VOLUME 23 · NUMBER 4 · FEBRUARY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Review of Exercise Intervention Studies in Cancer Patients

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Submitted June 14, 2004; accepted October 14, 2004.

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0732-183X/05/2304-899/$20.00

DOI: 10.1200/JCO.2005.06.085

ABSTRACT

Purpose
To present an overview of exercise interventions in cancer patients during and after treatment and evaluate dose-training response considering type, frequency, volume, and intensity of training along with expected physiological outcomes.

Methods
The review is divided into studies that incorporated cardiovascular training, combination of cardiovascular, resistance, and flexibility training, and resistance training alone during and after cancer management. Criteria for inclusion were based on studies sourced from electronic and nonelectronic databases and that incorporated preintervention and postintervention assessment with statistical analysis of data.

Results
Twenty-six published studies were summarized. The majority of the studies demonstrate physiological and psychological benefits. However, most of these studies suffer limitations because they are not randomized controlled trials and/or use small sample sizes. Predominantly, studies have been conducted with breast cancer patients using cardiovascular training rather than resistance exercise as the exercise modality. Recent evidence supports use of resistance exercise or "anabolic exercise" during cancer management as an exercise mode to counteract side effects of the disease and treatment.

Conclusion
Evidence underlines the preliminary positive physiological and psychological benefits from exercise when undertaken during or after traditional cancer treatment. As such, other cancer groups, in addition to those with breast cancer, should also be included in clinical trials to address more specifically dose-response training for this population. Contemporary resistance training designs that provide strong anabolic effects for muscle and bone may have an impact on counteracting some of the side effects of cancer management assisting patients to improve physical function and quality of life.

J Clin Oncol 23:899-909. © 2005 by American Society of Clinical Oncology

INTRODUCTION

A progressive increase of cancer burden, with an estimated 15 million new cases and 10 million new deaths, is expected by the year of 2020.[1] In this context, prostate cancer is the sixth most common cancer in the world, representing 14.3% of cancers among men in developed countries with more than 80% of the cases occurring in men older than 65 years.[2] Breast cancer appears as the third most common cancer in the world, and it is ranked as the fifth most prevalent cause of death from cancer overall, being the leading cause of cancer mortality in women.[2] Treatments for cancer include surgery as well as systemic and radiation therapy and have successfully shown reductions in mortality rates. However, for cancer patients, the increased levels of fatigue during treatment remains a concern as it affects the majority of patients during radiotherapy and/or chemotherapy periods compromising their physical function and quality of life.[3-9] Dimeo[7,8] has proposed that the lack of physical activity during treatment may affect the increased levels of fatigue observed during and after cancer management. As such, several studies examining the role of exercise with cancer patients have linked the increased levels of physical activity during[10-23] and after cancer treatment[24-32] with positive effects on decreasing rates of fatigue, enhancing physical performance, and improving quality of life. However, the majority of the exercise interventions undertaken with this population have focused on cardiovascular training,[10,11,15,17-19,22-24,33-36] with few studies using the combination of aerobic and resistance exercises[12,16,25,29-31] or resistance exercise alone.[20,37] Therefore, little is known as to the effect of resistance training being a primary exercise choice to counteract some of the physiological conditions accompanied by cancer disease and the traditional treatments. Considering that most of the experimental exercise studies have incorporated breast cancer patients[11,18,19,21,38-40] and other types of cancer[10,17,23,24,37] but not prostate cancer, there is a particular lack of information on how prostate cancer patients undertaking traditional treatment would respond to an exercise program. Yet, given the documented effects of androgen deprivation therapy (ADT),[41-49] these patients should benefit particularly from resistance exercise. To date, only one published report has examined the effects of a short-term resistance exercise program on patients diagnosed with prostate cancer undertaking ADT.[20] Interestingly, they reported quite promising results. In view of the extensive scientific literature supporting resistance training as being the most effective method available for improving muscle strength and increasing lean tissue mass in different populations ranging from athletes to frail older adults,[50-60] resistance exercise may also have a great potential to counteract the side effects of prostate cancer during ADT by increasing muscle function, lean tissue mass, and bone mineral density with subsequent reduction in levels of fatigue.

There are specific training variables involving resistance exercise prescription that include number of sets and repetitions (volume), intensity of training (load), duration of rest between sets and exercises, frequency of training, and repetition velocity.[39,61,62] Currently, there is no information with regard to such training variables and possible variations with cancer patients undertaking resistance training programs. Interestingly, some of these variables have been examined in untrained older adults[54,63-66] and favorable responses in strength and function result from a variety of training regimens, even those that involve relatively low intensities,[54,64,67] frequencies,[65] and volume.[63,68] Considering the detrained state and high levels of fatigue of many cancer patients, it may be expected that even a training program consisting of lower intensity, volume, and frequency could significantly promote positive physiological and psychological adaptations increasing quality of life in this population.

The purpose of this article is to present a descriptive overview and chronological perspective of developments of the experimental exercise intervention studies undertaken during and after cancer management. The second aim of this review attempts to establish a dose response of training for this population considering type of exercise, frequency of training, volume of training, intensity of training and expected physiological outcome measures. In addition, we also highlight specific points that should be examined in the future with the goal of obtaining more information on exercise prescription for this population. This review reports 26 published studies appearing in the Medline (electronic version of Index Medicus) database, published by June of 2004 and searched by the terms: exercise; cardiovascular training; resistance training; rehabilitation; and cancer. Secondary searching involved scanning the reference lists from the papers identified above and then locating papers that appeared useful in reviewing the topic. A key criterion throughout this process was identifying studies that incorporated preintervention and postintervention assessment with statistical analysis of the data.

EXPERIMENTAL EXERCISE STUDIES DURING CANCER TREATMENT

A summary of the published studies examining the effect of exercise on cancer patients undertaking treatment is shown in Table 1. Of the 18 experimental exercise interventions under cancer treatment, 14 had used some type of cardiovascular training,[10,11,13-15,17-19,21,23,33-35,38,40] two had used a mixed training program using cardiovascular, resistance, and flexibility exercises[12,16] while the other two studies applied a structured resistance training program.[20,37] The main outcome measures from these studies include: levels of fatigue,[11,20,35,40,69] quality of life, emotional-related distress,[11,12,15,16,19,23,33,35] immunological parameters,[13,14,17,24], aerobic capacity,[10-12,14-19,21,23,33,35,39,40] and muscle strength.[12,16,20]

Cardiovascular Training

The first study by Winningham et al[38] examined the effect of a 10-week aerobic program performed three times per week on nausea responses of patients with breast cancer undertaking chemotherapy. Subjects were randomly assigned to a supervised aerobic exercise group three times per week, a placebo group that performed low-intensity supervised flexibility training once weekly, or a control nonexercise group. Nausea responses to training were assessed by a self-report system inventory (Symptom Checklist-90-R; Pearson Assessments, Eagan, MN). The exercise group improved significantly more on symptoms of nausea compared with control and placebo groups ($P < .05$). Considering that nausea is a consistent symptom experienced by

Table 1. Experimental Design Exercise Studies During Cancer Treatment

Study (Reference Number)	Duration	Frequency (weeks)	No. of Patients	Sex	Age (years)	Type of Cancer	Exercise Program	Intensity	Outcome Measures
Cunningham et al, 1986[49]	5	3-5/week	40	M, W	14-44	Leukemia	Resistance training	Unspecified	↓ Nitrogen balance ↔ Creatinine excretion ↔ AC
Winningham et al, 1988[50]	12	3/week	42	W	45-48	Breast	Cardiovascular cycling IT 20-30 minutes	60-85% MHR	↓ Nausea
Winningham et al, 1989[48]	12	3/week	24	W	45	Breast	Cardiovascular cycling IT 20-30 minutes	60-85% MHR	↑ Lean tissue mass ↓ 0.5% Body fat ↓ Skinfold sites
Macvicar et al, 1989[30]	10	3/week	45	W	43-46	Breast	Cardiovascular cycling IT	60-85% MHR	↑ 42% Vo_{2max}
Mock et al, 1997[23]	6	4-5/week	46	W	35-64	Breast	Cardiovascular walking 20-30 minutes	Self-paced	↑ 4% 12-MWT ↓ Fatigue ↓ Symptom experience
Dimeo et al, 1997[29]	~2	Daily	70	M, W	39-40	Breast, sarcoma, carcinoma, adenocarcinoma, neuroblastoma	Cardiovascular cycling IT 30 minutes	50% HRR	↓ 14% MP, ↓ Thro ↓ Neutro, ↓ Hosp
Dimeo et al, 1998[22]	6	5/week	5	M, W	18-55	Hodgkin's lymp., Non-Hodgkin's lymp., bronchial, breast, medulloblastoma	Progressive treadmill walking 30-35 minutes	3 mmol/L (LC) 80% MHR	↓ 100% LC ↓ 18% Heart rate ↑ 101% TD ↑ 12% MP
Dimeo et al, 1999[35]	*	Daily	59	M, W	40	Breast, lung Carcinoma, seminoma, Adenocarcinoma, Hodgkin's lymp.	Cardiovascular cycling IT 30 minutes	50% HRR	↓ Psychologic distress
Schwartz et al, 1999, 2000[46,47]	8	4/week	27	W	35-57	Breast	Cardiovascular walking 35 minutes	Self-paced accelerometers	↑ 10.4% 12-MWT ↓ Fatigue
Na et al, 2000[25]	2	5/week	35	*	28-75	Stomach	Cardiovascular arms and cycling ergometers 30 minutes	60% MHR	↑ 28% NKCA
Schwartz et al, 2001[52]	8	3–4/week	72	W	27-69	Breast	Cardiovascular walking 12 minutes	Self-paced accelerometers	↑ 15% 12-MWT ↓ Fatigue
Mock et al, 2001[31]	6-24	5-6/week	52	W	28-75	Breast	Cardiovascular walking 10-30 minutes	Self-paced	↑ 6% 12-MWT ↓ Fatigue ↓ Emotional distress
Segal et al, 2001[45]	26	5/week	123	W	51.4	Breast	Cardiovascular walking, home vs. non-home based	50–60% Vo_{2max}	↑ Physical functioning ↔ Quality of life ↔ Vo_{2max}
Kolden et al, 2002[24]	16	3/week	40	W	45–76	Breast	Cardiovascular walking, cycling, stepping, resistance training, flexibility	Unspecified	↑ 11% Flexibility ↑ 15.4% Vo_{2max} ↑ 34.5% UB ↑ 37% LB ↓ 5% RSBP ↑ Quality of life
Segal et al, 2003[32]	12	3/week	155	M	68.2	Prostate	Resistance training, 2 sets, 12 repetitions	60–70% 1-RM	↑ 42% UB ↑ 36% LB ↔ Body composition ↔ PSA, ↓ Fatigue ↑ Quality of life
Dimeo et al, 2003[26]	~ 2	Daily	66	M, W	20–73	Leukemia, Hodgkin's lymp., non-Hodgkin's lymp., myeloma	Cardiovascular walking	70% MHR	↔ Walking speed ↓ 6.7% HEM
Courneya et al, 2003[27]	16	3–5/week	102	M, W	61.1	Colorectal	Cardiovascular walking, flexibility	65–75% MHR	↔ Quality of life ↔ Cardiovascular capacity
Adamsen et al, 2003[28]	6	4/week	23	M, W	18–63	Leukemia, breast, colon, ovary, testis, cervix, Hodgkin's lymp., non-Hodgkin's lymp.	Resistance training, 3 sets, 5–8 repetitions; cardiovascular cycling; relaxation	60–100% MHR 85–95% 1-RM	↑ 32.5% WB ↑ 16% Vo_{2max} ↔ Quality of life

Abbreviations: M, men; W, women; ↔, no change; ↑, increase; ↓, decrease; *, not described; PSA, prostate-specific antigen; LC, lactate concentration; Vo_{2max}, maximum concentration of oxygen consumption; lymp., lymphoma; IT, interval training; TD, training distance; MHR, maximum heart rate; MP, maximal performance (MET); HEM, hemoglobin; AC, arm circumference; UB, upper body strength; LB, lower body strength; WB, whole body strength; RSBP, resting systolic blood pressure; NKCA, natural killer-cell cytotoxic activity; HRR, heart rate reserve; Neutro, duration of neutropenia; Thro, duration of thrombopenia; Hosp, duration of hospitalization.

cancer patients during treatment, these preliminary data showed that cardiovascular training can safely be incorporated during breast cancer traditional treatment and may decrease symptoms of nausea. Winningham et al[36] also presented data related to a subgroup of their earlier report,[38] which examined the effect of a 10- to 12-week aerobic training program on body composition responses of breast cancer subjects undertaking chemotherapy. Subjects were randomly allocated to an exercise group that trained three times per week for 20 to 30 minutes with intensity set at 60% to 80% of maximal heart rate or a control group that did not receive the exercise treatment. Although elementary techniques for body composition determination, such as skinfold measurement, were used in this intervention, the results were an increase in lean tissue mass for the training group compared with the control group. Considering the specificity of the training program in this study (aerobic exercise only), the relative increase in lean tissue mass may be attributed to the decreased fat tissue.

The effect of a 10-week aerobic interval training program was also investigated by MacVicar et al.[18] Forty-five women with breast cancer receiving chemotherapy were randomly assigned to an aerobic exercise group (cycling training), a flexibility training group, or a control group. Exercise intensity was set at 60% to 85% of the maximum heart rate reserve. Results demonstrated differences for maximum oxygen uptake ($\mathrm{V\dot{O}_{2MAX}}$) and testing time among groups; the aerobic training group improved significantly more than the flexibility and control groups.

Mock et al[11] examined the effect of a randomized controlled-trial home-based exercise program on 46 women with breast cancer undertaking radiotherapy. The exercise program consisted of a 20- to 30-minute self-paced walking program, four to five times per week over 6 weeks. A 12-Minute Walk Test, Symptom Assessment Scales, and the Piper Scale were used to assess physical function, symptoms experience, and fatigue, respectively. Results showed that subjects undertaking the exercise program improved significantly more in walking distance, symptom experience (anxiety, depression, and difficulty sleeping), and fatigue compared with controls.

The effect of a daily bed cycling program during high-dose chemotherapy treatment in cancer patients followed by autologous peripheral blood cell transplantation was reported by Dimeo et al.[17] Subjects from the control group experienced significantly higher loss of physical performance levels during hospitalization than the exercise group ($P < .05$). Moreover, other physiological parameters such as duration of neutropenia, thrombocytopenia, and severity of diarrhea were significantly reduced after the exercise intervention ($P < .05$). Dimeo et al[10] also reported the response of a 6-week cardiovascular exercise program on fatigue and physical performance in a small sample of cancer patients ($n = 5$) experiencing fatigue during treatment. A progressive walking treadmill program up to 30 to 35 minutes with intensity set to elicit a blood lactate level of 3 mmol/L in capillary blood was prescribed. At the end of the intervention, walking distance, walking maximal performance, heart rate, and lactate concentration were improved ($P < .05$) demonstrating once more the positive physiological responses accrued with cardiovascular training. In addition, the authors also noted a clear decrease in levels of fatigue at post-test. Subsequently, in 1999, the same group of investigators[23] also examined a daily exercise protocol consisting of a supine bike program followed by an interval training pattern for 30 minutes in cancer patients receiving high doses of chemotherapy. Outcome measures included psychological distress and levels of fatigue. It was demonstrated at the end of the intervention that subjects undertaking the exercise program significantly decreased psychological distress with no changes in fatigue levels.

Schwartz et al[34,35] reported results from a 8-week exercise intervention in 27 women with breast cancer undertaking chemotherapy. The exercise program included a home-based walking program with self-paced intensity measured by an accelerometer. Subjects who underwent the exercise program demonstrated greater response in the physical performance assessment (12-minute walk test), as well as decreasing levels of fatigue compared with subjects who did not adopt the training program ($P < .05$).

The short-term effect of cardiovascular training on natural killer-cell cytotoxic activity (NKCA) in patients with stomach cancer were reported by Na et al.[13] Subjects were assigned to an exercise group that performed 30 minutes of supervised cardiovascular training using arm and cycle ergometer or a nonexercise control group. Blood samples were collected at baseline, day 7, and day 14. At post-test, a significantly greater increase in NKCA was noted for the exercise group (27.9%) compared with the control group (13.3%; $P < .05$). Although the training period was short in duration, it is interesting to note that both groups had similar values for NKCA at the midpoint of intervention, with the differences between groups occurring during the second half of the training period.

Schwartz et al[40] also investigated the relationship of fatigue and exercise through a home-based aerobic exercise program consisting of a 12-minute walk in women undergoing chemotherapy treatment for breast cancer. Functional abilities were assessed through a 12-minute walk test and fatigue levels by a self-reported instrument. The exercise program increased functional ability by 15% whereas the nonexercisers decreased performance by 16%. In addition, decreased levels of fatigue ($P < .01$) for the exercise group were observed after the intervention. It is interesting to note that the exercise program was unsupervised with none of the sessions being accompanied by an exercise physiologist. Considering that training program variables were not well controlled during training, the results are somewhat attractive and one would expect even greater adaptations for an exercise program that incorporates a more controlled setting resulting in an enormous impact on the outcome measures with this population.

The effect of a similar home-based walking exercise intervention on patients with breast cancer undertaking either radiotherapy or chemotherapy was also examined by Mock et al.[19] The exercise program consisted of a progressive walking (10 to 30 minutes) program 5 to 6 days per week with an unspecified training intensity. Similar to Schwartz et al[40] and their previous report,[11] physical function was assessed by the 12-Minute Walk Test. In addition, fatigue and emotional distress were measured by the Piper Scale and Profile of Mood States (POMS), respectively. Consistent with their previous findings,[11] the exercise intervention lead to a significant improvement in physical performance by increasing walking distance. Additionally, fatigue and emotional distress were enhanced at post-test, indicating once more that positive psychological outcomes may be achieved with a simple home-based walking exercise program.

Segal et al[33] conducted a randomized controlled trial examining the effect of a supervised and unsupervised walking program on patients with breast cancer undertaking treatment (radiotherapy, hormonal therapy, or chemotherapy) over 26 weeks. Aerobic capacity, body weight, and generic and disease-specific health-related quality of life were assessed (MOS SF-36) at baseline and post-test. Results demonstrated that physical function measured by the MOS SF-36 decreased in the control group while it increased in both training groups ($P < .05$). At post-test, no differences among groups were detected for quality of life, aerobic capacity, or body weight. However, when groups were stratified by type of adjuvant therapy, in this case not receiving chemotherapy, differences in improvement were observed between the supervised and control group for aerobic capacity ($P < .01$). It is relevant to point out that the small changes in aerobic capacity (3.5%) may be related to the nonspecific aerobic capacity test protocol (stepping ergometer) utilized by the authors to assess chronic response of a walking program.

The effect of 2 weeks of cardiovascular training on a mixed cancer population undergoing conventional or high-dose chemotherapy during hospitalization was examined by Dimeo et al.[14] The training program consisted of a daily walking treadmill interval training program with intensity set at 70% of the maximum heart rate. Submaximal stress test results demonstrated that physical performance remained unaltered during treatment with significant reductions in hemoglobin levels at hospital discharge ($P < .05$). Although physical performance did not change at post-test, results demonstrated that cardiovascular training may assist on preserving performance status during intensive chemotherapy.

Finally, Courneya et al[15] conducted a randomized controlled trial examining the effect of a home-based exercise program on quality of life and cardiovascular capacity of colorectal cancer patients undertaking adjuvant therapy. The exercise group was instructed to perform cardiovascular and flexibility activities three to five times per week over 16 weeks whereas the control group was advised to not participate in any exercise activity during the study period. No significant differences were observed between groups for quality of life and cardiovascular capacity at the end of the intervention. The failure to detect differences between groups is primarily explained by the fact that 51.6% of the control group did not comply with the study and exercised during the study period. The nature of the exercise itself (home-based program) was pointed out by the authors as being one possible reason of the high contamination during the intervention with little effectiveness.

Cardiovascular, Resistance, and Flexibility Training

Kolden et al[12] examined the effect of an exercise training intervention including cardiovascular, resistance, and flexibility training over 16 weeks in patients with breast cancer undertaking some type of adjuvant therapy (radiotherapy, chemotherapy, or hormonal therapy). Subjects were tested for resting blood pressure, body composition, aerobic capacity, flexibility, and strength. In addition, numerous psychological outcomes were also examined using the Beck Depression Inventory, State-Trait Anxiety Inventory, Positive and Negative Affect Schedule, Hamilton Scale for Depression, Quality of Life, and Global Assessment Scale. At the end of the intervention, there was an observed effect for time for upper and lower body strength, cardiovascular capacity (estimated $\dot{V}O_{2max}$), flexibility, and resting systolic blood pressure ($P < .05$). Additionally, subjects experienced positive psychological adaptations with training improving some of the quality-of-life measures.

Recently, Adamsen et al,[16] examined the effect of a high-intensity supervised exercise program on a mixed cancer population over 6 weeks. The training program included interval training with intensity set at 60% to 100% of the maximal heart rate, resistance exercises performed at 85% to 95% of 1 repetition maximum (RM) for five to eight repetitions, and relaxation training. The results demonstrated an increase of 32.5% in maximal strength ($P < .0001$) and 16% improvement in $\dot{V}O_{2max}$ ($P < .001$). Several measures of quality of life were also improved; however, no statistically significant values were noted. It is relevant to highlight that this is the first study that incorporates a higher intensity training design; however, the absence of a control group and the short duration of the intervention limited the interpretation of the data.

Resistance Training

The earliest published study examining the effects of resistance exercise was a short-term intervention involving patients with acute leukemia undertaken by Cunningham et al.[37] Subjects were randomly assigned to two exercise groups performing the program either three or five times weekly or a nonexercising control group. The training program consisted of several upper and lower body exercises including the chest press, biceps curl, triceps extension, straight leg raises, knee extension, hip extension, hip abduction, shoulder retractors, and sit-ups performed with 15 repetitions at an unspecified intensity. Outcome measures included skinfold measures, arm circumference, nitrogen balance, and creatinine excretion. Results indicated that groups did not change arm circumference and skinfold measures over the course of the intervention. Although there were no differences among groups for nitrogen balance during the course of the study, the authors suggested that the exercise program favored both training groups with the control group decreasing levels of creatinine excretion from pretest to post-test ($P < .05$).

Recently, Segal et al[20] reported the results from a 12-week whole body resistance training intervention in patients with prostate cancer undergoing ADT. The resistance training program consisted of two sets of 8 to 12 repetitions at 60% to 70% of 1 RM for six upper body and three lower body exercises performed three times per week. Outcome measures included fatigue, disease-specific quality-of-life assessment, and muscle strength and body composition. Results showed positive effects of resistance training on decreasing fatigue levels, health-related quality of life, and muscle strength with no changes in body composition by the subjects embarking on the exercise program. The fact that body composition was unaffected by the training program may be related in part to the elementary body composition methods used to assess changes in muscle and fat tissue. In addition, it is well known that strength gains during the first stages of resistance training are predominantly caused by neural factors with gains in muscle size becoming dominant as training continues.[70-72] Consequently, the shorter duration of the intervention and the limitations on body composition assessment methods indicated that increases in strength were likely to be related to neural alterations rather than muscle morphological changes. These preliminary data showed optimistic outcomes with a resistance training program that is characterized primarily by anaerobic rather than aerobic energy sources. Taking into consideration that immunological parameters were not assessed in this particular study, it remains to quantify if resistance training may positively alter the immune system of patients under cancer treatment. In addition, it would be interesting to examine how other types of cancer patients would respond with resistance exercises.

EXPERIMENTAL EXERCISE STUDIES AFTER CANCER TREATMENT

Experimental studies examining the effect of exercise on patients with cancer after treatment are presented in Table 2. Four studies had used cardiovascular exercise programs[24,26-28,32] whereas the other four implemented a mixed training program using cardiovascular, resistance, and flexibility exercises.[25,29-31] Levels of fatigue, muscle strength,[29,31] cardiovascular function,[24,26-31] immunological parameters,[24,27,28,31] symptoms of emotional-related distress, and quality of life[25,27,29,30,32] were the major outcome measures from these studies.

Cardiovascular Training

Sharkey et al[26] conducted the first experimental exercise study examining the chronic response of a 12-week cardiovascular training program on children and young adults with mixed cancer diagnosis who had completed chemotherapy for at least 1 year. Outcome measures included cardiovascular and pulmonary physiological responses. Although none of the physiological parameters changed with training, exercise tolerance assessed by exercise time was increased significantly ($P < .05$).

The effect of cardiovascular training on NKCA, monocytes, and personality was examined in a group of breast cancer survivors by Peters et al.[27,28] Their training program consisted of 30 to 40 minutes of cycling at approximately 60% of maximum heart rate performed five times per week during the first 5 weeks of training with a subsequent reduction of training frequency for the following 6 months completing a total 7-month training period. Although NKCA cell numbers were unaltered over the course of the intervention, an increase in the cytotoxic activity was noted at post-test. While the total number of leukocytes was unchanged after the training program, significant changes in leukocyte subpopulations were detected with an increased number of granulocytes and a decreased number of lymphocytes and monocytes ($P < .05$). The authors suggested that cardiovascular training would possibly alter the number of specific receptors in the surface membrane on monocytes. Moreover, satisfaction of life increased in the first 5 weeks of training with a subsequent decrease during the other 6 months of the intervention.

Dimeo et al[24] examined the effects of a cardiovascular training program on maximal performance and hemoglobin levels of cancer patients directly after hospital discharge. The exercise program consisted of 6 weeks of treadmill walking every weekday with intensity set to elicit a blood lactate level of 3 mmol/L in capillary blood. Results indicated that subjects that underwent the exercise program showed a significant increase in maximal performance and hemoglobin concentration compared with controls ($P < .05$).

The effects of 10 weeks of cardiovascular exercises on women who had undergone breast cancer treatment were examined by Segar et al.[32] Subjects were randomly allocated to an exercise group, exercise plus behavior modification group, or a control group in an experimental crossover design. Symptoms of depression, state of anxiety, and self-esteem were assessed by the Beck Depression Inventory, the State

Table 2. Experimental Design Exercise Studies After Cancer Treatment

Study	Duration	Frequency (weeks)	No. of Patients	Sex	Age (years)	Type of Cancer	Exercise Program	Intensity	Outcome Measures
Sharkey et al, 1993[38]	12	2/week	10	M, W	19	Leukemia, Ewings tumor, neuroblastoma Wilms' tumor, rhabdomyosarcoma	Cardiovascular *	60–80% MHR	10% ET, ↔ AT ↔ Peak OX ↔ Peak HR
Peters et al, 1994, 1995[39, 40]	28	2-5/week	24	W	49	Breast	Cardiovascular cycling	~ 60% MHR	↑↓ Satisfaction of life ↔ NKCA ↔ Leukocytes ↓ 2.1% Lymphocytes ↓ 1.1% Monocytes ↑ 4.1% Granulocytes
Nieman et al, 1995[43]	8	3/week	12	W	61	Breast	Cardiovascular resistance training	75% MHR	↔ NKCA ↔ LB ↑ 6-minute Walk Test
Dimeo et al, 1997[36]	6	5/week	36	M, W	39–42	Non-Hodgkin's lymp., breast, sarcoma, seminoma, lung	Cardiovascular walking 30 minutes	3 mmol/L (LC)	↑ 32% MP ↑ 30% HEM
Segar et al, 1998[44]	10	4/week	24	W	30–65	Breast	Cardiovascular 30–40 minutes	= 60% MHR	↓ Depression ↓ Anxiety
Durak et al, 1998[41]	10	2/week	20	M, W	50	Carcinoma, lymphoma, leukemia	Cardiovascular resistance training, flexibility	Own RPE	↑ 43% WB, 41.4% ↑ MP ↑ Quality of life
Durak et al, 1999[42]	20	2/week	25	M, W	44-71	Prostate carcinoma, leukemia	Cardiovascular resistance training	Unspecified	↔ Aerobic capacity ↑ 45% WB
Porock et al, 2000[37]	4	*	9	M, W	51-77	Bowel, breast, oral, pancreas, melanoma	Cardiovascular resistance training	Unspecified	↓ Depression ↓ Anxiety ↔ Fatigue

Abbreviations: M, men; W, women; ↔, no change; ↑, increase; ↓, decrease; ↑↓, increased at week 5 and decreased at posttest; *, not described; LC, lactate concentration; MHR, maximum heart rate; MP, maximal performance (MET); HEM, hemoglobin; LB, lower body strength; WB, whole body strength; NKCA, natural killer-cell cytotoxic activity; ET, exercise tolerance; AT, anaerobic threshold; peak OX, peak oxygen uptake; peak HR, peak heart rate.

Anxiety Inventory, and the Rosenberg Self-Esteem Inventory, respectively. At post-test, it was observed that the exercise group had significantly less depression and state of anxiety compared with controls with no differences between exercise and exercise plus behavior modification groups. After the crossover, the controls also showed optimistic changes by decreasing depression and state of anxiety showing positive psychological response accrued with cardiovascular training.

Cardiovascular, Resistance, and Flexibility Training

The effects of an exercise program on breast cancer survivors who had undergone surgery, radiation, and chemotherapy were examined by Nieman et al.[31] Subjects were randomly assigned to an exercise or control group. In addition to physical performance measures that included symptoms-limited exercise testing on the treadmill, 6-minute walk test and lower body strength, immunological training response was also assessed by measuring NKCA and concentrations of circulating immune cells. The training program included 30 minutes of walking at 75% of heart rate maximum and seven different resistance exercises performed for 12 repetitions at an unspecified intensity. Results indicated significant improvement for the exercise group on 6-minute walk distance test compared with controls ($P < .05$). However, differences between groups were neither observed for lower body strength nor for NKCA. It should be noted that the small sample size ($n = 6$ per group) limited the ability to detect significant difference between groups.

Durak et al[29] conducted an exercise intervention in a mixed cancer patient population over 10 weeks. The exercise program was performed twice weekly and consisted of cardiovascular training at their own perceived exertion, resistance training machines using unspecified intensity, and flexibility exercises. Outcome measures included quality of life (Modified Rotterdam Quality of Life Survey), endurance capacity, and a four- to six-repetition maximum strength test. Results demonstrated an average increase of 43% for both upper and lower body strength combined and a 41.4% increase in MET level from the first to the last session of the exercise program. In addition, the quality of life assessment indicated a significant improvement in participants' ability to perform daily functions. The same group of investigators[30] also examined the effect of a 20-week cardiovascular and resistance training program on survivors of prostate cancer, carcinoma, and leukemia. The exercise protocol was described with little detail in the original manuscript; therefore it is unclear what intensity and volume were applied during the exercise intervention for both cardiovascular and resistance exercises. In addition, neither strength maximum nor cardiovascular capacity tests were implemented at pretest and post-test; therefore it was extremely difficult to analyze the authors' presented data. At post-test, subjects completed a quality-of-life survey with the same questionnaire being reassessed in a 2-year follow-up period. It was reported that the training protocol induced an increase of 38% and 52% for overall strength in the prostate cancer and carcinoma/leukemia groups, respectively. No significant change was noted for aerobic capacity. It is interesting to point out the high level of adherence to the exercise program from both groups with subjects from the prostate cancer group having 100% compliance to the training program whereas the carcinoma/leukemia group recorded 65% of adherence over the 2-year period.

Finally, Porock et al[25] investigated the effect of a short-term home-based exercise intervention in a mixed population of cancer patients. The training program appears to include both cardiovascular and resistance exercises but lacked an exact description of training program variables (intensity, frequency, and volume). Outcome measures included fatigue, anxiety, depression, symptoms of distress, and quality of life. Results indicated positive adaptations for depression and anxiety with no change in fatigue levels. It should be noted that the short-term duration of the intervention and the small sample size (n = 9) limited the ability to detect significant changes with training.

DISCUSSION

The primary aim of this article was to present an overview of published studies undertaken with any cancer population during and after treatment. Unfortunately, most of these studies suffer limitations because they are not randomized controlled trials, use small sample sizes, and/or report insufficient scientific methodological criteria. Despite this, it appears that there is a reasonable amount of data in the literature that underline preliminary positive physiological and psychological benefits from exercise when undertaking during or after traditional cancer treatment. It is interesting to point out that the early published report on cancer and exercise by Cunningham et al[37] used resistance exercises as the training modality that was based on the original work by Delorme,[73,74] who introduced the model of progressive workload with resistance exercises. Subsequently, the majority of studies examining the effect of exercise on cancer patients undertaking treatment completed from the late 1980s to 2003 implemented the cardiovascular training modality[10,11,13,15,17-19,23,33-36,38,40] with only two interventions using the combination of resistance, flexibility, and cardiovascular training.[12,16] Therefore, particular attention should be taken of the recent report from Segal et al[20] who reported positive effects of resistance exercises alone on rates of fatigue, health-related quality of life, and muscle strength in patients with prostate cancer undertaking ADT. Although these results support positive psychological and physical outcomes, it remains to be examined how specific physiological parameters such as muscle tissue mass and bone mineral density would respond with resistance exercises in this population, especially in long-term trials. Recently, Smith et al[43] reported an increase of 11% of fat mass and a decrease of 3.8% of lean-free bone tissue mass from a year-long prospective assessment of the effects of ADT on body composition responses evaluated by dual energy x-ray absorptiometry. Further, the concern related to the negative effects of ADT on accelerating bone loss has been extensively reported in the literature.[46,75-83] As an alternative, resistance exercise studies in older adults have consistently shown it to be a safe and effective strategy to counteract sarcopenia[50,54-57,59,84,85] and preserve or induce gains in bone mineral density[84,86-88]. Recently, Villareal et al[86] reported positive effects of a 9-month resistance training program on bone mineral density in older women undertaking hormonal replacement. A meta-analysis undertaken by Wolff et al[89] also proposes that resistance training preserves or reverses bone loss of up to 1% per year in both femoral neck and lumbar spine sites for pre- and postmenopausal women. Taking into consideration the long-term benefits of this exercise modality on bone response, resistance training may have an important role on reducing the effect of bone loss rate in men with prostate cancer undertaking ADT. Moreover, considering that, traditionally, ADT varies from 2 to 3 years but can also take up to 20 years,[90] the role of resistance exercise may be even more relevant by improving psychological and physiological parameters and, therefore, improving quality of life.

In the context of maintaining or increasing lean tissue content in healthy elderly and various patient populations in which muscle and bone loss are problematic, resistance exercise might be more appropriately termed "anabolic exercise." It is not surprising, therefore, that the many cardiovascular exercise interventions with cancer patients have produced mixed results as such exercise does not provide a strong anabolic effect for muscle and bone and may not elicit the changes in endocrine status that are desirable in these patients.

It is interesting to note that, among the different cancer types, breast cancer has been the most common cancer type examined during exercise trials. Of the 18 studies undertaken during treatment, nine had used exclusively breast cancer subjects[11,12,18,19,21,33-35,38,40] with three studies including breast cancer plus a mix of cancer populations[10,17,23] and few other experiments using leukemia, stomach cancer, prostate, colorectal, and a mix population of cancer types.[13,15,16,20,37] A similar figure can be observed with the experimental trials undertaken after cancer treatment where three studies were

Table 3. Guidelines and Possible Physiological Outcomes from Exercise in Cancer Patients

Exercise Modality	Intensity	Frequency (/week)	Volume	Dosage	Cancer Relevant Expected Outcomes
Cardiovascular exercises	55-90% MHR 40-85% MHRR	3-5	20-60 minutes	Continuous or intermittent	↑ Cardiopulmonary function ↑ Insulin sensitivity*, ↑ HDL*, ↓ LDL* ↓ Fat mass, ↓ Fatigue
Anabolic/resistance exercises	50-80% 1-RM 6-12 RM	1-3	1-4 sets per muscle group		↑ Muscle mass*, ↑ Muscle strength ↑ Muscle power*, ↑ Muscle endurance ↑ BMD*, ↑ FP, ↓ Fatigue ↑ Resting metabolic rate*, ↓ Fat mass*
Flexibility exercises	?	2-3	2-4 sets per muscle group	10-30 seconds	↑↔ Range of motion

Abbreviations: ↑, increase; ↓, decrease; ↔, no change; MHR, maximum heart rate; MHRR, maximum heart rate reserve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMD, bone mineral density; FP, functional performance; RM, repetition maximum.
*Data not available with cancer population, recommendation based from studies undertaken with noncancer population.

conducted with breast cancer patients,[27,28,31,32] three in a mixed cancer population including breast cancer,[24,25,29] and two in a mixed cancer population not including breast cancer.[26,30] Therefore, future studies aiming to examine the role of exercises in cancer populations should also include other cancer types than breast to reveal possible physiological and psychological benefits from exercise among other cancer groups.

As a secondary purpose of this review, we attempted to establish a training dose-response with this population based on the existing literature. The importance of scientific exercise principles has been extensively reported.[39,61,62,91] It is well known that manipulation of the training program variables of frequency of training, intensity of training, specificity of training, and rest period between sets and exercise sessions produces clearly differentiated effects on specific physiological adaptations for both cardiovascular and resistance exercise. Nevertheless, long-term trials comparing different training models are rare even in healthy adult populations as reported by the American College of Sports Medicine position stand on the recommended quantity and quality of exercise prescription in healthy adults.[39] Therefore, most of the studies presented in this review that aim to elucidate training response for cancer patients during and after treatment, were short in duration[10,13,14,16,18,20,24,25,29,31,32,34-38,40] with some interventions still not controlling elementary training variables.[12,25,29,30,92] The short-term nature of these interventions would likely limit the ability to detect specific physiological responses with training. Moreover, considering that exercise has been endorsed as a crucial component of a healthy lifestyle and is viewed as a lifelong behavior that may prevent and control various disease conditions,[93-96] further studies undertaken for longer periods are needed. Additionally, the specific training dose for this population and how it would differentiate from many of the cancer types, treatment modalities, and stages of treatment remains an open area for prospective trials. Despite the work by Segal et al[33] and Cunningham et al,[37] which compared a home-based versus supervised exercise and five times versus three times weekly resistance exercises, respectively, none of these studies had actually used more than one training protocol, attempting to compare differences in training response due to various intensities, frequencies, volume, and type of training. Consequently, a requirement for future studies on this topic should include randomized controlled trials comparing how various types of cancer undergoing different treatments and stages of the disease would respond to different training stimuli.

Finally, the majority of the studies involving resistance training did not draw on the wealth of scientific research that has been published in regard to resistance training for muscle hypertrophy and strength gain. In all cases excepted one,[16] the intensity of exercise in particular was inferior to the 6 to 10 RM load that has been deemed optimal for muscle growth and strength enhancement.[61,62] One of the better designed resistance training interventions addressed in this review was by Cunningham et al[37] and yet their model was based on research completed around 1950.[73,74] Moreover, the only study that incorporated a better-quality training intensity limited the program to 6 weeks and performed no more than three resistance exercises.[16] Although much more research is required in this important area, some guidelines and possible physiological outcomes are provided in Table 3. Future research into exercise interventions with cancer patients should involve contemporary resistance training program designs incorporating adequate intensity, periodization, selection of functional exercises involving large muscle groups, and manipulation of rest period and recovery strategies to maximize the anabolic effect on muscle and bone as well as positive endocrine responses.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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