CVD-related death.¹⁴ Peak $\dot{V}O_2$ was defined as the highest values of oxygen uptake that were averaged among every 15-second interval during the graded exer-

cise test using a modified Bruce protocol.¹⁵ The criteria for a valid test included volitional exhaustion as the primary criterion, respiratory exchange ratio greater than 1.15, age-predicted maximum heart rate within 5 beats per minute, and rated perceived exertion higher than 7 (on a 0-10 scale, with 0 indicating no exertion at all and 10 indicating extremely strong).¹⁶ The exercise test was conducted on a treadmill (4Front; Woodway), along with direct measures of gas exchange and cardiorespiratory variables using a metabolic cart (TrueOne 2400; Parvo Medics). Peak $\dot{V}O_2$ is reported herein in both relative terms (milliliters per kilogram per minute) and absolute terms (liters per minute).

The secondary outcomes included serum prostate-specific antigen (PSA) concentrations and kinetics (ie, PSA doubling time [PSADT] and PSA velocity [PSAV]), sex hormone levels, functional fitness, and anthropometrics. Blood samples were collected after 12 hours of fasting at the Kaye Edmonton Clinic Laboratory Services. Serum PSA and testosterone levels were analyzed on fresh blood at the central processing facility, and the results were made available in the electronic medical record of the center. Two additional 6-mL blood samples in EDTA tubes were collected for research purposes and sent to the biochemistry laboratory in the Li Ka Shing Centre for Health Research Innovation at the University of Al-

berta. Both PSADT and PSAV were calculated according to the guidelines of the Prostate Specific Antigen Working Group¹⁷ and using the 3 most recent PSA values in the electronic medical record, with the first and last values being at least 3 months apart. The formula was based on the natural logarithm of 2 (0.693) divided by the slope from fitting a linear regression of the natural log of PSA.

In addition to PSA levels and PSA kinetics, the effect of exercise on the proliferation of plasma prostate cancer cell line LNCaP was examined. LNCaP cell line was grown in ATCC-formulated RPMI 1640 medium (ATCC) and was supplemented with 5% FCS (fetal calf serum) and 1% penicillin-streptomycin. To determine cell proliferation, we seeded LNCaP cells (100 μ L) at a concentration of 50 000/mL in a 96-well plate that contained either 5% FCS or 5% human plasma from test participants in triplicate for 48 hours. All samples were tested using the LNCaP cells at the same phase of growth. To determine final cell numbers, we removed supernatant and fixed the LNCaP cells with 100 μ L of 4% paraformaldehyde in the plate for 20 minutes. Fixed cells were then incubated for an additional 20 minutes with 100 μ L of 2% crystal violet (Fisher Scientific) dye solution (0.1%, wt/vol, with ethanol 2%, vol/vol in 0.5 M Tris-Cl, pH 7.80).⁸ The stained cells were washed in tap water and then solubilized with a sodium dodecyl sulfate solution (0.1%, wt/vol, with ethanol 50%, vol/vol, in 0.5 M Tris-Cl, pH 7.8; 100 μ L/well) for 30 minutes. The crystal violet dye was released by the fixed cells into the supernatant, and the absorbance was measured by a spectrophotometer (Molecular Devices LLC) at 600 nm.

Functional fitness was assessed using the Senior Fitness Test.¹⁸ Anthropometrics included weight, height, and waist and hip circumference and were identified using scales and tape measures in accordance with the standardized protocols.¹⁹

Demographic, Behavioral, and Medical Variables

Demographic and behavioral information was self-reported at baseline and included smoking status, alcohol consumption, and exercise behavior.²⁰ Race was self-identified with defined and open-ended options to identify the racial representation of the participants. Medical information, including tumor pathology and clinical stage, was extracted from the electronic medical record.

Statistical Analysis

The originally planned sample size of 66 participants (33 per group) was estimated to provide 80% power using a 2-tailed $\alpha < .05$ to detect a statistically significant between-group difference of 1 metabolic equivalent task (3.5 mL/kg/min) on the primary outcome of peak $\dot{V}O_2$, assuming an SD of 5.6 mL/kg/min, a 10% dropout rate, and an adjustment for baseline value and other prognostic covariates.²¹ This sample size was also sufficient for detecting differences in the secondary outcomes of biomarkers, functional fitness, and anthropometrics.

Analyses of covariance were performed for the primary and secondary outcomes to determine the between-group mean differences at the postintervention period after adjusting for covariates. Covariates were selected a priori and included the

baseline values of the outcome and other variables that were unbalanced between groups. All statistical analyses were based on the intention-to-treat principle and included all participants who had baseline and follow-up data. No missing data strategy was used because of minimal loss of data (<10%), and no adjustment was made for multiple comparisons.

Results

A total of 52 male patients were randomized to the HIIT group ($n = 26$) or the usual care group ($n = 26$) (Figure 1). Of these participants, the mean (SD) age was 63.4 (7.1) years and 46 (89%) self-identified as White. In all, 46 participants (88%) completed the postintervention peak $\dot{V}O_2$ assessment and 49 (94%) completed the postintervention blood draw.

Other demographic, medical, and behavioral characteristics of the participants at baseline are presented in Table 1. Baseline mean (SD) resistance exercise behavior was unbalanced between groups (HIIT group: 18 (42) min/wk; usual care group: 44 (62) min/wk) and adjusted for in the analyses because of its prognostic association with PSA^{22,23} and fitness outcomes.²⁴ Because of the outbreak of COVID-19 and the impending closure of the facilities we used, we completed postintervention assessments 2 weeks earlier than planned (ie, at 10 weeks) for the last 6 participants (3 in each group). Participants attended 880 of 918 planned exercise sessions (96%) with 100% adherence to intensity and duration. Eight participants (15%) reported aggravation of previous medical issues, including joint pain ($n = 6$), chest discomfort ($n = 1$), and light-headedness ($n = 1$), that were potentially related to HIIT. One participant (2%) reported stomach bleeding of a Dieulafoy lesion that was not related to HIIT.

Changes in Cardiorespiratory Fitness and Functional Outcomes

The primary outcome of peak $\dot{V}O_2$ increased by 0.9 mL/kg/min in the HIIT group and decreased by 0.5 mL/kg/min in the usual care group (adjusted between-group mean difference, 1.6 mL/kg/min; 95% CI, 0.3-2.9; $P = .01$) (Table 2). Compared with the usual care group, the HIIT group also significantly increased peak $\dot{V}O_2$ in liter per minute, upper body strength, and lower body flexibility (eTable in Supplement 2).

Changes in Prostate Cancer-Related Biochemical Outcomes

Changes in serum PSA levels, PSADT, PSAV, testosterone, and LNCaP cell growth are provided in Table 2 and illustrated in Figure 2 and Figure 3. Compared with the usual care group, the HIIT group showed a significant decrease in PSA levels (adjusted between-group mean difference, $-1.1 \mu\text{g/L}$; 95% CI, -2.1 to 0.0 ; $P = .04$) and PSAV (adjusted between-group mean difference, $-1.3 \mu\text{g/L/y}$; 95% CI, -2.5 to -0.1 ; $P = .04$). The PSADT favored the HIIT group but did not reach statistical significance (adjusted between-group mean difference, 17.9 months; 95% CI, -3.8 to 39.6 ; $P = .10$). No adjusted between-group mean difference in testosterone was found (1.0 nmol/L ; 95% CI, -0.7 to 2.6 ; $P = .24$). LNCaP cell growth was significantly inhibited in the HIIT group compared with the usual care group (ad-

Table 1. Baseline Characteristics of Participants

Variable	Overall (N = 52)	HIIT group (n = 26)	Usual care group (n = 26)
Sociodemographic profile			
Age, mean (SD), y	63.4 (7.1)	63.9 (7.5)	62.8 (6.9)
White race, No. (%)	46 (89)	25 (96)	21 (81)
Married status, No. (%)	37 (71)	17 (65)	20 (77)
Completed university or college, No. (%)	20 (39)	9 (35)	11 (42)
Employed status, No. (%)	32 (63)	12 (48)	20 (77)
Family income of >\$100 000/y, No. (%)	21 (40)	9 (35)	12 (46)
Medical profile			
Weight, mean (SD), kg	89.1 (16.3)	89.3 (18.7)	88.8 (14.0)
BMI, mean (SD)	29.0 (4.7)	29.0 (5.7)	29.0 (3.5)
Waist circumference, mean (SD), cm	102.3 (13.4)	101.4 (14.4)	103.3 (12.6)
Waist-hip ratio, mean (SD)	0.99 (0.08)	0.98 (0.09)	1.01 (0.07)
No. of comorbidities, No. (%)			
0	9 (17)	4 (15)	5 (19)
1	14 (27)	7 (27)	7 (27)
2	16 (31)	8 (31)	8 (31)
≥3	13 (25)	7 (27)	6 (23)
Most common comorbidities, No. (%)			
Arthritis or arthralgia	31 (60)	16 (62)	15 (58)
Hypertension	16 (31)	8 (31)	8 (31)
Metabolic condition	9 (17)	4 (15)	5 (19)
Prostate cancer profile			
Clinical stage, No. (%)			
T1c	47 (90)	24 (92)	23 (89)
T2a	4 (8)	2 (8)	2 (8)
T2b	1 (2)	0	1 (4)
Gleason grade, No. (%)			
1 (3 + 3 = 6)	50 (96)	25 (96)	25 (96)
2 (3 + 4 = 7)	2 (4)	1 (4)	1 (4)
PSA level, mean (SD), µg/L	7.3 (3.2)	6.0 (2.3)	8.6 (3.5)
Prostate volume, mean (SD), cc	52.9 (21.5)	55.6 (24.8)	50.3 (17.6)
PSA density, mean (SD), µg · L ⁻¹ · cc ⁻¹	0.13 (0.07)	0.11 (0.06)	0.16 (0.08)
Positive cores, mean (SD), %	21.6 (13.0)	22.9 (14.2)	18.3 (10.5)
Time on active surveillance, mean (SD), mo	23.0 (25.8)	26.7 (27.0)	19.4 (24.4)
Behavioral profile			
Smoking status, No. (%)			
Current smoker	1 (2)	1 (4)	0
Former smoker	29 (56)	15 (58)	14 (54)
Alcohol consumption, No. (%)			
Regular drinker	6 (12)	3 (12)	3 (12)
Social drinker	39 (75)	19 (73)	20 (77)
Exercise behavior, mean (SD)			
Vigorous aerobic exercise, min/wk	0	0	0
Moderate aerobic exercise, min/wk	61 (99)	59 (74)	62 (120)
Resistance exercise, min/wk	31 (54)	18 (42)	44 (62)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HIIT, high-intensity interval training; PSA, prostate-specific antigen.

justed between-group mean difference, -0.13 optical density unit [95% CI, -0.25 to -0.02 ; $P = .02$], or -5.1%).

Discussion

To our knowledge, the ERASE trial was the first randomized clinical trial to examine the efficacy of HIIT in men with localized prostate cancer undergoing active surveillance. As we

hypothesized, a supervised 12-week HIIT program significantly improved cardiorespiratory fitness and indicators of prostate cancer biochemical progression. These improvements appear to be meaningful and may translate into better outcomes for patients with prostate cancer who are being managed by active surveillance.

One cohort study reported an approximately 3-fold increased risk of CVD-related death compared with prostate cancer death in men under active surveillance.² Given that greater

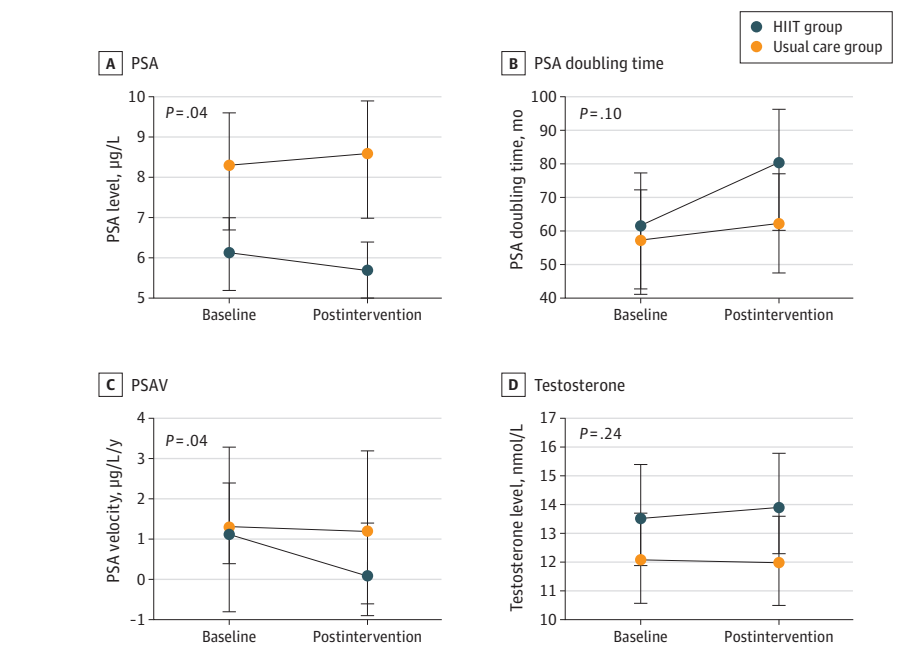
Table 2. Effects of 12 Weeks of HIIT on Cardiorespiratory Fitness and Prostate Cancer–Related Biomarkers in Patients Under Active Surveillance

Variable	Mean (SD)		Mean (95% CI)		P value for adjusted between-group difference ^a
	Baseline value	Postintervention value	Mean change	Adjusted between-group difference ^a	
Cardiopulmonary fitness					
Peak $\dot{V}O_2$, mL/kg/min					
HIIT group (n = 23)	29.6 (5.8)	30.4 (6.1)	0.9 (0.0 to 1.7)	1.6 (0.3 to 2.9)	.01
Usual care group (n = 23)	28.4 (6.9)	27.9 (7.0)	-0.5 (-1.4 to 0.4)		
Peak $\dot{V}O_2$, L/min					
HIIT group (n = 23)	2.55 (0.56)	2.60 (0.58)	0.05 (-0.01 to 0.12)	0.12 (0.00 to 0.20)	.03
Usual care group (n = 23)	2.51 (0.64)	2.46 (0.64)	-0.05 (-0.13 to 0.03)		
Biochemical outcomes					
PSA level, $\mu\text{g/L}$					
HIIT group (n = 24)	6.1 (2.2)	5.7 (1.7)	-0.4 (-0.8 to 0.0)	-1.1 (-2.1 to 0.0)	.04
Usual care group (n = 25)	8.3 (3.2)	8.6 (4.2)	0.3 (-0.7 to 1.3)		
PSADT, mo					
HIIT group (n = 23)	61.3 (39.1)	80.2 (49.5)	18.9 (-1.2 to 38.9)	17.9 (-3.8 to 39.6)	.10
Usual care group (n = 24)	57.3 (37.6)	62.0 (36.5)	4.7 (-7.0 to 16.5)		
PSAV, $\mu\text{g/L/y}$					
HIIT group (n = 23)	1.1 (3.3)	0.1 (1.7)	-1.0 (-2.1 to 0.1)	-1.3 (-2.5 to -0.1)	.04
Usual care group (n = 24)	1.3 (5.0)	1.2 (5.2)	-0.1 (-1.0 to 0.8)		
Testosterone, nmol/L					
HIIT group (n = 22)	13.5 (4.6)	13.9 (3.9)	0.4 (-1.0 to 1.7)	1.0 (-0.7 to 2.6)	.24
Usual care group (n = 23)	12.1 (3.9)	12.0 (3.7)	-0.1 (-1.2 to 1.0)		
LNCaP proliferation, ODU					
HIIT group (n = 23)	0.23 (0.02)	0.21 (0.02)	-0.02 (-0.02 to -0.01)	-0.13 (-0.25 to -0.02)	.02
Usual care group (n = 24)	0.22 (0.03)	0.22 (0.03)	0.00 (-0.01 to 0.01)		

Abbreviations: HIIT, high-intensity interval training; ODU, optical density unit; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity; $\dot{V}O_2$, oxygen consumption.

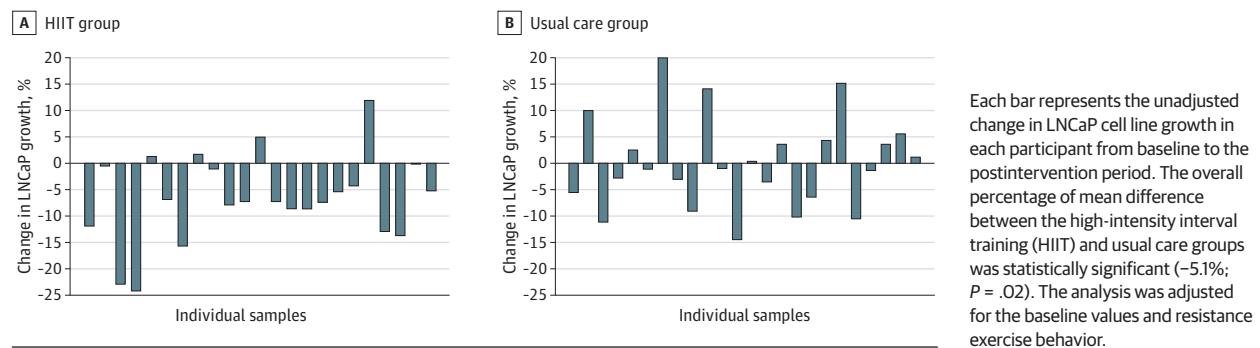
^a Between-group difference was adjusted for the baseline values of the outcome and resistance exercise behavior.

Figure 2. Changes in Prostate-Specific Antigen (PSA), PSA Doubling Time, PSA Velocity, and Testosterone



Means are based on unadjusted data. Error bars indicate 95% CIs, and P values indicate between-group difference at the postintervention period adjusted for the baseline values of the outcome and resistance exercise behavior. HIIT indicates high-intensity interval training; PSAV, PSA velocity.

Figure 3. Changes in LNCaP Cell Line Growth



cardiorespiratory fitness of 3.5 mL/kg/min has been shown to decrease the risk of all-cause mortality by 13%,¹⁴ the increase in peak $\dot{V}O_2$ of 1.6 mL/kg/min after 12 weeks of HIIT in the ERASE trial suggests a potential long-term cardioprotective benefit. This finding is consistent with results of a meta-analysis of randomized clinical trials indicating that aerobic exercise training significantly improved peak $\dot{V}O_2$ by 2.4 mL/kg/min before treatment, 1.4 mL/kg/min during treatment, and 2.5 mL/kg/min after treatment in patients with cancer.²⁵

We observed inhibitory effects of HIIT on the biochemical progression of prostate cancer. The decreased PSA level in this trial is in contrast to findings in most exercise trials among patients with prostate cancer who reported no significant changes in PSA level.²⁶⁻³² This discrepancy may be attributed to patients in previous studies undergoing androgen deprivation therapy and/or radiation therapy, which can substantially lower PSA levels. One exploratory exercise study that was conducted in patients with prostate cancer on active surveillance reported no changes in PSA concentration after a year-long, home-based exercise intervention.¹² In comparison, the exercise program in the present study focused on high-intensity aerobic training (ie, 85%-95%) for a shorter-term (ie, 12 weeks), which can exert greater physiological changes (eg, sympathetic activation and mobilization of cytotoxic immune cells).^{33,34} The data suggest that high-intensity aerobic exercise might be necessary to produce changes in biochemical outcomes in prostate cancer.

Both PSAV and PSADT are associated with prostate cancer progression and mortality, independent of PSA.^{35,36} A PSAV that is greater than 0.75 $\mu\text{g/L/y}$ has been used as a criterion of progression to radical treatment in active surveillance settings,³⁷ and the change in PSAV in this trial of -1.3 $\mu\text{g/L/y}$ may be clinically meaningful. Similarly, we found a nonsignificant but meaningful between-group difference in PSADT of 17.9 months. Previous studies have shown that higher fitness levels are associated with longer PSADT in patients with prostate cancer, which suggests that HIIT may have the potential to delay the progression of prostate cancer.⁹ However, PSA kinetics have been examined mostly in patients with advanced prostate cancer³⁸ and are still under investigation in the active surveillance setting.³⁹ Therefore, caution is required when interpreting PSA kinetics in patient cohorts under active surveillance.

Furthermore, HIIT suppressed the proliferation of LNCaP cells by 5.1%, compared with usual care, suggesting that HIIT may have played an inhibitory role in prostate cancer cell growth in this setting. This finding is consistent with results of a study by Rundqvist et al,⁸ which showed a 31% inhibition of LNCaP cell proliferation in postexercise serum when compared with rest in healthy men. A few lifestyle trials have also suggested the inhibitory effects of combined exercise and diet interventions on LNCaP cell growth by 30% to 44% in healthy men⁴⁰ and by 70% in men with prostate cancer on active surveillance.⁴¹ We believe the ERASE trial was the first to show the suppressive effects of exercise alone on LNCaP along with decreased PSA levels and PSAV.

The biological mechanisms of the effects of exercise on prostate cancer are unclear. One plausible mechanism is the enhanced immunosurveillance after exercise training or even during a single bout of exercise.^{42,43} Specifically, exercise can mobilize cytotoxic natural killer cells into circulating blood and can redistribute these cells into tumor cells with assistance from the exercise-induced increases in circulating norepinephrine and IL-6³⁴; this process appears to require endurance exercise at high intensity.^{9,42} Other possible explanations include that exercise could suppress prostate cancer progression by modulating systemic inflammatory mediators,⁴⁴ metabolic biomarkers,⁸ and tumor vascularization and perfusion.⁴⁵ More research in active surveillance clinical settings is necessary to identify the biophysiological associations between exercise and prostate cancer⁴⁶ and to further explore potential tumor-related biomarkers.⁴⁷

Given that no statistical adjustment for multiple testing on the PSA-related secondary outcomes was made, confirmatory studies are needed to support the findings in this trial. Larger randomized clinical trials are warranted to determine whether improvements in cardiorespiratory fitness and prostate cancer-related markers translate into better long-term clinical outcomes in men with prostate cancer on active surveillance.⁴⁸

Strengths and Limitations

This study has strengths. These strengths include the understudied cancer setting, the novel exercise intervention, the randomized clinical trial design, high adherence to the interven-

tion, minimal loss to follow-up, and assessment of prostate cancer-related biochemical outcomes.

This study also has limitations. These limitations include potentially low statistical power due to failure to achieve the target sample size (87%), some missing data (6%-12%), and a shortened intervention period for 3 participants. Additional limitations are the potential recruitment bias (eg, more fit and active men), unblinded outcome assessors for the primary outcome, and lack of long-term follow-up for clinical outcomes.

Conclusions

To our knowledge, the ERASE trial was the first to demonstrate that HIIT increases cardiorespiratory fitness and inhibits the biochemical progression of prostate cancer in men on active surveillance. To support the findings of this trial and to determine whether the improvements can translate into better long-term clinical outcomes, larger randomized clinical trials are warranted.

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