

## Physical Exercise in Cancer Patients During and After Medical Treatment: A Systematic Review of Randomized and Controlled Clinical Trials

Ruud Knols, Neil K. Aaronson, Daniel Uebelhart, Jaap Fransen, and Geert Aufdemkampe

From the Department of Rheumatology and Institute of Physical Medicine, University Hospital Zurich, Zurich, Switzerland; Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam; Department of Rheumatology, University Medical Center, Nijmegen; University of Professional Education, Department of Health, Faculty Chair of Health and Lifestyle and Department of Physical Therapy, Utrecht, the Netherlands.

Submitted February 20, 2004; accepted February 1, 2005.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Ruud Knols, MSc, PT, Department of Rheumatology and Institute of Physical Medicine, University Hospital Zurich, Gloriastrasse 25, 8091 Zurich, Switzerland; e-mail: ruud.knols@usz.ch.

© 2005 by American Society of Clinical Oncology

0732-183X/05/2316-3830/\$20.00

DOI: 10.1200/JCO.2005.02.148

### A B S T R A C T

#### Purpose

To systematically review the methodologic quality of, and summarize the evidence from trials examining the effectiveness of physical exercise in improving the level of physical functioning and psychological well-being of cancer patients during and after medical treatment.

#### Methods

Thirty-four randomized clinical trials (RCTs) and controlled clinical trials were identified, reviewed for substantive results, and assessed for methodologic quality.

#### Results

Four of 34 trials met all (seven of seven) methodologic criteria on the Delphi criteria list. Failure to conceal the sequencing of treatment allocation before patient recruitment, failure to blind the outcome assessor, and failure to employ an intention-to-treat analysis strategy were the most prevalent methodologic shortcomings. Various exercise modalities have been applied, differing in content, frequency, intensity, and duration. Positive results have been observed for a diverse set of outcomes, including physiologic measures, objective performance indicators, self-reported functioning and symptoms, psychological well-being, and overall health-related quality of life.

#### Conclusion

The trials reviewed were of moderate methodologic quality. Together they suggest that cancer patients may benefit from physical exercise both during and after treatment. However, the specific beneficial effects of physical exercise may vary as a function of the stage of disease, the nature of the medical treatment, and the current lifestyle of the patient. Future RCTs should use larger samples, use appropriate comparison groups to rule out the possibility of an attention-placebo effect, use a comparable set of outcome measures, pay greater attention to issues of motivation and adherence of patients participating in exercise programs, and examine the effect of exercise on cancer survival.

*J Clin Oncol* 23:3830-3842. © 2005 by American Society of Clinical Oncology

### INTRODUCTION

Cancer and its treatment are associated with numerous physical and psychological symptoms and adverse effects.<sup>1-3</sup> Exercise has been proposed as a promising strategy for the treatment of some of these physical and psychological complaints, and various exercise interventions are currently available for use both during and after cancer treatment.<sup>4-8</sup> One of

the major challenges for researchers in the field of rehabilitation is to provide empirical evidence of the efficacy of these programs.

Earlier work has reviewed the evidence regarding physical exercise and health-related quality of life (HRQOL) in cancer patients during and after treatment.<sup>9-17</sup> These reviews found evidence supportive of the role of exercise in attenuating a range of physical and psychosocial problems associated with cancer and

its treatment, but also indicated numerous methodologic limitations that hampered the interpretation of the results of the studies. The most common limitations reported were the use of small convenience samples resulting in limited statistical power, the absence of appropriate control groups, and the diversity of measures that made it difficult to compare results across studies.

Well-designed and properly executed randomized controlled trials (RCTs) provide the best evidence on the effectiveness of health care interventions. Trials with inadequate methodologic approaches may produce exaggerated treatment effects and biased results, and may lead to misinformed decision making at all levels of health care, from treatment decisions for the individual patient to the formulation of national public health policies. Critical appraisal of the quality of clinical trials is possible only if the design, conduct, and analysis of RCTs are described thoroughly and accurately in published reports. Unfortunately, the reporting of RCTs is often incomplete and thus may obfuscate problems arising from poor methodology.<sup>18-21</sup>

This review was undertaken to systematically evaluate the methodologic quality of, and summarize the evidence from RCTs and controlled clinical trials (CCTs) that have investigated the effectiveness of physical exercise in cancer patients during and after medical treatment. It incorporates several recently published RCTs that were not included in previous reviews, and uses a more structured approach to evaluating the methodologic quality of studies than has been used previously.

## METHODS

### Search Strategy

A computer-aided search<sup>22</sup> of Medline (Wingspurs, PubMed, Gateway; 1966 to June 2004), CINAHL (1982 to 2004), the Cochrane Library (2004), CancerLIT (2004), and PEDro (all up to June 2004) was performed to identify relevant RCTs and CCTs. CCTs are defined as intervention studies with a control group, but without explicit use of randomization for purposes of group allocation. The following search terms were used: cancer, neoplasm, randomized or randomised, tumor or tumour\* (where \* is a truncation sign), malignanc\*, sports, exercise\*, physical activity, graded activity, physical function, body mass, fat-free mass, symptom\*, depressive disorder, fatigue, anxiety, depressive, mood status, psychology, and quality of life. The reference lists of the studies identified were searched for additional suitable studies. Furthermore, an effort was made to retrieve unpublished studies, including those with negative results. Toward this end, a letter was sent to 20 experts who had published earlier in the area of physical exercise in cancer inquiring as to whether they or any of their colleagues had any unpublished reports concerning exercise trials among cancer patients that they would be willing to share with us.

No restrictions were made regarding the language of the publication.

### Inclusion Criteria and Data Collection

To be included in the review, all RCTs and CCTs had to have examined the effects of physical exercise after surgery or during or after chemotherapy, radiotherapy, and/or hormonal therapy. In this review, an intervention during cancer treatment was defined as one that took place during the time period between the initiation of cancer treatment and either 2 weeks after the last radiation treatment or 4 weeks after the last cycle of chemotherapy.<sup>10</sup> An intervention after cancer treatment was defined as one that took place at least 2 weeks after completion of radiotherapy and/or at least 4 weeks after the last cycle of chemotherapy. Studies were reviewed that used interventions to improve endurance or muscular strength. Examples include walking (either outdoor or on a treadmill), cycling, swimming, and strengthening exercises (using free weights, isokinetic machines, or weight machines), performed either within a hospital-based rehabilitation unit or in a home-based program. Studies of relaxing exercises (eg, yoga or tai-chi) were excluded. Studies using at least one of the following types of outcome were included: oxygen consumption per unit of time ( $\dot{V}O_2$  maximum or oxygen uptake), fatigue, body composition, exercise levels or level of physical activity, walking distance, psychological distress, or self-reported HRQOL. A *P* value of less than .05 was used as the criterion for statistically significant results. One reviewer (R.K.) performed the initial search to identify studies that met the eligibility criteria. A senior associate of the library service of the University Hospital Zurich verified this search. Disagreement regarding inclusion of the studies was resolved by consensus between authors (R.K. and J.F.). The arbitration of a third reviewer (N.K.A.), as recommended by van Tulder et al,<sup>23</sup> was to be used in the event of any disagreement between the two reviewers regarding the methodologic quality of a trial.

### Assessment of Methodologic Quality

Two reviewers (R.K. and G.A.) independently assessed the methodologic quality of the studies according to the Delphi criteria list,<sup>24</sup> a set of nine criteria for quality assessment: use of randomization; concealment of treatment allocation (ie, concealing the group assignment sequence until a potential study participant has been approached and has provided informed consent); equivalence (or similarity) of groups at baseline regarding the most important prognostic indicators; specification of the eligibility criteria; blinding of the outcome assessors; blinding of the care providers; blinding of the patients; reporting of point estimates and measures of variability for the primary outcome measures; and use of an intention-to-treat analysis. In the current analysis, seven of the nine quality criteria were evaluated. Two of the three criteria relating to the use of blinding procedures were not rated because it is difficult, if not impossible, to blind patients and care providers to treatment assignment.<sup>25</sup> However, blinding of external assessors or raters was included as one of the quality criteria.

For each quality criterion, three rating categories were available: yes, met criteria; no, did not meet criteria; and do not know. Although summary scores across quality criteria are sometimes calculated to classify studies qualitatively as being of high or low quality, the use of such rating procedures in assessing the quality of physical therapy trials has been discouraged because of the absence of clear decision rules for establishing threshold or cutoff scores.<sup>26</sup> Therefore, in this review, the methodologic quality of the identified trials was analyzed and is presented for each quality criterion separately (Tables 1 and 2).

Percentage agreement and Cohen's Kappa statistic were calculated with GRAPHPAD software (Version 2002; GRAPHPAD

**Table 1.** Methodologic Quality of Studies Conducted During Cancer Treatment

Study	Item							Total Items Reported
	Was a Method of Randomization Performed?	Was the Treatment Allocation Concealed?	Similarity of Groups at Baseline?	Eligibility Criteria Specified?	Blinding of Outcome Assessor?	Point-Estimates and Measures of Variability for Primary Outcome?	Intention-to-Treat Analyses?	
<b>Exercise during treatment in breast cancer</b>								
Segal et al <sup>34</sup> (2001) RCT	+	+	+	+	-	+	+	6
Mock et al <sup>35</sup> (2001) RCT	+	+	+	+	-	+	-	5
Schwartz et al (submitted for publication A) RCT	+	-	+	+	-	+	+	5
Pickett et al <sup>45</sup> (2002) RCT	+	+	+	+	-	-	-	4
Mock et al <sup>41</sup> (1997) CCT	-	-	+	+	-	+	-	3
Mock et al <sup>31</sup> (1994) RCT	+	-	-	+	-	+	-	3
Winningham et al <sup>29</sup> (1989) RCT	+	-	+	+	-	-	-	3
Winningham et al <sup>28</sup> (1988) RCT	+	-	+	+	-	-	-	3
MacVicar et al <sup>30</sup> (1989) RCT	+	-	-	-	-	-	-	1
<b>Exercise during bone marrow and peripheral stem-cell transplantation</b>								
Coleman et al <sup>38</sup> (2003) RCT	+	+	-	+	-	+	+	5
Dimeo et al <sup>32</sup> (1997) RCT	+	-	+	+	-	+	+	5
Cunningham et al <sup>27</sup> (1986) RCT	+	+	+	+	-	+	-	5
Mello et al <sup>37</sup> (2003) RCT	+	-	+	+	-	+	-	4
Hayes et al <sup>44</sup> (2003) CCT	-	-	+	+	-	+	+	4
Dimeo et al <sup>42</sup> (1999) CCT	-	-	+	+	-	+	+	4
Dimeo et al <sup>40</sup> (1997) CCT	-	-	+	+	-	+	-	3
Hayes et al <sup>43</sup> (2003) CCT	-	-	+	+	-	+	-	3
<b>Exercise during treatment in a mixed solid tumor population</b>								
Segal et al <sup>36</sup> (2003) RCT	+	+	+	+	+	+	+	7
Schwartz et al (submitted for publication B) RCT	+	-	+	+	+	+	+	6
Young-Moo et al <sup>33</sup> (2000) RCT	+	-	+	+	-	-	+	4
Moneely et al <sup>39</sup> (2004) RCT	+	-	+	+	-	+	-	4
Huang et al (submitted for publication) RCT	+	-	-	+	+	+	-	4

NOTE. The criteria items blinding of the care provider and blinding of the patient were all scored as not applicable. Abbreviations: RCT, randomized clinical trial; +, reported item; -, not reported item; CCT, controlled clinical trial.

Software Inc, San Diego, CA), and were interpreted in accordance with Landis and Koch's benchmarks for assessing the agreement between raters: poor (< 0), slight (0.0 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), and almost perfect (0.81 to 1.0).<sup>58</sup>

## RESULTS

### Study Characteristics

The literature search yielded 31 reports<sup>27-57</sup> that met the basic eligibility criteria of being either an RCT or a CCT, and in which physical exercise was used as a means of improving physical fitness and/or psychological well-being of cancer patients during or after treatment. Three studies, all from a single source, were added as a result of a direct inquiry sent to authors within the area of research (Schwartz et al, submitted for publication A; Schwartz et al, submitted for publication B; Huang et al, submitted for

publication). All of these latter studies had been submitted for publication at the time of inquiry. Of the 34 studies included in the review, 17 RCTs (Schwartz et al, submitted for publication A; Schwartz et al, submitted for publication B; Huang et al, submitted for publication)<sup>27-39,45</sup> and five CCTs<sup>40-44</sup> examined the effectiveness of physical exercise during medical treatment, whereas 10 RCTs<sup>46-55</sup> and two CCTs<sup>56,57</sup> were focused on the period after medical treatment. The studies during medical treatment were divided into three subcategories: exercise during breast cancer treatment, exercise during bone marrow and peripheral stem-cell transplantation, and 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. These categories of studies reflect not only differences in cancer diagnosis and the timing of the

**Table 2.** Methodologic Quality of Studies Conducted After Cancer Treatment

Study	Item							Total Items Reported
	Was a Method of Randomization Performed?	Was the Treatment Allocation Concealed?	Similarity of Groups at Baseline?	Eligibility Criteria Specified?	Blinding of Outcome Assessor?	Point Estimates and Measures of Variability for Primary Outcome?	Intention-to-Treat Analyses?	
<b>Exercise after breast cancer treatment</b>								
Courneya et al <sup>52</sup> (2003) RCT	+	+	+	+	+	+	+	7
Fairey et al <sup>53</sup> (2003) RCT	+	+	+	+	+	+	+	7
Mckenzie et al <sup>50</sup> (2003) RCT	+	-	+	+	-	-	+	4
Pinto et al <sup>51</sup> (2003) RCT	+	-	+	+	-	+	-	4
Berglund et al <sup>57</sup> (1993) CCT	-	-	+	+	-	+	+	4
Segar et al <sup>56</sup> (1998) CCT	-	-	+	+	-	+	-	3
Nieman et al <sup>46</sup> (1995) RCT	+	-	+	-	-	+	-	3
<b>Exercise after treatment in a mixed solid tumor population</b>								
Courneya et al <sup>54</sup> (2003) RCT	+	+	+	+	+	+	+	7
Courneya et al <sup>55</sup> (2003) RCT	+	-	+	+	+	+	+	6
Burnham and Wilcox <sup>49</sup> (2002) RCT	+	-	+	+	-	+	-	4
Berglund et al <sup>47</sup> (1994) RCT	+	-	+	+	-	+	-	4
Berglund et al <sup>48</sup> (1994) RCT	+	-	+	+	-	+	-	4

NOTE. The criteria items blinding of the care provider and blinding of the patient were all scored as not applicable. Abbreviations: RCT, randomized clinical trial; +, reported item; -, not reported item; CCT, controlled clinical trial.

physical exercise programs, but also possible differences in motivation, safety, feasibility, and efficacy of exercise.<sup>14</sup>

In total, 1,844 patients were included in these studies (1,164 patients during medical and 680 patients after medical treatment). Of the 22 trials that examined physical exercise during cancer treatment, 12 were performed in the United States, three in Germany, three in Canada, one in Brazil, two in Australia, and one in South Korea. Of the 12 trials of the effect of exercise after cancer treatment, four were performed in the United States, five in Canada, two in Sweden, and one in Germany.

A variety of physical exercise modalities were employed, differing in type (walking,<sup>31,34,35,40,41,45,54-56</sup> cycling,<sup>28-30,32,33,42,51,53,54-56</sup> swimming,<sup>54,55</sup> resistive exercises,<sup>27,36,39</sup> or combined exercises [Schwartz, submitted for publication B; Huang, submitted for publication]<sup>37-39,43,44,46-50,52,57</sup>); intensity, with most programs at 50% to 90% of the estimated  $\dot{V}O_2$  maximum heart rate; frequency, ranging from two times a week up to two times daily; and duration, ranging from 2 weeks up to 1 year. In some studies, the experimental or intervention group was compared with a group that received some form of training of a lesser intensity, frequency, and/or duration. Examples of control or comparison group activities included stretching,<sup>28,30,43,44</sup> self-directed exercises,<sup>34</sup> strength exercises (Schwartz et al, submitted for publication A; Schwartz et al, submitted for publication B; Huang et al, submitted for publication),<sup>27</sup> usual care (Schwartz et al, submitted for publication A; Schwartz et al, submitted for publication B; Huang et al, submitted for publication),<sup>27,31,32,34,35,40,41,45</sup> aerobic exercise of a lesser intensity,<sup>49</sup> swimming,<sup>54</sup> and

behavioral therapy.<sup>54</sup> In other studies, the comparison group did not receive any exercise program or advice, or were on a waiting list<sup>28-30,33,36-38,42,46-53,55,57</sup> or participated in a cross-over trial.<sup>39,56</sup>

### **Exercise During Breast Cancer Treatment**

Physical exercise was performed during (adjuvant) chemotherapy in five studies (Schwartz, submitted for publication A)<sup>28-31</sup>; chemotherapy, radiotherapy, or hormone therapy in one study<sup>34</sup>; radiotherapy or chemotherapy in two studies<sup>35,45</sup>; and radiotherapy alone in one study (Table 3).<sup>41</sup> The sample sizes ranged from 14 to 123 patients. These studies yielded a wide range of statistically significant outcomes favoring exercise, including body composition (body fat,<sup>29</sup> lean mass,<sup>29</sup> and bone mineral density [Schwartz, submitted for publication A]), functional capacity (Schwartz, submitted for publication A),<sup>30,40</sup> muscle strength (Schwartz, submitted for publication A), walking distance,<sup>31,35,41</sup> and self-reported outcomes including, symptom relief (nausea,<sup>28,31</sup> fatigue,<sup>31,35,41</sup> difficulty sleeping<sup>41</sup>), psychological well-being,<sup>31</sup> mood status,<sup>35,41</sup> and quality of life.<sup>35</sup> In one study, no statistically significant differences between groups were observed for changes in aerobic capacity, body weight, and self-reported quality-of-life scores.<sup>34</sup>

### **Exercise During High-Dose Chemotherapy Following Bone Marrow and Peripheral Bone Stem-Cell Transplantation**

The effect of physical exercise was investigated during high-dose chemotherapy, radiotherapy and bone marrow transplantation (BMT) in one study,<sup>27</sup> during high-dose chemotherapy following peripheral bone stem-cell

**Table 3.** Description of Studies of Physical Exercise During Breast Cancer Treatment

Study	Design	Sample	Exercise Intervention	Outcome Variable	Results	P
Segal et al <sup>34</sup> (2001)	RCT with two intervention groups (supervised and self-directed) and usual care controls	Breast cancer patients; stage I-II (randomized, n = 123; completed program, n = 99) during chemotherapy, radiotherapy, or hormone therapy	Supervised progressive walking program, 50%-60% of $\dot{V}O_2$ maximum and home exercises 3/wk; self-directed exercise group, home-based program 5 d/wk during 26 wk	SF-36, FACT-G, aerobic capacity, body weight	Physical functioning subscale (of the SF-36) improved in the self-directed exercisers when only 83 participants receiving chemotherapy were considered, compared with nonexercising controls*	.03*
Mock et al <sup>35</sup> (2001)	RCT with usual care controls	Breast cancer patients; stage I-III (randomized, n = 52; completed program, n = 48) with outpatient radiotherapy or chemotherapy	Supported walking exercise, 5-7 months, 5-6/wk, 15-30 minutes at moderate intensity	PFS, fatigue diary, POMS, SF-36, 12-minute walking test	Fatigue assessed with fatigue diary* and POMS** was lower in HIW v LIW; 12-minute walking test** increased in HIW; depression*** and anxiety** were lower in HIW; QOL increased in HIW†	.01* .00** .03*** .02†
Pickett et al <sup>45</sup> (2002)	RCT with usual care controls	Breast cancer patients; stage I-III (randomized, n = 52; completed program, n = 48) with outpatient radiotherapy or chemotherapy	Home-based 10- to 30- minute walking exercise sessions, at least 5-6 d/wk at 60%-80% of $\dot{V}O_2$ maximum	Adherence to exercise, occurrence of disease symptoms	33% of the walking group did not exercise on the prescribed levels; 50% of the usual care group reported maintaining or increasing to a moderate level; there were no clinically relevant differences between the usual care group and the walkers for disease symptoms	
Schwartz (submitted for publication A) RCT	RCT with three intervention groups: aerobic exercise, resistant exercise, and usual care controls	Pre- and postmenopausal breast cancer patients; stage I-III (randomized, n = 66; completed program, n = 60) beginning adjuvant chemotherapy	Home-based aerobic exercise group, 6-month walking or jogging 15-30 minutes, 4 d/wk at moderate intensity; home-based resistant exercise group, 6 month, 4 d/wk + usual care control	BMD of lumbar spine, aerobic capacity, muscle strength	Aerobic exercisers demonstrated lower % BMD loss than controls*; premenopausal woman demonstrated greater declines in BMD than postmenopausal woman**; aerobic exercisers covered a greater distance on the 12-minute walk test than the other groups* and demonstrated an increase in leg extension strength***	.02* .03** .01***
Mock et al <sup>41</sup> (1997)	CCT with usual care controls	Breast cancer patients; stage I-II (randomized, n = 50; completed program, n = 46) scheduled for radiotherapy	Self-paced 20- to 30-minute progressive walking program, 6 weeks, 4-5/wk	12-minute walking test, SAS, PFS	The exercise group scored higher than the usual care group on physical functioning (12-minute walking test*); fatigue,** difficulty sleeping,† and anxiety* decreased in exercisers	.003* .018** .027†
Mock et al <sup>31</sup> (1994)	RCT and usual care controls	Breast cancer patients; stage I-II (completed program, n = 14) during adjuvant chemotherapy	Supported walking exercise program 3-5/wk 30 minutes at moderate intensity	12-minute walking test, functional performance (Karnofsky), PAIS, BSI, TSCS, BIVAS, SAS	Walking group showed increased walking distance,* PAIS,** less nausea,** fatigue,** and depression***	< .05* .02** .01***
Winningham et al <sup>29</sup> (1989)	RCT with waiting list controls	Breast cancer patients; stage II (randomized, n = 24; completed program, n = 24) within 1-6 months of adjuvant chemotherapy	Supervised cycle ergometer interval protocol 10-12 weeks, 3/wk, 20-30 minutes at 60%-85% $\dot{V}O_2$ maximum	Body composition by skinfold measure	There was a decrease of body fat* and an increase of lean mass** in the exercise group compared with controls	.008* .033**
Winningham et al <sup>28</sup> (1988)	RCT with an exercise, placebo (stretching exercises), and waiting list controls group	Breast cancer patients; stage II-IV (randomized, n = 42; completed program, n = 42) within 3-6 months of adjuvant chemotherapy	Supervised cycle ergometer interval protocol 10 weeks, 3/wk, 20-30 minutes at 60%-85% $\dot{V}O_2$ maximum	SCL-90-R, nausea	Less nausea* and somatization* was reported by the exercise group than the placebo and controls	< .05*

(continued on following page)

**Table 3.** Description of Studies of Physical Exercise During Breast Cancer Treatment (continued)

Study	Design	Sample	Exercise Intervention	Outcome Variable	Results	P
MacVicar et al <sup>30</sup> (1989)	RCT with a placebo group (stretching exercises) and waiting list controls	Breast cancer patients; stage II (randomized, n = 49; completed program, n = 45) during chemotherapy	Supervised cycle ergometer interval protocol 10 weeks, 3/wk, 20-30 minutes at 60%-85% $\dot{V}O_2$ maximum	Functional capacity, HR, test time to estimate $\dot{V}O_2$ maximum, maximum workload achieved during the test	All variables improved significantly in the exercise group <sup>*</sup> ; placebos and controls showed no improvement	< .05 <sup>*</sup>

NOTE. The symbols (\*, \*\*, \*\*\*, etc) connect the P values with the corresponding statements in the Results column.

Abbreviations: RCT, randomized clinical trial; SF-36, Rand 36-item health survey;  $\dot{V}O_2$ , oxygen consumption per unit of time; FACT-G, Functional Assessment of Cancer Therapy-General; POMS, Profile of Mood Status; HIW, high-intensity walkers; LIW, low-intensity walkers; CCT, controlled clinical trial; QOL, quality of life; BMD, bone mineral density; SAS, Symptom Assessment Scale; PFS, Piper Fatigue Scale; PAIS, Psychological Adjustment to Illness Scale; BSI, Brief Symptom Inventory; TSCS, Tennessee Self-Concept Scale; BIVAS, Body Image Visual Analogue Scale; SCL-90-R, Symptom Checklist 90 Revised; HR, heart rate.

transplantation (PBSCT) in six studies,<sup>32,38,40,42-44</sup> and immediately after bone marrow transplantation in one study (Table 4).<sup>37</sup> The sample sizes ranged from 12 to 70 patients. Positive results were reported for body composition (weight,<sup>38,43</sup> body mass index,<sup>43</sup> total body water,<sup>43</sup> total energy expenditure,<sup>43</sup> fat-free mass<sup>43</sup>), muscle strength,<sup>37</sup> functional capacity<sup>40</sup>; creatinine excretion,<sup>27</sup> neutropenia,<sup>32</sup> hemoglobin<sup>40</sup>; symptoms of medical treatment including pain<sup>32</sup> and diarrhea,<sup>32</sup> and days in hospital<sup>32</sup>; and self-reported psychological well-being and mood status.<sup>42</sup> No statistically significant effects were reported for triceps skinfold, arm circumference, nitrogen balance, or 3-methylhistidine excretion.<sup>27</sup> Lymphocytes and cell counts improved but remained lower than normative data.<sup>44</sup>

### Exercise in a Mixed Solid Tumor Population During Medical Treatment

Five studies investigated the effect of physical exercise among mixed solid tumor populations (Table 5). These included studies of physical exercise directly after stomach cancer surgery,<sup>33</sup> during hormone therapy,<sup>36</sup> directly after neurectomy in head and neck cancer patients,<sup>39</sup> and in mixed cancer populations beginning chemotherapeutic regimens with catabolic steroids (Schwartz, submitted for publication B; Huang, submitted for publication). The sample sizes ranged from 12 to 155 patients. Positive results were reported for increased physical fitness,<sup>36</sup> aerobic capacity (Schwartz, submitted for publication B), bone mineral density (Schwartz, submitted for publication B), range of motion of the shoulder,<sup>39</sup> natural-killer cell activity,<sup>33</sup> pain,<sup>39</sup> fatigue (Huang, submitted for publication),<sup>36</sup> completion rate of the exercise program,<sup>39</sup> and self-reported quality of life (Schwartz, submitted for publication B).<sup>36</sup> Statistically significant results were not reported between groups for body composition (including weight, body mass index, waist circumference, and sum of skinfolds),<sup>36</sup> muscle strength (Schwartz, submitted for publication B; Huang, submitted for publication), fatigue (Schwartz, submitted for publication B), and quality of life.<sup>39</sup>

### Exercise After Breast Cancer Treatment

A wide range of statistically significant outcomes were reported in studies of exercise after breast cancer treatment,

including aerobic capacity,<sup>51</sup> cardiopulmonary changes,<sup>52</sup> physical strength,<sup>57</sup> walking distance,<sup>46</sup> and blood pressure (Table 6).<sup>51</sup> The effects of exercise on insulin-like growth factors (IGF1)<sup>53</sup> and binding proteins (IGFBP-3, IGFBP-1: IGFBP-3 molar ratio) were reported in one study.<sup>53</sup> Statistically significant results were reported for self-reported outcomes including mood status,<sup>51</sup> fatigue,<sup>52,56</sup> depression,<sup>56</sup> anxiety,<sup>56</sup> happiness,<sup>52</sup> self-esteem,<sup>52</sup> and quality of life.<sup>50,52,57</sup> One study reported the effect of support received from the physicians.<sup>56</sup> Patients who were encouraged by their oncologist exercised significantly more than patients who did not receive such encouragement.<sup>56</sup> Other outcomes for which no statistically significant results were reported included muscle strength,<sup>46</sup> physical capacity,<sup>57</sup> arm circumference,<sup>50</sup> body composition (including weight, body mass index, sum of skinfolds),<sup>52</sup> natural-killer cell cytotoxic activity,<sup>46</sup> fasting insulin, glucose, insulin resistance, IGF2, IGFBP-1,<sup>53</sup> subjects' positive and negative affect,<sup>51</sup> and anxiety.<sup>56</sup> The sample size of these studies ranged from 11 to 60 patients.

### Exercise in Mixed Solid Tumor Populations After Medical Treatment

These studies included a mix of patients with breast, colon, ovarian, brain and lung cancer, and non-Hodgkin's lymphoma (Table 7). The sample size ranged from 18 to 199 patients. Positive results were reported for several physical and psychological variables, including physical strength,<sup>47,48</sup> aerobic capacity,<sup>49</sup> decrease in body fat,<sup>49</sup> anxiety,<sup>55</sup> body avoidance,<sup>47</sup> sleeping problems,<sup>47</sup> fighting spirit,<sup>48</sup> body flexibility,<sup>49</sup> and self-reported quality of life.<sup>49,55</sup>

### Assessment of Methodologic Quality

The reviewers agreed on 288 of 306 methodologic ratings (94.1%). The remaining disagreements were resolved after discussions among the reviewers. The inter-reviewer  $\kappa$  statistic was 0.88 (95% CI, 0.83 to 0.94). The median criteria score on the Delphi list (range, 1 to 7) was 4 for both studies of exercise during and after cancer treatment (Tables 1 and 2, respectively). The studies of Segal,<sup>36</sup> Courneya,<sup>52,54</sup> and Fairey<sup>53</sup> were rated positively on all seven methodologic criteria. Nine of 34

**Table 4.** Description of Studies of Physical Exercise During Bone Marrow and Peripheral Stem-Cell Transplantation

Study	Design	Sample	Exercise Intervention	Outcome Variable	Results	P
Coleman et al <sup>38</sup> (2003) RCT	RCT with nonexercise controls	Multiple myeloma patients (randomized, n = 24; completed program, n = 13) receiving high-dose chemotherapy and PBSCT	Home-based combined aerobic (walking or jogging) 20 minutes, 3/wk and a strength exercise program with stretch resistive bands	POMS, sleep, body composition, muscle strength, and aerobic capacity	For body weight, the average difference between the exercisers and the nonexercisers group was significant*; all other measures were not significant	.01*
Dimeo et al <sup>32</sup> (1997) RCT	RCT with usual care controls	Mixed solid tumor patients (randomized, n = 70; completed program; n = 51) during high-dose chemotherapy and PBSCT	Supervised biking with a bed ergometer, daily 30 minutes at 50% of the cardiac reserve	Treadmill stress test, hematologic values, cancer symptoms, days in hospital	In the exercise group neutropenia,* pain,* and diarrhea*** decreased; days in hospital*** were reduced for exercisers only	.01* .04** .03***
Cunningham et al <sup>27</sup> (1986) RCT	RCT with two intervention groups (3/wk v 5/wk and usual care controls)	Leukemia patients (randomized, n = 40; completed program, n = 30) after HD chemotherapy, total body radiation, and bone marrow transplantation	Supervised resistance training (30 minutes) during 5 weeks, 3 or 5/wk	Body composition: triceps skinfold, arm circumference, nitrogen balance, creatinine excretion, 3-methylhistidine excretion	Creatinine excretion was significantly lower* in both intervention groups than in usual care controls	.039*
Mello et al <sup>37</sup> (2003) RCT	RCT with nonexercise controls	Patients (randomized, n = 32; completed program, n = 18) participating in an exercise program immediately after bone marrow transplantation	6 weeks active exercise program for upper and lower limb mobility, stretching exercises, and treadmill walking initiated during in hospital phase and continued when patient was at home	Maximal isometric strength for upper- and lower-extremity muscle groups	The exercise group showed higher strength values for dominant shoulder abductors,* and flexors,** nondominant shoulder abductors,** and flexors,** dominant elbow flexors,** nondominant elbow flexors*** and extensors,* dominant† and nondominant‡ knee flexors,†† dominant‡ and nondominant* ankle flexors; the nonexercisers showed improvements in dominant knee flexors‡‡ and nondominant knee flexors**	.002* .001** .000*** .008† .004†† .005‡ .033‡‡
Hayes et al <sup>44</sup> (2003) CCT	CCT with controls (stretching exercises)	Mixed cancer diagnosis, HD chemotherapy after PBSCT (completed program, n = 12)	3-month aerobic exercises, treadmill walking, and stationary cycling 70%-90% maximum HR 3/wk + resistive exercises 2/wk between 8 and 20 repetitions	Lymphocytes CD3 <sup>+</sup> , CD4 <sup>+</sup> , CD8 <sup>+</sup> counts; CD3 <sup>+</sup> cell function	First, CD8 <sup>+</sup> increased, but at the end of the study, returned to normal; CD3 <sup>+</sup> + CD4 <sup>+</sup> , and CD3 <sup>+</sup> /CD4 <sup>+</sup> ratio remained lower than normative data,* with 66%, 100%, and 100% of the participating group reporting counts and ratio, respectively, below the normal range	< .01*
Dimeo et al <sup>42</sup> (1999) CCT	CCT with controls	Mixed solid tumor patients (enrolled onto program, n = 59; completed program, n = 47) during HD chemotherapy and autologous PBSCT	Supervised biking with a bed ergometer, daily 30 minutes at 50% of the cardiac reserve	POMS, SCL-90-R	Obsessive-compulsive traits,* anxiety,** interpersonal sensitivity,† and phobic anxiety†† decreased in exercisers	.005* .01** .0004† .02††
Dimeo et al <sup>40</sup> (1997) CCT	CCT with usual care controls	Mixed solid tumor patients (enrolled onto program, n = 36; completed program, n = 32) after HD chemotherapy and autologous PBSCT	Supervised treadmill walking 5/wk, 6 weeks 80% of HR maximum	Physical performance, speed, hemoglobin, HR, lactate	Improvement of physical performance* and hemoglobin* were significantly higher for the exercisers than for controls	.04*
Hayes et al <sup>43</sup> (2003) CCT	CCT with controls (stretching exercises)	Mixed cancer diagnosis, HD chemotherapy after PBSCT (completed program, n = 12)	3-month aerobic exercises, treadmill walking, and stationary cycling 70%-90% maximum HR 3/wk + resistive exercises 2/wk between 8 and 20 repetitions	Height, weight, BMI, TBW, TEE, FFM, %BF	TEE increased in the exercise group,* weight and BMI at 3-month follow-up remained lower* than pretransplantation measures for both exercisers and controls; exercisers showed FFM increases* and reduction in %BF**	< .01* < .05**

NOTE. The symbols (\*, \*\*, \*\*\*, etc) connect the P values with the corresponding statements in the Results column.

Abbreviations: RCT, randomized clinical trial; PBSCT, peripheral blood stem-cell transplantation; CCT, controlled clinical trial; POMS, Profile of Mood Status; HD, high dose; SCL-90-R, Symptom Checklist 90 Revised; BMI, body mass index; TBW, total body water; TEE, total energy expenditure; FFM, fat-free mass; %BF, % body fat; HR, heart rate.

**Table 5.** Description of Studies of Physical Exercise During Medical Treatment in a Mixed Solid Tumor Population

Study	Design	Sample	Exercise Intervention	Outcome Variable	Results	P
Segal et al <sup>36</sup> (2003) RCT	RCT with controls	Prostate cancer patients during hormone therapy, stage I-IV (enrolled onto program, n = 155; completed program, n = 135)	RE 60%-70% of repetition maximum, 3/wk; total 12 weeks	FACT-F, FACT-P, standard load test, body composition	Exercisers had less interference from fatigue* and higher QOL** compared with the control group; exercisers had higher upper*** and lower body fitness†	.002* .001** .009*** .001†
Schwartz (submitted for publication B) RCT	RCT with three intervention groups: AE, RE, and C	Newly diagnosed cancer patients (enrolled onto program, n = 101; completed program, n = 89) beginning chemotherapy regimens with catabolic steroids	12 months home-based RE (4 d/wk), with resistive rubber tubing, or AE (15-40 minutes, 4 d/wk) at moderate intensity; C, usual activities	SCFS, SIP, muscle strength, aerobic capacity, bone mineral density	There were clinically, but not statistically significant differences in fatigue between AE and RE/C; QOL (SIP)* and return to work sooner after treatment** improved in the AE; aerobic capacity improved in the AE compared with the C group*; bone mineral density was preserved in the AE group* at 6 months, but the effect disappeared at study end	.05* .01**
Young-Moo et al <sup>33</sup> (2001) RCT	RCT with two groups	Stomach cancer patients (enrolled onto and finished program, n = 35) after surgery	Arm and bicycle ergometers; 2/d during 14 days at 60% of the cardiac reserve	NKCA	At day 14 after the operation, NKCA in the exercise group increased compared with the controls*	< .05*
Moneely <sup>39</sup> (2004) RCT	RCT cross-over trial	Head and neck cancer patients (enrolled onto program, n = 20; completed program, n = 17) with shoulder dysfunction caused by neuropraxia or neurectomy	Individual adapted progressive RE, 3/wk during 12 weeks	Primary outcomes, feasibility completion rate; secondary outcomes, ROM, SPADI, QOL, and FACT H + N	Completion rate: 85% (17 of 20 patients; exercisers 93%); improvements were found in favor of the exercise group in active shoulder rotation,* shoulder pain,** and overall score for pain and disability†	.001* .038** .045†
Huang et al (submitted for publication) RCT	RCT with three intervention groups: AE, RE, and C	Newly diagnosed cancer patients (enrolled onto program, n = 96); beginning chemotherapy regimens with catabolic steroids	12 months home-based RE (4 d/wk with resistive rubber tubing) or AE training (4 d/wk at moderate intensity); C, usual activities	POMS, SCFS, POMS-F, POMS-V, muscle strength	Patients in the C group had a lower fatigue score (SCFS), than RE or AE group*; after 1 year, POMS-F, SCFS, and POMS-V scores were not statistically significantly different among groups; there were no statistically significant differences for muscle strength among groups; the relationships between fatigue and muscle strength appeared to be weak (r = -0.3)	.021*

NOTE. The symbols (\*, \*\*, \*\*\*, etc) connect the P values with the corresponding statements in the Results column. Abbreviations: RCT, randomized clinical trial; RE; resistive exercise; FACT-F, Functional Assessment of Cancer Therapy–Fatigue; FACT-P, Functional Assessment of Cancer Therapy–Prostate Cancer; QOL, quality of life; AE, aerobic exercise; C, control; SCFS, Schwartz Item Fatigue Scale; SIP, Sickness Impact Profile Scale; NKCA, natural killer cell activity; ROM, range of motion; SPADI, Shoulder Pain and Disability Index; FACT H + N, Functional Assessment of Cancer Therapy–Head and Neck; POMS, Profile of Mood Status; POMS-F, POMS–Inertia; POMS-V, POMS–Vigor Activity.

trials<sup>27,34–36,38,45,52–54</sup> avoided potential selection bias by using an appropriate method to generate the random allocation sequence. Thirty of 34 trials reported group similarity at baseline regarding the most important prognostic indicators (Schwartz, submitted for publication A; Schwartz, submitted for publication B).<sup>27–29,32–37,39–57</sup> Thirty-two of 34 trials explic-

itly stated the eligibility criteria (Schwartz, submitted for publication A; Schwartz, submitted for publication B; Huang, submitted for publication).<sup>27–29,31–39,40–45,47–57</sup> The outcome assessors were blinded in seven of 34 trials (Schwartz, submitted for publication B; Huang, submitted for publication).<sup>36,52–55</sup> Twenty-eight of 34 trials (Schwartz, submitted

Table 6. Description of Studies of Physical Exercise After Breast Cancer Treatment

Study	Design	Sample	Exercise Intervention	Outcome Variable	Results	P
Courneya et al <sup>52</sup> (2003)	RCT with nonexercise controls	Breast cancer survivors (enrolled onto program, n = 53; completed program, n = 52) after surgery, chemotherapy, radiotherapy	Aerobic walking and cycling exercises 70%-75% $\dot{V}O_2$ maximum; 3/wk; total 15 weeks	Primary changes: peak oxygen outcome; QOL: FACT-B, FACT-G; secondary cardiopulmonary changes: changes in peak power output, oxygen consumption, oxygen consumption at the ventilatory equivalent for oxygen, oxygen consumption at the ventilatory equivalent for carbon dioxide; secondary QOL changes: changes in happiness, self-esteem, fatigue; secondary body composition: changes in body weight, body mass index, sum of skin folds	Peak oxygen uptake* increased significantly in the exercise group and decreased in the control group; overall QOL increased in the exercise group*; changes in peak power output,* in oxygen consumption at the ventilatory equivalent for carbon dioxide** and oxygen consumption at the ventilatory equivalent for oxygen increased in the exercise group*; changes in happiness,*** self-esteem,t and fatigue†† increased in the exercise group	< .001* < .03** .019*** .01† .006††
Fairey et al <sup>53</sup> (2003)	RCT with nonexercise controls	Postmenopausal breast cancer survivors (enrolled onto trial, n = 53; completed trial, n = 52); 14 months (standard deviation, 6 months) after surgery and/or chemotherapy and/or radiation and/or hormone treatment	15 weeks aerobic cycling exercises, 70%-75% $\dot{V}O_2$ maximum starting at 15 minutes for weeks 1-3 and increasing 5 minutes every 3 weeks to 35 minutes; controls, no exercise	Changes in fasting insulin, glucose, insulin resistance, IGF1, IGF2, IGFBP-1, IGFBP-3, and IGFBP-1:IGFBP-3 molar ratio	Significant differences in the exercise group were observed for changes in IGF1,* IGFBP-3,** and IGFBP-1:IGFBP-3 molar ratio***	.045* .021** .017***
Mckenzie et al <sup>50</sup> (2003)	RCT with nonexercise controls	Breast cancer survivors stage I or II (enrolled onto program, n = 14) more than 6 months after surgery	8 weeks aerobic arm cycling and progressive arm resistance exercises	Arm volume changes, SF-36	No changes in arm circumference or volume; the subscales physical functioning,* general health,** and vitality† increased in the exercisers	.05* .048** .023†
Pinto et al <sup>51</sup> (2003)	RCT with waiting list controls	Breast cancer patients; stage 0, I, or II, completed surgery, chemotherapy, and/or radiation (enrolled onto program, n = 24; completed program, n = 21)	Aerobic exercise 30 minutes, 3/wk during 12 weeks at 60%-70% of cardiac reserve	Blood pressure (baseline and peak), heart rate, POMS, PANAS, body esteem scale	Baseline blood pressure (systolic and diastolic),* peak systolic blood pressure,* heart rate at 75 W,* physical condition, and weight concern subscale of body esteem scale** improved in the exercisers	.05* .03**
Berglund et al <sup>57</sup> (1993)	CCT with nonexercise controls	Breast cancer survivors (enrolled onto program, n = 60) after surgery with chemotherapy and/or radiation	Physical training to increase mobility, muscle strength, and general fitness; no information about the intensity of the training program; 11 sessions lasting 2 hours for 7 weeks	Exercise scale (variables): work and sick leaves, physical strength and exercise, QOL, CIPS, activities, symptoms, MACS, and HADS	Physical training,* physical strength,* and global health† increased and tiredness decreased** in exercisers; patients' appraisal of having received sufficient information improved during follow-up year*	.0001* < .0005** < .01‡
Segar et al <sup>56</sup> (1998)	CCT cross-over trial	Breast cancer survivors (enrolled onto trial, n = 30; completed trial, n = 24) after surgery	Self-paced aerobic exercise (60% of heart rate maximum) 30 minutes, 4/wk; total 10 weeks	BDI, STAI, RSE	Exercisers had less depression* and state and trait anxiety** over time compared with controls; participants with exercise recommendations from the oncologists exercised significantly more than exercisers without recommendations***	< .01* < .02** < .03***
Nieman et al <sup>46</sup> (1995)	RCT with nonexercise controls	Breast cancer survivors (enrolled onto program, n = 6; completed program, n = 12) within previous 4 years after surgery and/or chemotherapy and/or radiation	Supervised weight training, two sets and 12 repetitions, seven different exercises, 60 minutes + aerobic exercise of indoor track walking (75% of heart rate maximum) 30 minutes, 3/week; total 8 weeks	6-minute walking test, leg extension strength, treadmill test	The 6-minute walking test improved in the exercise group*; no significant changes in NKCA, body composition, or muscle strength	.02*

NOTE. The symbols (\*, \*\*, \*\*\*, etc) connect the P values with the corresponding statements in the Results column.

Abbreviations: RCT, randomized clinical trial;  $\dot{V}O_2$ , oxygen consumption per unit of time; FACT-B, Functional Assessment of Cancer Therapy–Breast Cancer; FACT-G, Functional Assessment of Cancer Therapy–General; QOL, quality of life; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; SF-36, Rand 36-item health survey; POMS, Profile of Mood Status; PANAS, Positive and Negative Affect Scale; CCT, controlled clinical trial; CIPS, Cancer Inventory of Problems Situation; MACS, Mental Adjustment to Cancer Scale; HADS, Hospital Anxiety and Depression Score; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; RSE, Rosenberg Self-Esteem Inventory; NKCA, natural killer cell activity.

**Table 7.** Description of Studies of Physical Exercise After Medical Treatment in a Mixed Solid Tumor Population

Study	Design	Sample	Exercise Intervention	Outcome Variable	Results	P
Courneya et al <sup>54</sup> (2003)	RCT with a combined exercise and group psychotherapy condition v exercise alone	Breast, colon, ovarian, non-Hodgkin's, brain, lung cancers; stage I-IV (enrolled onto trial, n = 108; completed program, n = 96); at the time of intervention, 34.1% were receiving chemotherapy and 19.3% were receiving radiotherapy treatment	10 weeks home-based walking program 3-5/wk during 20-30 minutes at 65%-75% or self-preferred exercises such as swimming, cycling, and/or group psychotherapy	FACT-G, SWLS, CES-D, STAI, FACT-F, physical fitness for cardiovascular endurance, skin folds, sit and reach test, Physical Exercise Leisure Score Index (Godin)	There was a significant time by condition interaction for functional well-being,* fatigue,* and sum of skin folds*	.04*
Courneya <sup>55</sup> (2003)	RCT with waiting list controls	Colon cancer patients (enrolled onto trial, n = 102; completed program, n = 93) within the last of 3 months after surgery	Home-based, personalized, exercise program, at least 3-5/wk, 20-30 minutes at 65%-75% of cardiac reserve	FACT-C, satisfaction with life, TOI depression, anxiety, fatigue, cardiovascular fitness, body composition, and flexibility	FACT-C* and anxiety** scores improved in the exercise group	.038* .005** .044***
Burnham and Wilcox <sup>49</sup> (2002)	RCT with nonexercise controls, low and moderate exercisers	Mixed solid tumor survivors (enrolled onto trial, n = 21; completed trial, n = 18), minimal 2 months after chemotherapy and/or radiation and/or surgery	10 weeks, 10-32 minutes each session, low-intensity exercise cycling group, 25%-35% of maximum heart rate; moderate-intensity exercise group, 40%-50% of maximum heart rate; controls, no exercise	Peak aerobic capacity, body composition, lower body flexibility, VAS, QOL, LASA	Peak aerobic capacity,* body flexibility (sit and reach)** and QOL* improved in the exercisers; there was a decrease in body fat*	< .001* .027**
Berglund et al <sup>47</sup> (1994)	RCT with nonexercise controls	Mixed solid tumor survivors (enrolled onto trial, n = 199; completed trial, n = 188) after radiation, adjuvant chemotherapy, and in few cases, hormonal therapy	Physical training to increase mobility, muscle strength, and general fitness; no information about the intensity of the training program; 11 sessions lasting 2 hours for 7 weeks	Exercise scale (variables): work and sick leaves, physical strength, and exercise; QOL, CIPS, activities, symptoms, MACS, HADS	Physical strength,** body avoidance,* appraisal of having received sufficient information,† and frequency of sleeping problems** improved in the exercise group	.05* .001** .01†
Berglund et al <sup>48</sup> (1994)	RCT with nonexercise controls	Mixed solid tumor survivors (enrolled onto trial, n = 199; after 12 months, n = 176) after radiation, adjuvant chemotherapy, and in few cases, hormonal therapy	Physical training to increase mobility, muscle strength, and general fitness; no information about the intensity of the training program; 11 sessions lasting 2 hours for 7 weeks	Exercise scale (variables): work and sick leaves, physical strength, and exercise; QOL, CIPS, activities, symptoms, MACS, HADS	Patients' appraisal of having received sufficient information* and of physical strength,** physical training,† and fighting spirit,‡ were improved in the exercise group compared with the controls during entire follow-up year	.0001* .005** .0005† .0001‡

NOTE. The symbols (\*, \*\*, \*\*\*, etc) connect the P values with the corresponding statements in the Results column.

Abbreviations: RCT, randomized clinical trial; FACT-G, Functional Assessment of Cancer Therapy-General; SWLS, Satisfaction with Life Scale; CES-D, Center for Epidemiological Studies-Depression; STAI, State-Trait Anxiety Inventory; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; FACT-C, Functional Assessment of Cancer Therapy-Colon Cancer; TOI, Trial Outcome Index; VAS QOL, visual analog scale for quality of life; LASA, linear analog self-assessment; CIPS, Cancer Inventory of Problems Situation; MACS, Mental Adjustment to Cancer Scale; HADS, Hospital Anxiety and Depression Score.

for publication A; Schwartz, submitted for publication B; Huang, submitted for publication)<sup>27,31,32,34-44,46-49,51-57</sup> provided point estimates and measures of variability for the primary outcome(s). An intention-to-treat analysis was performed in 15 of 34 trials (Schwartz, submitted for publication A; Schwartz, submitted for publication B).<sup>32-34,37,38,42,44,50,52-55,57</sup>

## DISCUSSION

This systematic review summarizes the substantive results and evaluates the methodologic quality of 34 reports of

27 RCTs and seven CCTs of physical exercise programs designed for cancer patients during and after medical treatment. Of the studies conducted during cancer treatment, five RCTs satisfied five of the seven criteria for methodologic quality (Schwartz, submitted for publication A),<sup>27,32,35,38</sup> two RCTs satisfied six of the criteria (Schwartz, submitted for publication B),<sup>34</sup> and one trial<sup>36</sup> satisfied all seven of the criteria. The highest methodologic quality score for a CCT was 4 of 7, found in two trials of physical exercise during the treatment in a mixed solid tumor population.<sup>42,44</sup> Of the studies examining physical

exercise after treatment, there was one RCT that satisfied six of seven criteria for methodologic quality,<sup>55</sup> and there were three RCTs<sup>52-54</sup> in cancer survivors that satisfied all of the criteria for methodologic quality. Overall, nine of the trials<sup>28-31,40,41,43,46,56</sup> satisfied three criteria or fewer on the Delphi criteria list. The most commonly observed problems were with concealment of treatment allocation (25 of 34), blinding of the outcome assessor (27 of 34) and failure to employ an intention-to-treat data analysis strategy (19 of 34). Overall, the RCTs and CCTs included in this review were of moderate methodologic quality. However, there appears to be a trend toward more methodologic rigor in more recent studies.<sup>36,52-54</sup> The reporting of future RCTs may be improved if authors provide all of the information requested by the Consort checklist<sup>19</sup> before submitting manuscripts for publication.

The results of this review suggest that cancer patients in specific populations may benefit from physical exercise both during and after cancer treatment. Positive results have been observed for a diverse set of outcomes, including physiologic measures, objective performance indicators, self-reported functioning and symptoms (particularly fatigue), psychological well-being, and overall HRQOL. However, these results need to be interpreted with some caution. Many of the positive outcomes were observed in some, but not all trials. Variability in outcomes may be due to differences in study design (RCT v CCT), sample size and resulting statistical power, and the specific study measures employed. From a substantive perspective, the studies were quite heterogeneous with regard to the nature, intensity, timing, and duration of the exercise program being evaluated. There was also a good deal of variability in the medical context in which the exercise programs were implemented and evaluated. Given that many of the trials reviewed used small sample sizes, we considered statistical pooling of data across trials. This was ultimately deemed not to be feasible because of the heterogeneity in the types of exercise programs investigated, in the types of comparison groups used (eg, placebo, minimal intervention, no intervention), in the outcomes assessed, and in the periods of follow-up.

Quality-of-life and longevity benefits resulting from increased physical activity may vary as a function of the type and stage of cancer, the medical treatment, and the patients' current lifestyle. For example, early-stage breast cancer patients may benefit from a moderate aerobic exercise program, both during and after completion of medical treatment, in terms of the improved physical, functional, and social well-being, reduced symptom distress (particularly fatigue), and increased levels of life satisfaction. Among this population of patients, exercise might be combined with dietary changes (eg, a low-fat diet). Dietary fat reduction can result in a lowering of serum estradiol levels and such dietary modification may contribute to the prevention of breast cancer.<sup>59</sup> Currently, it is unknown whether physical exercise, eventually combined with a low-fat

diet, can lower the risk of breast cancer recurrence. This might be investigated by following up certain biomarkers (ie, IGF-1 and IGFBP-3) in women who have participated previously in clinical trial-based exercise programs, or could be studied in future clinical trials. Diet, nutrition, and other lifestyle features affect the expression and production of IGF-1.<sup>60</sup> IGF-1 has potent mitogenic and antiapoptotic properties in normal and malignant breast epithelial cells in vitro, whereas IGFBP-3 restricts the availability and biologic activity of IGF-1.<sup>60</sup> High levels of IGF-1 and low levels of IGFBP-3 are associated with cancer recurrence and adverse prognostic factors.<sup>61</sup> The study by Fairey et al<sup>53</sup> showed that physical exercise has a significant effect on IGF-1 and IGFBP-3 in postmenopausal breast cancer survivors. However, the clinical implications of these findings and their potential impact on overall survival in breast cancer patients remain to be defined.

Patients with breast,<sup>62</sup> colorectal,<sup>63</sup> and prostate<sup>64</sup> cancer who are overweight have been found to be at increased risk of cancer recurrence and death. The results of this review suggest that a physical exercise intervention alone is not sufficient to influence significantly the weight of cancer patients during the period after medical treatment, although one study reported a significant decrease in body fat after a physical exercise intervention.<sup>49</sup> Among survivors of solid tumors, weight loss can probably best be achieved by combining physical exercise with dietary management strategies aimed at promoting healthy eating habits, and strategies for improving body image and self-acceptance.<sup>65</sup>

Among patients with advanced disease, a resistive exercise program combined with protein supplements may increase muscle strength and maintain patients' functional ability.<sup>65,66</sup> The increased efficiency of protein use may be important for wasting diseases such as cancer, particularly in patients suffering from sarcopenia.<sup>67</sup>

Self-reported HRQOL improved in the intervention groups in most of the studies reviewed. Although this may be attributed to the exercise programs, it could also be the result of increased attention paid by health care personnel, and might reflect benefits accrued from group activities with fellow patients.<sup>68</sup> Such alternative explanations are particularly relevant in those studies that employed a no-treatment control group. Two studies<sup>34,54</sup> employed a research design capable of addressing this issue. Segal et al<sup>34</sup> compared the effects of supervised exercise versus self-directed exercise versus usual care (control group) among patients undergoing adjuvant chemotherapy or hormonal therapy. HRQOL, as assessed with the Rand 36-item health survey (SF-36), improved significantly over a 26-week period in both the supervised and self-directed exercise groups, whereas it declined in the control group. Posthoc analyses indicated a significant difference between the self-directed and the supervised exercise group in favor of the self-directed exercisers. Courneya et al<sup>54</sup> compared psychotherapy alone with psychotherapy plus a home-based physical exercise program.

Significant group differences over time in favor of the combined psychotherapy and exercise group were observed in fatigue and functional well-being. Taken together, the two studies suggest that the salutary effect of physical exercise on patients' HRQOL cannot be attributed to nonspecific program characteristics such as increased attention received from health care providers or support received from fellow patients.

As has been described by Courneya et al<sup>68</sup> the exercise preferences of cancer patients can have an important effect on both their initial motivation to participate in formal physical exercise programs and their adherence to such programs. Adherence of cancer patients to short-term physical exercise interventions is slightly below that of other patient populations, and may explain, in part, the lack of effect observed in some of the studies reviewed.<sup>45</sup> In future RCTs, the motivation of patients and their exercise history should be assessed and perhaps used as either stratification variables before randomization or as covariates in the statistical analysis. Similarly, patients' adherence with exercise programs should be carefully monitored and reported because this may influence significantly the effectiveness of such programs in improving physical and psychosocial health outcomes.<sup>69</sup>

In conclusion, this review indicates that many of the RCTs and CCTs undertaken to date to evaluate the efficacy of exercise programs in cancer patients have been of only moderate methodologic quality. However, there appears to be

some improvement over time, with the most recent studies evidencing the highest methodologic quality. Although positive results have not always been observed consistently across studies, the general pattern of results indicates that exercise can be effective in reducing symptoms and improving the physical and psychosocial functioning of patients with cancer. It is important to note that the positive effects of exercise may vary significantly as a function of the type of cancer; the stage of disease; the medical treatment; the nature, intensity, and duration of the exercise program; and the lifestyle of the patient. Future RCTs should use larger samples, include appropriate comparison groups to rule out the possibility of an attention-placebo effect, standardize both the mode and intensity of exercise used, use a comparable set of outcome measures, and pay greater attention to issues of motivation and adherence of patients participating in exercise programs. Finally, studies with longer follow-up are needed to investigate the possible effects of exercise on cancer recurrence and survival.

### Acknowledgment

We thank Pius Estermann for verifying the search strategy and Leanne Pobjoy for assistance in preparing the final manuscript.

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

## REFERENCES

- Lindley C, Vasa S, Sawyer W, et al: Quality of life and preferences for treatment following systemic adjuvant therapy for early-stage breast cancer. *J Clin Oncol* 16:1380-1387, 1998
- Meuser T, Pietruck C, Radbruch L, et al: Symptoms during cancer pain treatment following WHO-guidelines: A longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain* 93:247-257, 2001
- Hanson-Frost M, Suman V, Rummans T, et al: Physical, psychological and social well-being of women with breast cancer: The influence of disease phase. *Psychooncology* 9:221-231, 2000
- Schwartz A: Daily fatigue patterns and effect of exercise in women with breast cancer. *Cancer Pract* 8:16-24, 2000
- Schwartz A: Fatigue mediates the effects of exercise on quality of life. *Qual Life Res* 8:529-538, 1999
- Schwartz A, Mori M, Gao R, et al: Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. *Med Sci Sports Exerc* 33:718-723, 2001
- Courneya K, Keats M, Turner A: Physical exercise and quality of life in cancer patients following high dose chemotherapy and autologous bone marrow transplantation. *Psychooncology* 9:127-136, 2000
- Dimeo F, Rumberger B, Keul J: Aerobic exercise as therapy for cancer fatigue. *Med Sci Sports Exerc* 30:475-478, 1998
- Courneya K, Friedenreich C: Physical exercise and quality of life following cancer diagnosis: A literature review. *Ann Behav Med* 21:171-179, 1999
- Courneya K: Exercise interventions during cancer treatment: Biopsychosocial outcomes. *Exerc Sports Sci Rev* 29:60-64, 2001
- Friedenreich C, Courneya K: Exercise as rehabilitation for cancer patients. *Clin J Sport Med* 6:237-244, 1996
- Pinto B: Exercise in the rehabilitation of breast cancer survivors. *Psychooncology* 8:191-206, 1999
- Courneya K: Exercise in cancer survivors: An overview of research. *Med Sci Sports Exerc* 35:1846-1852, 2003
- Dimeo F: Effects of exercise on cancer related fatigue. *Cancer* 15:1689-1693, 2001 (suppl 6)
- Fairey A, Courneya K, Field CJ, et al: Physical exercise and immune system function in cancer survivors: A comprehensive review and future directions. *Cancer* 94:539-551, 2002
- Oldervoll L, Kaasa S, Hjerstad M, et al: Physical exercise results in the improved subjective well-being of a few or is effective rehabilitation for all cancer patients? *Eur J Cancer* 40:951-962, 2004
- Irwin M, Ainsworth B: Physical activity interventions following cancer diagnosis: Methodologic challenges to delivery and assessment. *Cancer Invest* 22:30-50, 2004
- Bentzen S: Towards evidence based radiation oncology: Improving the design, analysis, and reporting of clinical outcome studies in radiotherapy. *Radiother Oncol* 46:5-18, 1998
- Moher D, Schulz K, Altman D: The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet* 357:1191-1194, 2001
- Schulz K, Chalmers I, Hayes R, et al: Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 273:408-412, 1995
- Moher D, Cook D, Eastwood S, et al: Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement—Quality of reporting of meta-analyses. *Lancet* 354:1896-1900, 1999
- Dickersin K, Scherer R, Lefebvre C: Identifying relevant studies for systematic reviews. *BMJ* 309:1286-1291, 1994
- Van Tulder M, Assendelft W, Koes B, et al: Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. *Spine* 22:2323-2330, 1997
- Verhagen A, de Vet H, de Bie R, et al: The Delphi list: A criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 51:1235-1241, 1998
- van Tulder M, Malmivaara A, Esmail R, et al: Exercise therapy for low back pain: A systematic review within the framework of the Cochrane collaboration back review group. *Spine* 25:2784-2796, 2000

26. Colle F, Rannou F, Revel M, et al: Impact of quality scales on levels of evidence inferred from a systematic review of exercise therapy and low back pain. *Arch Phys Med Rehabil* 83:1745-1752, 2002
27. Cunningham B, Morris G, Cheney C, et al: Effects of resistive exercise on skeletal muscle in marrow transplant recipients receiving total parenteral nutrition. *JPEN J Parenter Enteral Nutr* 10:558-563, 1986
28. Winningham M, MacVicar M: The effect of aerobic exercise on patient reports of nausea. *Oncol Nurs Forum* 15:447-450, 1988
29. Winningham M, MacVicar M, Bondoc M, et al: Effect of aerobic exercise on body weight and composition in patients with breast cancer on adjuvant chemotherapy. *Oncol Nurs Forum* 16:683-689, 1989
30. MacVicar M, Winningham M, Nickel J: Effects of aerobic interval training on cancer patients functional capacity. *Nurs Res* 38:348-351, 1989
31. Mock V, Burke M, Sheehan P, et al: A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. *Oncol Nurs Forum* 21:899-908, 1994
32. Dimeo F, Fetscher S, Lange W, et al: Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood* 90:3390-3394, 1997
33. Young-Moo N, Min-Young K, Young-Kyumn K, et al: Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery. *Arch Phys Med Rehabil* 81:777-779, 2000
34. Segal R, Evans W, Johnson D, et al: Structured exercise improves physical functioning in women with stages I and II breast cancer: Results of a randomized controlled trial. *J Clin Oncol* 19:657-665, 2001
35. Mock V, Pickett M, Ropka M, et al: Fatigue and quality of life outcomes of exercise during cancer treatment. *Cancer Pract* 9:119-127, 2001
36. Segal R, Reid R, Courneya K, et al: Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* 21:1653-1659, 2003
37. Mello M, Tanaka C, Dulle F: Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplant* 32:723-728, 2003
38. Coleman E, Coon S, Hall-Barrow J, et al: Feasibility of exercise during treatment for multiple myeloma. *Cancer Nurs* 26:410-419, 2003
39. Mcneely M, Parliament M, Courneya K, et al: A pilot study of a randomized trial to evaluate the effects of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurectomy in head and neck cancer survivors. *Head Neck* 26:518-530, 2004
40. Dimeo F, Tilmann M, Bertz H, et al: Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer* 79:1717-1722, 1997
41. Mock V, Dow K, Meares C, et al: Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncol Nurs Forum* 24:991-1000, 1997
42. Dimeo F, Stieglitz R, Novelli-Fischer U, et al: Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer* 85:2273-2277, 1999
43. Hayes S, Davies PS, Parker T, et al: Total energy expenditure and body composition changes following peripheral blood stem cell transplantation and participation in an exercise programme. *Bone Marrow Transplant* 31:331-338, 2003
44. Hayes SC, Rowbottom D, Davies PS: Immunological changes after cancer treatment and participation in an exercise program. *Med Sci Sports Exerc* 35:2-9, 2003
45. Pickett M, Mock V, Ropka M, et al: Adherence to moderate-intensity exercise during breast cancer therapy. *Cancer Pract* 10:284-292, 2002
46. Nieman D, Cook V, Henson D, et al: Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients. *Int J Sports Med* 16:334-337, 1995
47. Berglund G, Bolund C, Gustafsson UL, et al: One-year follow-up of the 'Starting Again' group rehabilitation programme for cancer patients. *Eur J Cancer* 30A:1744-1751, 1994
48. Berglund G, Bolund C, Gustafsson UL, et al: A randomized study of a rehabilitation program for cancer patients: The starting again group. *Psychooncology* 3:109-120, 1994
49. Burnham T, Wilcox A: Effects of exercise on physiological and psychological variables in cancer survivors. *Med Sci Sports Exerc* 34:1863-1867, 2002
50. McKenzie D, Kalda A: Effect of upper extremity exercise on secondary lymphedema in breast cancer patients: A pilot study. *J Clin Oncol* 21:463-466, 2003
51. Pinto B, Clark M, Maruyama N, et al: Psychological and fitness changes associated with exercise participation among women with breast cancer. *Psychooncology* 12:118-126, 2003
52. Courneya K, Mackey J, Bell G, et al: Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. *J Clin Oncol* 21:1660-1668, 2003
53. Fairey A, Courneya K, Field C, et al: Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: A randomized controlled trial. *Cancer Epidemiol Biomarkers Prev* 12:721-727, 2003
54. Courneya K, Friedenreich C, Sela R, et al: The group psychotherapy and home-based physical exercise (group-hope) trial in cancer survivors: Physical fitness and quality of life outcomes. *Psychooncology* 12:357-374, 2003
55. Courneya K, Friedenreich CM, Quinney HA, et al: A randomized trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care (Engl)* 12:347-357, 2003
56. Segar M, Katch V, Roth R, et al: The effect of aerobic exercise on self-esteem and depressive and anxiety symptoms among breast cancer survivors. *Oncol Nurs Forum* 25:107-113, 1998
57. Berglund G, Bolund C, Gustavsson U, et al: Starting again: A comparison study of a group rehabilitation program for cancer patients. *Acta Oncol* 32:15-21, 1993
58. Landis J, Koch G: The measurement of observer agreement for categorical data. *Biometrics* 33:159-174, 1977
59. Wu A, Pike M, Stram D: Meta-analysis: Dietary fat intake, serum estrogen levels, and the risk of breast cancer. *J Natl Cancer Inst* 91:529-534, 1999
60. Yu H, Berkel H: Insulin-like growth factors and cancer. *J La State Med Soc* 151:218-223, 1999
61. Vadgama J, Wu Y, Datta G, et al: Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women. *Oncology* 57:330-340, 1999
62. Chlebowski R, Aiello E, Mctiernan A: Weight loss in breast cancer patient management. *J Clin Oncol* 20:1128-1143, 2002
63. Davidow A, Neugut A, Jacobson J, et al: Recurrent adenomatous polyps and body mass index. *Cancer Epidemiol Biomarkers Prev* 5:313-315, 1996
64. Amling C, Riffenburgh R, Sun L, et al: Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. *J Clin Oncol* 22:439-445, 2004
65. Brown J, Byers T, Doyle C, et al: Nutrition and physical activity during and after cancer treatment: An American Cancer Society guide for informed choices—American Cancer Society. *CA Cancer J Clin* 53:268-291, 2003
66. Fearon K, Luff R: The nutritional management of surgical patients: Enhanced recovery after surgery. *Proc Nutr Soc* 62:807-811, 2003
67. Evans W: Effects of exercise on senescent muscle. *Clin Orthop Relat Res* Oct: S211-S220, 2002 (suppl 403)
68. Courneya K, Friedenreich C, Sela R, et al: Correlates of adherence and contamination in a randomized controlled trial of exercise in cancer survivors: An application of the theory of planned behavior and the five factor model of personality. *Ann Behav Med* 24:257-268, 2002
69. Samarel N, Fawcett J, Krippendorff K, et al: Women's perceptions of group support and adaptation to breast cancer. *J Adv Nurs* 28:1259-1268, 1998