



# Impact of Physical Exercise Program Interventions on Erectile Function and Cardiovascular Health in Males with Prostate Cancer

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Prostate cancer (PC) and its associated treatments can cause significant cardiovascular and sexual dysfunctions. While structured exercise interventions can induce positive outcomes in males with PC, there are limited data on its effects on cardiovascular health, erectile function, or the combination of these outcomes. It has been proposed that positive changes in biomarkers of cardiovascular health through physical exercise programs, can result in cardiovascular remodelling and improve penile haemodynamic and erectile function recovery in those with metabolic syndrome and/or cardiovascular diseases, although the data is accruing in males who are diagnosed and/or treated for PC. While the results of this review article support structured physical exercise interventions to effectively prevent and mitigate the development of both sexual and cardiovascular dysfunctions in males with PC, appropriate caution should be maintained and future clinical research should focus on the development of standardised and evidence-based exercise guidelines in the setting of PC survivorship.

**Keywords:** Cardiovascular system; Erectile dysfunction; Exercise; Prostate cancer; Treatment outcomes

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## INTRODUCTION

Prostate cancer (PC) is a common malignancy and its associated treatments often result in various complications including male sexual dysfunction [1,2]. Similar to the higher incidence of PC with age, older males are more likely to report erectile dysfunction (ED) too [1,3]. There is a strong association between ED and cardiovascular disease (CVD) [4,5] since they share similar risk factors and pathophysiologic mechanisms [6,7]. The use of androgen deprivation therapy (ADT) in males with PC has been shown to increase subsequent risk of

CVD due to adverse changes in body composition, metabolic profile, vascular hemodynamic, and biomarkers [6,7].

Published literature shows that a significant proportion of males with PC on active surveillance have ED [2] whilst those undergoing active PC treatment invariably have a higher rate of male sexual dysfunction [2,8]. Furthermore, there is a higher rate of cardiovascular-related morbidity and mortality in males who receive ADT [9]. Some of the proposed pathophysiologic mechanisms for ED relating to various PC treatments include neurovascular injury, inflammatory changes,

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damage to surrounding structures, corporal hypoxia, and penile fibrosis, the adverse impact from urinary or bowel complications, as well as alterations in metabolic profile, psychosocial and relationship dynamics [8].

Penile rehabilitation is accepted as the standard of care in males following radical prostatectomy [10,11] and there is growing evidence to advocate its role in males receiving radiation therapy and ADT too [12]. While established pharmacotherapy for penile rehabilitation can be effective in restoring erectile function (EF), they may not affect underlying endothelial dysfunction which is thought to be the underlying basis for ED. Several publications have highlighted the role of lifestyle interventions and modification of these metabolic factors could improve CVD and alleviate ED [13-16]. In general, aerobic exercise involves endurance-type exercise for a sustained period and increases physical endurance and cardiac health; while anaerobic exercise consists of short, intensive levels of physical activity that improves muscle mass and strength [17,18]. There is some evidence that shows these physical activity interventions can improve sexual function in the cancer population [16,17] although its effects on cardiovascular health, EF, or the combination of these outcomes are uncertain in PC males [18,19]. The following review article examines the current understanding of the role of physical exercise program interventions on EF recovery and cardiovascular remodelling in males with PC.

## **METHODS AND MATERIALS**

This review included research on ED and physical exercises in males with PC. Original articles, narrative reviews, systematic review and meta-analysis was undertaken on PUBMED search up to December 2020 based on the following keywords namely “erectile dysfunction”, “structured exercise program”, “cardiovascular”, “biomarkers”, and “prostate cancer”. This paper is not designed to provide systematic review or meta-analysis on this subject, nor offer a detailed description of each structured physical exercise program interventions in PC management.

## **CLINICAL EVIDENCE ON CARDIOVASCULAR REMODELLING AND ERECTILE FUNCTION RECOVERY FOLLOWING PHYSICAL EXERCISE PROGRAM INTERVENTIONS (TABLE 1)**

While the positive impact of physical activity on cardiometabolic modifications [20,21] and EF [16,22] are well established, there are limited well-designed clinical trials are analysing the effects of structured exercise interventional programs on sexual function in PC populations whether it is pre-treatment or following radical prostatectomy, radiation therapy, or ADT [23-25]. It has been proposed that changes in biomarkers of cardiovascular health through physical exercise programs can improve penile haemodynamic and alleviate sexual dysfunction [26]. A recent systematic review [16] highlighted that a supervised exercise training with moderate-to-vigorous exercise intensity may be effective in improving EF in clinical populations such as those with metabolic syndrome and/or CVDs, although this did not include PC males.

Published literature in this field that evaluates the relationship between physical activity and sexual function in males with PC have reported mixed findings. Among males who had completed active treatment (surgery, or surgery and radiation therapy), no significant between-group differences were observed for sexual function for either the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and its PC-specific module (EORTC QLQ-PR25) (-5.8,  $p=0.412$ ) or the International Index of Erectile Function (IIEF)-5 scores (-2.8,  $p=0.431$ ) at 15 months despite low-to-moderate intensity supervised aerobic and resistance exercise training [27]. Both the exercise and control groups experienced a significant improvement in sexual function as assessed by the EORTC QLQ-PR25 (+9.8,  $p=0.008$  and +15.6,  $p=0.008$ , respectively), but not in the IIEF-5 (both  $p>0.05$ ).

Preoperative exercise program on sexual function did not significantly improve EF in males who underwent radical prostatectomy at 6 months [28]. The same group [29] did not observe any acute effect of exercise on the cortical silent period on neuroimaging study that reflects self-reported vigour and positive mood. In a non-linear aerobic training study in males following radical

**Table 1.** Physical exercise program interventions on cardiovascular remodelling and erectile function recovery in male who received treatment for prostate cancer

Study (reference)	Type of prostate cancer treatment	Type of physical exercise program	Study design	Erectile function outcome	Cardiovascular parameters
Zoft et al [27]	Post-radical prostatectomy	Multi-modal intensity exercise	15-month program; randomised trial with 56 males received exercise and 29 males in control group	Improved IIEF-5 (p=0.008)	Improved VO <sub>2</sub> peak (p=0.018)
Mina et al [28]	Pre-radical prostatectomy	Physical activity guidelines per American College of Sports Medicine	Non-blinded (retrospective); 234 males met vs. 275 not met guideline	Improved erectile function (p=0.049)	Not reported
Jones et al [30]	Post-radical prostatectomy	Aerobic exercise	Randomised trial, 25 males in each group	Improved IIEF-5 (p=0.406)	Improved VO <sub>2</sub> peak (p=0.017) and FMD (p=0.07)
Dahn et al [31]	Radiation	Normal physical activity	11 males non-randomised	Improved IIEF-5 (better for EBRT than brachytherapy)	No data
Ben-Josef et al [32]	Radiation	Twice-weekly yoga class	Randomised trial, 22 received yoga and 28 in control group	Improved IIEF-5 (p=0.033)	No data
Dieperink et al [33]	Radiation and androgen deprivation therapy	Pelvic floor exercise	Randomised trial, 79 received physical therapist and 82 in control group	Improved sexual function	Improved SF-12 physical component summary (p=0.002)
Cormie et al [34]	Androgen deprivation therapy	Aerobic and resistance exercise	Randomised trial, 29 in active group and 28 in control group	Improved sexual activity (p=0.045)	No data
Cormie et al [35]	Androgen deprivation therapy	Aerobic and resistance exercise	Randomised trial, 32 in active group and 31 in control group	Improved sexual function (p=0.028)	Improved VO <sub>2</sub> peak (p=0.004), muscular strength (p≤0.026), and total cholesterol: high-density lipoprotein-cholesterol ratio (p=0.028)
Pernar et al [36]	Newly diagnosed prostate cancer	Walking exercise	Randomised trial, 21 in walking group and 20 in control group		Improved high-density lipoprotein (p=0.04), low-density lipoprotein (p=0.08), and systolic blood pressure (p=0.18).

IIEF: International Index of Erectile Function, VO<sub>2</sub> peak: peak oxygen uptake, FMD: brachial artery flow-mediated dilation, EBRT: external beam radiation therapy, SF-12: quality-of-life Short-form-12 questionnaire.

prostatectomy, Jones et al [30] reported that the prevalence of ED (IIEF score  $\leq 21$ ) decreased by 20% in the aerobic training group with significant between-group differences were observed for changes in brachial artery flow-mediated dilation and peak oxygen uptake ( $VO_{2peak}$ ), favouring aerobic training, although there were no group differences in other markers of cardiovascular risk profile or patient-reported outcomes.

For males who received radiation therapy, Dahn et al [31] observed males who maintained habitual physical activity levels were more likely to respond to erectile drugs, and those who had external beam radiation therapy for PC fared better than males who receive brachytherapy or combination treatments. Similarly, Ben-Josef et al [32] showed that a twice-weekly yoga class was associated with a significant reduction in pre-existing and radiation therapy-related sexual dysfunction in males who had external beam radiation therapy. On the other hand, a home-based 20-week pamphlet-based pelvic floor strengthening and resistance training intervention in males who had completed radiation therapy four weeks before study randomisation, did not result in any significant improvement on sexual function, as assessed by the Expanded Prostate Cancer Index Composite (EPIC)-26 scores ( $p=0.117$ ) [33].

In the group of males on ADT who underwent a 12-week twice-weekly supervised moderate-to-vigorous intensity aerobic and resistance exercise training intervention, combined with home-based aerobic exercise training, Cormie et al [34] found the exercise group maintained good sexual activity scores, especially on sexual libido pre- to post-intervention, whereas control group participants experienced a worsening in sexual activity over the same study period. Non-linear exercise program involving aerobic and resistance exercise when initiating ADT has been shown to significantly reduce treatment toxicity while improving social functioning and mental health [35]. Sexual activity did decrease in both groups, but to a lesser extent in the exercise group. Blood pressure parameters were maintained in the exercise group, while the control group did experience a significant increase in diastolic blood pressure.

A more sedentary exercise program by Pernar et al [36] also did not show significant between-group improvements in blood pressure parameters or sexual function (based on a visual analogue scale with the

associated question '*Do you have problems with your sex life?*'). Interestingly, this study observed a non-significant within-group reduction in sexual function in the walking group (+25.8%) and non-significant within-group improvement in the usual care group (-28.6%) which may be explained in part by the self-reported level of social support provided to participants by their partners. Perceptions of both partner support and patient self-confidence in performing sexual activities may support the explanation for the above-mentioned clinical finding. Couple-based approaches with the involvement of the partner in exercise programs engage males and females as equal to improve their own and their partner's physical health and allow for relationship-focus strategies [37-39]. This in turns may improve physical intimacy and other relational outcomes. Integration of pharmacotherapy and couple-based psychotherapy with structured exercise programs has been shown to enhance sexual outcomes too [40].

Collectively, the above-mentioned articles suggest that structured physical exercise interventions have a positive effect on cardiovascular health and can be effective in promoting improvements in sexual function in males with PC. Whether it is supervised higher-intensity aerobic exercise or more casual physical activity, the beneficial changes in sexual health outcomes should encourage adoption of these exercise interventions as a standard of care in PC survivorship. Nonetheless, it should be acknowledged that male sexual dysfunction in males with PC is a complex interplay of various factors beyond just penile erection and cardiovascular dysfunction [8]. Alterations in urinary and bowel functions, coupled with changes in psychosocial and relationship dynamics can affect sexual function in males following PC treatment [2].

Further clinical trials should explore various exercise interventions of differing durations, intensities and frequencies to identify the optimal exercise 'dose' for maximum positive effects on cardiovascular remodeling and sexual health in PC populations. The adoption of consistent, formal standards for methods and data reporting in exercise testing is needed to ensure high-quality research in the field of clinical oncology. The engagement of highly-trained allied health professionals with appropriate qualifications in sexual health and rehabilitation [41] are required to personalise these physical interventions for optimal clinical outcomes. Additional studies incorporating more novel biomark-

ers of CVD coupled with more objective evaluations of sexual function including use of penile colour Duplex ultrasonography or cortical neuroimaging study [42] should be conducted to further delineate the effects of physical activity on CVD risk remodelling and recovery of sexual function in this population.

## CONCLUSIONS

Treatments for PC can cause significant cardiovascular and sexual dysfunctions. Physical exercise program interventions have a positive impact on cardiovascular remodelling and sexual function in men, and PC survivors should be encouraged to be physically active. While the results of this review article support structured physical exercise interventions to effectively prevent and mitigate the development of both sexual and cardiovascular dysfunctions in PC patients, appropriate caution should be exercised due to significant heterogeneity in exercise intervention designs and studied PC groups within the included articles. Further research is needed to develop standardised and evidence-based exercise guidelines to optimise the prevention and mitigation of cardiovascular and sexual dysfunctions in the setting of PC survivorship.

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## Conflict of Interest

The authors have nothing to disclose.

## Author Contribution

Conceptualization: EC. Data curation: EC, HR. Formal analysis: EC, HR. Methodology: EC, HR. Supervision: EC. Writing – original draft: EC. Writing – review & editing: EC, HR.

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