



Fatigue  
Systematic Reviews / Meta-analysis Table

Review Author	Study Information	Conclusions and Implications
<b>Exercise: PEP Weight of Evidence Category: Recommended for Practice</b>		
<p>Courneya &amp; Friedenreich, 1999<sup>3</sup></p>	<p><b>Search strategy:</b> MEDLINE®, CancerLit, CINAHL®, Heracles, PsychINFO, SPORT Discus through 1997</p> <p><b>Trials evaluated:</b> 18 intervention studies (10 quasi-experimental and 8 experimental designs) of physical exercise designed to improve cardiovascular and/or muscular fitness; the sample sizes ranged from 8–70 participants. Studies restricted solely to movement therapy and/or stretching or flexibility exercises for rehabilitation of range of motion were excluded. Studies also were excluded if they presented insufficient detail to allow for critical review.</p> <p><b>Sample:</b> Most of the studies were conducted in patients with or survivors of breast cancer who predominantly had stage I or II disease. A few studies evaluated exercise in patients with leukemia following allogeneic stem cell transplantation and patients with solid tumors following autologous stem cell transplantation. Single studies were found for survivors of head and neck cancer and survivors of colorectal or childhood cancer.</p> <p><b>Outcome(s):</b> fatigue, health-related quality of life, symptom distress, immune function, physical exercise capacity (VO<sub>2</sub> max), and other physical performance measures</p> <p><b>Treatment evaluated:</b> cycle ergometer (8 studies), walking alone or in combination with some other exercise mode (6 studies), resistance training (1 study), or unspecified (3 studies); the length of the intervention was 12 weeks or less in 14 studies, four to six months in three studies, and one year in one study. Exercise was supervised (13 studies), unsupervised and home based (3 studies), and partially supervised (2 studies).</p>	<p>The reviewed studies indicate promising effects on physiologic and psychological outcomes. Three studies reported a significant reduction in fatigue. Although effect sizes could not be summarized across studies because of the diversity of outcomes with small numbers of effect sizes, the effects appear to be robust and clinically significant. Major study limitations include the use of small convenience samples, the absence of appropriate control groups, the restricted range of cancer sites, and the short intervention period (in most studies, the exercise treatment lasted 12 weeks or less). Additional studies are needed to examine the effect of exercise specifically on the endpoint of fatigue.</p>
<p>Stricker et al., 2004<sup>2</sup></p>	<p><b>Search strategy:</b> MEDLINE, CINAHL, and the Database of Abstracts of Reviews Effects through October 2003; proceedings of the annual meetings of the American Society of Clinical Oncology, American College of Sports Medicine, and Oncology Nursing Society</p> <p><b>Trials evaluated:</b> 20 experimental studies (9 randomized clinical trials and 11 quasi-experimental studies), sample sizes ranging from 9–11 participants</p> <p><b>Sample:</b> adults with breast cancer, mixed solid tumors, or hematologic malignancies; patients receiving active treatment, including stem cell transplantation, radiation, chemotherapy, and palliative care; and long-term survivors</p> <p><b>Outcome(s):</b> fatigue</p> <p><b>Treatment evaluated:</b> physical activity or exercise; group or individual</p>	<p>Strong evidence supports the effectiveness of home-based exercise programs performed by middle-aged women undergoing adjuvant chemotherapy or radiation therapy for nonmetastatic breast cancer. Some evidence indicates that exercise may be equally beneficial in other cancer populations, including individuals with solid tumor and hematologic malignancies, and cancer survivors. Based on the current evidence, low-intensity exercise individualized to patient comfort is the only type of exercise that can be considered safe for patients in palliative care settings. Evidence supports the efficacy of aerobic laboratory-based interval training in individuals receiving peripheral blood stem cell transplantation. All studies had some design limitations, including small sample sizes, a lack of random assignment, the absence of control groups, and a failure to control for anemia levels, intensity of chemotherapy, and the timing of the fatigue measurement in relationship to chemotherapy treatments.</p>
<p>Oldervoll et al., 2004<sup>6</sup></p>	<p><b>Search strategy:</b> PubMed, PsychInfo, CancerLit, and the Cochrane Library through May 2003</p> <p><b>Trials evaluated:</b> 12 randomized trials, with sample sizes ranging from 21–155 patients;</p>	<p>The reviewed studies indicate promising effects on physiologic and psychological outcomes. However, the studies differed widely in the length of the exercise program and its intensity, content, and frequency, as well as the timing of the interventions in relation to patients' disease and treatment. Three studies reported a significant reduction in fatigue. One study</p>

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	<p>nonrandomized trials, pilot studies, and studies in which exercise was combined with other therapies such as cognitive therapy or diet were excluded.</p> <p><b>Sample:</b> Nine studies included patients with breast cancer, mostly stage I or II. The remaining studies used samples with mixed diagnoses, prostate cancer, and acute leukemia. In 10 of 12 studies, the intervention was conducted when patients were undergoing radiation therapy and/or chemotherapy treatment; two trials implemented exercise after the treatment was finished. Eleven studies were performed with patients receiving treatment with curative intent, whereas one study included a mix of patients receiving treatment with curative or palliative intent.</p> <p><b>Outcome(s):</b> fatigue, health-related quality of life, physical exercise capacity (VO<sub>2</sub> max), and other physical performance measures</p> <p><b>Treatment evaluated:</b> aerobic exercise training (10 studies) and resistance exercise (2 studies)</p>	<p>observed a significant reduction in fatigue, although it did not reach statistical significance. In another study, no statistical analyses were performed to examine between-group differences. In many of the studies reporting data on quality of life, too many outcomes were listed (range = 2–12), and only four trials defined which variables were the primary endpoints.</p> <p>Randomized clinical studies tended to be small in scope, and focused mainly on patients with breast cancer. Complete knowledge about the type of physical exercise that is most beneficial for patients at different stages of disease is lacking. Future exercise intervention studies should identify fewer and more specific endpoints.</p>
<p>Stevinson et al., 2004<sup>1</sup></p>	<p><b>Search strategy:</b> MEDLINE, Embase, Cochrane Controlled Trials Register, CancerLit, CINAHL, PsycInfo, and SportDiscus through December 2003</p> <p><b>Trials evaluated:</b> 33 studies (25 randomized trials and 8 nonrandomized studies) reported in 40 different articles were included in the review. Data were pooled for 10 trials that assessed physical functioning and 12 trials that assessed fatigue. Trials were included if they tested interventions involving regular exercise of any type (e.g., aerobic, resistance, flexibility). Exercise could be the sole intervention or combined with other interventions (e.g., diet counseling). Trials of single exercise sessions that measured acute effects were excluded, as were trials that investigated the effects of physiotherapy only. Prospective trials with a control arm were included. Control arms could comprise no intervention (e.g., usual care), an alternative intervention (e.g., counseling, relaxation), or a different type of exercise (e.g., aerobic versus flexibility exercises). Trials with healthy or historic control groups were excluded. Based on a priori decision, both nonrandomized and randomized trials were included. No restrictions were included on the outcomes assessed in trials.</p> <p><b>Sample:</b> 13 trials involved patients with breast cancer during or after adjuvant therapy. Eleven trials included adult patients with any cancer, and one involved pediatric cancer survivors. The remaining trials included patients undergoing treatment for prostate, lung, colorectal, or stomach cancers; multiple myeloma; or leukemia.</p> <p><b>Outcome(s):</b> Physical function, fatigue, body composition, immune function, hemoglobin/hematocrit, fasting insulin, glucose and insulin resistance, testosterone and prostate-specific antigen levels, treatment related symptoms, psychosocial outcomes, adherence to exercise interventions, tolerability.</p> <p><b>Treatment evaluated:</b> 19 studies tested aerobic exercise interventions: Eight used cycle ergometers, and eight used walking programs. Three trials tested resistive exercise, 10</p>	<p>Reductions in cancer-related fatigue were reported in 10 studies; however, in three studies, statistical significance was not reached or not tested. No differences between groups were reported for fatigue in six trials immediately after the intervention or several months later. Pooling the data from 12 trials that assessed fatigue suggested that no overall effect of exercise was found on symptoms of fatigue (standardized [standard deviation] mean difference in fatigue –0.15 (–0.38, 0.09). Heterogeneity between studies was not related to randomization, allocation concealment, intention-to-treat analysis, or choice of control. The effect did appear to vary by population type; some evidence exists in trials that recruited patients with any type of cancer that no effect of exercise on fatigue symptoms was found and trials that recruited patients with breast cancer that a modest reduction in symptoms of fatigue was found among patients allocated to exercise (standardized [standard deviation] mean difference in fatigue –0.52 –0.95, –0.09). There was no evidence in this meta-analysis of small study bias, as determined by the Beggs rank-order correlation test and the Egger regression approach.</p> <p>The authors generally concluded that methodologic limitations were associated with many of the studies and that the limitations may have contributed to inconsistencies among the results. The limitations included lack of randomized allocation, failure to conceal allocation, failure to specify the primary outcome measures, small sample sizes, and multiple statistical testing without adjustment of significance values. Two studies may have included participants in the control group who had declined to undertake the intervention, and five studies were unclear regarding whether eligibility (including willingness to participate) was determined prior to group allocation or whether the control group may have solely or partly consisted of those who declined to be allocated to exercise.</p>

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	<p>had combined aerobic and resistive programs, and one was based on team sport activities. Most trials compared an exercise intervention with no intervention; in six trials that did not, information training, psychological therapy, stretching, or tai chi was used as a comparison arm. Exercise interventions lasted for 10 weeks or more in 17 trials and two weeks or less in four studies. The longest intervention period of any trial was 26 weeks. Trial quality was assessed by recording whether the following features were incorporated in the study design: randomization, allocation concealment, blinding of the main outcome assessment, and intention-to-treat analysis.</p>	
<p>Schmitz et al., 2005<sup>7</sup></p>	<p><b>Search strategy:</b> MEDLINE through February 2005 was used to identify intervention studies designed to increase physical activity in adults. Only studies with a concurrent comparison group and results presented separately for treatment and comparison groups were included.</p> <p><b>Trials evaluated:</b> The quality of 32 studies was assessed using prespecified criteria for internal validity. Twenty-two of the 32 studies were rated as being of high methodologic quality and were retained for qualitative and quantitative analysis. The outcomes of physical activity interventions in patients receiving active treatment were analyzed separately from the studies of physical activity after treatment was concluded.</p> <p><b>Sample:</b> The average sample size for the intervention group was 28 participants, and the most common diagnosis included in the studies was breast cancer. The majority of the studies focused on the time period during or immediately following active cancer therapy. None focused on palliation.</p> <p><b>Outcome(s):</b> fatigue, health-related quality of life, symptom distress, immune function, hematocrit, body composition, physical exercise capacity (VO<sub>2</sub> max), and other physical performance measures</p> <p><b>Treatment evaluated:</b> aerobic physical activity of moderate to vigorous intensity three to five times per week for 20–30 minutes per session; most of the interventions were five weeks to three months long, with no follow-up at the end of the intervention. Most used a control group in which no physical activity or other treatment was prescribed, although a few studies provided an intervention for the comparison group.</p>	<p>A consistent positive effect of physical activity on fatigue is noted using qualitative study review techniques, but effect size calculations did not reveal an effect of physical activity on fatigue during treatment (weighted mean effect size 0.13, 95% confidence interval –0.06 to 0.33, p = 0.18) or after treatment (weighted mean effect size 0.16, 95% confidence interval –0.23 to 0.54, p = 0.43) or for vigor or vitality during treatment (weighted mean effect size 0.43, 95% confidence interval –0.07 to 0.94, p = 0.09). A large positive effect of exercise on vigor or vitality post-treatment was noted (weighted mean effect size 0.82, 95% confidence interval 0.05–1.6, p = 0.04). When fatigue and vigor or vitality were combined into one category (under the assumption that fatigue and vitality are the same attribute) and all studies were combined across treatment timing, the weighted mean effect size was still small (weighted mean effect size 0.19, p = 0.03).</p> <p>Limitations of the meta-analysis include that the reviewed studies used small, self-selected samples; were heterogeneous in terms of the outcome measures and interventions; and had gaps in the level of detail reported about individual study procedures and results. Results nevertheless support the conclusion that after treatment is complete, physical activity shows a large positive effect on vigor or vitality. Some support exists from qualitative analysis of a consistent effect of physical activity on fatigue, although the magnitude of the effect may be too small to be clinically meaningful. The study findings also support a preliminary conclusion that physical activity is generally well tolerated during and after cancer treatment, although the available literature does not allow conclusions to be drawn regarding adverse events from participation.</p>
<p>Knols et al., 2005<sup>5</sup></p>	<p><b>Search strategy:</b> MEDLINE, CINAHL, Cochrane Library, CancerLit, and PEDro through June 2004 to identify randomized, controlled trials and controlled trials (i.e., those with a comparison group but without explicit use of randomization for purposes of group allocation); to be included in the review, the trials had to have examined the effects of physical exercise after surgery or during or after chemotherapy, radiotherapy, and/or hormonal therapy. Only exercise interventions designed to improve endurance or muscular strength were included. Studies of relaxing exercises (e.g., yoga, tai chi) were excluded.</p> <p><b>Trials evaluated:</b> The methodologic quality (using the Delphi criteria list, a set of nine criteria for quality assessment of clinical trials) and substantive results of 34 randomized, controlled trials and controlled trials were examined. Of the 34 studies examined, 22</p>	<p>A clinically significant or statistically significant positive effect of physical activity specifically on fatigue was noted during (3 studies) or after (2 studies) breast cancer treatment and during (3 studies) or after treatment (1 study) in a mixed solid tumor population.</p> <p>The median score on the Delphi criteria list assessing methodologic quality (range 1–7) was 4 for both studies of exercise during treatment and exercise after cancer treatment. 25 trials satisfied more than three criteria on the Delphi criteria list. The most commonly observed methodologic problems were with concealment of treatment allocation, blinding of the outcome assessor, and failure to employ an intention-to-treat data analysis strategy. Overall, the authors concluded that the trials included in the review were of moderate methodologic quality, with a trend toward more methodologic rigor in more recent studies.</p>

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	<p>evaluated the effectiveness of physical exercise during medical treatment and 12 focused on the period after medical treatment.</p> <p><b>Sample:</b> The studies during medical treatment were divided into three categories: (1) exercise during breast cancer treatment, (2) exercise during bone marrow and peripheral blood stem cell transplantation, and (3) exercise during medical treatment for mixed solid tumors. The studies after medical treatment were divided into those involving exercise after breast cancer treatment and exercise after medical treatment for other solid tumors. The authors used this strategy to reflect not only the differences in cancer diagnosis and the timing of physical exercise programs but also possible differences in motivation, safety, feasibility, and efficacy of exercise. The sample sizes for the intervention groups ranged from 12–188 participants.</p> <p><b>Outcome(s):</b> fatigue, health-related quality of life, symptom distress, psychological distress, body composition, physical exercise capacity (VO<sub>2</sub> max), self-reported exercise or physical activity level, and other physical performance measures such as walk time</p> <p><b>Treatment evaluated:</b> A variety of physical exercise modalities were employed, differing in type (e.g., walking, cycling, swimming, resistive exercises, combined exercises), intensity (i.e., most programs were at 50%–90% of the estimated VO<sub>2</sub> maximum heart rate), frequency (i.e., ranging from two times per week to as many as two times daily), and duration (i.e., ranging from two weeks to one year). In some studies, the experimental group was compared with a group that received some form of training of a lesser intensity, frequency, and/or duration (e.g., stretching, self-directed exercises, strength exercises, aerobic exercise of a lesser intensity, swimming, behavioral therapy). In other studies, the comparison group did not receive any exercise program or advice, were on a waiting list, or participated in a crossover trial.</p>	
Galvao & Newton, 2005 <sup>4</sup>	<p><b>Search strategy:</b> MEDLINE through June 2004 to identify experimental and quasi-experimental studies of exercise (cardiovascular and/or resistance training) during and following cancer treatment; 26 published studies, 18 experimental or quasi-experimental trials of exercise during cancer treatment and 8 studies of exercise after cancer treatment, were identified.</p> <p><b>Trials evaluated:</b> 26 published studies; of the 18 experimental or quasi-experimental trials during treatment, 14 used some type of cardiovascular training; 2 used mixed training with cardiovascular, resistance, and flexibility exercise; and 2 studies applied a structured resistance training program. Of the eight trials of exercise after cancer treatment, all used cardiovascular or cardiovascular plus resistance training. The duration of the intervention ranged from 2–28 weeks, and the frequency of the exercise intervention ranged from daily to two times per week.</p> <p><b>Sample:</b> Most of the studies were conducted in women with breast cancer or in samples with mixed solid tumors; single studies in patients with prostate cancer, colorectal cancer, or hematologic malignancies were noted. Sample sizes ranged from 5–155, and average</p>	<p>Five of 18 studies of exercise during cancer treatment specifically found improvements in fatigue, and most of the studies were among women with breast cancer. Of note, a trial of resistance training three times per week in men with prostate cancer undergoing androgen-depletion therapy showed improvements in fatigue after a 12-week program. Of the eight studies of exercise following cancer treatment, none reported statistically significant improvements in fatigue, although improvements did exist in functional status, quality of life, psychological distress, strength, and capacity.</p> <p>Although recent evidence supports the use of resistance exercise during cancer management as an exercise mode to counteract the side effects of disease and treatment, most of the studies were conducted using cardiovascular training. Promising results in terms of fatigue and other outcomes and of a short-term resistance exercise program among patients diagnosed with prostate cancer and undertaking androgen-depletion therapy have been reported.</p>



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	<p>participant age ranged from 19–77 years.</p> <p><b>Outcome(s):</b> fatigue, health-related quality of life, symptom distress, psychological distress, body composition, physical exercise capacity (VO<sub>2</sub> max), immunologic parameters, and muscle strength</p> <p><b>Treatment evaluated:</b> cardiovascular and/or resistance exercise</p>	