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Review Article

The Impact of Exercise during Radiation Therapy for Prostate Cancer on Fatigue and Quality of Life: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Radiation therapy (RT) is clinically proven to improve survival in men with prostate cancer. Despite these advantages, it is known to cause adverse effects such as fatigue. This review proposes to summarize the totality of evidence from randomized controlled trials regarding the effectiveness of exercise on fatigue in men with prostate cancer as a primary outcome. Quality of life was a secondary outcome.

Methods: RCTs that explored the effect of exercise during RT on fatigue for men with prostate cancer were searched using MEDLINE, Embase, CINAHL, Cochrane Library, AMED, ClinicalTrials.gov, and ISRTCN registry. Reference lists of included studies and reviews were also examined. Trials were excluded if they included a mixed cohort of patients where data could not be extracted for prostate cancer patients alone or if the intervention took place after RT had finished. Preferred Reporting Items for Systematic Reviews and Meta-Analyses standardized reporting guidelines were followed to ensure the standardised conduct and reporting of the research.

Results: The search strategy yielded a total of 278 studies, of which five met the inclusion criteria. A meta-analysis pooled data of 392 participants using the Cochrane Review Manager 5.3 random-effects model (DerSimonian-Laird approach) with the post-test means of the control and intervention groups and associated standard deviations. Exercise was significant at alleviating fatigue when compared to the control group (standardized mean differences, −1.03; 95% confidence interval, −1.82 to −0.24).

Conclusion: Exercise during RT is an effective approach to alleviate fatigue in men with prostate cancer. The effect on quality of life was not significant, possibly because of considerable heterogeneity across studies.

RÉSUMÉ

Introduction/contexte : Il a été cliniquement démontré que la radiothérapie augmente le taux de survie chez les hommes ayant un cancer de la prostate. Malgré ces avantages, on sait aussi qu'elle a des effets secondaires, comme la fatigue. Cette étude propose de résumer l'ensemble des données probantes provenant des essais randomisés contrôlés (ERC) concernant l'efficacité de l'exercice sur la fatigue chez les hommes ayant un cancer de la prostate comme premier résultat. La qualité de vie était un résultat secondaire.

Méthodologie : les ERC qui explorent les effets de l'exercice durant un traitement de radiothérapie ont fait l'objet d'une recherche dans MEDLINE, EMBASE, CINAHL, Cochrane Library, AMED, ClinicalTrials.gov et le registre de l'ISRTCN. Les listes référencées d'études et d'examen ont également été examinées. Les essais étaient exclus s'ils comprenaient une cohorte mixte de patients dont il n'était pas possible d'extraire les données pour les seuls patients atteints d'un cancer de la prostate ou si l'intervention a eu lieu après la fin des traitements de radiothérapie. Les lignes directrices normalisées de PRISMA pour l'établissement de rapports ont été suivies pour assurer que la conduite de la recherche et l'établissement du rapport soient faits de façon normalisée.

Résultats : La stratégie de recherche a produit 278 résultats, dont cinq études répondant aux critères d'inclusion. Une méta-analyse a permis de regrouper les données de 392 patients à l'aide du modèle d'effets aléatoires de Cochrane Review Manager 5.3 (approche de DerSimonian-Laird) avec un contrôle postérieur de la moyenne du groupe de contrôle et du groupe d'intervention, avec les écarts-types connexes. L'exercice a eu un effet marqué sur l'atténuation de la fatigue en comparaison du groupe de contrôle (SMD −1,03, 95% IC −1,82, −0,24).

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Conclusion : L'exercice durant un traitement de radiothérapie constitue une approche efficace pour atténuer la fatigue chez les hommes atteints d'un cancer de la prostate. L'effet sur la qualité de vie n'était pas significatif, possiblement en raison d'une forte hétérogénéité entre les études.

Keywords: Exercise; prostate cancer; radiotherapy; fatigue; quality of life

Introduction

Prostate cancer is the second most common cancer diagnosed in men worldwide [1]. In 2012, there were an estimated 307,500 mortalities related to prostate cancer, making it the fifth most common cause of death from cancer in men globally [1]. Active treatment strategies vary depending on the extent of the disease, but radiation therapy with or without androgen deprivation therapy (ADT) is widely used across all risk groups as per National Comprehensive Cancer Network guidelines.

Despite the benefits of radiation therapy (RT), it is associated with various adverse effects for patients, including gastrointestinal and genitourinary problems as well as fatigue. Some studies report fatigue as the most common side effect of RT [2,3]. It is general consensus that cancer-related fatigue (CRF) increases in severity in the proportion of 78%–89% of patients during RT [2,4]. CRF is described as the "subjective sensation of lacking energy or being exhausted because of cancer or cancer treatment that is not proportional to recent activity and interferes with daily activities" [5]. Adverse effects such as fatigue are also commonly reported with ADT [5] and can therefore worsen fatigue experienced by patients undergoing combined RT and ADT [6].

Presently, the causes for CRF are not fully understood. Investigations have found correlations of fatigue with hemoglobin [7] and albumin [8] levels as well as psychological conditions such as depression [9]. Though biological conditions such anaemia are predictors for CRF [10], they do not completely explain the occurrence of CRF in the cancer population [11]. One hypothesis of the cause of CRF during RT is the activation of the proinflammatory cytokine network and subsequent increases in biomarkers of proinflammatory cytokine activity caused by RT [11].

In the past, cancer patients who experienced fatigue as a treatment side effect were often advised to avoid strenuous activities and take rest by health care professionals [10]. Dimeo et al. [12] reported that rest is likely to be counterproductive at alleviating fatigue as inactivity leads to muscle wasting and reduced cardiorespiratory fitness, both of which increase fatigue. To this end, several studies have explored the benefits of exercise on CRF. Recent reviews, the majority of which were conducted on breast cancer, have shown benefits of physical activity on fatigue [13–15].

A Cochrane review [16] of 4,068 participants across 56 trials examining breast, prostate, hematological, colorectal, and head and neck cancers found that aerobic exercise significantly reduced fatigue, but resistance training and other forms of exercise did not have a statistically significant effect. A possible reason for this was the smaller sample of participants that underwent resistance training. This review was not specific to RT nor prostate cancer patients. In addition, it included RCTs where the exercise intervention was carried out after treatment was completed. The authors recommended further research to be carried out to establish the optimum type, intensity, and timing of an exercise intervention.

The primary aim of this review was to systematically search, select, appraise, and synthesise the evidence from RCTs focusing on the effects of exercise on fatigue during RT among men with prostate cancer, using meta-analysis. The results of this review may determine the optimal exercise prescription parameters for these men during RT.

Methods

Search Strategy for Identification of Studies

See Appendix A for detailed search strategy.

The following databases were searched for relevant RCTs, from the initiation of each individual database:

- MEDLINE (1966 to 03/10/16)
- EMBASE (1980 to 03/10/16)
- CINAHL (1982 to 03/10/16)
- AMED (1985 to 03/10/16)
- Cochrane Library (1993 to 03/10/16)
- ClinicalTrials.gov
- ISRTCN Registry

A manual search of reference lists of the included trials and review articles relating to exercise and prostate cancer radiotherapy was also carried out.

Type of Studies

Only randomized controlled trials (RCT's) including cluster and quasi trials were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses [17] standardised reporting guidelines were followed to ensure the standardised conduct and reporting of the research.

Type of Participants

Eligible trials included participants above 18 years of age, with histologically confirmed stage I–IV prostate cancer, actively receiving RT with or without adjuvant hormone therapy. Trials were deemed unsuitable if participants had already completed RT.

Trials with a mixed cohort of cancer patients where data could not be extracted for prostate cancer alone were excluded.

Type of Interventions

Trials assessing the impact of exercise that is defined as "a physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" [18] were included. Aerobic exercise, resistance training, qigong, tai chi, yoga, and Pilates interventions were therefore eligible.

Eligible trials examined the effects of exercise during RT and not after RT. The intervention could take place in any setting (home-based or supervised).

Included trials compared exercise with usual care (routine treatment received by patients for disease) or no exercise. Studies that investigated an exercise programme accompanied by attempts to promote participant engagement were included (eg, waitlist controls).

Exercise interventions for each study were analysed to establish their efficacy in providing an adequate training stimulus. Type, duration, intensity, and frequency of the intervention were assessed. Analysis of training stimuli followed the American College for Sport Medicine (ACSM) for exercise testing and prescriptions and the Physical Activity Guidelines for Americans as recommended by ACSM for prostate cancer survivors [19]. Exercise interventions were considered adequate if 3 of 4 predefined requirements were met, as per previous review [20].

Type of Outcomes

Fatigue was assessed as the primary outcome in this review. Health-related quality of life (QOL) was assessed as a secondary outcome in this study. Quality of life (QOL) was measured using self-reported questionnaires such as the Functional Assessment of Cancer Therapy: FACT-G (FACT-An, FACT-B, FACT-C, FACT-P), EORTC-QLQ-30, expanded prostate cancer index composite, or the Short Form (36) Health Survey (SF-36).

Methodological Quality Assessment

The methodological quality of included RCTs was assessed using the PEDro scale [21]. Ten items are accounted for in the PEDro score, resulting in score ranges of 0–10. Blinding of subjects and therapists was excluded from assessment as per previous review [22] as it was deemed unfeasible for exercise interventions [23]. Studies were scored ranging 0–8.

RCTs were considered high quality with a score ≥ 4 [24].

Publication Bias

Risk of publication bias for included studies was assessed using a funnel plot. In the absence of publication bias, the funnel plot should show symmetry [25].

Statistical Analysis

For each RCT, the number of participants, post-test mean, and associated standard deviations (SD) for each outcome were extracted for meta-analysis, as per previous review [16]. Post-test means were more readily available in the studies and were therefore used instead of change data (change in fatigue from baseline to after RT). Where reported outcomes had a scale with a lower value indicative of a better outcome, the reported values were multiplied by -1 so that in all analyses, a higher value indicated a better outcome.

The meta-analysis was performed using Cochrane Review Manager Software (RevMan 5.3).

Treatment effect on fatigue and QOL was calculated using standardised mean differences (SMD) with 95% confidence intervals (CI). The pooled effects were calculated using the random-effects model (DerSimonian-Laird approach), which accounts for within- and between-study differences (assessment scales, exercise parameters). SMD were considered statistically significant at the 5% level ($P < .05$). SMD were categorised as small (0.1–0.3), medium (0.3–0.6), or large (≥ 0.6) [26]. Heterogeneity was determined between studies using the I^2 statistic. High, moderate, and low levels of heterogeneity corresponded to values of 75%, 50%, and 25%, respectively [27].

Sensitivity Analysis

The sensitivity analysis was performed on the basis of methodological quality to assess whether excluding studies on the basis of PEDro score would significantly change the main results on exercise and fatigue at the end of the study.

Results

Description of Studies

A total of 278 studies were identified after a comprehensive search strategy. Figure 1 shows the flow of studies and reasons for exclusion. Five RCTs [28–32] met the inclusion criteria and were included in this review. The characteristics of included studies are summarised in Table 1.

High levels of heterogeneity between studies on assessed variables meant it was not feasible to assess outcomes other than fatigue and QOL. Other outcomes assessed in studies included sleep disturbances, cardiac fitness, depression, muscular strength, and immune function.

Characteristics of Included Study

The five included studies provided data for 392 participants, with 192 participants receiving an exercise intervention and the remaining 200 participants undergoing usual care. Trials took place in Canada, Scotland, Poland, and the United States of America. Mean age of participants ranged from 64–69 years across the five studies.

Two studies assessed aerobic exercise [30,32], one study assessed aerobic exercise and resistance training individually [31], one study assessed qigong and light exercise individually [29], and one study combined aerobic exercise and resistance training [28]. The frequency, duration, and intensity of the exercise interventions is reported in Table 1.

Training stimuli were deemed adequate in all studies, with the exception of one study where the duration and intensity of the qigong and light exercise interventions were not reported [29].

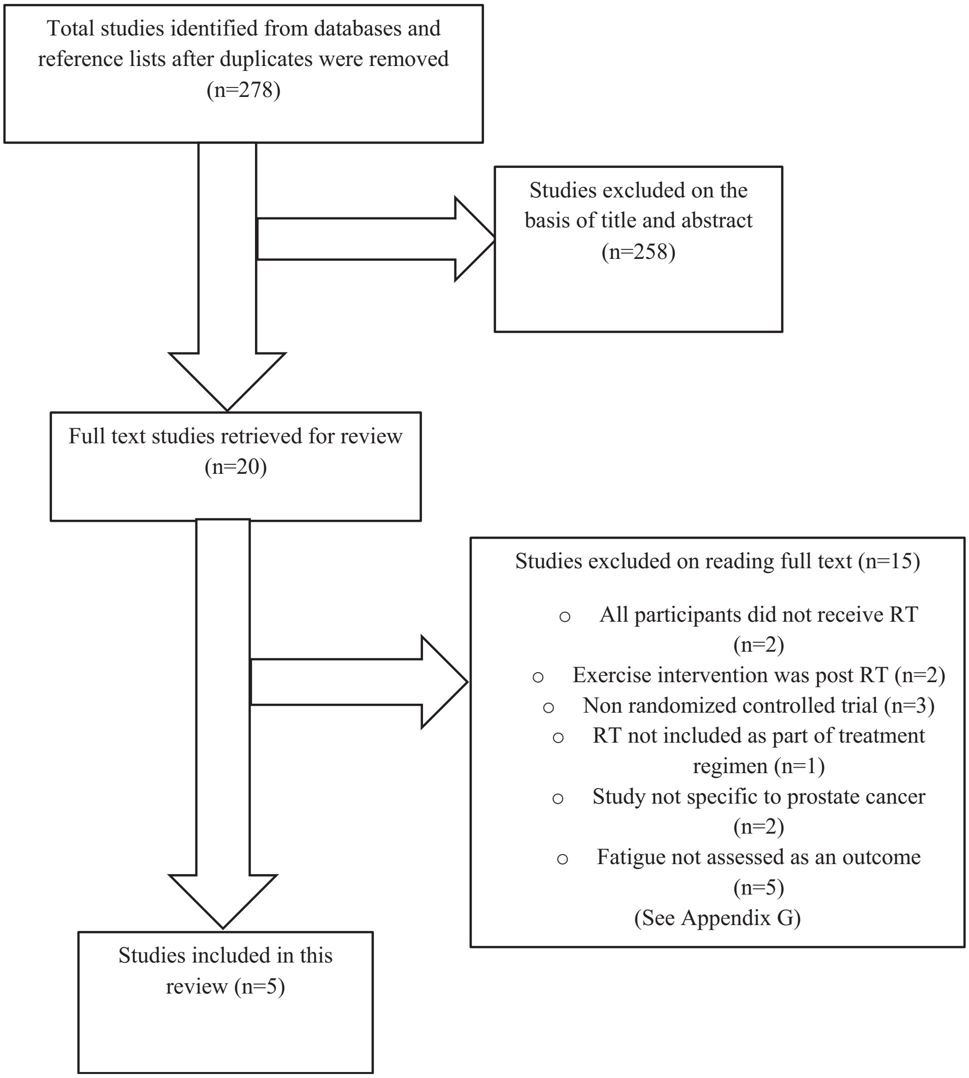

Figure 1. Flowchart of included and excluded studies.

All studies compared exercise with no exercise. Four studies investigated supervised exercise programmes [28–31], whereas one study explored home-based exercise [32].

Owing to the high levels of clinical heterogeneity between studies relating to exercise parameters (intensity, duration, frequency), it was not feasible to explore the effect of these individual parameters and thus to determine optimal prescription parameters in alleviating fatigue in men with prostate cancer.

Endpoints varied according to the RT schedule of the included participants, which ranged for 4–8 weeks across four studies [28–30,32]. The intervention in the other study [31] was carried on after RT had finished for a total of 24 weeks.

Outcomes

All studies used reliable and valid measures of fatigue. Fatigue was assessed with the FACT-F [28,31], the revised Piper Fatigue Scale [30], and the brief fatigue inventory [29,32].

QOL was assessed in four studies [28–31] using FACT-General [28,31], FACT-Prostate [30], and EPIC [29]. Three studies provided data suitable for meta-analysis, and one study only provided subscale values [29] and was not included in the meta-analysis.

The SDs were obtained from the reported standard error as per Cochrane handbook (section 7.7.3.2) [25] in one study [29].

Adverse outcomes were reported in two studies [28,31], whereas the remaining three studies did not report any adverse events [29–31].

Risk of Bias in Included studies

Methodological Quality Assessment

All RCTs were considered high quality with a PEDro score $\geq$ 4 (range, 4–7). Withdrawals and dropouts from included studies are recorded in Table 1.

Adherence and Contamination

Adherence to the exercise interventions was reported in four studies as seen in Table 1. Contamination was not reported in any study.

Table 1
Characteristics of Included Studies (n = 5) in Relation to Participants (Men With Prostate Cancer Undergoing RT), Intervention (Exercise and Control), and Outcomes (Fatigue and QOL)

Study (Y)	Sample Size (n)	Treatment Regimen	Patient Characteristics	Intervention (Type; Setting)	Duration Intervention	Intensity	Assessment Fatigue	Adherence (%)	Adverse Events (n)	Dropouts After Treatment (n)
Windsor (2004)	Total: 66 I: 33 C: 33	RT: 66; Three Field techniques. 50 Gy/20#/4 wk (12 patients). 52 Gy/20#/4 wk (53 patients) Adjuvant ADT: 19	Stage: localised Age: mean 69 (range, 52–82)	Aerobic (walking); Home based	4 wk (duration of RT)	3 per wk; 30 mins; 60%–70% HRmax	BFI	100% completed intervention	0	1/66. End of treatment: EG (32) UC (33)
Monga (2007)	Total: 21 I: 11 C: 10	RT: 21; Four Field box techniques 68–70 Gy in 34–38#'s at 1.8–2.8 Gy per#	Stage: localised Age: mean 69 (range, 62–80)	Aerobic (walking); Supervised	8 wk (duration of RT)	50-min classes 3 per wk 65% HRmax	r-PFS	82% completed intervention	0	No dropouts
Hojan (2016)	Total: 55 I: 27 C: 28	RT: 55; 76 Gy in 38#'s Adjuvant ADT: 55	Stage: I–III Mean age: 68.5	Combined aerobic and resistance; Supervised	8 wk	50–55 mins 5 per wk 70%–75% 1-RM 64%–70% HRmax	FACT-F	Median of 95% completed 38/40 sessions	1	1/55. End of treatment: EG (27) UC (27)
Segal (2009)	Total: 121 RE: 40 AE: 40 C: 41	RT: 121; no technique reported Adjuvant ADT: 74	Stage: I–IV Age: mean 66 (SD: 7.0)	AE + RE groups; Supervised	24 wk	AE: 3 per wk, 15–45 min, 50%–75% VO2max RE: 2 per wk, 2 × 8–12 reps, 60%–70% 1-RM	FACT-F	Median adherence 85.5%	3	Dropout: 11/121 End of treatment: RE (33), AE (37), UC (40)
McQuade (2016)	Total: 76 *Qigong: 26 †LE: 26 C: 24	RT: 63; IMRT: 27; Protons: 39 Adjuvant ADT: 49 (details provided on analysed participants only)	Stage: I–III Mean age: 64	Qigong + LE groups; Supervised and home practice encouraged	6 or 8 wk (depending of RT duration)	3 per wk; 40-min classes with home practise encouraged	BFI	63.5% attended all classes. 80.8% attended >50% of classes	0	Dropout: 14/76 End of treatment: QGTC (21), LE (19), WL (22).

ADT, androgen deprivation therapy; AE, aerobic exercise; BFI, brief fatigue inventory; EG, exercise group; FACT-F, functional assessment of cancer therapy-fatigue; FACT-P, functional assessment of cancer therapy-prostate; HR, heart rate; IMRT, intensity-modulated radiation therapy; LE, light exercise; QOL, quality of life; QGTC, Qigong/Tai–chi; RE, resistance exercise; rPFS, revised piper fatigue scale; RM, repetition maximum; RT, radiation therapy; UC, usual care.

* Qigong/tai-chi: Ancient Chinese practices that combine slow, deliberate movements, meditation, and breathing exercises. In the included study, this intervention involved preparation exercises consisting of guided breathing, the great Tai Chi circle, and grounding and centering exercises. The main programme consisted of eight-form Yang-style tai chi along with ending exercises which included tai chi ball form.

† Light exercise: This programme focused on light resistance training and stretching exercises with a goal of maintaining muscle strength and range of motion. Participants were given tailored prescriptions based on baseline function.

Effect of Interventions

Fatigue, All Studies

The pooled results of the five studies showed a significant reduction ($P = .01$) in fatigue in favour of the exercise group with large statistical heterogeneity (SMD, −1.03; 95% CI, −1.82 to −0.24; heterogeneity: $P < .00001$; $I^2 = 92\%$) (Figure 2A). Sensitivity analysis showed that removing any individual study on the basis of methodological quality did not alter the results significantly although I^2 did decrease to 28% when the studies with PEDro score six were removed [32] [28]. Evidence of publication bias was found as the funnel plot showed asymmetry (Figure 3A).

Fatigue, Supervised (All Interventions)

A subgroup analysis was conducted on all supervised interventions (Figure 2B). The pooled results of this group (n = 327) showed a large sized, significant reduction in fatigue favouring the exercise groups (SMD, −1.19; 95% CI, −2.15 to −0.22; heterogeneity: $I^2 = 93\%$; $P = .03$).

Fatigue, Supervised, Aerobic Exercise

Two studies investigated the effect of a supervised walking intervention programme on fatigue [30,31]. The pooled results of these studies (n = 102) showed a large sized, nonsignificant reduction in fatigue (SMD, −0.75; 95% CI, −1.92 to 0.42; heterogeneity: $I^2 = 79\%$; $P = .02$) (Figure 2C).

As only single studies examined resistance, combined aerobic and resistance, light exercise, qigong, and home-based interventions, it was not feasible to further analyse these groups in this review.

Long-term Outcomes

As the duration of the exercise programme in one study was 24 weeks [31], its postintervention results showed that resistance exercise was superior to usual care but aerobic walking was not when change in fatigue scores from baseline to follow-up were examined between the groups. One other study [29] reported a 3-month follow-up where the exercise intervention had stopped after RT had finished. Nonsignificant benefits were demonstrated for both qigong ($P = .16$) and light exercise ($P = .31$) groups.

Quality of Life

The pooled results of the three studies [28,30,31] examining four interventions showed a nonsignificant improvement in QOL ($P = .10$; SMD, −1.01; 95% CI, −2.19 to +0.18) (Figure 2D). However, there was a significant heterogeneity across the studies ($P < .00001$; $I^2 = 94\%$). The combined aerobic-resistance group was the only intervention to generate significance. The study that was not included in the meta-analysis as only subscale values were reported found nonsignificant improvements to hormonal, bowel, and urinary functions for both qigong and light exercise groups when compared with the control group. Evidence of publication bias was found as the funnel plot showed asymmetry (Figure 3B).

Discussion

This review examines the impact of different exercise interventions on fatigue and QOL experienced by men with prostate cancer undergoing RT. A meta-analysis pooled results from five different studies with a total of seven different exercise interventions demonstrating a significant reduction in fatigue in favour of the exercise groups. No significant improvement was reported in QOL among the participants.

Exercise has been proven to be advantageous in the management of other chronic illnesses such as coronary disease [33]. Cochrane reviews to this end have illustrated the benefit of supervised exercise programmes over home-based interventions [34,35], Further noncancer RCTs strengthen this finding [36]. A cancer review by Velthius et al [22] on multiple cancer sites also highlighted the benefit of supervised programmes compared with that of home-based interventions in breast cancer patients. The authors alluded to the reasoning of this to the possibility of poor adherence in the home-based programme. This reasoning is further supported in noncancer studies [37] where various efforts were used to maximise adherence such as providing activity logs, telephone contact, and regular clinic visits. Though adherence is reported to be 100% in the home-based study included in this review, one must always be cautious interpreting such a result as adherence is undoubtedly a flaw of such an intervention. As only one study explored a home-based intervention in this current review, it was impossible to determine whether a supervised intervention was superior to a home-based intervention.

The findings of some noncancer studies [38,39] have illustrated that a combined intervention incorporating aerobic and resistance training is superior to either intervention alone. In the cancer literature, there are currently no other data available investigating men with prostate cancer with a combined intervention. However, a review of breast cancer patients found corresponding significant results (SMD, –0.41; 95% CI, −0.70 to −0.13) in favour of the combined intervention [40]. Previous reviews examining a wide range of cancer sites show nonsignificant benefits for mind-body and resistance exercise [16] on fatigue. In this review, only one study investigated each of these intervention types, and thus, more studies are needed to examine these interventions in prostate cancer patients to accurately analyse their effects in the context of the current literature.

The nonsignificant impact of aerobic interventions is contrary to the results of a previous review that included 38 studies and 2,646 participants with different types of cancer in the meta-analysis. The earlier review found that there was a significant effect of aerobic exercise on fatigue (SMD, −0.22 with 95% CI, −0.34 to −0.10) [16]. However, a breast cancer review [40] found corresponding results to the current one, and thus, the limited number of pooled studies in both the reviews may be a reason for such a result. The

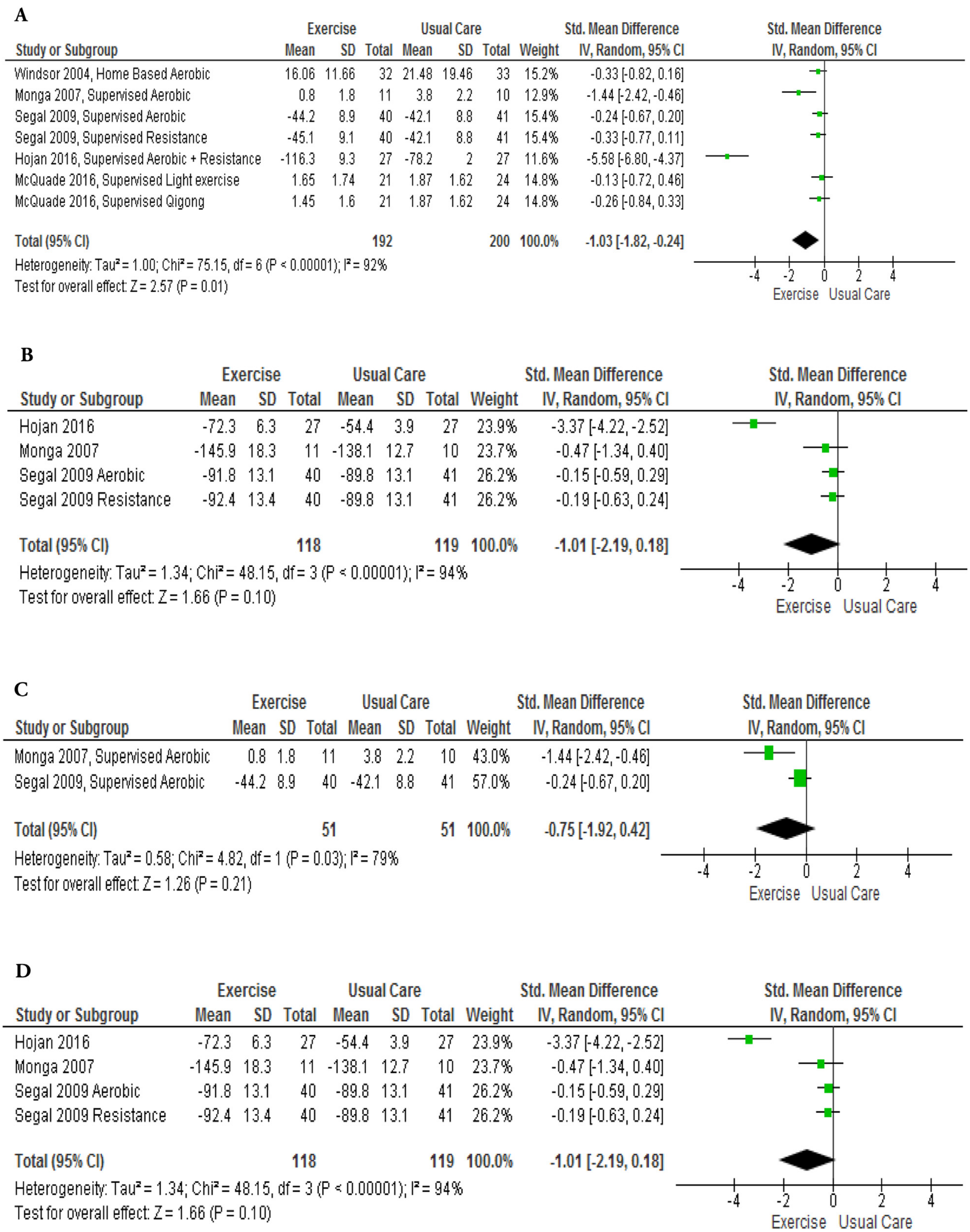

Figure 2. A, Forest plot showing effect estimate of exercise on fatigue. SMD with the associated 95%. The vertical line at 0 represents "no difference" between the exercise and usual care groups with respect to fatigue. Values to the left (negative values) favour the exercise intervention, whereas values to the right (positive values) favour the control group. Each square represents the SMD, and the attached horizontal line is the associated CI. Studies to the left of the line whose CI do not encompass the "no difference" line show significant benefit of exercise in reducing fatigue. Studies that have their CI touching the "no difference" line indicate nonsignificant benefit of exercise on fatigue. Each diamond represents the pooled effects for each subgroup, with the bottom one representing the pooled effects of all studies using the random-effects model. The diamond is to the left of the "no difference" line and does not incorporate it, thus indicating significant benefit of

limited data available for this intervention highlight an area for future research. Walking interventions were the only forms of aerobic activity examined in these studies which may allow future studies to also focus on other forms of aerobic activity.

Current literature examining the effects of exercise on QOL is conflicting and remains somewhat inconclusive. This is according to a Cochrane review of multiple cancer sites, where it was also addressed as a secondary outcome but without meta-analysis [16]. A more recent review on multiple cancer sites addressed QOL as a primary outcome and demonstrated a significant benefit to QOL (SMD, 5.55 with 95% CI, 3.19–7.9) in the exercise groups after meta-analysis of sixteen studies [41]. Both reviews included exercise interventions after treatment, and none were specific to men with prostate cancer. The findings of this review therefore reflect those of the current literature and highlight the need for further research into different modes of exercise. Limited data were available in this meta-analysis with two studies investigating supervised walking interventions, one study examining combined aerobic-resistance, and one study exploring resistance training. More data are therefore necessary to draw more conclusive results.

The results of this review highlight the importance of engagement in physical activity for men with prostate cancer undergoing RT. It further reflects the importance of involving different multidisciplinary team members to provide best advice in CRF management in this population. These findings are strengthened by a recent publication by the European School of Oncology [42] where physiotherapists are recommended to be included to reduce posttreatment complications and promote rehabilitation for these patients. The National Cancer Comprehensive Network has also developed guidelines to manage CRF [43]. Engagement in physical activity is one of their nonpharmacological recommendations in the document. Thus, this review supports their recommendation and should further reiterate to multidisciplinary team members the importance of engagement in physical activity for men with prostate cancer. Future studies may also focus on longer intervention programmes. The results of these studies may highlight the benefit of continued exercise engagement, such as one RCT included in this review, did with resistance training when change in fatigue scores were examined between the groups from baseline to follow-up [31].

Strengths and Weaknesses

First, to examine the totality of evidence related to the topic, studies were pooled from a wide variety of sources, enhancing the generalisability of this study. Robust and explicit methods were then used to identify, select, critically appraise, and synthesise the findings. Previous reviews focusing on exercise and fatigue in men with prostate cancer [16,22] also included men not treated with RT in their meta-analysis. Thus, a novel element to this specific review is its investigation into the impact of exercise during RT specifically in this patient group. Furthermore, additional modes of exercise interventions (combined aerobic-resistance training, qigong, and light exercise) have also been included in this review. However, the results must be interpreted in the context of the study limitations.

First, some study results were based on a small sample size. Only one study focused on exploring a home-based exercise intervention [32] while supervised resistance training, light exercise, qigong, and combined aerobic and resistance interventions also only included single studies. This limited volume of data may have led to an underestimation of the effectiveness of these interventions. By analysing only single studies, the results of this type of intervention may be misrepresented. This is why none of the interventions could be analysed individually and compared with those of the current literature.

Second, there was a degree of clinical heterogeneity and lack of standardised reporting among the included studies in this review and meta-analysis. Various fatigue and QOL scales were used as well at varying endpoints across all studies. Ideally, the same endpoints and outcome scales would have been used, making the data more comparable as a whole. Clinical heterogeneity also existed between the studies in terms of exercise intensity, duration, and type. This is similar to previous reviews that examine the impact of exercise interventions [16,22], and it is not known whether these may affect results. Evidence of publication bias was also found in this review with the funnel plots showing asymmetry. However, the limited number of studies found is no doubt a flaw of

exercise in alleviating fatigue. B, Forest plot showing effect estimate of exercise on QOL. SMD with the associated 95% CI was calculated for the random-effects model of meta-analysis. The vertical line at 0 represents "no difference" between the exercise and usual care groups with respect to QOL. Values to the left (negative values) favour the exercise intervention, whereas values to the right (positive values) favour the control group. Each square represents the SMD, and the attached horizontal line is the associated CI. Studies to the left of the line whose CI do not encompass the "no difference" line show significant benefit of exercise in QOL. Studies that have their CI touching the "no difference" line indicate nonsignificant benefit of exercise on QOL. The diamond at the bottom represents the pooled effects of the four different interventions using the random-effects model. The diamond is to the left of the "no difference" line and touches it, thus indicating a nonsignificant benefit of exercise on QOL. C, Subgroup analysis of supervised aerobic interventions. D, Forest plot showing effect estimate of exercise on QOL. SMD with the associated 95% CI was calculated for the random-effects model of meta-analysis. The vertical line at 0 represents "no difference" between the exercise and usual care groups with respect to QOL. Values to the left (negative values) favour the exercise intervention, whereas values to the right (positive values) favour the control group. Each square represents the SMD, and the attached horizontal line is the associated CI. Studies to the left of the line whose CI do not encompass the "no difference" line show significant benefit of exercise in QOL. Studies that have their CI touching the "no difference" line indicate nonsignificant benefit of exercise on QOL. The diamond at the bottom represents the pooled effects of the four different interventions using the random-effects model. The diamond is to the left of the "no difference" line and touches it, thus indicating a nonsignificant benefit of exercise on QOL. QOL, quality of life; SMD, standardised mean differences.

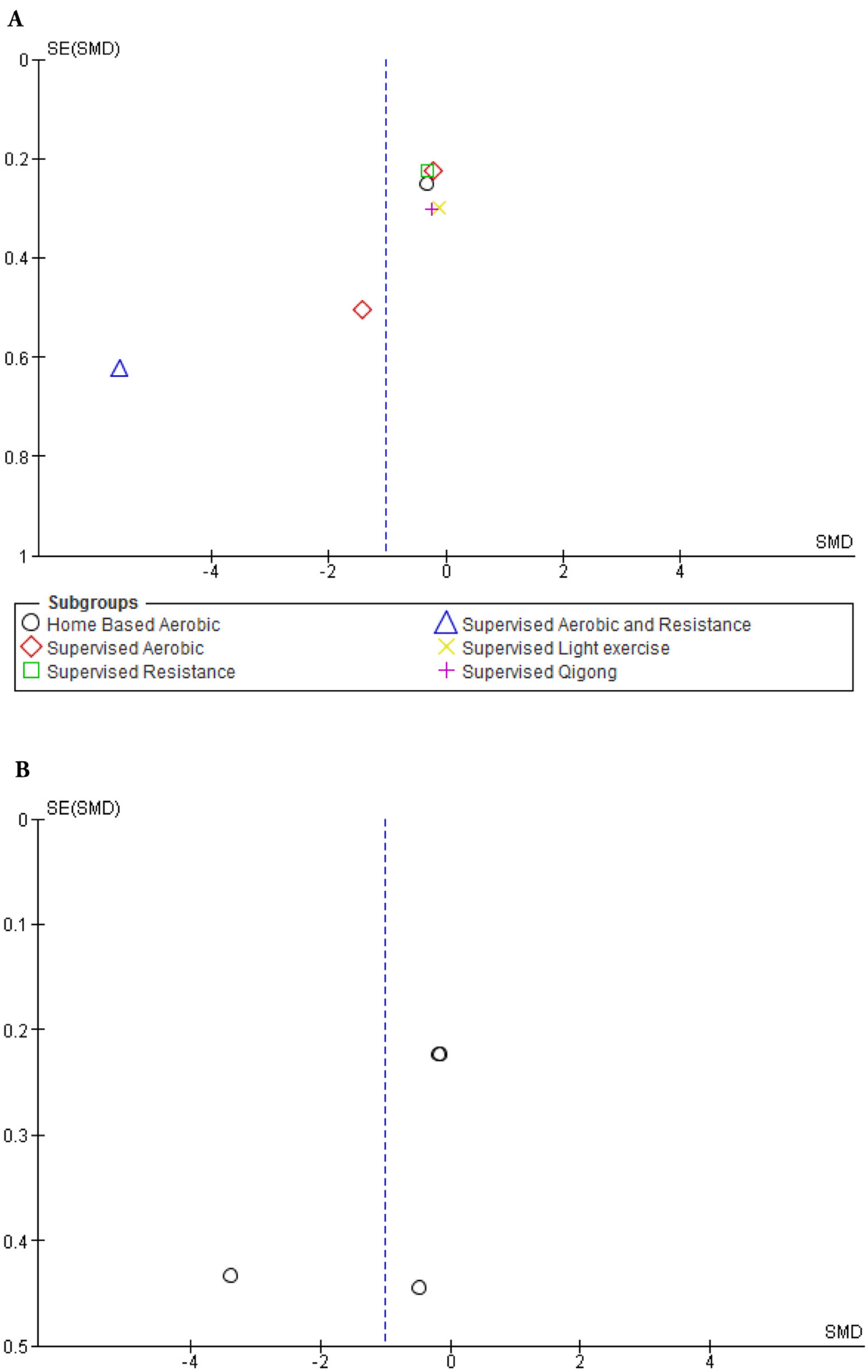

Figure 3. A, Funnel plot of standard error against SMD for the assessment of publication bias in the investigation of fatigue. The funnel plot shows asymmetry, indicating the presence of publication bias. B, Funnel plot of standard error against SMD for the assessment of publication bias in the investigation of QOL. The funnel plot shows slight asymmetry, indicating the presence of publication bias. QOL, quality of life; SMD, standardised mean differences.

such technique used to analyse publication bias as any one study may skew results to show asymmetry.

Finally, there was evidence of large statistical heterogeneity in the pooled effects of exercise on fatigue and QOL. A sensitivity analysis showed that this figure decreases significantly when studies with PEDro score six were removed [28,32] for fatigue. In one study [28], this may be related to the more strenuous intervention the participants were subject to, with both individual aerobic and resistant training components deemed as adequate intervention as per ACSM guidelines (scoring 4/4 each). It was likely that the home-based setting of the other study also contributed to this [32]. There was variability across the methodological quality of included RCTs, with a PEDro score range 4–7.

Areas for Further Research

Whereas these studies have explored the quantitative measures of fatigue, few studies have looked at the "lived-in" experience of managing fatigue among men with prostate cancer through the use of qualitative methods. A review exploring nonpharmacological interventions for cancer-related fatigue in men treated for prostate cancer [44] concluded that exercise and psychosocial interventions, including education and cognitive behavioural therapy, can be effective at alleviating fatigue for men with prostate cancer. The authors recommended further research to be carried out on psychosocial and educational interventions.

The majority of interventions included in this review were group-based interventions. Future research should be carried out on the role of interventions with peers and the role of informal carers as mediators of exercise delivery. This has been shown to be effective in other disciplines of health care. For example, in stroke rehabilitation, a study by Galvin et al [45] demonstrated the effective, beneficial, and active role family members may have as informal carers, providing exercise programmes to patients. Thus, there is a gap in the literature to investigate if this role would be effective in men with prostate cancer undergoing treatment.

Only one study investigated the effects of resistance training, low-intensity mind-body exercise and a combined aerobic-resistance intervention. Future investigations are necessary into all these types of interventions to draw more conclusive results regarding the optimum mode of exercise intervention to reduce fatigue. In addition, trials should adhere to the Consolidated Standards of Reporting Trials guidelines to standardise the conduct and reporting of these studies.

Finally, QOL was assessed as a secondary outcome in this review. Future reviews and meta-analyses should investigate QOL as the primary outcome and explore the effect of various exercise types and parameters (intensity, frequency, duration) for QOL.

Conclusion

Exercise during RT significantly reduces fatigue for men with prostate cancer. Further research is necessary to confirm this finding with more studies warranted to explore resistance, combined aerobic and resistance, light exercise, and qigong interventions to carry out more effective analysis. Future investigations into the optimal exercise prescription parameters for QOL are also necessary.

Footnotes

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Conflict of interest: The authors have no conflicts of interest to disclose. We have full control of all data, and this may be reviewed by the journal if requested.

Ethical approval: Not required.

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Appendix A

Detailed Search Strategy

MEDLINE:

1. "Physical Exertion"[Mesh] OR "Physical Education and Training"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Physical Endurance"[Mesh] OR "Exercise"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Motor Activity"[Mesh]
2. exercis*[tiab] OR train*[tiab] OR Physical activit*[tiab] OR fitness[tiab] OR physical performance[tiab] OR physical educat*[tiab] OR physical function*[tiab] OR Sport*[tiab] OR walk*[tiab] OR running[tiab] OR jogging[tiab] OR yoga[tiab]
3. #1 OR #2
4. "Radiotherapy"[Mesh]
5. Radiation therap*[Tiab] OR radiotherapy*[tiab]
6. #4 OR #5
7. "Prostatic Neoplasms"[Mesh]
8. Prostate cancer*[tiab] OR prostate neoplasm*[tiab] OR prostate tumour*[tiab] OR prostate tumor*[tiab] OR prostate carcinoma*[tiab] OR prostate adenocarcinoma*[tiab] OR Prostatic cancer*[tiab] OR prostatic neoplasm*[tiab] OR prostatic tumour*[tiab] OR prostatic tumor*[tiab] OR prostatic carcinoma*[tiab] OR prostatic adenocarcinoma*[tiab]
9. #7 OR #8
10. #3 AND #6 AND #9
11. randomized controlled trial [pt]
12. controlled clinical trial [pt]
13. randomized [tiab]
14. placebo [tiab]
15. drug therapy [sh]
16. randomly [tiab]
17. trial [tiab]
18. groups [tiab]
19. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20. animals [mh] NOT humans [mh]
21. #19 NOT #20
22. #10 AND #21

Key: tiab = title or abstract mh = Mesh term pt = publication type sh = subject heading

CINAHL:

1. (MH "Exercise+") OR (MH "Physical Fitness+") OR (MH "Sports+") OR (MH "Therapeutic Exercise+") OR (MH "Training Effect (Physiology)") OR (MH "Physical Activity") OR (MH "Physical Performance")
2. TI (Exercis* OR train* OR sport OR kinesotherapy OR walk* OR running OR yoga OR fitness) OR AB (Exercis* OR train* OR sport OR kinesotherapy OR walk* OR running OR yoga OR fitness)
3. TI (Physical N3 (activity OR performance OR fitness OR educat* OR function*)) OR AB (Physical N3 (activity OR performance OR fitness OR educat* OR function*))
4. S1 OR S2 OR S3
5. (MH "Radiotherapy+")
6. TI (‘Radiation therapy’ OR radiotherapy) OR AB (‘Radiation therapy’ OR radiotherapy)
7. S5 OR S6
8. (MH "Prostatic Neoplasms+")
9. TI (Prostat* N3 (tumor* OR tumour* OR cancer* OR neoplasm* OR carcinoma* OR adenocarcinoma*)) OR AB (Prostat* N3 (tumor* OR tumour* OR cancer* OR neoplasm* OR carcinoma* OR adenocarcinoma*))
10. S8 OR S9
11. S4 AND S7 AND S10

Cochrane:

1. [mh‘‘Physical Exertion’’]
2. [mh‘‘Physical Education and Training’’]
3. [mh‘‘Exercise Therapy’’]
4. [mh‘‘Physical Endurance’’]
5. [mh‘‘Physical Therapy Modalities’’]
6. [mh‘‘Motor Activity’’]
7. [mh‘‘Exercise Movement Techniques’’]
8. [mh‘‘Exercise’’]
9. (Exercis* OR train* OR sport OR kinesotherapy OR walk* OR running OR yoga OR fitness):ti,ab,kw
10. (Physical NEAR/3 (activity OR performance OR fitness OR educat* OR function*)):ti,ab,kw
11. {OR #1-#10}
12. [mh‘‘Radiotherapy’’]
13. (‘Radiation therapy’ OR radiotherapy):ti,ab,kw
14. #12 OR #13
15. [mh‘‘Prostatic Neoplasms’’]
16. (Prostat* NEAR/3 (tumor* OR tumour* OR cancer* OR neoplasm* OR carcinoma* OR adenocarcinoma*)):ti,ab,kw
17. #15 OR #16
18. #11 and #14 and #17

Key: ti = title, ab =abstract, kw = key word

EMBASE:

1. ‘physical activity, capacity and performance’/de OR ‘kinesiotherapy’/exp OR ‘motor activity’/exp OR ‘physical activity’/exp OR ‘physical fitness’/exp OR ‘exercise tolerance’/exp OR ‘exercise’/exp OR ‘physical performance’/exp OR ‘exercise’/exp OR ‘training’/exp Or ‘fitness’/exp OR ‘sport’/exp OR ‘physical education’/exp OR ‘kinesiotherapy’/exp OR ‘muscle exercise’/exp
2. (Exercis* OR train* OR sport OR kinesotherapy OR walk* OR running OR yoga OR fitness):ti,ab
3. (Physical NEAR/3 (activity OR performance OR fitness OR educat* OR function*)):ti,ab
4. #1 OR #2 OR #3
5. ‘radiotherapy’/exp
6. (‘Radiation therapy’ OR radiotherapy):ti,ab
7. #5 OR #6

8. ‘prostate cancer’/exp
9. (Prostat* NEAR/3 (tumor* OR tumour* OR cancer* OR neoplasm* OR carcinoma* OR adenocarcinoma*)):ti,ab
10. #8 OR #9
11. #4 AND #7 AND #10
12. ‘clinical trial’/de OR ‘randomized controlled trial’/de OR ‘randomization’/de OR ‘single blind procedure’/de OR ‘double blind procedure’/de OR ‘crossover procedure’/de OR ‘placebo’/de OR ‘prospective study’/de OR ‘randomi?ed controlled’ NEXT/1 trial* OR rct OR ‘randomly allocated’ OR ‘allocated randomly’ OR ‘random allocation’ OR allocated NEAR/2 random OR single NEXT/1 blind* OR double NEXT/1 blind* OR (treble OR triple) NEAR/1 blind* OR placebo*
13. #11 AND #12

clinicaltrials.gov:
radiotherapy AND exercise AND “prostate cancer”

ISRTCN Registry:
radiotherapy AND exercise AND “prostate cancer”