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ORIGINAL ARTICLE

Effects of Exercise on Cancer-related Fatigue and Quality of Life in Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: A Meta-analysis of Randomized Clinical Trials

Bo Yang* and Jiansheng Wang

Department of Urology, Xixi Hospital of Hangzhou, Hangzhou
310023, China

Key words: exercise; cancer related fatigue; prostate cancer; androgen deprivation therapy; meta-analysis

Objective To gain insight on how exercise affects the outcomes of prostate cancer patients treated with androgen deprivation therapy, specifically cancer-related fatigue (CRF) and quality of life (QoL).

Methods Systematic searches for randomized clinical trials (RCTs) evaluating the effects of exercise on CRF and QoL of prostate cancer patients receiving androgen deprivation therapy were carried out to identify the eligible studies from EMBASE, PubMed and Cochrane library. Related data were extracted from eligible studies and then subjected to Reviewer Manage 5.3 for analysis. Standardized mean differences (SMD) and its 95% confidence interval (CI) were calculated.

Results In all, 10 RCTs involving 841 prostate cancer patients (448 of whom exercised and 393 did not) were included in this study. With respect to CRF, there was good consistency among different studies, and it was remarkably reduced in the exercise group (SMD=-0.32, 95% CI: -0.45 to -0.18, $P<0.00001$, $n=784$). In regards to QoL, there was also good consistency among different studies, and it was also improved significantly in the exercise group (SMD=0.21, 95% CI: 0.08 to 0.34, $P=0.002$, $n=841$).

Conclusion Exercise both reduced CRF and improved QoL in prostate cancer patients receiving androgen deprivation therapy.

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CANCER-RELATED fatigue (CRF) is one of the most frequently reported symptoms in cancer patients,¹ which is also a distressing symptom associated with cancer treatment.² In the past, it was commonly accepted that patients with CRF should limit physical activity; however, there is increasing evidence that exercise brings substantial benefits to cancer patients' physical and mental health.³⁻⁵ Normally, quality of life (QoL) refers to a state of emotional and physical well-being, which can be affected throughout the course of cancer progression and treatment.⁶ Exercise has been shown to improve both physical and mental health; if the psychological and physical status of cancer patients (i.e., QoL) could be improved, it is possible that they will be more prepared to fight off disease. Therefore, exercise has won support from researchers in consideration of improving CRF and QoL of cancer patients.

The incidence of prostate cancer in Western and Northern Europe is high, accompanied by increasing incidence in less developed countries.⁷ Current treatment for prostate cancer mainly relies on androgen deprivation therapy targeting androgen receptor signaling,⁸ which improves both overall and disease-free survival.⁹ However, a prominent side effect of this therapy is decreased QoL, including fatigue.¹⁰ Recently, it was shown that a moderate amount of exercise could ameliorate some of the side effects of androgen deprivation treatment in prostate cancer.¹¹ Similar findings were reported in the study of Bourke *et al*,¹² where pragmatic exercise interventions resulted in health improvements in advanced prostate cancer patients receiving androgen deprivation therapy. Keogh and MacLeod¹³ found similar results, but in the context of group-based exercise with resistance training. Nevertheless, the sample sizes of studies advocating the benefits of exercise to prostate cancer patients undergoing androgen deprivation therapy are comparatively small. In addition, the voting for exercise in these patients suffered some doubts for making such conclusion with inadequate knowledge.¹⁴ Thus, it remains a question whether exercise could counteract some of the bad effects of androgen deprivation therapy.

This meta-analysis was carried out to obtain a pooled assessment of this issue focusing on randomized clinical trials (RCTs). A large population of prostate cancer patients who were receiving androgen deprivation therapy was enrolled. CRF and QoL were determined as the outcome measures. The study may provide valuable information for the future treatment of androgen deprivation therapy related side effects.

MATERIALS AND METHODS

Search strategy

A systematic literature search was conducted in PubMed (1966-2016. 9), EMBASE (1980-2016. 9), Cochrane library (1999-2016. 9) and Chinese journals full-text database (CNKI, 1980-2016. 9) from inception to September 2nd, 2016 to collect RCTs that investigated the influence of exercise on life quality of patients with prostate cancer receiving androgen deprivation therapy. The search strategy included the terms and key words "prostate cancer", "exercise", "physical activity", "resistance", "strength", "stretching", "androgen", and "androgen deprivation therapy". The reference lists of all eligible studies and previous meta-analyses were also screened.

Inclusion and exclusion criteria

Studies were included if they: (1) were RCTs that included adult male participants (≥ 18 years of age) with prostate cancer undergoing androgen deprivation therapy; (2) compared exercise intervention (any types of physical exercise, including aerobic exercise, strength training, flexibility exercises or combinations of these exercises) with no exercise, a usual care without emphasis on physical exercise or an alternative treatment with cancer in prostate cancer patients receiving androgen deprivation therapy; (3) had a primary outcome measure of CRF and QoL measured by validated questionnaires.

Studies were excluded if they: (1) did not report clear diagnosis and criteria of inclusion and exclusion on participants' selection; (2) were involved in other treatments beyond exercise intervention; (3) reported inaccurate or incomplete data and were unable to provide outcomes; (4) were duplicated.

Data extraction

In accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta analyses statement) guidance,¹⁵ two investigators independently extracted the following data from each study using a predefined information sheet: first author, publication year, sample size, duration of follow-up, outcome measures, and relevant baseline data, as well as data for the calculation of effect size. Any discrepancies during data extraction were resolved by discussion with a third investigator.

CRF and QoL served as the primary outcome measures. We considered the following validated tools for the measurement of fatigue levels: the Functional Assessment of Cancer Therapy-Fatigue Scale (FACT-F), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30), and the Fatigue

Severity Scale (FSS). Furthermore, we considered the following validated tools for the measurement of QoL level: the Functional Assessment of Cancer Therapy-Physical Scale (FACT-P), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30), the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), and the Functional Assessment of Cancer Therapy-General Scale (FACT-G). Pooled analysis for secondary outcomes was carried out if at least two studies were available for the outcome.

Quality assessment of the included studies

The quality of each included study was evaluated based on the RCT risk of bias assessment recommended by Cochrane Center (Cochrane Handbook version 5.1.0).¹⁶ Evaluation of the entries included the following seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each entry was then classified as low risk, unclear risk, or high risk.

Statistical analysis

Where possible, data were used to calculate the mean difference (MD) using the mean for continuous outcomes with the number of participants as the denominator for each outcome. When different scales were used, the standardized MD (SMD) was calculated. When the standard deviation (SD) of the change scores was not given, they were imputed using the SD from similar studies.

The heterogeneity across studies was examined by the

Cochran's Q statistic and the I^2 statistic.¹⁷ Fixed effects model was selected for homogeneous outcomes ($P \geq 0.05$ and $I^2 < 50\%$) and random effects model was applied for heterogeneous outcomes ($P < 0.05$ or $I^2 \geq 50\%$). SMD with 95% confidence intervals (CI) were calculated. Moreover, to evaluate the influence of each study on the overall outcome, sensitivity analysis was carried out by omitting each study at a time. Data analyses were performed with the Review Manager 5.3 version software (RevMan version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). A P -value ≤ 0.05 was considered to be statistically significant. All P values and 95% CIs were two-sided.

RESULTS

Search results

The process of study selection is shown in Figure 1. Finally, a total of 10 RCTs published between 2003 and 2015 were included in the present meta-analysis.^{11, 18-26}

Characteristics of the included studies

The characteristics of included studies are depicted in Table 1. In total, 841 prostate cancer patients (randomized population, 448 in the exercise group and 393 in the control group) receiving androgen deprivation therapy were involved in this meta-analysis. Mean participant ages ranged from 65 to 72 years, sample sizes ranged from 50 to 155 participants, and follow-up time varied from 12 weeks to 6 months. Treatment status of androgen deprivation therapy and characteristics of exercise intervention were varied among all studies.

Figure 1. Flow diagram of study inclusion strategy.

Table 1. Characteristics of included studie

Studies	Sample size	Mean age ^s (yrs)	ADT status	Exercise interventions	Control interventions	Outcome measures	Follow-up
Bourke <i>et al</i> ¹⁸	Exercise: 25	71.3±6.4	≥6 months ADT	12-week lifestyle intervention combined with supervised and self-directed exercise with dietary advice	Usual care	Fatigue [FACT-F]	12 weeks
	Control: 25	72.2±7.7				QoL [FACT-P]	
Bourke <i>et al</i> ¹⁹	Exercise: 43	71±6	≥6 months ADT	12-week lifestyle intervention consisting of aerobic and resistance exercise with parallel dietary advice	Usual care	Fatigue [FACT-F]	12 weeks
	Control: 43	71±8				QoL [FACT-P]	
Buffart <i>et al</i> ²⁰	Exercise: 29	69.7±7.3	≥2 months ADT	12-week lifestyle intervention consisting of aerobic and resistance exercise (program of chest press, seated row, shoulder press, triceps extension, leg press, leg extension, leg curl, and abdominal crunch)	Usual care	Fatigue [EORTC, QLQ-C30]	12 weeks
	Control: 28	70.1±7.3				QoL [SF-36]	
Cormie <i>et al</i> ²¹	Exercise: 32	69.6±6.5	≥3 months ADT	Twice weekly exercise sessions for 3 months consisting of an aerobic and resistance exercise program with parallel dietary advice	Usual care	Fatigue [FACT-F]	3 months
	Control: 31	67.1±7.5				QoL [SF-36]	
Culos-Reed <i>et al</i> ¹¹	Exercise: 53	67.2±8.8	≥6 months ADT	16-week supervised and unsupervised program of walking, stretching, light resistance and core strengthening	Usual care	Fatigue [FSS]	16 weeks
	Control: 476	68.0±8.4				QoL [EORTC-QOLC-30]	
Galvão <i>et al</i> ²²	Exercise: 29	69.5±7.3	≥2 months ADT,	12-week combined progressive resistance and aerobic training	Usual care	QoL [SF-36]	12 weeks
	Control: 28	70.1±7.3	Continuing for subsequent 6 months				

Studies	Sample size	Mean age ^s (yrs)	ADT status	Exercise interventions	Control interventions	Outcome measures	Follow-up
O'Neill <i>et al</i> ²³	Exercise: 47	69.7±6.8	≥6 months ADT	Walk at a brisk pace for at least 30 minutes per day, five or more days per week in line with UK physical activity guidelines for 6 months, and consume a diet commensurate with UK healthy eating guidelines	Usual care	Fatigue [FSS]	
	Control: 47	69.9±7.0				QoL [FACT-P]	
Segal <i>et al</i> ²⁴	Exercise: 82	68.2±7.9	≥3 months ADT	12-week program of 9 strength training exercises carried out under supervision 3 times per week	Usual care	Fatigue [FACT-F]	12 weeks
	Control: 73	67.7±7.5				QoL [FACT-P]	
Segal <i>et al</i> ²⁵	Resistance exercise: 40	66.4±7.6	≥16 weeks ADT	Resistance exercise: 24-week program of three sessions per week performing two sets of 8-12 repetitions of 10 different exercises	Usual care	Fatigue [FACT-F]	24 weeks
	Aerobic exercise: 40	66.2±6.8				QoL [FACT-G]	
	Control: 41	65.3±7.6					
Nilsen <i>et al</i> ²⁶	Exercise: 28	66 (range, 54-76)	2-6 months after the initiation of neo-adjuvant ADT, followed by 9-36 months adjuvant ADT	16-week program of 9 strength training exercises carried out under supervision 3 times per week	Usual care	Fatigue [EORTC-QOLC-30]	16 weeks
	Control: 30	66 (range, 54-76)				QoL [EORTC-QOLC-30]	

§: Plus-minus values are means±SD.

ADT: androgen deprivation therapy; FACT-F: Functional Assessment of Cancer Therapy-Fatigue Scale; FACT-P: Functional Assessment of Cancer Therapy-Physical Scale; EORTC-QOLC-30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30; QoL: quality of life; SF-36: The Medical Outcomes Study 36-Item Short Form Health Survey; FACT-F: Functional Assessment of Cancer Therapy-Fatigue Scale; FSS: Fatigue Severity Scale; FACT-G: Functional Assessment of Cancer Therapy-General Scale.

A summary of the bias risk of included studies is presented in Figure 2. Because of the nature of the interventions (self-report nature of subjective outcomes), most studies have high risk in the aspects of blinding of participants and intervention providers, except for two studies that were double-blinded.^{21, 23} There were two studies that referred to randomization, but no description was provided about how randomization was carried out,^{11, 20}

while other studies used a computer-generated random digital packet.^{18-19, 23-26} Overall, the studies enrolled in this meta-analysis had moderate quality.

Quantitative data analysis

CRF and QoL were reported in 9 studies and 10 studies, and the SD of the change scores were given in studies. The SMD and forest plot of pooled analysis is shown in Figure 3.

Figure 2. Analysis of bias risk of eligible studies.

Methodological quality summary-marks of interpretation: "+", low risk of bias; "-", high risk of bias; "?", unclear risk of bias.

Figure 3. Forest plot of cancer related fatigue and QoL in the exercise and non-exercise groups.

A. results for cancer related fatigue; B. results for QoL.

for resistance exercise; * for aerobic exercise.

SD: standard deviation; CI: confidence interval.

The fixed effects models were used to pool the CRF and QoL data, since there was no significant heterogeneity found between studies (CRF: $P=0.13$, $I^2=35\%$; QoL: $P=0.60$, $I^2=0$). The pooled results suggested significantly improved CRF ($SMD=-0.32$, 95% CI : -0.45 to -0.18 , $P<0.00001$, $n=784$) and QoL ($SMD=0.21$, 95% CI : 0.08 to 0.34 , $P=0.002$, $n=841$) in prostate cancer patients receiving androgen deprivation therapy and programmed exercise.

Sensitivity analysis

Sensitivity analysis was conducted by omitting one study at a time (Table 3). The pooled result for CRF was altered when omitting the study of Bourke *et al*¹⁹ or O'Neill *et al*.²³ Notably, more significantly improved results were obtained after omitting the study of Segal *et al*.²⁵ On the other hand, for QoL, the pooled result was not altered remarkably in the omission of any single study.

DISCUSSION

For cancer survivors, CRF is a common symptom, presenting as tiredness and exhaustion. The fatigue imposes on the patients' life quality by interfering with physical and mental performance. Some research has revealed that exercise is an effective intervention for increasing psychological well-being during and following cancer treatment. In this study, by pooling the data from 10 eligible studies, exercise intervention improved both CRF and QoL in prostate cancer patients undergoing androgen deprivation therapy.

For older adults and cancer patients, exercise is comparatively less expensive and complicated than radiation and chemical approaches to treating disease, with the added bonus of mental and social benefit.²⁷ It increases muscular endurance and strength, as well as cardiorespiratory fitness, which then stimulates the improvement in overall functional performance. The ability of cancer patients to lead an independent life is critical to their battle with the disease, and prevents additional complications from setbacks such as falling and other illness.²⁸ Gardner *et al*²⁹ conducted a systematic review in an attempt to make a comprehensive evaluation of exercise on patients receiving androgen deprivation therapy for prostate cancer. Ten RCTs and uncontrolled trials were investigated, and exercise was demonstrated to be effective in reducing androgen deprivation therapy induced fatigue.

There are some limitations in the current analysis. Firstly, different types of exercise were carried out in the included 10 studies. The studies were different in terms of exercise intensity, frequency, and intervention duration. Secondly, some newly published articles were not included in this study due to the lack of sufficient data. Therefore, the results of the current findings should be cautiously interpreted.

Our results provide additional evidence that exercise interventions significantly improve CRF and QoL for prostate cancer patients receiving androgen deprivation therapy. Further RCTs with consistent methodological quality need to be conducted in order to fully investigate the effect of various exercise types on the lives of cancer patients.

Table 3. Results of sensitivity analysis

Omitting study	CRF (fixed model)	QoL (fixed model)
	SMD (95% CI), P heterogeneity, I ² , n	SMD (95% CI), P heterogeneity, I ² , n
Bourke <i>et al</i> ¹⁸	-0.28 (-0.42 to -0.14), 0.32, 14%, 734	0.20 (0.07 to 0.34), 0.53, 0, 791
Bourke <i>et al</i> ¹⁹	-0.31 (-0.45 to -0.16), 0.09, 41%, 698	0.18 (0.04 to 0.32), 0.68, 0, 755
Buffart <i>et al</i> ²⁰	-0.27 (-0.41 to -0.13), 0.48, 0, 727	0.19 (0.05 to 0.33), 0.63, 0, 784
Cormie <i>et al</i> ²¹	-0.32 (-0.46 to -0.17), 0.09, 42%, 721	0.24 (0.1 to 0.38), 0.81, 0, 778
Culos-Reed <i>et al</i> ²¹	-0.33 (-0.48 to -0.18), 0.09, 41%, 684	0.20 (0.06 to 0.34), 0.51, 0, 741
Galvão <i>et al</i> ²²	-	0.19 (0.05 to 0.33), 0.63, 0, 784
O'Neill <i>et al</i> ²³	-0.32 (-1.47 to -0.17), 0.09, 42%, 690	0.23 (0.09 to 0.37), 0.60, 0, 747
Segal <i>et al</i> ²⁴	-0.36 (-0.51 to -0.21), 0.14, 34%, 629	0.22 (0.07 to 0.36), 0.51, 0, 686
Segal <i>et al</i> ²⁵	-0.32 (-0.48 to -0.17), 0.06, 49%, 663	0.22 (0.07 to 0.36), 0.41, 2%, 720
Nilsen <i>et al</i> ²⁶	-0.34 (-0.49 to -0.20), 0.15, 33%, 726	0.22 (0.08 to 0.36), 0.55, 0, 783

SMD: standardized mean difference; CRF: cancer-related fatigue; n: sample size; -: no data.

REFERENCES

1. Brown JC, Huedo-Medina TB, Pescatello LS, et al. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2011; 20:123-33.
2. Janda M, Gerstner N, Obermair A, et al. Quality of life changes during conformal radiation therapy for prostate carcinoma. *Cancer* 2000; 89:1322-8.
3. Kruijsen-Jaarsma M, Révész D, Bierings MB, et al. Effects of exercise on immune function in patients with cancer: a systematic review. *Exerc Immunol Rev* 2013; 19:120-43.
4. Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. *Brain Behav Immun* 2013; 30:S75-87.
5. Courneya KS, Segal RJ, McKenzie DC, et al. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med Sci Sports Exerc* 2014; 46:1744-51.
6. Victorson D, Barocas J, Song J, et al. Reliability across studies from the functional assessment of cancer therapy-general (FACT-G) and its subscales: a reliability generalization. *Qual Life Res* 2008; 17:1137-46.
7. Baade PD, Youlten DR, Cramb SM, et al. Epidemiology of prostate cancer in the Asia-Pacific region. *Prostate Int* 2013; 1:47-58.
8. Schroeder A, Herrmann A, Cherryholmes G, et al. Loss of androgen receptor expression promotes a stem-like cell phenotype in prostate cancer through STAT3 signaling. *Cancer Res* 2014; 74:1227-37.
9. Alberga AS, Segal RJ, Reid RD, et al. Age and androgen-deprivation therapy on exercise outcomes in men with prostate cancer. *Support Care Cancer* 2012; 20:971-81.
10. Shahinian VB, Kuo Y-F, Freeman JL, et al. Risk of the "androgen deprivation syndrome" in men receiving androgen deprivation for prostate cancer. *Arch Intern Med* 2006; 166:465-71.
11. Culos-Reed SN, Robinson JW, Lau H, et al. Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention. *Support Care Cancer* 2010; 18:591-9.
12. Bourke L, Doll H, Crank H, et al. Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: a feasibility study. *Cancer Epidemiol Biomarkers Prev* 2011; 20:647-57.
13. Keogh JW, MacLeod RD. Body composition, physical fitness, functional performance, quality of life, and fatigue benefits of exercise for prostate cancer patients: a systematic review. *J Pain Symptom Manage* 2012; 43:96-110.
14. Winters-Stone KM, Beer TM. Review of exercise studies in prostate cancer survivors receiving androgen deprivation therapy calls for an aggressive research agenda to generate high-quality evidence and guidance for exercise as standard of care. *J Clin Oncol* 2014; 32:2518-9.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; 151:W65-94.
16. Higgins J, Green S. *Cochrane handbook for systematic reviews of interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from: www.cochrane-handbook.org
17. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557-60.
18. Bourke L, Doll H, Crank H, et al. Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: a feasibility study. *Cancer Epidemiol Biomarkers Prev* 2011; 20:647-57.
19. Bourke L, Gilbert S, Hooper R, et al. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. *Eur Urol* 2014; 65:865-72.
20. Buffart LM, Galvão DA, Mai JC, et al. Mediators of the resistance and aerobic exercise intervention effect on physical and general health in men undergoing androgen deprivation therapy for prostate cancer. *Cancer* 2014; 120:294-301.
21. Cormie P, Galvão DA, Spry N, et al. Can supervised exercise prevent treatment toxicity in prostate cancer patients initiating androgen deprivation therapy: a randomised controlled trial. *BJU International* 2014; 115:256-66.
22. Galvão DA, Taaffe DR, Spry N, et al. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol* 2010; 28:340-7.
23. O'Neill RF, Haseen F, Murray LJ. A randomised controlled trial to evaluate the efficacy of a 6-month dietary and physical activity intervention for patients receiving androgen deprivation therapy for prostate cancer. *J Cancer Surviv* 2015; 9:431-40.
24. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2003; 21:1653-9.
25. Segal RJ, Reid RD, Courneya KS, et al. Randomized

- controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol* 2009; 27:344-51.
26. Nilsen TS, Raastad T, Skovlund E, et al. Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. *Acta Oncologica* 2015; 54:1-9.
27. Floyd A, Moyer A. Group *versus* individual exercise interventions for women with breast cancer: a meta-analysis. *Health Psychol Rev* 2010; 4:22-41.
28. Sherrington C, Whitney JC, Lord SR, et al. Effective exercise for the prevention of falls: a systematic review and meta-analysis. *J Am Geriatr Soc* 2008; 56:2234-43.
29. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. *J Clin Oncol* 2014; 32:335-46.