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ORIGINAL REPORT

Randomized Controlled Trial of Resistance or Aerobic Exercise in Men Receiving Radiation Therapy for Prostate Cancer

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Radiotherapy for prostate cancer (PCa) may cause unfavorable changes in fatigue, quality of life (QOL), and physical fitness. We report results from the Prostate Cancer Radiotherapy and Exercise Versus Normal Treatment study examining the effects of 24 weeks of resistance or aerobic training versus usual care on fatigue, QOL, physical fitness, body composition, prostate-specific antigen, testosterone, hemoglobin, and lipid levels in men with PCa receiving radiotherapy.

Patients and Methods
Between 2003 and 2006, we conducted a randomized controlled trial in Ottawa, Canada, where 121 PCa patients initiating radiotherapy with or without androgen deprivation therapy were randomly assigned to usual care (n = 41), resistance (n = 40), or aerobic exercise (n = 40) for 24 weeks. Our primary end point was fatigue assessed by the Functional Assessment of Cancer Therapy–Fatigue scale.

Results
The follow-up assessment rate for our primary end point of fatigue was 92.6%. Median adherence to prescribed exercise was 85.5%. Mixed-model repeated measures analyses indicated both resistance (P =.010) and aerobic exercise (P = .004) mitigated fatigue over the short term. Resistance exercise also produced longer-term improvements (P = .002). Compared with usual care, resistance training improved QOL (P = .015), aerobic fitness (P = .041), upper- ($P < .001$) and lower-body ($P < .001$) strength, and triglycerides (P = .036), while preventing an increase in body fat (P = .049). Aerobic training also improved fitness (P = .052). One serious adverse event occurred in the group that performed aerobic exercise.

Conclusion
In the short term, both resistance and aerobic exercise mitigated fatigue in men with PCa receiving radiotherapy. Resistance exercise generated longer-term improvements and additional benefits for QOL, strength, triglycerides, and body fat.

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INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men in North America and the second most common cause of cancer death in men older than 70 years.[1,2] Radiotherapy is an important modality for curative treatment in early-stage disease, and improves disease-free and overall survival in locally advanced or higher-risk disease.[3-6] The most common complaint of patients receiving radiotherapy is fatigue (60% to 80%), which tends to be cumulative and persistent even after treatment is completed.[7-12] Increased fatigue is associated with psychological distress, as well as reduced quality of life (QOL) and functional capacity. Interventions to reduce fatigue would be an important element of supportive care.

Previously, we showed that a 12-week program of resistance exercise training reduced fatigue and improved QOL and fitness in men with PCa receiving androgen deprivation therapy (ADT).[13] Here we report results from the Prostate Cancer Radiotherapy and Exercise Versus Normal Treatment study examining the effects of 24 weeks of resistance or aerobic training versus usual care on fatigue, cancer-specific QOL, physical fitness, body composition, and prostate-specific antigen (PSA), testosterone, and serum lipid levels in men with PCa receiving radiotherapy.

We hypothesized that both resistance and aerobic training would be superior to usual care for patient-rated fatigue and disease-specific QOL; resistance training would improve strength and body fat percentage, whereas aerobic training

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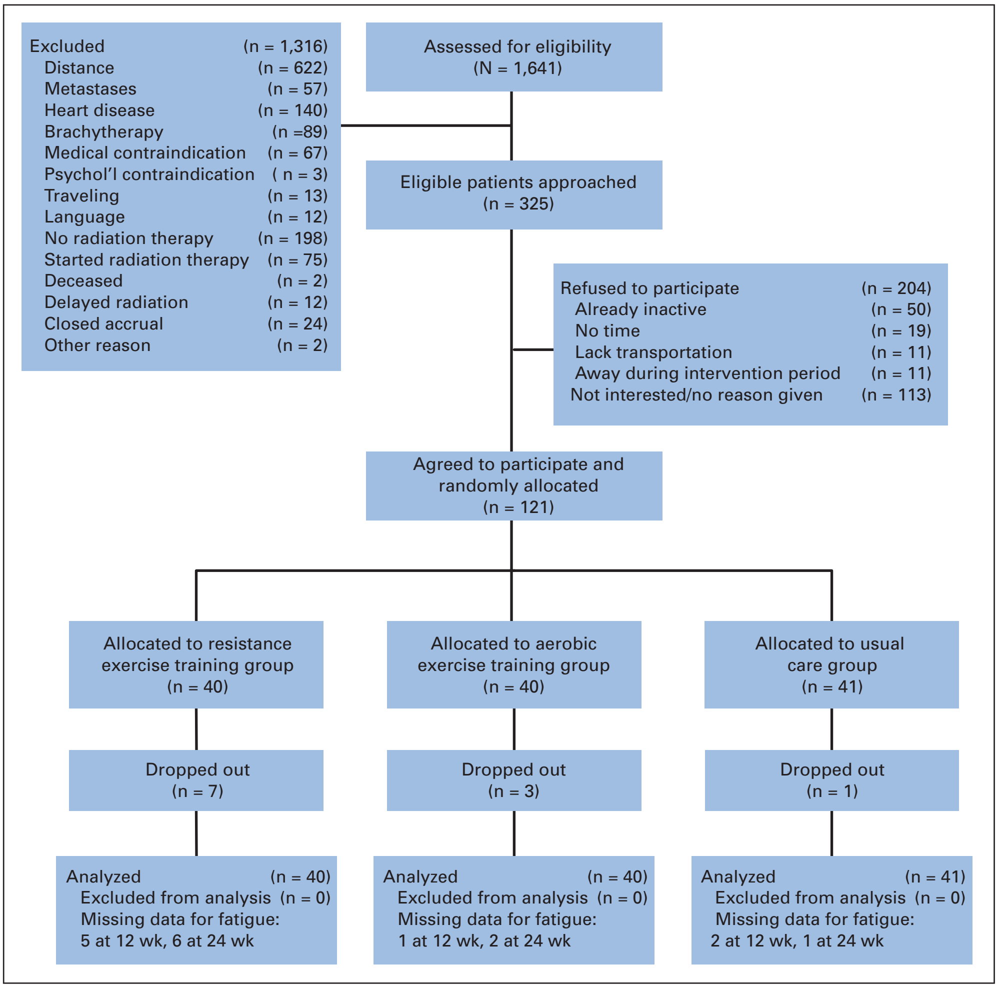

Fig 1. CONSORT diagram.

would improve aerobic fitness and body fat; and both exercise interventions would improve serum lipid levels and have no adverse effects on PSA, testosterone, or hemoglobin.

PATIENTS AND METHODS

Setting and Participants

The trial was conducted at the Ottawa Hospital Regional Cancer Centre, Ottawa, Canada. The protocol was approved by the institutional research ethics committee and all participants provided written informed consent. Men were eligible to participate if they had histologically documented PCa, were scheduled to receive radiotherapy with or without ADT, and if the treating oncologist approved. Men were excluded if they had severe cardiac disease (New York Heart Association functional class III or IV), uncontrolled hypertension, pain, psychiatric illness, or lived more than 1 hour away.

Design and Procedures

The study was a prospective, three-armed, randomized, controlled trial (Fig 1). Eligible participants were identified by their oncologist. Consenting participants completed a questionnaire, anthropometric measures, physical fitness tests, blood tests, and a dual energy x-ray absorptiometry scan (DEXA; added after 20 participants underwent random assignment).

Randomization

Participants were stratified by intended duration of ADT ($\leq$ 16 weeks/none *v* ADT $>$ 16 weeks) and randomly assigned to one of three groups: resistance training, aerobic training, or usual care using computer-generated numbers. Central random assignment was used, with allocation concealment before assignment. To ensure blinding of the research coordinator, an exercise specialist handled the random assignments.

Exercise Training Interventions

Participants in the exercise groups exercised for a total of 24 weeks. All exercise sessions were supervised by exercise specialists at the Cancer Rehabilitation Center. Warm-up and cool-down periods were 5 minutes of light aerobic activity and stretching. Resistance training participants exercised three times per week performing two sets of eight to12 repetitions of 10 different exercises (leg extension, leg curl, seated chest fly, latissimus pulldown, overhead press, triceps extension, biceps curls, calf raises, low back extension, and modified curl-ups) at 60% to 70% of their estimated one-repetition maximum (1 RM).[14] Resistance was increased by 5 lb when participants completed more than 12 repetitions. Aerobic training participants exercised three times per week on a cycle ergometer, treadmill, or elliptical trainer beginning at 50% to 60% of their predetermined peak oxygen consumption (VO_{2peak}) for weeks 1 to 4 and progressing to 70% to 75% for weeks 5 to 24. Exercise duration began at 15 minutes and increased by 5 minutes every 3 weeks until it reached 45 minutes. Exercise intensity was standardized using heart rate monitors. Usual-care participants were asked not to initiate exercise and were offered a program, postintervention assessments.

Assessment of Primary and Secondary End Points

Patient-rated outcomes were assessed at baseline before commencement of radiotherapy, in the middle (12 weeks), and at the end of intervention (24

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weeks). Fatigue, PCa-specific, and cancer-specific QOL were assessed by the Functional Assessment of Cancer Therapy–Fatigue (FACT-Fatigue), Prostate (FACT-P), and General (FACT-G) scales,[15] respectively.

Some objectively measured outcomes (aerobic fitness, strength, body weight, body fat percentage, serum lipids) were assessed at baseline and 24 weeks, whereas others (PSA, testosterone, and hemoglobin) were measured at all three time points. Aerobic fitness was evaluated using a maximal incremental exercise protocol on a treadmill. Whole-body oxygen uptake ($\dot{V}O_2$) was measured using expired gas samples. VO_{2peak} was determined by taking the highest values during a 15-second period. Muscular strength was assessed as the maximum weight that could be lifted eight times while maintaining proper form (8 RM) on the horizontal bench and leg press. This was used to estimate 1 RM.[14] Body weight to the nearest 0.1 kg and standing height to the nearest 0.5 cm were assessed without shoes using a balance beam scale. A DEXA scan (LUNAR EXPERT; General Electric, Princeton, NJ) assessed percent body fat. A blood sample to measure PSA, serum free testosterone, hemoglobin, and serum lipids (total cholesterol, low- and high-density lipoprotein cholesterol, and triglycerides) was obtained and processed by a centralized laboratory.

Assessment of Covariates, Exercise Adherence, and Adverse Events

Demographic and behavioral data were collected by self-report and medical data were abstracted from clinical records. Exercise specialists monitored adherence and adverse events. Nonprotocol exercise was assessed by self-report at 24 weeks.

Statistical Analyses and Sample Size Calculation

A priori, we calculated that with 37 participants per group, our trial had 80% power to detect a difference in change scores of 3.5 points (standard deviation = 5.8) on the FACT-Fatigue[16] with a loss to follow-up of 10%, a two-tailed level of significance of .05, and no adjustment for multiple testing.[17] Baseline comparisons were performed using univariate analysis of variance for continuous variables and χ^2 analyses for categoric variables. Mixed-model repeated measures analysis was used to compare the differences between groups over time. For the patient-rated outcomes assessed at baseline, midpoint, and postintervention, we used contrasts defined a priori to examine changes between baseline and midpoint (12 weeks) and baseline and post-test

Table 1. Baseline Characteristics of Volunteers Participating in Exercise Study

Characteristic	Overall Sample (N = 121) No.	Overall Sample %	Usual Care Group (n = 41) No.	Usual Care Group %	Resistance Exercise Training Group (n = 40) No.	Resistance Exercise Training Group %	Aerobic Exercise Training Group (n = 40) No.	Aerobic Exercise Training Group %
Demographic profile								
Age								
Mean	66.3		65.3		66.4		66.2	
SD	7.0		7.6		7.6		6.8	
Married	100	82.6	32	78.0	32	80.0	36	90.0
Completed university or college	62	51.2	21	51.2	19	47.5	22	55.0
Employed full-time	29	23.9	14	34.1	6	15.0	9	22.5
Medical profile								
Weight, kg								
Mean	86.3		86.5		84.3		88.1	
SD	12.2		15.2		9.9		10.9	
BMI, kg/m²								
Mean	28.6		29.0		28.1		28.9	
SD	12.2		4.2		3.5		3.4	
Testosterone, pmol								
Mean	7.8		7.8		6.4		9.3	
SD	7.3		7.1		6.2		8.5	
PSA, ng/mL								
Mean	3.1		3.9		3.0		2.5	
SD	4.3		5.5		3.3		3.8	
On androgen deprivation therapy	74	61.2	26	63.4	23	57.5	25	62.5
Cancer stage grouping								
Stage I	1	0.8	0	0.0	0	0.0	1	2.5
Stage II	95	78.5	35	85.4	31	77.5	29	72.5
Stage III	21	17.3	4	9.8	8	20.0	9	22.5
Stage IV	1	0.8	1	2.4	0	0.0	0	0.0
Unassignable group	3	2.4	1	2.4	1	2.5	1	2.5
Gleason score								
Mean	6.7		6.7		6.7		6.9	
SD	0.9		0.9		1.1		0.8	
Behavioral profile								
Current aerobic exerciser	44	36.4	16	39.0	14	35.0	14	35.0
Current weight trainer	13	10.7	3	7.3	4	10.0	6	15.0
Current smoker	5	4.1	2	4.9	0	0.0	3	7.5

Note: Data are presented as the mean and SD for continuous variables and the number and percentage for categorical variables.
Abbreviations: SD, standard deviation; BMI, body mass index; PSA, prostate-specific antigen.

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(24 weeks) for each outcome and to compare group differences in mean change (resistance *v* usual care and aerobic *v* usual care). Our primary analysis was unadjusted, but we also tested a model that adjusted for age, cancer stage, ADT (yes/no), and Gleason score. For all analyses, an intention-to-treat approach was followed. All analyses were done using SPSS Version 16.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient Flow and Follow-Up

Recruitment ran from February 2003 to April 2006 (Fig 1). We recruited 121 (37%) of 325 eligible participants. Common reasons for refusal were already active (n = 50), no time (n = 19), lacked transportation (n = 11), unavailable for more than 2 weeks during the intervention (n = 11), and no reason (n = 109). We obtained follow-up data from 112 (92.6%) of 121 participants. Loss to follow-up was similar between groups.

Baseline Characteristics

Groups were balanced at baseline (Table 1, online only). Resistance and aerobic participants completed a median of 88% (63 of 72 sessions) and 83% (60 of 72 sessions) of scheduled sessions, respectively (P = .845). Overall, 18 (15%) of 121 participants reported regular exercise outside treatment group assignment: eight resistance participants reported aerobic exercise ≥ three times/wk; five aerobic participants reported resistance exercise ≥ two times/wk; six usual-care participants reported aerobic exercise ≥ three times/wk (including one participant who also reported resistance exercise ≥ two times/wk).

Changes in Patient-Rated Outcomes

Table 2, online only, lists the patient-rated outcomes. The analysis for fatigue showed no main effect for group (F = 0.62; P = .540), but a significant main effect of time (F = 10.02; P < .001) and significant interaction between group and time (F = 3.84; P = .005). Planned contrasts showed fatigue was improved with resistance and aerobic training compared with usual care from baseline to 12 weeks. From baseline to 24 weeks, only resistance exercise was superior to usual care. PCa-specific QOL (FACT-P) declined over time (F = 19.17; P < .001) but there were no significant effects of group assignment. For cancer-specific QOL (FACT-G), there was no main effect for group (F = 0.16; P = .854), but there was a significant main effect of time (F = 5.11; P = .007) and a borderline significant interaction between group and time (F = 2.16; P = .076). Planned contrasts showed resistance exercise was superior to usual care for group differences in mean change between baseline and follow-up. All results were unchanged after covariate adjustment.

Changes in Objectively Measured Outcomes

Table 3, online only, lists physical fitness and body composition end points. VO_{2peak} was superior with resistance (P = .041) and aerobic training (P = .052) compared with usual care. After adjustment for covariates, resistance training remained superior in VO_{2peak} (P = .038), whereas aerobic training was borderline superior (P = .063). Lower- and upper-body strength were superior with resistance training (P < .001 for both). Results were unchanged after covariate adjustment. Resistance training attenuated increases in body fat percentage compared with usual care (P = .049). After covariate

Table 2. Effects of Aerobic and Resistance Exercise on Patient-Rated Outcomes in Prostate Cancer Patients Receiving Radiation Therapy

	Baseline		Midpoint		Post-Test		Change From Baseline to Midpoint (12 weeks)			Change From Baseline to Post-Test (24 weeks)			Unadjusted Group Difference in Mean Change From Baseline to Midpoint (12 weeks)			Unadjusted Group Difference in Mean Change From Baseline to Post-Test (24 weeks)		
Characteristic	M	SD	M	SD	M	SD	M	95% CI	P	M	95% CI	P	M	95% CI	P	M	95% CI	P
FACT–Fatigue Subscale																		
UC	44.6	8.7	39.0	8.9	42.1	8.8	−5.57	−7.80 to −3.34	< .001	−2.45	−4.50 to −0.40	.020						
RET	42.8	8.7	41.3	9.1	45.1	9.1	−1.46	−3.81 to 0.89	.220	2.33	0.13 to 4.53	.040		RET *v* UC			RET *v* UC	
													4.11	0.87 to 7.35	.010	4.78	1.77 to 7.78	.002
AET	44.1	8.7	43.1	8.8	44.2	8.9	−0.93	−3.17 to 1.31	.410	0.20	−1.90 to 2.29	.850		AET *v* UC			AET *v* UC	
													4.64	1.47 to 7.80	.004	2.65	−0.29 to 5.58	.080
FACT–Prostate Symptom Subscale																		
UC	37.1	6.4	32.9	6.5	36.0	6.4	−4.17	−5.97 to −2.38	< .001	−1.13	−2.70 to 0.43	.154						
RET	37.4	6.4	35.5	6.7	37.7	6.7	−1.91	−3.79 to −0.02	.047	0.27	−1.41 to 1.95	.750		RET *v* UC			RET *v* UC	
													2.26	−0.34 to 4.87	.088	1.40	−0.89 to 3.70	.228
AET	37.5	6.4	34.3	6.5	37.8	6.5	−3.17	−4.98. to 1.37	< .001	0.31	−1.29 to 1.90	.703		AET *v* UC			AET *v* UC	
													1.00	−1.55 to 3.54	.440	1.44	−0.80 to 3.68	.205
FACT–General Scale																		
UC	90.0	13.0	87.5	13.2	89.8	13.1	−2.48	−5.16 to 0.21	.070	−0.17	−2.53 to 2.19	.886						
RET	88.2	13.0	90.5	13.4	92.4	13.4	2.27	−0.55 to 5.11	.113	4.17	1.62 to 6.70	.002		RET *v* UC			RET *v* UC	
													4.76	0.86 to 8.65	.017	4.34	0.88 to 7.80	.015
AET	89.5	13.0	90.2	13.1	91.8	13.1	0.75	−1.95 to 3.44	.585	2.35	−0.06 to 4.77	.055		AET *v* UC			AET *v* UC	
													3.22	−0.58 to 7.02	.096	2.52	−0.85 to 5.90	.141

Abbreviations: M, mean; SD, standard deviation; FACT, Functional Assessment of Cancer Therapy; UC, usual care; RET, resistance exercise training; AET, aerobic exercise training.

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Table 3. Effects of Aerobic and Resistance Exercise on Physical Fitness and Body Composition in Prostate Cancer Patients Receiving Radiation Therapy

Characteristic	Baseline		Post-Test		Mean Change			Unadjusted Group Difference in Mean Change From Faseline to Post-Test (24 weeks)			Adjusted Group Difference in Mean Change From Baseline to Post-Test (24 weeks)		
	M	SD	M	SD	M	95% CI	*P*	M	95% CI	*P*	M	95% CI	*P*
VO_{2peak}, ml/kg/min													
UC	28.8	5.1	27.6	5.1	−1.4	−2.4 to −0.4	.008						
RET	28.2	6.9	29.1	6.6	+0.14	−0.9 to 1.2	.785		RET *v* UC			RET *v* UC	
								+1.5	0.06 to 3.0	.041	+1.6	1.0 to 3.1	.037
AET	29.4	6.5	29.6	6.4	+0.04	−.98 to 1.1	.941		AET *v* UC			AET *v* UC	
								+1.4	−.01 to 2.8	.052	+1.4	.08 to 2.8	.063
8-RM leg, kg													
UC	117.3	53.5	119.2	55.9	+0.41	−6.3 to 7.1	.905						
RET	104.6	37.7	134.1	41.6	+25.6	18.7 to 32.6	< .001		RET *v* UC			RET *v* UC	
								+25.2	15.6 to 34.9	< .001	+25.1	15.3 to 34.9	< .001
AET	125.6	55.8	128.0	60.9	+4.4	−2.4 to 11.2	.205		AET *v* UC			AET *v* UC	
								+4.0	−5.6 to 13.6	.412	+3.7	−6.0 to 13.4	.45
8-RM chest, kg													
UC	55.2	13.3	52.9	14.6	−2.5	−4.5 to −.60	.011						
RET	49.5	11.1	60.8	14.0	+10.9	8.8 to 13.0	< .001		RET *v* UC			RET *v* UC	
								+13.5	10.6 to 16.3	< .001	+13.7	10.7 to 16.6	< .001
AET	53.4	12.1	54.9	13.0	+1.3	−.68 to 3.3	.193		AET *v* UC			AET *v* UC	
								+3.9	1.1 to 6.6	.007	+4.0	1.2 to 6.9	.006
Weight, kg													
UC	86.5	15.2	87.7	15.9	+1.25	0.43 to 2.1	.003						
RET	84.3	9.9	85.2	10.5	+.86	0.03 to 1.7	.042		RET *v* UC			RET *v* UC	
								−.39	−1.6 to 0.78	.514	−.52	−1.7 to 0.67	.390
AET	88.1	10.9	88.6	11.6	+.46	−.38 to 1.3	.281		AET *v* UC			AET *v* UC	
								−.79	−2.0 to 0.39	.186	−.88	−2.1 to 0.32	.148
Body fat, %													
UC	31.7	8.4	33.3	8.1	+1.6	0.56 to 2.6	.003						
RET	31.7	5.6	31.3	7.1	−.04	−1.2 to 1.1	.947		RET *v* UC			RET *v* UC	
								−1.5	−3.1 to −.01	.049	−1.5	−3.1 to 0.03	.055
AET	31.0	5.9	32.3	7.1	+1.4	0.27 to 2.6	.016		AET *v* UC			AET *v* UC	
								−.19	−1.7 to 1.3	.808	−.15	−1.7 to 1.4	.847

NOTE. Adjusted for age, cancer stage, androgen deprivation therapy (yes/no), and Gleason score. *P* values presented only for hypothesized comparisons.
Abbreviations: M, mean; SD, standard deviation; FACT, Functional Assessment of Cancer Therapy; UC, usual care; RET, resistance exercise training; AET, aerobic exercise training; VO_{2peak}, peak volume of oxygen consumed; RM, repetition maximum.

adjustment, the difference between resistance training and usual care was borderline significant ($P = .055$).

Table 4, online only, lists hemoglobin, PSA, and testosterone data. The analysis for hemoglobin showed no main effect for group ($F = 0.51$; $P = .606$), but a significant main effect of time ($F = 54.28$; $P < .001$). The interaction between group and time ($F = 0.99$; $P = .414$) was not significant. Hemoglobin levels declined over time in all groups and results were unchanged after adjustment. For testosterone, there was no main effect for group ($F = 0.49$; $P = .611$), but there was a significant main effect of time ($F = 5.11$; $P < .001$) and a significant interaction between group and time ($F = 2.64$; $P < .035$). Planned contrasts showed a trend ($P = .090$) for less reduction in testosterone with resistance training in the analysis of group differences in mean change from baseline to 12 weeks. The between-group difference was reduced (to 1.17 pmol; $P = .267$) after covariate adjustment. For PSA, there was no main effect of group ($F = 1.13$; $P = .326$); however, there was a significant main effect for time ($F = 26.88$; $P < .001$). The interaction between group and time was not significant ($F = 1.21$; $P = .309$). Planned contrasts showed less reduction in PSA with resistance training in the analysis of group differences in mean changes from baseline to 12 weeks. The between-group difference was increased (to 1.59 ng/mL; $P = .031$) after covariate adjustment.

At baseline, mean levels (and standard deviations) of total cholesterol, low- and high-density lipoprotein cholesterol, and triglyceride levels were 5.4 ± 1.0, 3.3 ± 0.8, 1.4 ± 0.3, and 1.6 ± 0.9 mmol/L, respectively. There were no significant between-group differences. During the intervention, total and low-density lipoprotein cholesterol levels trended lower in all groups (0.1 ± 0.8 and 0.2 ± 0.6 mmol/L, respectively); however, there were no significant between-group differences. High-density lipoprotein values remained unchanged in all groups. Triglyceride levels increased by 0.3 ± 0.7 mmol/L in both the aerobic and usual-care groups, and decreased by 0.1 ± 0.6 mmol/L with resistance training. The change in triglycerides between the resistance training and usual care was significant ($P = .036$).

Adverse Events

Three participants experienced adverse events related to exercise; only one was deemed serious (ie, resulting in hospitalization or disability). In the resistance group, one man experienced chest pain during exercise. Subsequent cardiologic investigations were negative. In the aerobic group, one man had syncope before his treadmill exercise test. No underlying cause was identified. He later completed testing without incident. The lone serious adverse event occurred in

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Table 4. Effects of Aerobic and Resistance Exercise on Serology Outcome Indicators in Prostate Cancer Patients Receiving Radiation Therapy

	Baseline		Midpoint		Post-Test		Change From Baseline to 3 Months			Change From Baseline to 6 Months			Unadjusted Group Difference in Mean Change From Baseline to Midpoint (12 weeks)			Unadjusted Group Difference in Mean Change From Baseline to Post-Test (24 weeks)		
Characteristic	M	SD	M	SD	M	SD	M	95% CI	P	M	95% CI	P	M	95% CI	P	M	95% CI	P
Hemoglobin																		
UC	147.1	12.1	140.6	12.2	141.8	12.2	−6.46	−8.70 to −4.21	< .001	−5.25	−7.72 to −2.79	< .001						
RET	145.1	12.1	139.3	12.4	139.9	12.5	−5.35	−7.72 to −2.98	< .001	−5.16	−7.81 to −2.52	< .001		RET *v* UC			RET *v* UC	
													1.10	−2.15 to 4.37	.503	0.09	−3.52 to 3.70	.960
AET	145.7	12.1	137.2	12.2	139.1	12.3	−8.53	−10.78 to −6.27	< .001	−6.64	−9.18 to −4.11	< .001		AET *v* UC			AET *v* UC	
													−2.07	−5.25 to 1.11	.201	−1.39	−4.93 to 2.14	.437
Testosterone, pmol																		
UC	7.68	7.28	5.99	7.30	5.50	7.30	−1.70	−3.14 to −0.25	.021	−2.18	−4.02 to −0.34	.020						
RET	6.43	7.25	6.52	7.43	6.08	7.61	0.10	−1.40 to 1.61	.892	−0.34	−2.31 to 1.63	.734		RET *v* UC			RET *v* UC	
													1.80	−0.29 to 3.89	.090	1.84	−0.85 to 4.54	.177
AET	9.62	7.29	6.36	7.31	6.97	7.38	−3.26	−4.73 to −1.80	< .001	−2.65	−4.54 to −0.76	.006		AET *v* UC			AET *v* UC	
													−1.57	−3.62 to 0.49	.134	−0.46	−3.10 to 2.17	.728
Prostate-specific antigen, ng/dL																		
UC	3.86	3.04	1.31	3.09	0.57	3.07	−2.54	−3.52 to −1.57	< .001	−3.29	−4.46 to −2.11	< .001						
RET	2.94	3.03	1.84	3.20	1.19	3.31	−1.11	−2.13 to −0.09	.033	−1.76	−3.01 to −0.51	.006		RET *v* UC			RET *v* UC	
													1.43	0.02 to 2.86	.046	1.53	−0.18 to 3.25	.090
AET	2.54	3.03	0.86	3.07	0.40	3.10	−1.69	−2.67 to −0.71	< .001	−2.14	−3.34 to −0.94	< .001		AET *v* UC			AET *v* UC	
													0.86	−0.52 to 2.24	.223	1.14	−0.53 to 2.82	.181

Abbreviations: M, mean; SD, standard deviation; FACT, Functional Assessment of Cancer Therapy; UC, usual care; RET, resistance exercise training; AET, aerobic exercise training.

the aerobic group, where a man suffered an acute myocardial infarction. The patient was on the third day of the training protocol. Fifteen minutes after completion of the session he collapsed and was found to be in ventricular fibrillation. He was resuscitated and made a full recovery, although he did not complete the intervention. His ECG at hospital admission showed ST-segment elevation consistent with acute anterior wall myocardial infarction. No previous cardiac history had been reported.

DISCUSSION

In the short term, both resistance and aerobic exercise mitigated fatigue in men with PCa receiving radiotherapy, but resistance training also produced longer-term improvements; our main hypothesis was partially supported. Resistance training provided additional benefits for QOL, muscular strength, triglycerides, and body fat percentage. Aerobic training preserved aerobic fitness, but unexpectedly, so did resistance training. There was less reduction in PSA with resistance training compared with usual care. Other than for triglyceride levels, no training effects on serum lipid levels were observed.

Between-group differences were the result of a worsening of fatigue in the usual-care group, whereas symptoms remained stable or improved in the exercise groups. The observed 4.1- to 4.8-point improvements in fatigue with exercise intervention are clinically important[16] and are of greater magnitude than the 3.0-point improvement reported previously by our group.[13] They are also similar to the 4.2-point change in FACT-Fatigue associated with a ≥ 2 g/dL increase in hemoglobin after treatment with erythropoietic agents.[18] Given that erythropoietin agents have been associated with thromboembolic complications in anemic patients[19] and are contraindicated in non-anemic patients, it is encouraging that exercise is an effective alternative for managing cancer-related fatigue. Improvements in fatigue were associated with improvements in upper-body strength ($r = .21$; $P = .03$), but not hemoglobin ($r = .14$; $P = .13$). This suggests that exercise training may improve fatigue by improving neuromuscular efficiency and reducing muscular fatigue.[9] Other mechanisms by which exercise might improve fatigue include reduced depression, improved sleep, and increased socialization. It is also possible that the observed effects of training were placebo effects.

To our knowledge, only one other published study[20] has examined the effects of exercise training on fatigue in men receiving similar treatment. Windsor et al[20] randomly assigned 66 men before radiotherapy for PCa either to exercise or control. Moderate-intensity, home-based walking was performed 3 days/wk during radiotherapy. There was a trend toward less fatigue in the exercise group. Another published study has examined the effects of exercise on fatigue in men receiving ADT, but not radiotherapy: Culos-Reed et al[21] found fatigue was significantly reduced after 12 weeks of home-based exercise in an uncontrolled study of 31 men with PCa on ADT. The present study provides strong evidence of the benefits of both resistance and aerobic exercise for mitigating fatigue over the short term during radiotherapy in men with PCa; resistance training also produced longer-term improvements.

Our data showed resistance training improved cancer-specific QOL; however, neither exercise intervention improved PCa-specific concerns related to radiotherapy. Previously, we found resistance training improved PCa-specific QOL measured by the combined FACT-G and FACT-P.[13] In the present study, we divided the FACT-P into its prostate cancer–specific symptom component and the general cancer–specific QOL component, and found that the benefits of resistance training were related to improvement in general cancer–specific QOL. The 4.3- to 4.8-point difference between resistance training and usual care exceeds the minimal clinically important difference of 4.0 points observed in FACT-G.[16]

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Resistance and aerobic training mitigated a reduction in VO_{2peak} compared with usual care. Between-group differences indicated an approximate 5% advantage to either resistance or aerobic training compared with usual care. The relatively modest effect of aerobic training on aerobic fitness may be partially explained by the fact that six usual-care participants "dropped in" to aerobic training, possibly reducing between-group changes in VO_{2peak}. The benefit of resistance training on VO_{2peak} was unexpected. Again, one reason may be the fact that eight resistance training participants reported vigorous aerobic exercise in addition to their assigned training. Resistance training is not generally considered a primary means for developing VO_{2peak}; however, studies evaluating circuit weight training show an average improvement in VO_{2peak} of 6%.[22] With resistance training, upper- and lower-body muscular strength were also improved by 22% and 24%, respectively, compared with usual care. These improvements are somewhat smaller than reported in a previous uncontrolled pilot study of 10 men with PCa on ADT.[23] In our previous 12-week study of resistance training in men with PCa receiving ADT, we found changes in upper- and lower-body muscular fitness averaging 42% and 32%, respectively.[13]

Neither exercise intervention prevented weight gain, but resistance training helped avoid an increase in body fat, a common side effect of ADT.[24] To our knowledge, only one previous study[23] has reported body fat percentage changes on the basis of DEXA analysis during exercise intervention in PCa patients, with no observed change after 20 weeks of resistance training. Using a randomized design and a larger sample size, our study confirms the benefits of resistance training for preserving body composition.

The smaller reduction over time in PSA levels in the resistance training group is probably not clinically important, but caution is warranted. One reason may be that PSA levels in the usual-care group were higher at baseline and had farther to decline during the intervention period. Previous studies of men with PCa participating in resistance training[13,23] have not reported adverse effects on PSA levels. To our knowledge, the present study is the first to provide information on changes in PSA, testosterone, and hemoglobin during aerobic training in men with PCa.

A serious exercise-related adverse cardiovascular event occurred during aerobic exercise. The American College of Sports Medicine[25] recommends symptom-limited exercise stress testing to screen for ischemic heart disease in previously sedentary men age 45 years or older who wish to begin a vigorous exercise program, in men with symptoms of coronary artery disease, or with known cardiac, pulmonary, or metabolic disease. Screening for the presence and severity of cardiovascular disease in men with PCa before embarking on the types of vigorous exercise programs used in this study should be considered.

The strengths of our trial include the comparison of aerobic or resistance exercise training to usual care; the large sample size; the well-defined population; supervised exercise; and a comprehensive assessment of important end points with validated measures, intention-to-treat analysis, and limited loss to follow-up. Limitations include the well-educated, ethnically homogenous sample and the lack of long-term follow-up.

In summary, our trial demonstrates that both resistance and aerobic exercise mitigated fatigue in men with PCa receiving radiotherapy over the short term. Resistance exercise also produced longer-term improvements in fatigue and additional benefits for QOL, muscular strength, triglycerides, and body fat percentage. Resistance and aerobic exercise training use should be considered as supportive care therapies to preserve QOL and vigor in men undergoing radiotherapy for PCa.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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