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Research Article

Lifestyle Intervention in Men with Advanced Prostate Cancer Receiving Androgen Suppression Therapy: A Feasibility Study

Liam Bourke[1], Helen Doll[2], Helen Crank[1], Amanda Daley[3], Derek Rosario[4], and John M. Saxton[5]

Abstract

Background: Healthy lifestyle behaviors could have a role in ameliorating some of the adverse effects of androgen suppression therapy (AST) in men with prostate cancer. The primary aim of this study was to assess the feasibility of a tapered supervised exercise program in combination with dietary advice in men with advanced prostate cancer receiving AST.

Methods: Advanced prostate cancer patients receiving AST for a minimum of 6 months were randomized to a 12-week lifestyle program comprising aerobic and resistance exercise, plus dietary advice ($n = 25$), or standard care ($n = 25$). Exercise behavior, dietary macronutrient intake, quality of life, fatigue, functional fitness, and biomarkers associated with disease progression were assessed at baseline, after the intervention, and at 6 months.

Results: The lifestyle group showed improvements in exercise behavior ($P < 0.001$), dietary fat intake ($P = 0.001$), total energy intake ($P = 0.005$), fatigue ($P = 0.002$), aerobic exercise tolerance ($P < 0.001$), and muscle strength ($P = 0.033$) compared with standard care controls. Although a high rate of attrition (44%) was observed at 6 months, the improvements in key health outcomes were sustained. No effects on clinical prostate cancer disease markers were observed.

Conclusions: This preliminary evidence suggests that pragmatic lifestyle interventions have potential to evoke improvements in exercise and dietary behavior, in addition to other important health outcomes in men with advanced prostate cancer receiving AST.

Impact: This study shows for the first time that pragmatic lifestyle interventions are feasible and could have a positive impact on health behaviors and other key outcomes in men with advanced prostate cancer receiving AST. *Cancer Epidemiol Biomarkers Prev; 20(4); 647–57. ©2011 AACR.*

Introduction

Androgen suppression therapy (AST) remains the mainstay of treatment for advanced prostate cancer (1). With earlier diagnosis driven by prostate-specific antigen (PSA) testing, duration of AST treatment has increased to several years in a significant proportion of men (2). AST reduces disease-specific mortality (1), but long-term treatment is associated with side effects, such as fatigue (3, 4), reduced bone mineral density (5), increased fracture risk (6, 7), and a decrease in skeletal muscle mass (3) which impact quality of life (QoL; ref. 8). Moreover, AST has been associated with the development of metabolic syndrome/insulin resistance (9–11) and an increase in adverse cardiovascular events (12–14).

Lifestyle interventions could play an important role in ameliorating the side effects of AST and decreasing comorbidity risk. High total energy intake (15) and dietary saturated fat content (16, 17) have been linked to disease progression and an increased risk of developing fatal disease, but data on the impact of dietary interventions in men with advanced prostate cancer on AST are limited. The effect of exercise training in men with prostate cancer receiving AST has been evaluated, with home-based aerobic exercise (18), supervised resistance exercise training (19), and combined supervised resistance and aerobic exercise (20) have been shown to

Authors' Affiliations: [1]Faculty of Health and Wellbeing, Sheffield Hallam University, and NIHR Cardiovascular Biomedical Research Unit, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield; [2]School of Medicine, Health Policy and Practice, University of East Anglia, Norwich; [3]Department of Primary Care Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham; [4]Academic Urology Unit, Department of Oncology, Royal Hallamshire Hospital, University of Sheffield, Sheffield; and [5]School of Allied Health Professions, University of East Anglia, Norwich, United Kingdom

Note: D. Rosario and J.M. Saxton share senior authorship.

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Corresponding Author: John M. Saxton, School of Allied Health Professions, University of East Anglia, Norwich NR4 7TJ, United Kingdom. Phone: 01603-593098. E-mail: john.saxton@uea.ac.uk

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result in short-term improvements in exercise behavior, QoL, fatigue, and functional capacity. However, given the costs associated with intensive, supervised facility-based exercise programs, there is a need to evaluate pragmatic lifestyle interventions designed to equip men with the necessary skills and confidence in order to transform these short-term improvements into longer-term changes in independent health behavior. Further studies aimed at investigating the feasibility of interventions for improving exercise and dietary behavior are clearly warranted.

The primary aim of this study was to assess the feasibility of a tapered supervised exercise program in combination with dietary advice in men with advanced prostate cancer receiving AST, in terms of recruitment rate, willingness of the participants to be randomized, compliance and attrition due to the intervention, and reporting on outcome SDs to assist in sample size estimates for a larger-scale trial (21). Second, to obtain preliminary data on the impact of the intervention on physical activity levels, fatigue, physical/functional fitness, QoL, and circulating biomarkers associated with prostate cancer progression in comparison with patients randomized to a standard care control group. We hypothesized that men with prostate cancer undergoing AST randomized to the lifestyle intervention would experience improvements in these outcomes in comparison with a standard care control group over the period of the intervention and at 6-month follow-up.

Methods

Participants and design

With Local Ethics Committee approval, sedentary men with histologically confirmed, nonlocalized prostate cancer who had been receiving AST for at least 6 months were identified from outpatient clinics and randomized either to a combined exercise and dietary advice intervention or to standard care. Those with unstable angina, uncontrolled hypertension, recent myocardial infarction, pacemakers, and painful or unstable bony metastases and those already undertaking regular physical activity (men engaging in purposeful exercise or physical activity of at least a moderate intensity of 30 minutes or more, 3 times per week) were excluded. Randomization was carried out remotely, using nQuery statistical software (nQuery Advisor 6.01; Statistical Solutions), without disclosure of the sequence to the researcher responsible for the running of the trial until after completion of the baseline assessments.

Lifestyle intervention

The 12-week lifestyle intervention combined supervised and self-directed exercise with dietary advice. Men attended a dedicated exercise suite for supervised exercise sessions comprising 30 minutes of aerobic exercise [intensity of 55%–85% of age-predicted maximum heart rate and/or ratings of perceived exertion, 11 to 15/fairly light to hard, on the Borg Rating of Perceived Exertion (RPE) Scale; ref. 22), and between 2 and 4 sets of resistance exercises (body weight resistance and free weights) targeting large skeletal muscle groups with an experienced exercise physiologist, twice weekly for the initial 6 weeks and then once weekly for the following 6 weeks. Emphasis was placed on providing tuition on the correct performance of exercises, effective technique, and individual capability, with guidance on exercise intensity monitoring by using heart rate and perceived exertion. In addition, they were required to undertake self-directed exercise (e.g., brisk walking, cycling, and gym exercise) for at least one 30-minute session per week during the initial 6 weeks and at least 2 sessions per week for the final 6 weeks, using a log book (23) to record activity. To help improve compliance, a behavioral component included exploring with patients how they could incorporate regular physical activity within their daily lives, what social support structures were available to them, and which types of physical activity they preferred to engage in. Participants were encouraged to achieve up to a total of 5 sessions per week of exercise.

A nutrition advice pack encouraging reduction of saturated fat and refined carbohydrate and increase of dietary fiber intake with moderation of alcohol was provided and small-group healthy eating seminars, lasting approximately 15 to 20 minutes, were carried out fortnightly throughout the 12-week intervention.

This intervention was pragmatic in nature, in that the intensity of the prescribed exercise was light to moderate, the supervision element of the program was tapered off to 1 session per week after 6 weeks, and the dietary intervention was delivered as "advice," with participants free to engage with as much or as little of this as they chose. No specific support or training was delivered to either group after the cessation of the lifestyle intervention (the first 12 weeks). Individuals in both groups were free to change or maintain the lifestyle they felt most appropriate.

Men randomized to standard care were followed up in the urology clinic as normal and seen by an oncology nurse specialist and urologist. No members of the research team had any contact with the standard care group during routine clinical follow-up. No specific training courses, exercise sessions, and no advice about diet or exercise from the research team were delivered to men in the standard care arm. The treating physicians were informed that the man was participating in a lifestyle intervention study and that further information would be available on application. These men were asked to continue their current exercise/dietary behaviors as normal.

Outcome measures

Outcome measures included total exercise behavior [supervised and self-directed exercise assessed by the

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Godin Leisure Score Index (LSI) questionnaire; ref. 24], dietary macronutrient intake (3-day diet diaries analyzed using NetWisp 3.0; Tinuviel Software), fatigue [functional assessment of cancer therapy-fatigue (FACT-F); ref. 25], QoL [FACT-Physical (FACT-P) and FACT-General (FACT-G); ref. 26], physiologic/functional fitness, and anthropometric variables, which were assessed at baseline, 12 weeks (end of lifestyle intervention: end point), and 6 months in both groups. Responses of the self-administered questionnaires were checked for completeness by the researcher (L.B.) in the presence of the respondent. Physiologic and functional fitness outcomes were assessed by a trained technician blinded to group allocation. Aerobic exercise tolerance was assessed using the Bruce ramp protocol (27). Time on the treadmill to number 15 ("hard") on the Borg RPE Scale was recorded, at which point the test was terminated. Muscle strength was assessed by maximum voluntary torque (MVT) by isokinetic dynamometry (Biodex) of the quadriceps. Three maximum isometric muscle actions for more than 5 seconds were done at 75-degree flexion, allowing 60-second recovery between repetitions and with the highest value being recorded. Functional fitness was assessed as the maximum number of repetitions in 30 seconds of a standardized chair sit-to-stand test (28). Body mass index (BMI) was calculated from height (wall-mounted stadiometer) and weight (Weylux beam balance scales). Fasting blood samples (15 mL) were drawn at baseline and end of the intervention for measurement of plasma insulin-like growth factor (IGF) I, IGFBP-I, and IGFBP-3 (ELISA; R&D Systems), and plasma insulin levels (ultrasensitive ELISA; IDS Ltd.). Serum PSA, testosterone, free androgen index, and sex hormone–binding globulin were analyzed at the Department of Clinical Chemistry at the Royal Hallamshire Hospital, Sheffield, UK.

Data analysis

Blinded data analysis was done by a statistician (H.D.) independent of the trial, using SPSS for Windows version 17.0 (SPSS Inc.) and Stata version 11 (StataCorp). Change from the baseline score at 12 weeks and 6 months of follow-up was calculated for each variable. Data were assessed for normality, using the Shapiro–Wilk test, with nonnormal data being transformed to normality as appropriate. Outcomes (change in score) were compared between study groups at each assessment point, using either analysis of covariance (ANCOVA), with baseline values as the covariate (29), or Mann–Whitney tests for nonnormally distributed data (which could not be transformed to normality). Repeated-measures ANCOVAs were used for variables assessed more than twice. Data are presented as mean (SD) scores at each time point and as the between-group differences in change scores between time points (mean diff Δ; adjusted for baseline score). Statistical significance was set at $P < 0.05$ throughout, with 95% CIs used to express the uncertainty in the estimates.

Intention-to-treat analysis was used, with data missing at random (determined using Little's χ^2 tests) imputed using the SPSS Expectation Maximization (EM) procedure. This method depends on the assumption that the pattern of missing data is related to the observed data only, with the conditional expectation of the missing data being found from the observed values and these expectations substituted for the missing data. This method is superior to other methods of imputing missing data, particularly the last value carried forward (LVCF) method in which the assumption is made that the response remains constant at the last observed value. This assumption can be biased if the timing and rate of withdrawal are related to the treatment. Group mean differences calculated using the LVCF approach rather than the EM approach were observed to slightly favor the intervention group.

Results

Attrition and compliance with intervention

Fifty men (mean age = 72 years, range = 60–87 years) were randomized to lifestyle intervention ($n = 25$) or the standard care control group ($n = 25$). Baseline characteristics were comparable between the 2 groups (Table 1). Of those randomized to intervention, 2 men dropped out within the 12-week intervention period (with increasing family commitments) and 2 were excluded (following randomization due to previously undiagnosed cardiac conditions). Attendance (for the remainder) at the supervised exercise sessions was 360 of 378 sessions (95%). Compliance to the self-directed exercise aspect of the lifestyle intervention was also very good, with 329 of 378 sessions (87%) completed (i.e., patients reporting at least 25–30 minutes of aerobic exercise in their log books). Three men randomized to the standard care control arm self-excluded after learning that they had not drawn intervention. At 6 months, a further 6 men from the intervention group and 9 from the standard care control group were lost to follow-up, giving response rates of 60% and 52%, respectively (Fig. 1). Missing data were found to be missing at random and were imputed using the EM procedure.

Exercise and dietary behavior

Figure 2 shows that total exercise behavior was higher in the intervention group than in controls at the end of the intervention period (33.8 vs. 17.4 Godin LSI points, respectively, mean diff Δ = 16.3, 95% CI = 8.8–23.8; $P < 0.001$) and at 6 months of follow-up (25.9 vs. 15.6 Godin LSI points, respectively, mean diff Δ = 11.3, 95% CI = 5.0–17.5; $P = 0.001$). One patient in each group failed to return a baseline diet diary. There were reductions in total energy intake (mean diff Δ = −285.5 kcal, 95% CI = −32.5 to −484.5; $P = 0.005$), total fat (mean diff Δ = −19.8 g, 95% CI = −7.3 to −32.3; $P < 0.001$), saturated fat (mean diff Δ = −8.6 g, 95% CI = −3.7 to −13.5;

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Table 1. Baseline characteristics of intervention and control arms of the study

	Mean (SD)		*P*
	Control group	Intervention group	
Age, y	72.2 (7.7)	71.3 (6.4)	0.664
Body mass, kg	82.2 (8.1)	83.1 (10.9)	0.736
Height, cm	173.1 (6.6)	172.4 (6.9)	0.694
BMI, kg/m^2	27.4 (2.7)	28.0 (3.2)	0.533
Waist-to-hip ratio	0.96 (0.07)	0.96 (0.05)	0.985
Exercise behavior (Godin LSI)	15 (10)	13 (9)	0.612
Systolic BP, mmHg	148.1 (18.8)	146.7 (19.0)	0.803
Diastolic BP, mmHg	84.0 (11.4)	85.9 (7.8)	0.500
PSA, ng/mL	5.0 (10.2)	3.3 (6.8)	0.907
Length of AST, mo	30 (31)	30 (31)	0.972
Gleason score	7 (1.1)	7 (1.3)	0.981
No. of patients with metastatic disease	7	6	

$P < 0.001$), and monounsaturated fat intake (mean diff $\Delta = -6.6$ g, 95% CI $= -2.0$ to -11.2; $P < 0.001$) in the intervention compared with the standard care control group (Table 2).

Fatigue and QoL

An improvement in fatigue (FACT-F) was observed at 12 weeks in the intervention group compared with control (mean diff $\Delta = 5.4$, 95% CI $= 0.8$–10.0; adjusted $P = 0.002$), and this was maintained at 6 months (mean diff $\Delta = 3.1$, 95% CI $= -0.3$ to 6.4; adjusted $P = 0.006$). Table 3 shows that there was no difference between groups in FACT-P and FACT-G at 12 weeks (end of intervention; $P = 0.21$ and $P = 0.25$, respectively) or at 6 months ($P = 0.45$ and $P = 0.36$).

Physiologic, functional fitness, and anthropometric variables

Knee pain prevented completion of the isokinetic dynamometry test in 1 participant from each group and the chair sit-to-stand test in 1 member of the standard care control group. Men in the intervention group achieved an improvement in aerobic exercise tolerance (mean diff $\Delta =$ 133.4 seconds, 95% CI $= 92.4$–174.4; adjusted $P < 0.001$), chair sit-to-stand test (mean diff $\Delta = 3.79$ repetitions, 95% CI $= 1.7$–5.9; adjusted $P = 0.002$), and MVT (mean diff $\Delta =$ 9.97 Nm, 95% CI $= -0.9$ to 20.8; adjusted $P = 0.033$) compared with controls at 12 weeks. Improvements in aerobic exercise tolerance (mean diff $\Delta = 102.2$ seconds, 95% CI $= 56.8$–147.6; adjusted $P < 0.001$), chair sit-to-stand test (mean diff $\Delta = 3.66$ repetitions, 95% CI $= 1.71$–5.60; adjusted $P = 0.001$), and MVT (mean diff $\Delta = 8.20$ Nm, 95% CI $= -0.9$ to 17.3; adjusted $P = 0.035$) were maintained at 6 months of follow-up (Table 4). No significant changes in anthropometric variables were observed over the intervention period or at 6 months (Table 4).

Blood markers

There was no significant group difference in the change in circulating levels of insulin, IGF axis peptides, PSA, testosterone, free androgen index, or sex hormone–binding globulin over the course of the intervention period (Table 5).

Discussion

Feasibility of the lifestyle intervention

This study evaluated the feasibility of a combined pragmatic exercise and dietary intervention on lifestyle behaviors and associated health outcomes in men with advanced prostate cancer receiving AST. A total of 50 men were recruited for this trial from a potential cohort of 78 individuals who were identified as eligible and invited for familiarization. This recruitment rate of 64% compares favorably with previous randomized control trials investigating the effects of an exercise intervention in men receiving AST that reported rates of 59% (20) and 31% (19), respectively. The majority of eligible patients were identified via nurse-led outpatient clinics (52%) and requesting medical notes from AST treatment schedule folders (24%). These methods also resulted in the majority of successfully randomized patients (clinics = 52% and treatment folders = 24%). However, these recruitment strategies were labor intensive and required a great deal of time dedicated to the process of screening medical notes and assessing eligibility. Patient recruitment into clinical trails is one of the most difficult and time-consuming elements and can be a potentially rate-limiting factor in overall productivity (30). Hence, an important finding from this study is that future trials invest in adequate human resources to achieve the recruitment targets.

Adherence to the supervised and independent exercise components of the lifestyle intervention was good, with

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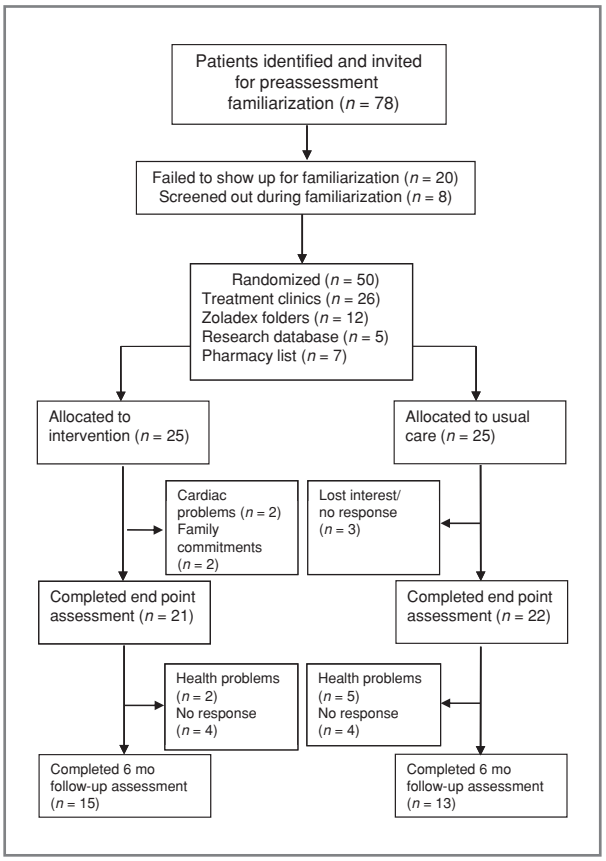

Figure 1. CONSORT recruitment flow diagram for men with prostate cancer receiving AST.

360 of 378 sessions attended (95%) and 329 of 378 bouts of independent exercise (87%) completed. These data match well with previous supervised exercise trials that reported 79% and 94% attendance, using resistance exercise only (19) and combined exercise interventions (20), respectively. The lifestyle intervention was also successful in increasing total exercise behavior (+19.7 Godin LSI points). This finding is similar to a recent randomized controlled trial (18) in men with prostate cancer on AST that reported improvements in physical activity behavior (+18.7 Godin LSI points) resulting from a home-based combined aerobic and resistance exercise program.

Attrition over the period of the lifestyle intervention was 7 of 50 men (14%), with 4 men leaving the lifestyle intervention (2 through previously undiagnosed cardiac conditions and 2 were unable to continue due to increasing family commitments). Three individuals who were randomized to the standard care control arm ceased correspondence after learning that they were not included in the exercise sessions. Despite study researchers making an attempt to contact these men via telephone or mail to explore their reasons for doing so, they chose not to respond to our enquiries. It is reasonable to speculate that, potentially, the reason for this was that these men were disappointed to be allocated to the standard care arm of the trial. A 14% attrition rate is similar to that reported in a previous supervised exercise intervention (13%; ref. 19) and much lower than the 34% dropout rate reported by others investigating the impact of a combined aerobic and resistance exercise intervention in men with prostate cancer undergoing AST (18). We observed a more substantial loss to follow-up at 6 months, with 44% of the cohort not assessed. Reasons for this increased attrition included the development of unrelated health problems ($n = 7$) and nonresponse to contact ($n = 8$). This high attrition might be associated with the lack of financial provision for trial participation (e.g., inclusion of reimbursement for the travel costs of visiting the center) on 2 further occasions. There was a slightly higher dropout rate in the standard care group than among men who undertook the lifestyle intervention (12 vs. 10, respectively), suggesting that attrition was not due to the demands of the intervention or increased independent exercise behavior.

Overall, the lifestyle intervention achieved acceptable recruitment (64%), compliance (95% and 87%), and attrition (14%) rates. Furthermore, 47 of 50 men complied with their randomization allocation. We have also presented data, with SDs, that could be used to inform sample size estimates for future larger-scale studies. A caveat must be added about the 6-month follow-up. With 44% of the cohort not being assessed, it is crucial that future trials compensate participants for travel and associated costs of attending assessment sessions. Sheffield is the fourth largest city of England and with volunteers taken from an expansive geographic area, it could be that nonresponders deemed the travel costs too much to continue with their involvement in the trial beyond the intervention phase. In addition, given that all support was withdrawn from study participants after the initial 12-week period, future programs should ensure that continued support systems are built in to reduce attrition and facilitate longer-term changes in health behaviors. We observed higher attrition in the control arm: future trials could utilize patient preference study designs which remove the undesirable potential for being allocated to standard care. However, such decisions need to be weighed against the loss of scientific robustness which is associated with the conventional randomized control trial.

Effect of the lifestyle intervention

There was partial support for our hypotheses about efficacy outcomes, with significant improvements in exercise and dietary behavior, aerobic exercise tolerance, functional capacity, and fatigue. However, prostate-specific QoL and biomarkers associated with disease progression did not change as a result of the intervention.

Reductions in total energy intake (−258.5 kcal), total fat (−19.8 g), and saturated fat (−8.6 g) were observed as a result of the lifestyle intervention in comparison with standard care. Saturated fat intake is linked to positive energy balance, greater BMI, and obesity, which have

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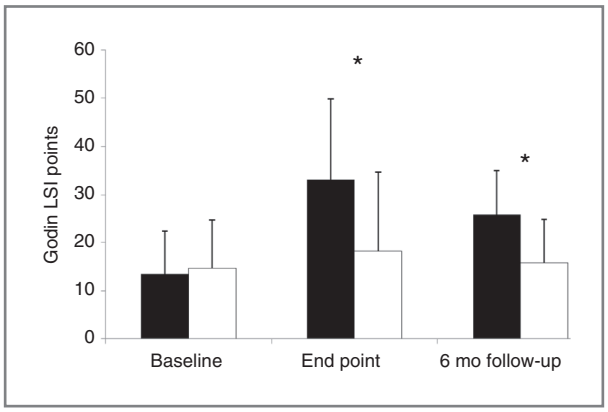

Figure 2. Exercise behavior within each group at each assessment as assessed by the Godin LSI. Data shown are means with SD bars. ■, lifestyle intervention; □, usual care controls. *, $P < 0.001$ compared with baseline (repeated-measures ANCOVA adjusting for baseline score, overall effect of group $P < 001$).

been associated with aggressive prostate cancer (15, 31). In addition, saturated fat intake has been linked to an increased risk of disease progression and death in men with prostate cancer (16, 17). There are several potential mechanisms by which saturated fat intake might influence disease progression, including its influence on circulating sex steroid hormones (32) and providing an advantage for tumor cell survival and proliferation (33).

Although a cautious approach needs to be applied when interpreting outcome data from feasibility trials, the positive changes in exercise and dietary behavior were accompanied by sustained changes in health outcomes. Men in the intervention group experienced reduced levels of fatigue (FACT-F) in comparison with the standard care controls at the intervention end point and at 6 months. As AST commonly causes an increase in prevalence and severity of fatigue (3), interventions that can ameliorate this adverse side effect are likely to have a substantial impact on daily physical and social functioning. A difference in FACT-F of 3.0 points is considered to be clinically relevant (34) and the mean difference in FACT-F score between groups at the end of the intervention and 6 months of follow-up was 5.4 and 3.1 points, respectively. This suggests that the pragmatic lifestyle intervention has much potential for evoking and maintaining a clinically relevant reduction in fatigue, though the 6 months data need to be interpreted with caution because of the high rate of attrition. Other studies have reported reduced levels of fatigue following combined programs of aerobic and resistance exercise, using different instruments (20) but at shorter follow-up.

Table 2. Dietary intake at baseline and end point in the intervention and usual care groups

Variable	Mean (SD)				Group mean difference in Δ[a] (95% CI)	P[b]
	Baseline		End point			
	Usual care	Intervention	Usual care	Intervention		
Total energy, kcal	2,012.4 (622.6)	1,957.2 (456.5)	1,983.2 (559.9)	1,669.4 (350.7)	−258.5 (−32.5 to −484.5)	0.005
Macronutrients						
Total fat, g	77.9 (28.0)	75.6 (23.7)	82.4 (25.7)	60.4 (16.9)	−19.8 (−32.3 to −7.3)	<0.001
Saturates, g	27.8 (11.2)	26.5 (7.5)	30.7 (11.5)	20.8 (7.3)	−8.6 (−13.5 to −3.7)	<0.001
Monounsaturates, g	24.4 (11.1)	22.5 (7.7)	25.7 (7.9)	17.2 (6.1)	−6.6 (−11.2 to −2.0)	<0.001
Polyunsaturates, g	11.3 (4.7)	10.3 (4.5)	10.4 (3.1)	8.8 (4.0)	−0.53 (−2.9 to 1.8)	0.21
Cholesterol, mg	273.8 (141.9)	247.6 (97.7)	272.7 (130.5)	209.4 (74.5)	−37.1 (−115.5 to 41.3)	0.064
Omega 3, mg	0.15 (0.19)	0.24 (0.40)	0.18 (0.35)	0.17 (0.23)	−0.11 (−0.29 to 0.07)	0.48
Omega 6, mg	0.87 (0.92)	0.84 (0.80)	0.78 (0.95)	0.81 (1.10)	0.07 (−0.56 to 0.69)	0.85
Carbohydrate, g	238.2 (55.7)	230.3 (56.4)	227.9 (61.3)	208.7 (50.9)	−11.3 (−39.8 to 17.3)	0.28
Sugars, g	106.7 (37.0)	100.4 (42.3)	98.9 (39.4)	93.6 (35.7)	1.1 (−18.1 to 20.3)	0.87
Starch, g	127.5 (26.9)	125.3 (35.0)	124.5 (25.7)	112.7 (28.9)	−9.2 (−28.2 to 8.9)	0.14
Alcohol, g	14.5 (23.0)	12.6 (12.8)	12.5 (21.9)	8.0 (11.2)	−2.7 (−8.6 to 3.19)	0.26
Fiber, g	15.7 (5.5)	14.4 (5.7)	15.0 (6.9)	15.1 (6.0)	1.4 (−1.6 to 4.41)	0.48
Protein, g	80.0 (29.1)	81.8 (18.7)	75.3 (16.7)	72.5 (15.1)	−4.6 (−16.5 to 7.3)	0.38
Micronutrients						
Vitamin E, mg	7.8 (3.2)	7.4 (2.9)	7.2 (3.0)	6.6 (2.4)	−0.26 (−1.6 to 1.1)	0.51
Vitamin C, mg	130.5 (81.4)	105.4 (99.6)	121.7 (94.1)	118.6 (93.7)	22.0 (−25.0 to 68.9)	0.56

[a]Δ (delta) from baseline in intervention group minus Δ from baseline in usual care group. A negative score indicates a greater decrease in the intervention group, and a positive score a greater increase.
[b]ANCOVA of end point score adjusting for baseline score, effect of group.

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Table 3. Fatigue and QoL outcomes at baseline, end point, and 6-month follow-up in the intervention and usual care groups

	Mean (SD)				Group mean difference in Δ^a (95% CI)	Adjusted P^b	Mean (SD)		Group mean difference in Δ^a (95% CI)	Adjusted P^c
	Baseline		End point				6-mo follow-up			
	Usual care	Intervention	Usual care	Intervention			Usual care	Intervention		
FACT-P	125 (19)	127 (13)	121 (25)	128 (14)	5.5 (−4.2 to 15.3)	0.21	122 (26)	125 (20)	1.0 (−8.6 to 10.6)	0.45
FACT-G	89 (13)	91 (9)	86 (18)	91 (10)	3.6 (−3.9 to 11.0)	0.25	87 (17)	90 (13)	1.8 (−5.1 to 8.6)	0.36
FACT-F	43 (8)	44 (6)	42 (8)	48 (4)	5.4 (0.8–10.0)	0.002	40 (8)	43 (7)	3.1 (−0.3 to 6.4)	0.006

NOTE: Because 95% CI in the previous column is calculated on unadjusted data, the *P* value, which is adjusted for baseline score, will not necessarily be consistent with the CI.

[a]Δ (delta) from baseline in intervention group minus Δ from baseline in usual care group. A negative score indicates a greater decrease in the intervention group, and a positive score a greater increase.

[b]ANCOVA of end point score adjusting for baseline score, effect of group.

[c]ANCOVA of end point and 6-month follow-up scores adjusting for baseline score, effect of group.

We observed a nonsignificant improvement in FACT-P in the intervention group at 12 weeks (mean diff $\Delta = 5.5$ points; $P = 0.21$). A clinically meaningful change in FACT-P is estimated to be between 6 and 10 points (35), and a significant difference between intervention and control groups (mean diff $\Delta = 5.3$) was previously reported following a 12-week program of resistance exercise in men with prostate cancer receiving AST (19). The magnitude of change approaches a clinically meaningful effect, but this did not reach statistical significance because of lack of power for this outcome.

Men in the intervention group exhibited improvements in aerobic fitness, muscle strength, and functional capacity. The improvement in strength is congruent with the results of previous exercise interventions in men with prostate cancer (20, 36), but the increased aerobic fitness is not consistent with results from the only randomized controlled exercise trial to include an aerobic exercise component in men with advanced prostate cancer undergoing AST (20). It is unclear why an improvement in aerobic fitness was not observed in the latter trial, but the difference could be due to a more intense aerobic exercise component in this study (i.e., 30 minutes of aerobic exercise at 11–15 on the Borg scale). Improvements in physical fitness parameters could have significant impact on perceptions of fatigue. As observed for fatigue, the improvements in physical fitness outcomes in the intervention group were maintained at 6 months of follow-up. This contrasts with the only other exercise trial to include a longer-term follow-up assessment in men with prostate cancer receiving AST (37). Although caution in interpretation of the 6 months follow-up data is needed because of the higher rate of attrition, the lasting improvements in physical fitness outcomes may have resulted from a sustained increase in independent physical activity (as indicated by the self-report measure).

In accordance with previous resistance exercise trials in prostate cancer patients receiving AST (19), there were no changes in any of the anthropometric variables (body mass, BMI, or waist-to-hip ratio). Quantification of changes in body composition by using BMI and girth measurements is fraught with difficulty, and more precise measures, such as dual energy X-ray absorptiometry (DEXA) or MRI are preferable to assess changes. Indeed, evidence of improvement in skeletal muscle mass via DEXA scanning following combined resistance and aerobic exercise training in such a cohort has been reported previously (20). The efficacy of lifestyle interventions for evoking changes in body composition is important, as higher levels of body fat have been associated with higher grade tumors and disease progression (31). Where possible, future studies should assess these parameters by using more precise anthropometric measurement techniques.

Circulating levels of insulin, IGF axis peptides, and PSA were also unchanged. IGF axis peptides have been

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Table 4. Physical function, fitness, and anthropometric outcomes at baseline, end point, and 6-month follow-up in the lifestyle intervention and usual care groups

	Mean (SD)				Group mean difference in Δ[a] (95% CI)	Adjusted *P*[b]	Mean (SD)		Group mean difference in Δ[a] (95% CI)	Adjusted *P*[c]
	Baseline		End point				6-mo follow-up			
	Usual care	Intervention	Usual care	Intervention			Usual care	Intervention		
Fitness and function										
Exercise tolerance, s	368.6 (129.1)	351.1 (110.8)	379.8 (129.2)	495.8 (125.0)	133.4 (92.4–174.4)	<0.001	351.0 (114.4)	435.8 (118.5)	102.2 (56.8–147.6)	< 0.001
Chair-sit-to-stand (reps)	12.3 (3.7)	11.1 (2.3)	13.4 (4.3)	16.0 (3.7)	3.79 (1.68–5.90)	0.002	13.6 (3.8)	16.1 (4.1)	3.66 (1.71–5.60)	0.001
MVT, Nm	170.8 (52.0)	181.9 (42.7)	169.2 (48.8)	190.3 (40.9)	9.97 (−0.92 to 20.8)	0.033	176.2 (53.8)	195.5 (43.6)	8.20 (−0.90 to 17.3)	0.035
Anthropometry										
Weight, kg	82.2 (8.1)	83.1 (10.9)	82.0 (8.1)	82.2 (10.4)	−0.72 (−1.8 to 0.35)	0.20	81.5 (8.2)	81.8 (10.2)	−0.64 (−2.2 to 0.87)	0.27
BMI, kg/m^2	27.4 (2.7)	28.0 (3.2)	27.0 (3.2)	27.6 (3.0)	0.09 (−0.85 to 1.01)	0.76	27.3 (2.7)	27.6 (3.1)	−0.23 (−0.67 to 0.22)	0.88
Waist-to-hip ratio	0.96 (0.07)	0.96 (0.05)	0.95 (0.06)	0.96 (0.05)	0.01 (−0.01 to 0.03)	0.39	0.95 (0.05)	0.95 (0.05)	0.001 (−0.02 to 0.02)	0.56

NOTE: Because 95% CI in the previous column is calculated on unadjusted data, the *P* value, which is adjusted for baseline score, will not necessarily be consistent with the CI.

[a]Δ (delta) from baseline in intervention group minus Δ from baseline in usual care group. A negative score indicates a greater decrease in the intervention group and a positive score a greater increase.

[b]*P* value for effect of group from an ANCOVA of end point score adjusting for baseline score.

[c]*P* value for effect of group from an ANCOVA of end point and 6-month follow-up scores adjusting for baseline score.

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Table 5. Blood markers at baseline and end point in the intervention and usual care groups

	n	Mean (SD)				Group mean difference in Δ[a] (95% CI)	*P*[b]
		Baseline		End point			
		Usual care	Intervention	Usual care	Intervention		
Insulin, mU/L	42	10.8 (12.7)	10.4 (13.2)	11.7 (14.2)	8.91 (8.4)	−2.3 (−12.5 to 7.8)	0.46
IGFBP-3, ng/mL	42	3,052.5 (750.7)	3,098.1 (738.2)	2,964.7 (796.2)	2,875.7 (827.3)	−134.6 (−503.9 to 234.6)	0.49
IGF-1, ng/mL	42	77.6 (25.8)	74.5 (21.5)	79.4 (27.2)	78.3 (22.6)	1.9 (−6.9 to 10.8)	0.72
IGFBP-1, ng/mL	42	34.5 (24.4)	32.6 (25.9)	38.4 (26.2)	36.4 (26.4)	−0.18 (−12.1 to 11.7)	0.91
PSA, ng/mL	50	5.02 (10.2)	3.32 (6.83)	6.24 (13.6)	4.55 (8.74)	0.01 (−2.2 to 2.2)	0.61
Serum testosterone, nmol/L	40	3.19 (6.97)	4.12 (8.69)	3.85 (8.67)	4.50 (8.01)	−0.28 (−1.8 to 1.2)	0.68
Free androgen index	39	8.52 (19.4)	12.4 (24.3)	9.44 (21.5)	13.5 (22.8)	0.22 (−3.3 to 3.8)	0.87
Sex hormone–binding globulin, nmol/L	40	45.1 (13.6)	41.6 (13.2)	46.8 (14.0)	40.8 (11.8)	−2.5 (−6.4 to 1.5)	0.13

[a]Δ (delta) from baseline in intervention group minus Δ from baseline in usual care group. A negative score indicates a greater decrease in the intervention group and a positive score a greater increase.
[b]ANCOVA of end point score adjusting for baseline score, effect of group.

associated with prostate cancer risk in observational studies (38) and evidence describes an association with disease progression (39), but these markers are not specific for prostate cancer and circulating levels can vary greatly between individuals (40). A 15-week program of thrice-weekly aerobic exercise has previously been shown to evoke positive changes in circulating levels of IGF-I and IGFBP-3 in postmenopausal breast cancer survivors (41). The exercise prescription was of similar duration and intensity as that used in this study, but differences in gender, cancer type, and/or treatment strategies between the cohorts (AST vs. surgery, radiotherapy, and/or chemotherapy) could account for the discordant findings. The utility of IGF axis peptide markers for prospective intervention studies in men with prostate cancer is unknown, and it is unlikely that this study was adequately powered to show changes in these exploratory outcomes. Nevertheless, these data could be useful for informing sample size calculations for future larger-scale prospective intervention trials. The absence of any change in PSA is consistent with other exercise studies in this patient group (19, 20). Although PSA is a specific marker for progression of prostate cancer following treatment, the magnitude of change does not correlate well with disease progression in such a cohort. Hence, further long-term studies are needed to assess the impact of such lifestyle interventions on prostate cancer progression.

The results and conclusions from this feasibility trial should be interpreted in the context of a number of limitations. First, the high rate of attrition at 6 months (44%) increases the possibility of differential selection bias and means that caution needs to be taken when interpreting the 6-month follow-up data. Second, the absence of more precise anthropometric measures (e.g., DEXA, MRI) limits any conclusions that can be drawn about changes in body composition. Third, although the observed reductions in total energy and saturated fat consumption were encouraging, it should be acknowledged that there is inherent error in using diet diaries over such a short period of time (just 3 days) and a longer duration analysis (e.g., >7 days) might have produced more reliable data. In addition, incorporating analysis of nutritional biomarkers such as serum lipids, lycopene, carotenoids, and tocopherols would provide more objective measures of dietary change.

In conclusion, this study provides evidence that pragmatic lifestyle interventions are feasible and have much potential to evoke improvements in exercise and dietary behavior and a range of other important health outcomes in men with advanced prostate cancer receiving AST. Our results suggest that future larger-scale definitive trials should incorporate enhanced support systems that could help to reduce attrition and facilitate longer-term changes in independent health behaviors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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