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Impact of Aerobic and Resistance Training on Fatigue, Quality of Life, and Physical Activity in Prostate Cancer Patients: A Systematic Review and Meta-Analysis

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Highlights

- Prostate cancer patients struggle with fatigue, limited activity, and low quality of life.
- This systematic review investigates how resistance and aerobic exercise impact fatigue, quality of life, and physical activity in prostate cancer patients, presenting a comprehensive analysis of twenty studies.
- Exercise improved prostate cancer patients' quality of life compared to the control group.
- There was a lack of association between exercise and fatigue, the 6-meter walk test, or up-and-go time.
- Our analysis encourages further research exploring additional strategies to address fatigue and promote physical activity in prostate cancer demographics.

Abstract

Background: Prostate cancer (PCa) is a prevalent cancer with significant morbidity and mortality rates. In most cases, prostate cancer remains asymptomatic until advanced disease manifests with symptoms, such as benign prostate hyperplasia (BPH). Timely detection and better management have improved overall survival in patients with prostate cancer, and fatigue, reduced physical activity, and impaired quality of life (QoL) remain major challenges that impact daily life.

Objective: This study aimed to systematically review and conduct a meta-analysis to evaluate the impact of aerobic and resistance training on fatigue, quality of life, and physical activity in prostate cancer patients undergoing treatment.

Material & Methods: A comprehensive literature search was conducted using the PubMed, Cochrane Library, and clinicaltrials.gov databases, adhering to the PRISMA guidelines. Twenty studies, involving 1393 participants, were included in the final analysis. The inclusion criteria were Studies that evaluated the effects of exercise interventions relative to passive controls in patients with prostate cancer were included. The primary outcomes of interest were fatigue, QoL, and PA.. Data from eligible studies were extracted, and a meta-analysis was performed using RevMan 5.40.

Results: Twenty studies met our inclusion criteria. Data Analysis of the included studies demonstrated a significant improvement in quality of life among prostate cancer patients in the exercise group compared to the control group (SMD = 0.20, 95% CI = 0.07 to 0.34, P = 0.003). However, there was no significant association between exercise and fatigue (SMD = 0.07, 95% CI = -0.13, 0.26, P = 0.51). Sensitivity analysis did not alter these findings. Regarding physical activity outcomes, the control group exhibited superior performance in the 400-meter walk test ($P < 0.05$). No significant associations were found between exercise and the 6-meter walk test or up-and-go time.

Conclusion: This systematic review revealed that aerobic and resistance training enhance the quality of life of patients with prostate cancer, although it has a limited impact on fatigue and physical activity levels. These findings advocate a shift in clinical practice and positioning exercise as a core component of comprehensive cancer care. Tailoring exercise regimens according to individual patient needs and treatment stages should become the norm in treatment planning. This approach goes beyond physical wellness and addresses the psychological and emotional facets of cancer management. Moreover, there is an evident need for further research to develop holistic exercise interventions that effectively address the complex dynamics of fatigue, physical activity, and QoL in this patient group.

Keywords: Cancer Rehabilitation, Exercise Therapy, Oncology, Physical Endurance, Quality of Life, Resistance Training

Introduction

Globally, prostate cancer is the second most common cancer in males and the fourth most common cancer overall, with over 1.4 million new cases reported in 2020. While it remained more prevalent in high-income countries such as France, Ireland, and Sweden, Zimbabwe reported the highest death count in 2020(1). Although the precise pathogenesis of prostate cancer is complex, several factors are known to contribute, including increasing age, ethnicity, obesity, increased height, hypertension, sedentary lifestyle, smoking, and chronically elevated testosterone levels. Similarly, several genetic mutations have been linked to it, including those in hereditary prostate cancer (HPC) gene 1, HPC 2, CAPB, and TMPRSS2-ETS gene families (2).

In most cases, prostate cancer remains asymptomatic until advanced disease manifests with symptoms, such as benign prostate hyperplasia (BPH). The disease may present with urinary urgency, frequency, difficulty in voiding, compromised renal function, impotence, or features of metastatic disease involving the bones, lymph nodes, rectum, and nervous system. Digital rectal examination (DRE) is an integral part of prostate cancer screening; however, its positive predictive value (PPV) is lower than that of prostate-specific antigen (PSA). However, DRE may have a lower PPV and still has significant clinical value, especially in identifying advanced-stage diseases. DRE can be effective for detecting prostate cancer that has progressed to a more advanced and palpable stage. Serum PSA level plays a pivotal role in determining high-risk prostate adenocarcinoma patients, with a positive predictor potential depending on the cut-off values. In patients with clinical suspicion, a transrectal ultrasound-guided needle biopsy sample was obtained to reach a definitive histological diagnosis. Similarly, the Prostate health index (Phi), which statistically combines tPSA, fPSA, and [-2] pro-PSA to offer better specificity and sensitivity, can also be employed(3).

Following diagnosis, prostate cancer was classified using the American Joint Committee on Cancer Tumor Node Metastasis (AJCC TNM) staging system. Staging uses the extent of the primary tumor (T), spread to lymph nodes (N), metastasis (M), PSA levels, and Gleason score grade group to categorize tumors into stages I, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, and IVb(4).

Although several management options are available, radical prostatectomy, with or without radiotherapy, remains the mainstay of treatment for localized diseases. This may be accompanied by lymph node removal, depending on sentinel lymph node involvement. Additionally, external beam radiotherapy can be used independently to manage low-, intermediate-, and high-risk patients following prostatectomy. Brachytherapy offers the benefit of delivering tumor-focused radiation therapy while sparing the surrounding tissues and can be either used alone or in conjugation with external beam therapy(5). Androgen deprivation therapy (ADT) impairs testosterone and other male hormone production, and prevents the stimulation of tumor growth. This can be accomplished via bilateral orchiectomy or medical castration induced by a series of drugs such as flutamide and chlormadinone acetate (CMA). Finally, chemotherapy with agents such as Docetaxel and Cabazitaxel can also be used in cases of advanced disease(6).

Timely detection and better management have improved overall survival in patients with prostate cancer; fatigue, reduced physical activity, and impaired quality of life remain major challenges that impact daily life(7). According to one study, 78% of patients seeking treatment for prostate cancer reported significant fatigue that impacted their routine life activities(8). In this systematic review and meta-analysis, we evaluated the impact of aerobic and resistance training relative to usual care on fatigue, quality of life, and physical activity in patients with prostate cancer undergoing treatment.

The American College of Sports Medicine (ACSM) defines aerobic exercise as an activity that utilizes large muscle groups while maintaining them and is performed rhythmically. These exercises use aerobic metabolism for energy generation. Aerobic exercises include cycling, running, swimming, etc.(9). These exercises improve cardiovascular fitness and enhance the ability of the body to use oxygen efficiently. Resistance training is a form of periodic physical activity that involves the use of external weights or resistance against force to provide muscles with a progressive overload. It is a form of anaerobic exercise(10).

Thus, this systematic review aimed to evaluate the effects of aerobic and resistance training on fatigue, quality of life, and physical activity in prostate cancer patients, providing a thorough synthesis of the current research findings.

Material and Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)(11) and Assessing the

Methodological Quality of Systematic Reviews (AMSTAR) guidelines(12), and the protocol was registered in PROSPERO ;

Data Source and Search Strategy:

The authors conducted a thorough literature search from inception till 30th May 30, 2023, using PubMed, the Cochrane Library, and clinicaltrials.gov. To obtain comprehensive search results, similar terms, synonyms, and spelling variants were employed. Our search string comprised of the following terms: physical activity, Exercise, Aerobic exercise, resistance training, physical inactivity, prostate carcinoma, prostate neoplasm, and prostate cancer. Following a preliminary search, duplicates were removed using Zotero, a manual duplicate removal tool, and the recruited articles were screened for their full length.

Inclusion and Exclusion Criteria:

Studies were included only if they evaluated the impact of aerobic and/or resistance training relative to passive control on fatigue, quality of life, and physical activity among patients undergoing prostate cancer treatment. We did not limit the studies to the presence or absence of metastasis or the effects evaluated in patients receiving any particular management. We included only original studies, such as randomized controlled trials, cohort observational studies, and case-control studies.

Studies were excluded if they evaluated the impact of combined interventions such as exercise and medicine, if an active control was used, or if they studied the impact on non-desired outcomes such as inflammatory biomarkers. Similarly, articles that employed physical interventions other than aerobic and resistance training were deemed ineligible for inclusion. Finally, all case reports, single-arm studies, reviews, and meta-analyses were excluded.

Data Extraction and Quality Assessment:

Following a comprehensive literature search, relevant information from the recruited articles was tabulated using an Excel spreadsheet. The following measurements were recorded: author's name, study year, number of participants, intervention, control, intervention exercise details, and outcomes.

To assess the quality of included trials, the Cochrane Risk of Bias tool (The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration) was used which categorizes each study as either high-risk, low-risk, or unclear across the following domains: random sequence generation, allocation concealment, selective reporting, blinding of participants/personnel, blinding of outcome assessment, incomplete outcome data, and any other source of bias.

Outcomes:

This systematic review and meta-analysis aimed to evaluate the impact of aerobic or resistance training relative to control in patients with prostate carcinoma. The primary outcomes of interest were fatigue, QoL, and PA.. We used the 400-m walk, 6-m walk, and up-and-go tests to assess physical activity levels. Furthermore, these studies were not limited to the scales and tools employed to assess the desired outcomes.

Statistical Analysis:

To determine the pooled effects, Review Manager (RevMan) 5.40 (The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration, 2014) was used. Given the variations in exercise programs and tools employed to assess outcomes, a random-effects model was used to determine the standard mean difference, confidence interval, and p-value. Heterogeneity was assessed using I2, and a value greater than 75% was considered significant.

Results

Literature Search

Our initial electronic database search yielded 9320 articles. After removing duplicates and screening by title and abstract, 435 articles were excluded, of which 19 articles could not be retrieved. Finally, 416 articles were considered eligible for full-length review. Following a thorough assessment of these articles, 20 were ultimately considered eligible for inclusion in this systematic review and meta-analysis(13–32). All studies included in this meta-analysis met our predefined inclusion criteria, as described in the Materials and Methods section. The results of our literature review are summarized in the PRISMA flowchart (Figure 1).

Study Characteristics

A total of 1393 patients (I=731, C=662) were included in our study. The mean age for the intervention and control groups were 69.42±7.6 and 68.98±8.05 respectively while BMI was 28.13±4.1 kg/m² for intervention while 27.48±3.43 kg/m² for the control group. Four of our studies employed aerobic training, five had resistance, while ten had both aerobic and resistance training. Only one study had high load strength as its training component. The details of the included studies' characteristics are tabulated in Table 1, and the outcomes are presented in Table 2.

Risk of Bias

Most of our studies were low risk in six of the seven components of the Cochrane ROB tool. One exception was the component of blinding of participants/personnel, in which 15/20 studies were marked as high-risk, while two studies were categorized as low-risk and three as unclear. The detailed risk of bias is presented in Table 3.

Publication Bias: The Publication bias was assessed using a funnel plot (Figure 3). The plots showed some degree of asymmetry, which may be reflective of reporting bias. Consequently, it is difficult to estimate the effect size.

Results of Meta-Analysis

A) Quality of Life

Of the 20 studies included in this review, 13 reported this outcome. There were 854 patients in the exercise group, consisting of 434 patients whereas there were 420 patients assigned to the control group. However, two studies could not be included in the analysis(13,21) because of the lack of data needed for analysis. The pooled results revealed a statistically significant association between the exercise group compared to the control group in improving the quality of life of the patients (SMD= 0.20, 95%CI= 0.07 to 0.34, P= 0.003, I2=0%).

B) Fatigue

This outcome was reported in fifteen studies. However, 4 studies(13,14,21,27) could not be included in the final analysis because of a lack of relevant data. Of the 830 patients included in this study, 427 were in the intervention group and 403 were in the control group. A non-significant effect of exercise on fatigue was observed compared to the control (SMD= 0.07, 95%CI= -0.13, 0.26, P=0.51, I2=49%). Similarly, sensitivity analysis was performed by removing the study by Monga et al. However, no statistically significant differences were observed between the groups.

C) 400 Meter Walk test

Our third outcome, a 400-meter walk test, was reported in only five of the recruited articles. In total, 344 patients with 174 assigned to the exercise and control groups. Surprisingly, the pooled results significantly favored the control group for the 400-meter walk test compared to the interventional group.

D) 6 Meter walk test

This outcome was reported in four of the 20 recruited studies. In total, 244 patients with 124 assigned to the exercise and control groups. Our analysis showed no significant association between exercise and the 6-meter walk test when compared to the control group (SMD= -0.08, 95%CI= -0.53 − 0.38, p=0.74, I2=64%). Similarly, the sensitivity analysis showed no benefit.

E) Up and Go Time

This outcome was reported in only two studies, with a total of 77 patients. The exercise and control groups included 38 and 39 patients, respectively. Our analysis showed no significant association between exercise and up-and-go time when compared with the control group (SMD= 0.12, 95%CI= -0.48, 0.72, p=0.70, I2=35%).

Discussion:

This study aimed to evaluate the association between exercise and its effects in patients with prostate cancer. Our study results established a significant association between exercise and overall elevation in the quality of life (QoL) (p= 0.003) which is in line with the study by Bourke et al., where a significant relationship was quantified between exercise and cancer specific (QoL)(28). In contrast to previous studies, the most recent meta-analysis yielded a different result, indicating an association that favored exercise; however, it was statistically insignificant (p=0.718)(33). This could be explained by the fact that our analysis did not include any overlapping interventions (dietary, psychological, etc.), which may have led to different results, indicating that exercise alone is far superior to mixed interventions for these demographics.

However, our analysis showed no positive interaction between exercise and fatigue (P=0.51), which contradicts the results of previous studies. Anderson et al. reported a relationship between the two, similar to Lopez et al., who showed that exercise has significant positive benefits in patients with prostate cancer (33,34). This might be attributed to differences in the inclusion criteria of the studies. Anderson et al.. included studies with mixed interventions (exercise with dietary changes), whereas Lopez et al.. only considered resistance training. However, our results strengthen the conclusion of Kelley et al., who pointed out the ambiguity in research across exercise and its effect on fatigue in their grand review, demonstrating that caution should be taken when establishing a relationship between them (35). The lack of significant association between exercise and fatigue is an intriguing finding that warrants further investigation. Fatigue reduction is an important aspect of QoL improvement. Fatigue can profoundly impact daily functioning, emotional well-being, and the overall quality of life. Therefore, it is reasonable to expect that exercise interventions aimed at improving QoL will lead to a reduction in fatigue levels. However, the results of this meta-analysis contradict those of other studies. This may be because of the specific exercise interventions employed in these studies. Different exercise modalities, intensities, and durations may have varying effects on fatigue levels. It should be noted that we did not include Languis et al. and Ashton et al. due to a lack of clarity of data, but overall, both demonstrated modest effects on the intervention on QoL and fatigue, respectively(13,21).

Another factor to consider is the potential impact of the various treatment techniques on fatigue. Patients with prostate cancer are frequently subjected to various therapies including surgery, radiation therapy, and chemotherapy, all of which can lead to fatigue. The presence of treatment-related weariness may have attenuated the benefits of exercise on fatigue, as observed in this meta-analysis. Furthermore, the association between exercise and exhaustion might be modified by individual patient features as well as the participants' general health status. Patients with prostate cancer can have a wide range of characteristics including differences in disease stage, comorbidities, and general fitness levels.

While the lack of a link between exercise and fatigue is notable, it is necessary to recognize that improving QOL involves a greater scope than fatigue reduction. Even if the specific symptoms of fatigue do not improve significantly, exercise therapies may have broader effects on psychological well-being, social relationships, and the overall QOL. Because of the significant relationship found between exercise and QOL in this meta-analysis, future research should focus on optimizing exercise interventions, investigating the potential synergistic effects of exercise with other treatment modalities, and identifying specific patient characteristics that may influence the exercise response.

Other outcomes of interest were the 400-meter walk test, the 6-meter walk test, and the up-and-go time, all of which were found to have no significant association with our intervention. The control group showed a significant improvement in the 400-meter walk test. It is crucial to note that the number of studies reporting this outcome was minimal, which may limit the generalizability of the findings. Further research is required to explore the potential reasons for this counterintuitive finding. Our results are contrary to those of another meta-analysis that reported a significant improvement in cardiovascular fitness(33). This could be explained by the fact that our study only evaluated cardiovascular fitness via walking tests, while previous studies assessed cardiovascular fitness with VO2 max combined with other modalities such as the 600-meter walk test, leading to mismatched results with ours.

It is important to consider that physical functioning outcomes are modifiable and, thus, can be influenced by various factors beyond exercise interventions alone. Patient characteristics, disease progression, and other interventions or treatments may interact with exercise interventions and impact observed outcomes. Additionally, the specific types and intensities of exercise interventions used in the included studies may have contributed to the lack of significant effects on physical functioning measures. It is imperative to mention that there are multiple exercises, such as Flexibility and Stretching Exercises, Balance and Coordination Exercises, Mind-Body Practices, Interval Training, and Functional Training, all of which may reproduce different results.

While the lack of significant associations between exercise and the 400-meter walk test, the 6-meter walk test, and the up-and-go time are intriguing, it is crucial to interpret these findings within the context of the available literature and the limitations of the included studies. Future research should explore alternative exercise interventions, consider the influence of other factors on physical functioning outcomes, and increase the number of studies reporting on these measures to provide more robust evidence.

Several limitations of the studies included in this meta-analysis should be noted. First, the studies included in this meta-analysis had high heterogeneity in terms of participant characteristics such as age, disease stage, treatment history, and overall health status. These variations can introduce confounding factors that may have influenced the outcomes and contributed to the inconsistencies observed across studies. Furthermore, the outcome assessment tools and specific exercise interventions used in the included studies varied significantly in terms of type, intensity, duration, and frequency. These variations can lead to differences in the effectiveness of the interventions, making it challenging to draw definitive conclusions regarding the effects of exercise on the outcomes of interest. Additionally, the sample sizes of individual studies were relatively small, which affected the statistical power to detect significant associations. Moreover, the limited number of studies reporting certain outcomes, such as the 400-meter walk test, the 6-meter walk test, and the up-and-go time, further restrict the generalizability and reliability of the findings for these specific measures. The small number of studies reporting these outcomes reduced the overall sample size and may limit the representativeness of the results. Lastly, an important consideration is potential publication bias, where studies with positive or significant results are more likely to be published, whereas studies with null or negative results may be underrepresented. This bias can skew the overall findings and lead to overestimation of the true effect sizes.

Conclusion:

This review highlights the critical role of exercise in improving the quality of life of patients with prostate cancer. These findings have broad implications for health care practices and policies. Clinically, integrating exercise into cancer rehabilitation programs is paramount and requires healthcare professionals to prescribe and oversee personalized exercise plans. A collaborative approach involving oncologists, physical therapists, and exercise physiologists is essential for safe and effective implementation of exercise. Policymakers and healthcare systems should invest in infrastructure to facilitate physical activity for cancer patients, including dedicated exercise spaces and community programmes. This study also acts as a springboard for future research to explore comprehensive exercise protocols and address challenges such as fatigue and physical activity in cancer treatment. Further research should examine the role of digital health technologies in enhancing exercise adherence. Overall, these insights underscore the importance of exercise in cancer care, enhancing patient outcomes, and overall quality of life.

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The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Figure 1: PRISMA Flow Chart

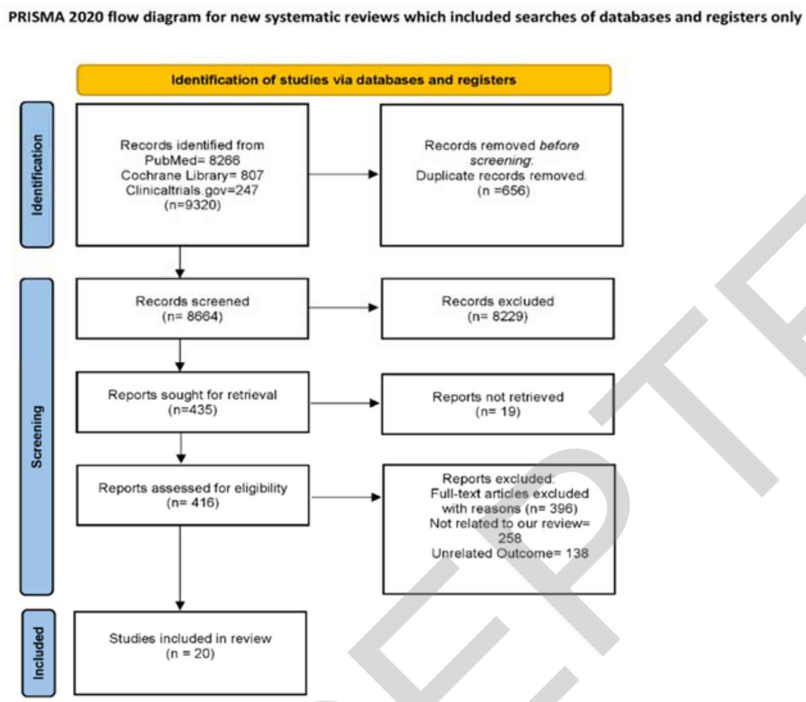


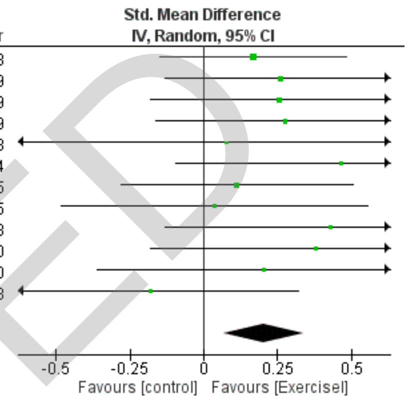
Figure 2: Forest Plots

A) QoL B) Fatigue C) 400-meter walk test D) 6-meter walk test E) Up and go time.

A)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Segal RJ et al.	120.2	15.9	82	117.6	14.9	73	18.2%	0.17 [-0.15, 0.48]	2003
Reed SNC et al.	73.12	15.96	53	69	15.12	47	11.7%	0.26 [-0.13, 0.66]	2009
Segal RJ et al (a)	37.7	6.7	40	36	6.4	41	9.5%	0.26 [-0.18, 0.69]	2009
Segal RJ et al (b)	37.8	6.5	40	36	6.4	41	9.5%	0.28 [-0.16, 0.71]	2009
Cormie P et al.	46.5	9.4	10	45.8	7.8	10	2.4%	0.08 [-0.80, 0.95]	2013
Winters-stone KM et al.	93.9	9	29	86.7	20.7	22	5.8%	0.47 [-0.09, 1.03]	2014
Buffart et al.	76.9	16	50	75	17.8	50	11.8%	0.11 [-0.28, 0.50]	2015
Nilsen et al.	79.6	17	27	78.9	20.7	30	6.7%	0.04 [-0.48, 0.56]	2015
Bourke L et al.	84	7.2678	25	79	14.5356	25	5.8%	0.43 [-0.13, 0.99]	2018
Ndjavera W et al.	126	15	24	120	16	26	5.8%	0.38 [-0.18, 0.94]	2020
Piraux E et al.	82.5	25.57	24	77.9	17.76	24	5.7%	0.21 [-0.36, 0.77]	2020
Sheill et al.	120.89	24.67	30	125.12	21.525	31	7.2%	-0.18 [-0.68, 0.32]	2023
Total (95% CI)			**434**			**420**	**100.0%**	**0.20 [0.07, 0.34]**	

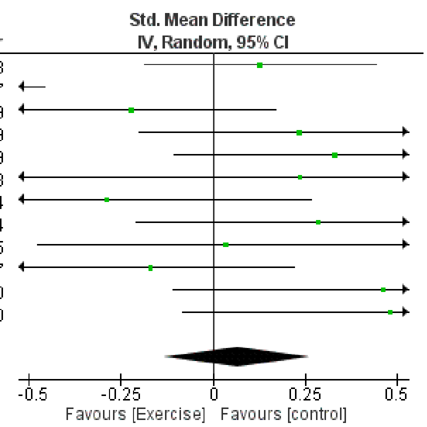
Heterogeneity: Tau² = 0.00; Chi² = 5.07, df = 11 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.93 (P = 0.003)



B)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Segal RJ et al.	41.6	10.5	82	40.3	9.4	73	12.6%	0.13 [-0.19, 0.45]	2003
Monga U et al.	0.8	1.8	11	3.8	2.2	10	3.3%	-1.44 [-2.42, -0.46]	2007
Reed SNC et al.	4.15	1.58	53	4.46	1.12	47	10.7%	-0.22 [-0.62, 0.17]	2009
Segal RJ et al (b)	44.2	8.9	40	42.1	8.8	41	9.8%	0.24 [-0.20, 0.67]	2009
Segal RJ et al (a)	45.1	9.1	40	42.1	8.8	41	9.7%	0.33 [-0.11, 0.77]	2009
Cormie P et al.	8.8	24.9	10	3.8	13.7	10	4.0%	0.24 [-0.64, 1.12]	2013
Winters-stone KM et al.	8.83	3.19	29	9.83	3.66	22	7.5%	-0.29 [-0.85, 0.27]	2014
Cormie P et al	43.8	6.8	32	41.4	9.5	31	8.6%	0.29 [-0.21, 0.78]	2014
Nilsen et al.	33.7	16.1	28	33	22.3	30	8.2%	0.04 [-0.48, 0.55]	2015
Taaffe DR et al.	17.7	15	54	20.3	15.3	48	10.8%	-0.17 [-0.56, 0.22]	2017
Piraux E et al.	40.5	9.8	24	35.3	12.1	24	7.3%	0.46 [-0.11, 1.04]	2020
Ndjavera W et al.	43.7	8.6	24	39.3	9.3	26	7.4%	0.48 [-0.08, 1.05]	2020
Total (95% CI)			**427**			**403**	**100.0%**	**0.07 [-0.13, 0.26]**	

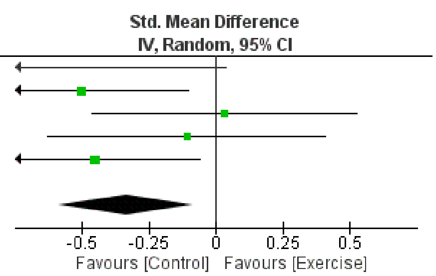
Heterogeneity: Tau² = 0.06; Chi² = 21.07, df = 11 (P = 0.03); I² = 48%
Test for overall effect: Z = 0.65 (P = 0.51)



C)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Cormie P et al.	246.9	32.9	10	286.5	50.5	10	6.8%	-0.89 [-1.82, 0.04]	2013
Galvao DA et al	270.4	7.3	50	274.1	7.3	50	27.1%	-0.50 [-0.90, -0.10]	2014
Cormie P et al	254.4	42.8	32	253	40.6	31	19.9%	0.03 [-0.46, 0.53]	2014
Galvao DA et al.	245.2	32.9	28	249.3	41	29	18.4%	-0.11 [-0.63, 0.41]	2018
Newton RU et al.	241.9	37.8	54	263.7	56.9	50	27.9%	-0.45 [-0.84, -0.06]	2020
Total (95% CI)			**174**			**170**	**100.0%**	**-0.34 [-0.59, -0.08]**	

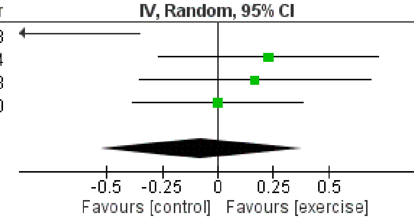
Heterogeneity: Tau² = 0.02; Chi² = 5.26, df = 4 (P = 0.26); I² = 24%
Test for overall effect: Z = 2.61 (P = 0.009)



D)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Cormie P et al.	4.23	0.33	10	4.76	0.42	10	13.9%	-1.34 [-2.34, -0.35]	2013
Cormie P et al	4.32	0.62	32	4.2	0.38	31	27.6%	0.23 [-0.27, 0.73]	2014
Galvao DA et al.	4.8	1	28	4.6	1.3	29	26.7%	0.17 [-0.35, 0.69]	2018
Newton RU et al.	4.4	0.6	54	4.4	0.5	50	31.8%	0.00 [-0.38, 0.38]	2020
Total (95% CI)			**124**			**120**	**100.0%**	**-0.08 [-0.53, 0.38]**	

Heterogeneity: Tau² = 0.13; Chi² = 8.27, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 0.34 (P = 0.74)



E)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Cormie P et al.	6.97	1.02	10	7.32	1.17	10	34.3%	-0.31 [-1.19, 0.58]	2013
Galvao DA et al.	7.5	2.5	28	6.8	1.4	29	65.7%	0.34 [-0.18, 0.87]	2018
Total (95% CI)			**38**			**39**	**100.0%**	**0.12 [-0.48, 0.72]**	

Heterogeneity: Tau² = 0.07; Chi² = 1.53, df = 1 (P = 0.22); I² = 35%
Test for overall effect: Z = 0.39 (P = 0.70)

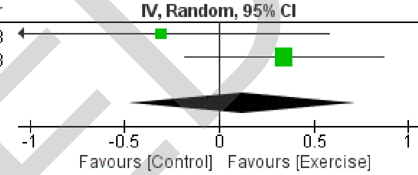
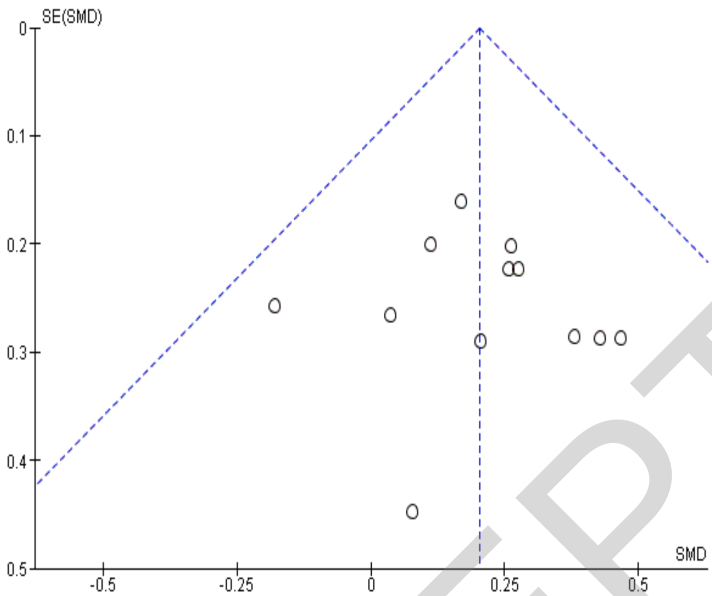


Figure 3: Funnel plots

1) **Fatigue 2) QoL**



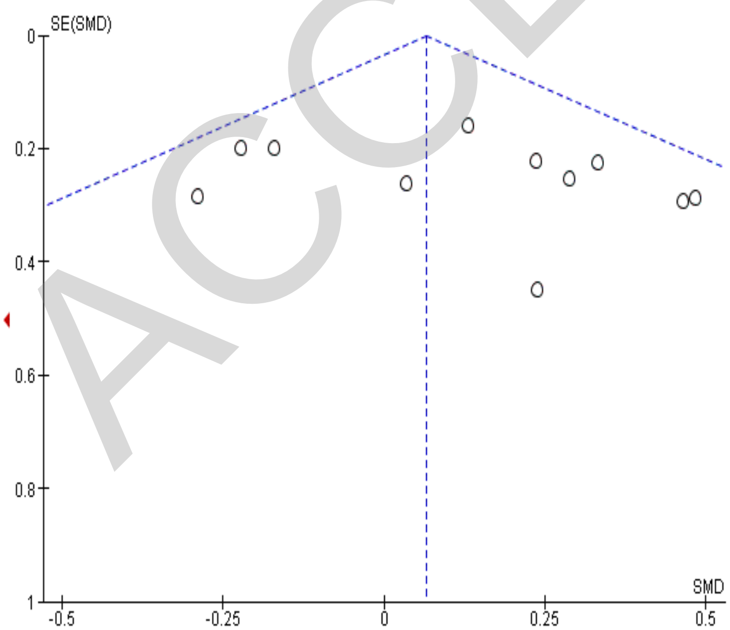


Table 1: Study characteristics

Author (year)	Study Type	Interventions	Intervention Details	Population Characteristics		Outcomes
				Intervention	Control	
Galvao DA et al. 2018[12]	RCT	Exercise (aerobic and resistance) vs stretching	12-week program with supervised intervention 3 times per week. Resistance exercise comprised 10-12 RM, which was increased at a rate of 5-10% for the next session. Aerobic exercise comprised 2-30 mins at 60-85% of maximal heart rate.	N= 28 Age= 69.7±7.6 BMI=28.9±4.1 ADT= 27(96.4)	N= 29 Age= 70.4±9.3 BMI= 28.5±4.0 ADT= 27 (93.1)	Fatigue, 6m walk test, 400m walk test, and up and go time
Newton RU et al. 2020[13]	RCT	Aerobic and resistance vs stretching	Resistance training was done at an intensity of 6-12 RM for 2-4 sets per exercise. The aerobic component consisted of jogging/walking on a treadmill, and	N= 54 Age= 69.0±6.3 BMI= 27.5±4.4	N= 50 Age=67.5±7.7 BMI= 28.3±3.9	6m walk test and 400m walk test.

			cycling or rowing at an intensity of 60-85% estimated maximum heart rate for 25-40 min.			
Piraux E et al. 2020[14]	RCT	Resistance training vs usual care	Resistance training comprised of 1-3 sets of 8-12 repetitions using resistance bands or dumbbells for about 30 min.	N= 24 Age= 67.9±7.1 BMI= 26.1±2.9	N= 24 Age= 71.9±8.1 BMI= 25.8±4.4	Fatigue and QoL
Cormie P et al. 2013[15]	RCT	Resistance training vs usual care	Twice weekly sessions for 12 weeks of 60 mins each with 5 min warmup and 110 min cool down period consisting of low aerobic exercise and stretching	N= 10 Age= 73.1±7.5 BMI= 29.1±3.1 Time for diagnosis of bone metastasis (years)= 1.0±1.1	N= 10 Age= 71.2±6.9 BMI= 28.3±4.0 Time for diagnosis of bone metastasis (years)= 1.0±1.0	Physical functions , Fatigue, and QoL
Ashton RE et al. 2021[11]	RCT	Resistance exercise vs usual care	Weekly sessions using resistance bands for 6 months. It was performed with 30-60s interpolated	N= 20 Age= 64.6±6.2 BMI= 28.1±3.5	N= 22 Age= 66.9±6.8 BMI= 28.3±4.1	QoL and Fatigue

			rest intervals until 3 sets of each exercise has been performed			
Ndjavera W et al. 2020[16]	RCT	Aerobic and resistance vs usual care	2 supervised session every week for 12 weeks. Each session lasted for 60 mins and consisted of aerobic interval exercise on a cycle ergometer followed by resistance training.	N= 24 Age= 71.4±5.4 BMI= 28.4±3.1	N= 26 Age= 72.5±4.2 BMI= 27.7±3.4	QoL and Fatigue
Winters-stone KM et al. 2014[17]	RCT	Intensity resistance training vs stretching	2 supervised sessions and 1 home-based session every week for 12 months	N= 29 Age= 69.9±59.3 BMI= 28.4±4.1	N= 22 Age= 70.5±7.8 BMI= 29.6±4.8	QoL and Fatigue
Taaffe DR et al. 2017[18]	RCT	Aerobic and resistance training vs usual care	Resistance training comprised of 2-4 sets of each exercise at an intensity of 6-12 RM. The aerobic component comprised of 20-30 mins of exercise at 60-75% of maximal heart rate.	N= 54 Age= 69±9.3 Time for diagnosis of bone metastasis (months)= 5.3±7.6	N= 48 Age= 68.4±9.1 Time for diagnosis of bone metastasis (months)= 3.7±3.7	Fatigue

Langlais CS et al. 2023[19]	RCT	Aerobic and resistance training vs usual care	Resistance exercise consisted of 3 sessions per week for 12 weeks and sets progressed from 1-4 of 4-14 repetitions. Aerobic sessions occurred 3 times a week using a cycle ergometer.	**Aerobic** N= 8 **Resistance** N= 7	N=10	Fatigue and QoL
Segal RJ et al. 2003[20]	RCT	Resistance training vs control	Supervised resistance sessions were carried out 3 times a week for 12 weeks at 60-70% of 1-RM.	N= 82 Age= 68.2±7.9 BMI= 29.0±3.5	N= 73 Age= 67.7±7.5 BMI= 28.5±3.7	Fatigue and QoL
Reed SNC et al. 2009[21]	RCT	Aerobic and light resistance vs wait-list	16 weeks of aerobic and light resistance training.	N= 53 Age= 67.2±8.8	N= 47 Age= 68.0±8.0	Fatigue and QoL
Segal RJ et al. 2009[22]	RCT	Aerobic, Resistance, and Control	Resistance training comprised of 3 sessions per week with two sets of 8-12 repetitions. Aerobic training participants exercised thrice weekly	**Aerobic** N= 40 Age= 66.2±6.8 BMI= 28.9±3.4 **Resistance**	N= 41 Age= 65.3±7.6 BMI= 29.0±4.2	Fatigue and QoL

			on a cycle ergometer, treadmill, or elliptical trainer beginning at 50% to 60% and later increasing to 70-75% of their predetermined peak oxygen consumption. The exercise program lasted for 24 weeks	N= 40 Age= 66.4±7.6 BMI= 28.1±3.5		
Galvao DA et al., 2014[30]	RCT	resistance and aerobic training vs physical activity	Progressive resistance and aerobic training twice per week for 6 months. The resistance exercises progressed in loading from 12- to 6-repetition maximum (RM) for two to four sets per exercise. The aerobic training included 20–30 min of cardiovascular exercises at 70–85% maximum heart rate and perceived	N= 50 Age= 71.9 (5.6) BMI=24.9 (3.3)	N= 50 Age= 71.5 (7.2) BMI= 24.9 (3.1)	400-meter walk test

			exertion at 11–13.			
Nilsen et al., 2015[29]	RCT	high-load strength training vs usual care	3 sessions/week for 16 weeks. The first two weeks included low resistance at 40–50% of 1 RM, the rest of the training programme followed a linear progression in training volume from one to three sets of 10RM on Mondays, and from two to three sets of 6RM on Fridays.	N= 28 Age= 66(6.6) ADT= 17 (8.7)	N= 30 Age= 66 (5) ADT= 18 (8.2)	QoL and Fatigue
Buffart et al., 2015[28]	RCT`	aerobic and resistance exercise vs physical activity	The resistance exercises progressed from 12 RM to 6 RM for 2 to 4 sets per exercise. Aerobic exercises were included for 20 to 30 minutes at 70% to 85% of the maximum heart rate. An additional 90 minutes of	N= 50 Age= 71.9 (5.6) BMI= 24.9 (3.3)	N= 50 Age= 71.5 (7.2) BMI= 24.9 (3.1)	QoL

			home-based aerobic exercise per week was advised to complement the 60 minutes of supervised aerobic exercise training using the same intensity as prescribed during supervised exercise sessions.			
Sheill et al. 2023[23]	Multi-centre two-armed randomised controlled trial (RCT)	Aerobic exercise vs standard care	The exercise group participated in a 6-month moderate to vigorous intensity aerobic exercise comprising a weekly class and a home-based aerobic exercise programme. Whereas the control group was offered the standard physical activity	N= 30 Age (years)= 69.8 ± 7.0 BMI (kg/m2) = 28.4 ± 4.84 Time since cancer diagnosis (months)= 37.36 (32.30)	N= 31 Age (years)= 69.9 ± 7.5 BMI (kg/m2) = 29.9 ± 4.35 Time since cancer diagnosis (months)=30.23	QoL
Cormie P et al.	RCT	Aerobic and Resistance training vs	The exercise intervention involved	N=32 Age, years=	N= 31 Age, years=	Fatigue, 6-meter walk test

2014[24]		usual care	twice weekly exercise sessions for 3 months. The sessions were ≈60 min in duration. The aerobic exercise component included 20–30 min of cardiovascula r exercise and target intensity was set at approximately 70–85% of the estimated maximum heart rate. The resistance training intensity was manipulated fa rom 6–12 repetition maximum and was increased by a 5–10% increment for the next set/training session.	69.6 ± 6.5 BMI, kg/m2= 29.3 ± 4.5 Time since ADT injection, days= 6.2 ± 1.6	67.1 ± 7.5 BMI, kg/m2= 29.6 ± 2.6 Time since ADT injection, days=5.6 ± 2.0	and 400-meter walk test
Windsor et al., 2004[25]	RCT	Aerobic training vs usual care	Home-based, moderate-intensity, continuous walking for 30 minutes on at least 3 days of each week of	N= 32 Age (yrs)= 68.3 ± 0.9 Weight= 81.6 ± 2.57	N= 33 Age (yrs)= 69.3 ± 1.3 Weight (kg)= 82.9 ± 1.76	Fatigue

			radiotherapy at a target heart rate of 60–70% calculated maximum heart rate (as a guide to the intensity of the activity).			
Bourke L et al., 2018[26]	RCT	Aerobic exercise vs usual care	Aerobic ET was undertaken for 12 months with intensity set at between 65% to 85% of age-predicted maximum heart rate or 12 to 17 on the Borg rating of perceived exertion (RPE) scale	N= 25 Age (years)=68 (6) BMI (Kg.m2) =26.7 (2.4)	N= 25 Age (years)=67 (9) BMI (Kg.m2)= 27.7 (3.2)	QoL
Monga U et al., 2007[27]	RCT	Aerobic training vs patient education	The exercise protocol consisted of a 10-minute warm-up, a 30-minute aerobic segment consisting of walking on a treadmill, and a 5- to 10-minute cool-down period	N= 11 Age (y)= 68+4.2 Weight (lb)= 177.3+29.1 PSA 7.4+5.7	N= 10 Age= 70.6+5.3 Weight (lb)= 80.1+28.8 Mean PSA= 6.4+5.0	Fatigue (PFS)

6MWT: 6-minute walk test; RM: Repetition maximum, PFS: Piper Fatigue Scale; FACT-P: Functional Assessment of Cancer Therapy-Prostate

Table 2: Outcomes

Author (year)	Fatigue	Quality of Life	Physical Functions
Galvao DA et al. 2018[12]	No change in fatigue (P=0.964) was assessed by the Functional Assessment of Chronic Illness therapy.	-	**6-m usual walk** **Exercise** Baseline:4.5±0.9 12weeks/3month:4.8±1.0 **Control** Baseline:4.6±1.1 12weeks/3month:4.6±1.3 **400-m walk** **Exercise** Baseline:249.1±38.7 12weeks/3month:245.2±32.9 **Control** Baseline:252.0±47.7 12weeks/3month:249.3±41.0 **Up and go** **Exercise** Baseline:7.5±2.4 12weeks/3month:7.5±2.5 **Control** Baseline:6.9±1.6 12weeks/3month:6.8±1.4

Newton RU et al. 2020[13]	-	-	**6-m usual walk** **Exercise** Baseline:4.2±0.6 6 months:4.4±0.6 **Control** Baseline:4.2±0.7 6 month:4.4±0.5 **400-m walk** **Exercise** Baseline:246.8±36.1 6 months:241.9±37.8 **Control** Baseline:258.7±53.8 6 months:263.7±56.9
Piraux E et al. 2020[14]	CTRF measured using FACIT-F **Exercise** Baseline:41.2±7.7 End:40.5±9.8 **Control** Baseline:41.1±9.0 End:35.3±12.1	Cancer-related QoL using **FACT-G.** **Exercise** Baseline:83.5 (95%CI=75.5-91.8) End:82.5 (95%CI=72.3-93.9) **Control**	

		Baseline:79.3 (95%CI=73.3-83.3) End:77.9 (95%CI=67.5-85.4)	
Cormie P et al. 2013[15]	**MFSI-SF** **Exercise** Baseline:5.2±16.8 12weeks:8.8±24.9 **Control** Baseline:6.0±12.3 12weeks:3.8±13.7	**SF-36** **Exercise** Baseline:44.2±9.0 12weeks:46.5±9.4 **Control** Baseline:45.0±11.4 12weeks:45.8±7.8	**6-m usual walk** **Exercise** Baseline:4.48±0.54 12weeks:4.23±0.33 **Control** Baseline:4.45±0.56 12weeks:4.76±0.42 **400-m walk** **Exercise** Baseline:252.1±40.8 12weeks:246.9±32.9 **Control** Baseline:280.8±53.0 12weeks:286.5±50.5 **Timed Up and go** **Exercise** Baseline:7.41±1.50 12weeks:6.97±1.02 **Control** Baseline:7.59±1.91 12weeks:7.32±1.17

Ashton RE et al. 2021[11]	**Brief Fatigue Inventory (BFI)** **Exercise** Baseline:1.2±1.2 **Control** Baseline:1.9±1.4 Mean Difference at 6 months: -0.1 (-0.9, 0.6)	**FACT-G** **Exercise** Baseline:91.9±10.0 **Control** Baseline:88.8±12.1 Mean Difference at 6 months: 0.9 (-4.0, 5.7)	-
Ndjavera W et al. 2020[16]	**FACIT-F** **Exercise** Baseline:41.8±10.2 6 months:43.7±8.6 **Control** Baseline:42.9±8.4 6 months:39.9±9.3	**FACT-P** Baseline:119±19 6 months:126±15 **Control** Baseline:123±16 6 months:120±16	-
Winters-stone KM et al. 2014[17]	**Schwartz Cancer Fatigue Scale** Baseline:9.87±4.47 12 months:8.83±3.19 **Control** Baseline:9.92±3.58 12 months:9.83±3.66	**QLQC30** Baseline:87.5±14.3 12 months:93.3±9.0 **Control** Baseline:89.7±15.3 12 months:86.7±20.7	-

Taaffe DR et al. 2017[18]	QLQC30 **Exercise** Baseline:23.4±18.1 6 months:21.9±18.4 **Control** Baseline:25.8±20.2 12 months:24.6±17.7		-
Langlais CS et al. 2023[19]	**Control** Baseline:24.4±20.2 12weeks: -2.2(12.6) Mean change (SD) **Resistance** Baseline:16.7±8.3 12weeks: 0.0(7.2) Mean change (SD) 12weeks vs control (95%CI): 2.2(-16.3,20.8) **Aerobic** Baseline:36.1±27.1 12weeks: 4.4(6.1) Mean change (SD) 12weeks vs control (95%CI): 6.7(-3.8,17.1)	**Control** Baseline:93.9±9.9 12weeks: -6.0(8.6) Mean change (SD) **Resistance** Baseline:96.7±5.6 12weeks: -1.1(5.0) Mean change (SD) 12weeks vs control (95%CI): 4.9(-2.4,12.2) **Aerobic** Baseline:91.7±5.9 12weeks: -1.3(9.9) Mean change (SD) 12weeks vs control (95%CI): 4.7(-7.6,16.9)	
Segal RJ et al.	**Exercise**	**FACT-P**	-

2003[20]	Baseline:40.8±10.6 12 weeks:41.6±10.5 **Control** Baseline:42.5±8.5 12 weeks:40.3±9.4	**Exercise** Baseline:118.2±16.7 12 weeks:120.2±15.9 **Control** Baseline:120.9±13.6 12 weeks:117.6±14.9	
Reed SNC et al. 2009[21]	**FSS** **Exercise (N=37)** Baseline:4.49±1.45 16 weeks:4.15±1.58 **Control (N=24)** Baseline: 4.50±1.33 16 weeks:4.46±1.12	**EORTC-30** **Exercise (N=40)** Baseline:70.42±17.39 16 weeks:73.12±15.96 **Control (N=25)** Baseline:71.33±18.65 16 weeks:69.00±15.12	-
Segal RJ et al. 2009[22]	**FACT-F** **Control** Baseline:44.6±8.7 24weeks: 42.1±8.8 **Resistance** Baseline:42.8±8.7 24weeks: 45.1±9.1 **Aerobic** Baseline:44.1±8.7 24weeks: 44.2±8.9	**FACT-P** **Control** Baseline:37.1±6.4 24weeks: 36.0±6.4 **Resistance** Baseline:37.4±6.4 24weeks: 37.7±6.7 **Aerobic** Baseline:37.5±6.4 24weeks: 37.8±6.5	-

Galvao DA et al., 2014[30]		**EORTC QLQ-C30** **Exercise** Baseline:77.3±16.7 12 months:76.9±16.0 **Control** Baseline:78.5±15.9 12 months:75.0±17.8	
Nilsen et al., 2015[29]	**EORTC QLQ-C30 symptom scales** **Exercise:** N= 28 Baseline: 34.5±15.2 16 weeks: 33.7±16.1 **Control:** N= 30 Baseline: 36.5±14.9 16 weeks: 33±22.3	**EORTC QLQ-C30** **Exercise:** N= 27 Baseline: 76.5±17.3 16 weeks: 79.6±17 **Control:** N= 30 Baseline: 66.7±19.6 16 weeks: 78.9±20.7	
Buffart et al., 2015[28]			**400-m Test** **Exercise:** Baseline: 288.0±7.6 12 months: 270.4±7.3 **Control:** Baseline: 276.5±7.6

			12 months: 270.4±7.3
Sheill et al. 2023[23]	-	**Exercise:** Baseline=120.3+21.096 6 months= 120.89+24.674 **Control:** Baseline=119.96+20.733 6 months=125.12+21.525	
Cormie P et al. 2014[24]	Fatigue (FACIT-Fatigue): **Exercise** Baseline= 43.7 (8.3) 3-months=43.8 (6.8) **Control** Baseline= 44.8 (8.5) 3-months= 41.4 (9.5)	-	**400-m walk, s:** **Exercise group:** Baseline= 260.9 (44.3) 3-months= 254.4 (42.8) **Control group:** Baseline= 248.5 (36.8) 3-months= 253.0 (40.6) **6-m walk – usual pace, s:** **Exercise group:** Baseline= 4.36 (0.65) 3-months=4.32 (0.62) **Control group:** Baseline= 4.04 (0.57) 6-months= 4.20 (0.38)
Windsor et al., 2004[25]	Men in the control group had significant increases in fatigue scores from baseline to the end of radiotherapy (P = 0.013), with no	-	-

	significant increases observed in the exercise group (P = 0.203).		
Bourke L et al., 2018[26]	-	**Intervention group:** Baseline= 71 (64, 79) 12-month= 84 (80, 87) **Control group:** Baseline= 71 (64, 78) 12-month= 79 (73, 85)	-
Monga U et al., 2007[27]	**Intervention group:** Pre-radiotherapy= 2.4+2.4 Post-radiotherapy= 0.8+1.8 Difference=-1.6+2.0 **Control Group:** Pre-radiotherapy= 1.1+1.9 Post-radiotherapy= 3.8+2.2 Difference=2.7+2.2	-	-

CTRF: Cancer Treatment-Related Fatigue, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, FACT-G: Functional Assessment of Chronic Illness Therapy-General, MFSI-SF: Multidimensional Fatigue Symptom Inventory Short Form, FACT-P: Functional Assessment of Cancer Therapy-Prostate, QLQC30: Quality of Life questionnaire, FACT-F: Functional Assessment of Cancer Therapy-Fatigue, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, FSS: Fatigue Subscale

Table 3: Risk of Bias

Author (year)	Random Sequence Generation	Allocation Concealment	Selective Reporting	Blinding of Participants/Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Other Sources of Bias
Galvao DA et al. 2018	Low Risk	Low Risk	Low Risk	High risk	Unclear	Low Risk	Low Risk
Newton RU et al. 2020	Low Risk	Low Risk	Low Risk	High risk	Unclear	Low Risk	Low Risk
Piraux E et al. 2020	Low Risk	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk
Cormie P et al. 2013	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk
Ashton RE et al. 2021	Low Risk	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk
Ndjavera W et al. 2020	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk
Winters-stone KM et al.	Low Risk	Unclear	Low Risk	High Risk	Unclear	Low Risk	Low Risk

2014							
Taafe DR et al. 2017	Low Risk	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk
Langlais CS et al. 2023	Low Risk	Unclear	Low Risk	High Risk	Low Risk	Low Risk	Low Risk
Segal RJ et al. 2003	Low Risk	Low Risk	Low Risk	High Risk	Unclear	Unclear	Low Risk
Reed SNC et al. 2009	Low Risk	High Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk
Sejal RJ et al. 2009	Low Risk	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk
Buffart et al., 2015	Low Risk	Low Risk	Low Risk	High risk	High risk	Low Risk	Low Risk
Nilsen et al., 2015	Low Risk	Low Risk	Low Risk	Unclear	Unclear	Low Risk	Low Risk
Galvao DA	Low Risk	Low Risk	Low Risk	Unclear	Unclear	Low Risk	Low Risk

et al., 2014							
Sheill et al. 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cormie P et al. 2014	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Windsor et al., 2004	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Bourke L et al., 2018	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Monga U et al., 2007	Unclear	Unclear	Low risk	High-risk	Low risk	Low risk	High-risk