Impact of Resistance Training in Cancer Survivors: A Meta-Analysis

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ABSTRACT

STRASSER, B., K. STEINDORF, J. WISKEMANN, and C. M. ULRICH. Impact of Resistance Training in Cancer Survivors: A Meta-Analysis. *Med. Sci. Sports Exerc.*, Vol. 45, No. 11, pp. 2080–2090, 2013. **Purpose**: Current evidence suggests many health benefits from physical activity during and after cancer treatment. However, the optimal exercise program for cancer survivors has not yet been established. The purpose of this meta-analysis was to summarize evidence for the efficacy of resistance training (RT) interventions to improve muscle strength and body composition among adult cancer survivors. We also investigate potential dose–response relationships between intensity, duration, and frequency of RT and assessed outcomes. **Methods**: A systematic literature review of the Clinical Trial Register, Cochrane Trial Register, MEDLINE, and EMBASE literature databases was undertaken. Studies were included if they were randomized controlled trials (RCT) comparing RT with an exercise or nonexercise control group in cancer survivors during and after treatment. Thirteen articles from 11 RCT met our inclusion criteria. We performed a random-effects meta-analysis to determine weighted mean differences (WMD) with 95% confidence intervals using the Cochrane Review Manager 5.0.25. A random-effects metaregression model was performed to examine dose–response relationships between RT variables and assessed outcomes. **Results**: Quantitative evidence shows a large effect of RT on lower-limb and upper-limb muscle strength (WMD: +14.57 kg, $P = 0.0005$ and +6.90 kg, $P < 0.00001$, respectively) and moderate effects on lean body mass and percentage of body fat (WMD: +1.07 kg, $P < 0.0001$ and −2.08%, $P = 0.003$, respectively). A small positive effect of RT was noted on Functional Assessment of Cancer Therapy–Fatigue ($P = 0.05$). Upper-limb muscle strength and percentage of body fat improved to a greater extent when RT interventions were of low to moderate intensity (≤75% one-repetition maximum, $P = 0.042$). **Conclusions**: RT was shown to be associated with clinically important positive effects on muscular function and body composition in patients during treatment or in long-term follow-up. **Key Words:** CANCER, EXERCISE, STRENGTH TRAINING, MUSCLE FUNCTION, QUALITY OF LIFE, SYSTEMATIC REVIEW

Cancer is the second leading cause of death in the United States, with breast and prostate cancer being the most frequently diagnosed cancers for women and men, respectively, (66). There are numerous side effects to cancer treatment, which often include muscle wasting or atrophy, reduced physical functioning, unfavorable changes in body composition, and depression and fatigue (17). A decrease in physical activity levels associated with other side effects, such as loss of appetite, can intensify muscular wasting and consequently loss of overall body strength, leading patients to experience a negative spiraling effect that further exacerbates the sense of fatigue. This loss of muscular strength together with a reduction in aerobic fitness makes it difficult to perform simple daily activities, significantly compromising the quality of life in cancer patients (37) as well as contributing to increased rates of mortality (27,28). Recent systematic reviews have shown that resistance training (RT) has the power to combat many of the side effects of cancer treatment and, thus, can be of significant benefit to patients in the short and long term (10,15,16).

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Benefits include improved muscle strength and physical functioning (73) and reduced fatigue (56), all potentially leading to improved quality of life (40). However, this has so far only been investigated for very few cancer types.

Normal aging is associated with a decline in muscle mass between 5% and 10% each decade after age 50 yr, averaging approximately 0.4 kg of lean weight loss per year after the fifth decade of life (33). Although weight loss occurs in roughly half of cancer patients, in cachexia, the weight loss represents a marked loss of predominantly skeletal muscle (58). In cachectic patients, a loss of 25% of body weight represents an approximately 75% reduction in skeletal muscle protein. Approximately 20% of cancer deaths are attributed to cachexia (65).

Numerous studies have demonstrated that relatively brief sessions of regular RT can increase muscle mass in adults of all ages through the 10th decade of life (71). Effects of RT are more pronounced if exercises are muscle site specific, high intensity, and when combined with calcium and vitamin D intake (8,31). Furthermore, RT can provide functional benefits and improvements in overall health and well-being, including increased bone mineral density (BMD) (38), improved physical performance (25,71), and cardiovascular health (63). Therefore, RT may have beneficial effects in cancer patients in terms of reducing muscle wasting or regaining lost muscle mass as well as improving muscle function and a diversity of biomarkers. In turn, this may lead to reduced fatigue levels and an overall enhancement in mental health.

The current systematic review was undertaken 1) to perform a meta-analysis of randomized controlled trials (RCT) regarding the effect of RT on muscle function, body composition, and fatigue both during and after cancer treatment and (2) to investigate the potential for a dose–response relationship between intensity, duration, and frequency of RT and assessed outcomes.

METHODS

Literature search. A systematic literature review of the Clinical Trial Register, Cochrane Trial Register, MEDLINE, and EMBASE literature databases was undertaken to identify relevant studies from earliest record to December 2012. The following key words were used alone, or in various combinations, within the systematic search: cancer, RT, muscle function, muscle strength, body mass, and fatigue. Reference lists from original and review articles were also reviewed to identify additional relevant studies. Only eligible full texts in English were considered for review.

Inclusion and exclusion criteria. All RCT comparing RT with an exercise or nonexercise control group in adult patients with cancer were examined. Participants may have been actively receiving treatment or be in long-term follow-up. Exclusion criteria for this review included the following: (i) studies with single-bout RT interventions; (ii) studies where the intervention was less than 6 wk in duration; (iii) pilot studies; (iv) studies with mere recommendations as intervention, without further detail; (v) studies where the RT was not either directly supervised or well documented; (vi) studies with a clinical cointervention in the experimental group that was not also applied to the control group; and (vii) studies with concomitant aerobic endurance training performed for more than 12 min per training session in the experimental group that was not also applied to the control group. Two researchers (B.S. and K.S.) independently performed the literature search, quality assessment, and data extraction. The third author (J.W.) provided additional review and insight. Any disagreements on inclusion of trials were resolved by discussion with the fourth author (C.U.).

The review comprises studies with both male and female adults. RCT with detailed RT prescriptions (relating to type, dose, intensity, frequency, and duration of RT) were included in the review. An inclusion criterion was the evaluation and report of the specific effects of RT on muscle strength and/or body composition. Included studies compared RT with no exercise, a usual care group (i.e., no specific exercise program prescribed), or an alternative treatment or exercise regime. Concentric and eccentric RT was considered for inclusion. On the basis of these criteria, 11 studies (13 publications) were included for review (2,5,12,35,49–51,54–57,73,74).

Assessed outcomes. The primary outcomes of our systematic review were lower-limb and upper-limb muscle strength measured in kilograms. Secondary outcomes included lean body mass (kg), fat mass (kg), percentage of body fat (%) determined by dual energy x-ray absorptiometry scan (DEXA), aerobic capacity measured in peak oxygen uptake ($\dot{V}O_{2max}$, $mL\cdot kg^{-1}\cdot min^{-1}$), or assessed by the 12-min walk test (m). Fatigue was evaluated in this set of studies and assessed by the Functional Assessment of Cancer Therapy–Fatigue (FACT-Fatigue) scale (points) (75).

Data extraction. A standardized data extraction form was developed to extract data from each study in the following areas: study population, intervention, and outcome. The form included the following items: 1) general information, including title, authors, source, setting, and year of publication; 2) trial characteristics, including study design and randomization; 3) characteristics of participants, such as inclusion criteria, exclusion criteria, total number in intervention/control groups, sex distribution, mean age, diagnostic criteria, other baseline characteristics, and dropouts; 4) intervention type, dose, intensity, and frequency as well as duration of the trial; 5) outcomes specified in the methods; and 6) results. For continuous variables, we extracted sample size as well as baseline and postintervention means with SD for the intervention and control groups. There were no dichotomous outcomes. Study characteristics were reported in evidence tables.

Quality assessment. The methodological qualities of RCT included in this review were assessed according to JADAD score (30). This 5-point quality scale includes points for randomization (described as randomized, 1 point; table of random numbers or computer-generated randomization, additional 1 point), double blinding (described as double

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blind, 1 point; use of making such as identical placebo, additional 1 point), and follow-up (the numbers and reasons for withdrawal in each group are stated, 1 point) within the report of an RCT. An additional point was accepted if the analysis was by intention to treat. Final scores between 0 and 2 were considered as low quality, whereas final scores of 3 or more were regarded to represent studies of high quality because the blinding of patients performing the exercise is not possible.

Statistical analysis. All data were analyzed with the software package Review Manager 5.0.25 from the Cochrane Collaboration. Heterogeneity between trial results was tested with a standard chi-square test (χ^2). The I^2 parameter was used to quantify any inconsistency ($I^2 = [(Q - df) / Q] \times 100\%$, where Q is the chi-square statistic and df is its degrees of freedom). A value for I^2 greater than 50% has been considered to be substantial heterogeneity (26). For each outcome of interest, a meta-analysis was performed to determine the pooled effect of the intervention in terms of weighted mean differences (WMD) between the postintervention values of the intervention and control groups. To consider heterogeneity, the random-effects model was used to estimate WMD with 95% confidence intervals (CI). Forest plots were generated to illustrate the study-specific effect sizes along with a 95% CI. Funnel plots were used to assess potential publication bias. To determine the presence of publication bias, we assessed the symmetry of the funnel plots in which mean differences were plotted against their corresponding SE. A random-effects meta-regression was performed to examine the association between duration, frequency, mean intensity (percentage of the one-repetition maximum [1RM]), and volume (sets per muscle group per week at the end of the intervention program) of RT exercises with changes in effect size. The P values for differences in effects between RT variables were obtained using STATA 11.0 (StataCorp, College Station, TX). Two-sided P values <0.05 were considered statistically significant. All presented CI refer to coverage of 95%.

RESULTS

Included Studies

After the selection of a total number of 259 full-text articles, 23 publications were considered potentially relevant. The application of all desired inclusion criteria resulted in a final inclusion of 11 RCT reported in 13 publications (2,5,12,35,49–51,54–57,73,74). A flow diagram of search and selection is shown in Figure 1 (see Figure, Supplemental Digital Content 1, http://links.lww.com/MSS/A277, which illustrates the selection process of eligible randomized controlled studies). The predominant reasons for exclusion were as follows: (a) the study had no control group (24,41), (b) studies did not report muscle strength or body composition as an outcome measure (11,34,40,48,69,76), or (c) multiple publication of studies (4,60). Two studies resulted in two publications each (2, 49 and 73, 74, respectively) but reported different strength outcomes and were thus included, although they were considered only as one trial. The characteristics of studies that were included, and detailed descriptions of the exact RT regimes are presented in Table 1.

Participants

The total number of participants included in the analysis of the 11 RCT was 1167 (74% women and 26% men) with 502 participating in an RT intervention, 491 control participants, and a further 174 participants participating in an aerobic endurance training intervention. The latter participants were not included for data extraction and meta-analysis. Seven studies (reported in nine publications) included only patients with breast cancer (2,5,12,49–51,54,73,74), two included only patients with prostate cancer (56,57), one included only patients with head and neck cancer (35), and the one remaining included patients with different types of cancer (55). Cancer treatments received by participants included various combinations of surgery, radiotherapy, chemotherapy, and androgen-deprivation therapy. Six of the

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ahmed 2006	37.6	1.3	23	28.6	1.2	22	18.1%	9.00 [8.27, 9.73]
Courneya 2007	31.9	10.8	77	24.6	7.8	73	13.5%	7.30 [4.30, 10.30]
McNeely 2008	51.4	20.6	27	37	21.1	25	2.9%	14.40 [3.05, 25.75]
Schmitz 2009	24	8.2	59	17.7	5.4	63	14.8%	6.30 [3.82, 8.78]
Schmitz 2010	24.5	5.4	61	19.5	5	63	16.3%	5.00 [3.17, 6.83]
Schwartz 2007	38.1	8.6	21	30.7	9.1	23	8.7%	7.40 [2.17, 12.63]
Schwartz 2009	44.9	13.2	34	32.2	15.8	33	6.2%	12.70 [5.72, 19.68]
Segal 2009	60.8	14	40	52.9	14.6	41	7.1%	7.90 [1.67, 14.13]
Winters-Stone 2012	28.7	6.9	36	27.7	7.6	31	12.3%	1.00 [-2.50, 4.50]
Total (95% CI)			**378**			**374**	**100.0%**	**6.90 [4.78, 9.03]**

Heterogeneity: Tau² = 6.35; Chi² = 37.85, df = 8 (P < 0.00001); I² = 79%
Test for overall effect: Z = 6.37 (P < 0.00001)

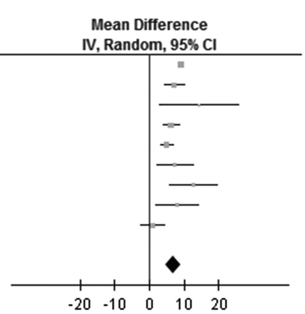

FIGURE 1—Forest plot showing the results of a meta-analysis as pooled WMD with 95% CI in upper-limb muscle strength (kg) for the nine included randomized controlled RT trials. For each RT trial, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of this effect. The area of the shaded square reflects the relative weight of the trial in the meta-analysis. The diamond at the bottom of the graph represents the pooled WMD with the 95% CI for the nine trial groups. Studies included Ahmed et al. (2), Courneya et al. (12), McNeely et al. (35), Schmitz et al. (50,51), Schwartz et al. (54,55), Segal et al. (57), and Winters-Stone et al. (73).

TABLE 1. Summary of articles included in the meta-analysis.

Study ID	Aim	Sample Size RT/Control	RT Intervention	Main Outcomes	Main Results RT Group
Winters-Stone et al. (73)	To evaluate the effects of RT on muscle strength and physical function	*N* = 67 (RT = 36, control = 31) breast cancer survivors	3 times per week for 52 wk. 10 RT exercises, 1–3 sets of 8–12 reps at 80% 1RM + impact exercise program with weighted vests	Max muscle strength: 1RM bench press/leg press; fatigue (CFS); physical function	Significant improvements in maximal muscle strength in the RT group compared with controls at 52 wk. RT did not improve fatigue
Winters-Stone et al. (74)	To evaluate the effects of RT on BMD, body composition	*N* = 67 (RT = 36, control = 31) breast cancer survivors	3 times per week for 52 wk. 10 RT exercises, 1–3 sets of 8–12 reps at 80% 1RM + impact exercise program with weighted vests	BMD: lumbar spine, total hip, trochanter, femoral neck; body comp: BF%, FM, LBM	Women in the RT group preserved BMD at the lumbar spine compared with controls at 52 wk. RT significantly increased LBM among women currently taking AI compared with controls not on this therapy
Schmitz et al. (50)	To evaluate the effects of RT on lymphedema onset, muscle strength, and body composition	*N* = 133 (RT = 60, UC = 63 for muscle strength; RT = 65, UC = 68 for body mass) survivors at risk for BCRL	2 times per week for 52 wk. 10 RT exercises, 3 sets of 10 reps; weight gradually increased	BCRL: >5% increase arm swelling; muscle strength: 1RM bench press/leg press; body comp: BF%, FM, LBM	RT did not result in increased incidence of BCRL compared with controls at 52 wk. Significant improvements in muscle strength and body fat compared with controls at 52 wk
Schmitz et al. (51)	To evaluate the effects of RT on limb swelling, muscle strength, and body composition	*N* = 129 (RT = 58, UC = 63 for muscle strength; RT = 65, UC = 64 for body mass) survivors with BCRL	2 times per week for 52 wk. 10 RT exercises, 3 sets of 10 reps; weight increased gradually	BCRL: >5% increase arm swelling; muscle strength: 1RM bench press/leg press; body comp: BF%, FM, LBM	RT had no significant effect on limb swelling and resulted in a decreased incidence of exacerbations of lymphedema at 52 wk. Further, significant improvements in muscle strength compared with controls
Schwartz et al. (55)	To evaluate the effects of RT or AET on aerobic capacity, muscle strength, and body composition	*N* = 101 (RT = 34, AET = 34, UC = 33) cancer survivors during/after CHT	4 times per week for 52 wk. 6 RT exercises, 3 sets of 12 reps or 2 sets of 18–20 reps; weight increased gradually	Max muscle strength: 1RM leg extension/seated row; 12-MWT; body comp: BF%	Significant improvements in muscle strength and aerobic capacity in the RT and AET group compared with UC. BF% significantly increased in the UC group compared with AET and RT at 52 wk
Segal et al. (57)	To evaluate the effects of RT or AET on fatigue, QOL, physical fitness, body composition, PSA, testosterone, lipids, and hemoglobin	*N* = 121 (RT = 40, AET = 40, UC = 41) prostate cancer patients receiving RAT	3 times per week for 24 wk. 10 RT exercises, 2 sets of 8–12 reps at 60%–70% 1RM	Muscle strength: 8-RM leg press/8-RM chest press; $\dot{V}O_{2max}$; body comp: BF%; QOL; fatigue (FACT)	RT significantly improved muscle strength, aerobic fitness, QOL, fatigue, and prevented body fat increases compared with usual care at 24 wk
McNeely et al. (35)	To evaluate the effects of RT on upper extremity pain and dysfunction	*N* = 52 (RT = 27, UC = 25) head and neck cancer survivors	2 times per week for 12 wk. 5–8 RT exercises, 2 sets of 10–15 reps, starting at 25%–30% 1RM progressing to 60%–70% 1RM	Max muscle strength: 1RM chest press/seated row; QOL; shoulder pain, ROM; fatigue (FACT)	Shoulder pain and muscle strength significantly improved after RT compared with usual care at 12 wk. QOL and fatigue showed nonsignificant improvements with RT
Battaglini et al. (5)	To evaluate the effects of RT on body composition	*N* = 20 (RT = 10, control = 10) breast cancer patients during treatment	2 times per week for 21 wk. 8–12 RT exercises, 3 sets of 6–12 reps at 40%–60% 1RM	Body composition: BF%, LBM%; muscle strength	Significant improvements in percent body fat, lean body mass, and muscle strength in the RT group compared with controls
Courneya et al. (12)	To evaluate the effects of RT or AET on physical fitness, body composition, QOL, and fatigue	*N* = 242 (RT = 82, AET = 78, UC = 82) breast cancer patients receiving CHT	3 times per week for the duration of CHT (9–24 wk). 9 RT exercises, 2 sets of 8–12 reps at 60%–70% 1RM	Max muscle strength: 1RM bench press/leg press; $\dot{V}O_{2max}$; body comp: BF%, FM, LBM; QOL; fatigue (FACT)	RT was superior to usual care for improving muscular strength, LBM, and CHT completion rate. RT did not significantly improve cancer-specific QOL and fatigue
Schwartz et al. (54)	To evaluate the effects of RT or AET on BMD	*N* = 66 (RT = 21, AET = 22, UC = 23) breast cancer patients receiving CHT	4 times per week for 24 wk. 8 RT exercises, 2 sets of 8–10 reps weight increased gradually	Max muscle strength: 1RM leg extension/seated row; 12-MWT; BMD	Significant improvements in muscle strength and aerobic capacity in the RT and AET group compared with UC. Weight-bearing AET preserved BMD significantly better compared with RT and UC at 24 wk
Ahmed et al. (2)	To evaluate the effects of RT on lymphedema onset or exacerbation and muscle strength	*N* = 45 (RT = 23, control = 22) breast cancer survivors	2 times per week for 24 wk. 9 RT exercises, 3 sets of 8–10 reps weight increased gradually	BCRL: >2% increase arm circumferences; max muscle strength: 1RM bench press/leg press	RT did not increase the risk for symptoms of lymphedema and resulted in significant improvements in muscle strength compared with controls at 24 wk
Schmitz et al. (49)	To evaluate the effects of RT on body size and biomarkers (glucose, insulin, IGF axis variables)	*N* = 81 (RT = 40, control = 41) breast cancer survivors	2 times per week for 24 wk. 9 RT exercises, 3 sets of 8–10 reps weight increased gradually	Body composition: BF%, FM, LBM; biomarkers: glucose, insulin, HOMA, IGF axis variables.	Significant improvements in LBM, BF% and IGF-II compared with controls at 24 wk
Segal et al. (56)	To evaluate the effects of RT on QOL and fatigue	*N* = 155 (RT = 82, control = 73) prostate cancer patients receiving ADT	3 times per week for 12 wk. 9 RT exercises, 2 sets of 8–12 reps at 60%–70% 1RM	QOL; fatigue (FACT); muscular fitness (rep)	Significant improvements in QOL, fatigue, and muscular fitness in the RT group compared with controls at 12 wk

ADT, androgen deprivation therapy; AET, aerobic endurance training; AI, aromatase inhibitor; BCRL, breast cancer–related lymphedema; BF%, % body fat; BMD, bone mineral density; CFS, Schwartz cancer fatigue scale; CHT, chemotherapy; FACT, Functional Assessment of Cancer Therapy; FM, fat mass; HOMA, homeostatic model assessment; IGF, insulin-like growth factor; LBM, lean body mass; RAT, radiation therapy; RM, repetition maximum; ROM, range of motion; RT, resistance training; UC, usual care; $\dot{V}O_{2max}$, peak oxygen uptake; QOL, quality of life; 12-MWT, 12-min walk test.

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studies investigated participants during cancer treatment (5,12,54–57), and in five studies (seven papers), the participants were considered to have completed cancer treatment (2,35,49–51,73,74).

The mean age of participants ranged from 47 yr (55) to 68 yr (56). Eight studies (reported in ten publications) recruited only women (2,5,12,49–51,54,55,73,74), two recruited only men (56,57), and one study recruited both (35).

Interventions

The duration of interventions ranged from 12 wk in two studies (35,56), 4–6 months in four studies (five papers) (2,5,49,54,57), and 1 yr in four studies (five papers) (50,51,55,73,74). One intervention was delivered throughout chemotherapy and had a mean duration of 17 ± 4 wk (12). Most interventions involved two (2,5,35,49–51) or three (12,56,57,73,74) training sessions per week, with RT occurring on nonconsecutive days. Two studies involved four sessions per week (54,55). The percentage of the 1RM or 10- to 15-repetition maximum (10–15RM) were scales used to define the intensity of RT. One set consisted of 10–15RM without interruption, until severe fatigue occurred and completion of further repetitions was impossible. The training load was systematically adapted to keep the maximum possible repetition per set between 10 and 15; 10–15RM is equivalent to 70%–80% 1RM for most exercises (72). The mean intensity of the interventions ranged from 50% 1RM (5) to 80% 1RM (73,74). The maximum number of sets for each muscle group per week (S/MG/W) at the end of the intervention program ranged from 4 S/MG/W (35) to 12 S/MG/W (55). The most common dose of RT at the end of the intervention was 6 S/MG/W. RT on a weight machine was most commonly used for progressive RT. In most studies, the RT program consisted of exercises for all major muscle groups. Exercises to strengthen the upper body included bench press (pectoralis), chest cross (horizontal flexion of the shoulder joint), shoulder press (trapezius), pulldowns (latissimus dorsi), bicep curls, tricep extensions, and exercises for abdominal muscles (sit-ups). Lower body exercises included leg press (quadriceps femoris). Two studies performed RT using elastic bands (54,55), and one study combined with plyometric jumps (73,74).

Pooled Outcomes

Lower-limb and upper-limb muscle strength was used as the principal outcome measure in this systematic review. Ten of 11 studies measured muscle strength, involving a total of 958 participants (2,5,12,35,50,51,54,55,57,73). Of these, 391 received the RT intervention. Of 11 studies, 8 reported results for percentage of body fat (5,12,49–51,55,57,74), 5 for fat mass (12,49–51,74), and 6 for lean body mass (5,12,49–51,74). Peak oxygen uptake ($\dot{V}O_{2max}$) and results for the 12-min walk test were reported in two studies each (12, 57 and 54, 55, respectively). Four of the studies provided data on FACT-Fatigue (12,37,58,59).

Figure 1 shows the results from each study group for upper-limb muscle strength, and Figure 2 shows the results for FACT-Fatigue change (WMD point estimate and 95% CI) in response to RT (graphically displayed as a forest plot). Table 2 summarizes the pooled results for all considered intervention effects. The meta-analysis demonstrated that the pooled effect of RT on lower-limb and upper-limb muscle strength was a significant weighted mean increase of 14.57 kg (95% CI = 6.34–22.80 kg, P = 0.0005) and 6.90 kg (95% CI = 4.78–9.03 kg, P < 0.00001), respectively. There were no significant differences between the RT group and the control group in $\dot{V}O_{2max}$ (WMD: 0.97 mL·kg^{-1}·min^{-1}, 95% CI = −0.53 to 2.47 mL·kg^{-1}·min^{-1}, P = 0.20), although the improvement in the 12-min walk test with RT was statistically significant (WMD: 143.7 m, 95% CI = 70.5–216.8 m, P = 0.0001). The percentage of body fat was reduced by 2.08%, which is statistically significant (95% CI = −3.46 to −0.70%, P = 0.003). There were no significant differences between the RT group and the control group in body fat mass (WMD: −0.83 kg, 95% CI = −1.87 to 0.21 kg, P = 0.12). The change in lean body mass with RT was statistically significant (WMD: 1.07 kg, 95% CI = 0.76–1.37 kg, P < 0.00001). This meta-analysis showed a significant improvement in FACT-Fatigue with RT (WMD: 1.86 points, 95% CI = −0.03 to 3.75 points, P = 0.05). We performed sensitivity analysis of pooled data in patients who had completed treatment for cancer in contrast to subjects during cancer treatment. RT resulted in a superior improvement in lower-limb muscle strength in the cancer survivor group (WMD: 18.24 kg, 95% CI = 7.16–29.32 kg, P = 0.001) compared with the during-treatment group (WMD: 9.38 kg,

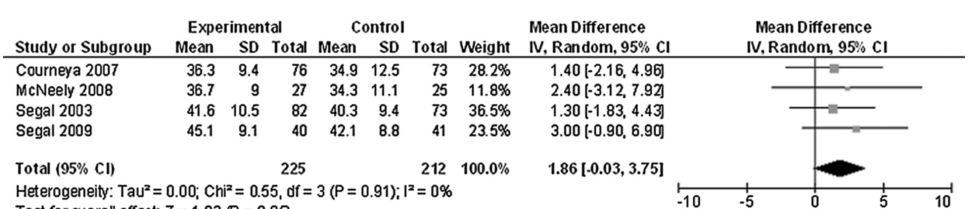

FIGURE 2—Forest plot showing the results of a meta-analysis as pooled WMD with 95% CI in FACT-Fatigue (points) for the four included randomized controlled RT studies. For each RT trial, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of this effect. The area of the shaded square reflects the relative weight of the study in the meta-analysis. The diamond at the bottom of the graph represents the pooled WMD with the 95% CI for the four study groups. Studies included Courneya et al. (12), McNeely et al. (35), and Segal et al. (56,57).

TABLE 2. Pooled estimates of effect size (95% CI) expressed as WMD for the effect of RT on muscle strength, aerobic capacity, body composition, and fatigue in cancer patients.

Outcomes	No. Studies	Sample Size	WMD	95% CI	P	Heterogeneity I^2 (%)
Muscle strength						
Upper limb (kg)	9	752	6.90	4.78 to 9.03	<0.00001	79
Lower limb (kg)	9	719	14.57	6.34 to 22.80	0.0005	91
Aerobic capacity						
$\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	2	231	0.97	−0.53 to 2.47	0.20	0
12-MWT (m)	2	111	143.65	70.46 to 216.83	0.0001	0
Body composition						
Body fat (%)	8	713	−2.08	−3.46 to −0.70	0.003	74
Body fat mass (kg)	5	545	−0.83	−1.87 to 0.21	0.12	12
Lean body mass (kg)	6	565	1.07	0.76 to 1.37	<0.00001	0
Fatigue						
FACT (points)	4	437	1.86	−0.03 to 3.75	0.05	0

FACT, Functional Assessment of Cancer Therapy; $\dot{V}O_{2max}$, peak oxygen uptake; 12-MWT, 12-min walk test.

95% CI = 4.22–14.54 kg, P = 0.0004). Otherwise, the percentage of body fat was reduced by a statistically significant 4.0% (95% CI = −5.51 to −2.50%, P < 0.00001) during treatment compared with 0.87% (95% CI = −2.18 to 0.48%, P = 0.19) after treatment. Aerobic capacity, body fat mass, lean body mass, and fatigue were not affected by the cancer treatments received by participants.

Additional Outcomes

BMD. Two studies assessed BMD as an outcome (54,74). In one study, women in the RT group preserved BMD at the lumbar spine at 52 wk compared with controls (74), whereas another study showed a significant better preservation of BMD with weight-bearing aerobic endurance training compared with RT and usual care at 24 wk (54).

Tumor-specific outcomes. Three studies that investigated the effects of RT on limb swelling and lymphedema onset in breast cancer survivors reported either no increase in incidence of breast cancer-related lymphedema (2,50) or a decreased incidence of exacerbations of lymphedema (51). Both studies that recruited participants with prostate cancer reported no significant differences between the RT group and the control group in terms of testosterone levels (56,57). One study aimed to evaluate the effects of RT on shoulder pain and dysfunction in people with head and neck cancer and reported beneficial effect on shoulder function (35).

Quality of life. Four studies assessed quality of life (QOL) as an outcome (12,35,56,57). Two studies demonstrated a significantly beneficial effect of RT on QOL compared with usual care (56,57). Two other studies reported trends for improved QOL in the RT group compared with the control group (12,35).

Study Quality

All selected trials were described as randomized. No trials reported significant differences in participant characteristics at the outset of the intervention (baseline). The median score for quality was 4, ranging from 3 to 5 (see Table, Supplemental Digital Content 2, http://links.lww.com/MSS/A278, which illustrates methodological quality of included RT trials). Four RCT (five publications) met all the quality criteria (35, 56, 57, 73, 74). The second methodological assessment criterion (blinding of the intervention) was not assessed as a quality criterion because blinding was not possible in this context. However, an additional point was given if the blinding of the study assessors was reported. The blinding of the outcome assessors was fulfilled in seven RCT (nine publications) (2, 35, 49–51, 56, 57, 73, 74). A review of the third methodological criteria demonstrated that drop-outs were reported in all studies. Drop-outs in the intervention group ranged from 0% in one study (5), 5%–10% in six studies (seven publications) (2,12,35,49,51,54,56), 11%–20% in three studies (50,55,57), to 30% in one study (reported in two publications) (73,74). Compliance with exercise, on the other hand, was between 60% and 80% in six studies (seven papers) (12,50,54–56,73,74), 90% in three studies (four papers) (2,49,51,57), and more than 90% in two trials (5,35).

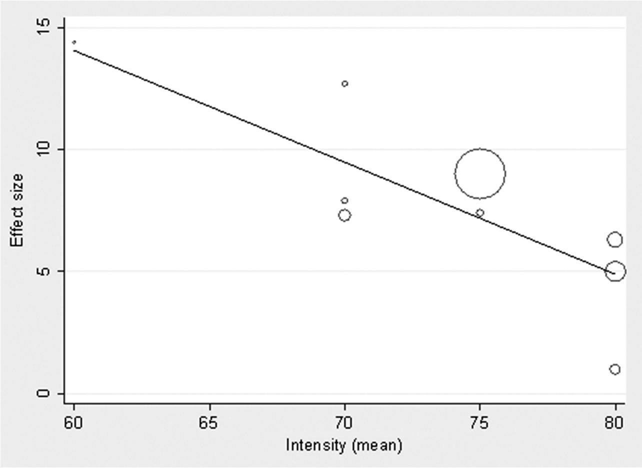

FIGURE 3—Bubble plot showing the dose–response relationship between the mean intensity (percentage of the 1RM) of RT intervention and effect size changes for upper limb muscle strength (kg) for the nine included randomized controlled RT trials (P = 0.042). For one single continuous variable, the fitted regression line together with circles representing the estimates from each trial, sized according to precision of each estimate in the fitted random-effects metaregression. Studies included Ahmed et al. (2), Courneya et al. (12), McNeely et al. (35), Schmitz et al. (50,51), Schwartz et al. (54,55), Segal et al. (57), and Winters-Stone et al. (73).

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Heterogeneity and Dose–Response Relationship

We found heterogeneity across trials concerning some outcomes, that is, upper limb muscle strength (I^2 = 79%), lower-limb muscle-strength (I^2 = 91%), and percentage of body fat (I^2 = 74%) (Table 2).

Metaregression revealed no statistically significant dose–response relationship between volume of RT at the end of the intervention program and effect size changes. The main factor that explained part of the heterogeneity was for one outcome duration and intensity of RT with a significant negative impact on upper limb muscle strength (decline in values) with increasing intensity (P = 0.042). We noted a significant positive impact on percentage of body fat (smaller effect size) with increasing intensity of RT (P = 0.02). Figures 3 and 4 show the dose–response relationship between intensity of RT and changes in effect size for upper limb muscle strength and percentage of body fat, respectively (graphically displayed as a bubble plot).

DISCUSSION

This meta-analysis was designed to investigate the effects of progressive RT on muscle strength and body composition in adult cancer patients. RT interventions resulted in a statistically significant improvement in muscle strength compared with controls. The increase of 14.6 kg for lower limb muscle strength (nine trials) and 6.9 kg for upper limb muscle strength (nine trials) was achieved during periods between 12 wk and 1 yr and compares well with reported improvements achieved in healthy elderly (61). The clinical significance of muscle strength for healthy adult and cancer survivors can be gauged by evaluating cross-sectional and longitudinal studies examining direct measurement of muscle strength in association with morbidity (3,29) and mortality (39,46). The Health, Aging, Body Composition Study study showed mortality to be associated with both lower limb and upper limb muscle strength, and this association remained significant even after adjustment for lean body mass (39). For quadriceps strength (per SD of 3.8 kg), the crude hazard ratio for men was 1.51 (95% CI = 1.128–1.79) and 1.65 (95% CI = 1.19–2.30) for women (29). Furthermore, the Aerobic Center Longitudinal Study noted that slightly higher levels of muscular strength (10.7 kg for leg press and 7.7 kg for bench press) were associated with 35% reduced cancer mortality in men, independent of body fat and cardiorespiratory fitness (46). Thus, the significant gain in muscle strength achieved in our review may increase life expectancy in cancer patients considerably. Although we found no significant differences between the RT group and the control group in $\dot{V}O_{2max}$ (two trials), the improvement in the 12-min walk test with RT was statistically significant in two trials by Schwartz et al. (54,55). This may be in part due to an increase in muscle oxidative capacity and/or anaerobic muscle metabolism with RT (23,32).

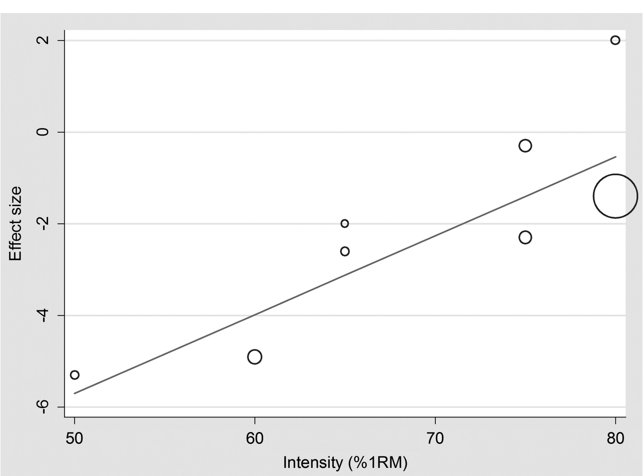

FIGURE 4—Bubble plot showing the dose–response relationship between the mean intensity (percentage of the 1RM) of RT intervention and effect size changes for percentage of body fat (%) for the eight included randomized controlled RT trials (*P* = 0.02). For one single continuous variable, the fitted regression line together with circles representing the estimates from each study, sized according to precision of each estimate in the fitted random-effects metaregression. Studies included Battaglini et al. (5), Courneya et al. (12), Schmitz et al. (49–51), Schwartz et al. (55), Segal et al. (57), and Winters-Stone et al. (74).

In addition to the increase in muscle strength, RT also resulted in a significant overall increase in lean body mass by 1.07 kg (six trials) compared with controls. This is in accordance with a recent meta-analysis by Peterson et al. (43) reporting a weighted pooled estimate of mean lean body mass change by 1.1 kg (95% CI = 0.9–1.2 kg) with RT (mean duration: 20.5 ± 9.1 wk) in healthy aging adults. Thus, RT twice a week increases muscle mass by 1–2 kg per 6 months and could prevent age-associated loss of muscle mass in both healthy adults (38) and patients with chronic disease (62). In our meta-analysis, an RT intervention resulted in a significant lowering of percentage of body fat by 2.08% (eight trials) compared with the controls, but there was no significant difference between groups in body fat mass (−0.83 kg). The observed between-group effect sizes in body fat are similar to the effect sizes observed with aerobic training in adult patients after completion of main cancer treatment (−0.8%, −1.5 kg) (22). This result is not unimportant because already small reductions in body fat mass (1.5 kg) are associated with reductions in plasma lipid peroxidation (68). Oxidative stress may be related to cancer prognosis and is closely associated with mitochondrial dysfunction, cytokine dysregulation, and disruptions in muscle metabolism, and all of them have been postulated as mechanistic underpinnings of cancer-related fatigue (47). RT increases muscle protein synthesis (45), improves cytokine response (44), and diminishes atrophy (21). Furthermore, reduced body fat may also impact cancer prognosis as there is some evidence for a positive association between body fat and increased cancer-related mortality or recurrence (67).

On the basis of this meta-analysis, an RT intervention resulted in a significant reduction in FACT-Fatigue (four trials) compared with controls. The pooled results of the four studies examining the effect of RT on symptoms of fatigue

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showed a small effect; however, statistically significant improvements in symptoms of fatigue were reported in only two studies (56,57). One study used the Schwartz cancer fatigue scale and noted no improvements in fatigue with RT (73). The observed 1.9-point improvement in FACT-Fatigue with RT was lower than the 3.0-point threshold for minimal clinically important differences (9). Only four meta-analyses have concluded that physical activity had significant effects on reducing fatigue in cancer survivors (6,13,14,59). They reported at least small effects of physical activity. Cramp and Daniel (13) identified in their recent systematic review significant benefits of aerobic endurance training on cancer-related fatigue but RT failed to reach significance. Interestingly, Brown et al. (6) reported that RT had a positive, quadratic, and exercise intensity dose–response effect on cancer-related fatigue. Exercise reduced fatigue especially in programs that involved RT exercise among adult cancer survivors and that were of moderate to high intensity (60%–80% 1RM) (6). Thus, the intensity of exercise could play an important role in its effects. Fong et al. (22) reported significantly larger effects of aerobic plus RT than aerobic training alone on cancer-related fatigue that might indicate a potential benefit of higher intensity. In one study by Segal et al. (57), improvements in fatigue were associated with improvements in upper-body strength, but not hemoglobin. This suggests that RT may improve fatigue by improving neuromuscular efficiency and reducing muscular fatigue.

How much RT is needed? Considering the benefits of RT on muscle function, body composition, and cancer-related fatigue, an important question is, how much RT (duration, intensity, and volume) is needed to confer such benefits? On the basis of this analysis, metaregression revealed no statistically significant dose–response relationship between the volume of RT and the effect size changes in assessed outcomes. For example, improvements in muscle strength were observed after low volume (4 S/MG/W) (35), moderate volume (6 S/MG/W) (12,57), and high volume (10 S/MG/W) (55) of RT. This is in accordance with data from a recent meta-analysis investigating the effectiveness of RT for strength improvement among adults ≥50 yr (42). However, we observed a significant negative impact on upper limb muscle strength with increasing intensity of RT intervention and a tendency toward a negative impact on upper limb muscle strength with increasing study duration. A possible reason might be a diminished increase in cross-sectional area per day with increasing length of the training period (70). Muscle size shows significant changes after 8–12 wk of regular RT (1). This adaptation appears to proceed in a linear manner during the first 6 months of training (36). It is intuitive that the growth of skeletal muscle must slow or plateau eventually, and at some point, further RT would provide no additional benefit or treatment effect. On the basis of current data, it appears that to facilitate progressive adaptation in muscle mass and strength, it is necessary to increase the prescription dosage as individuals become more familiarized with training (42). On the basis of our meta-analysis, prescription dosage (sets per muscle group per week) did not progressively increase over time in most studies. The only "progression" in training prescription was that of the absolute training load. It is therefore conceivable that the lack of increase in dosage may be the reason behind the negative impact on upper limb muscle strength with increasing study duration.

We observed a significant negative impact on upper limb muscle strength with increasing intensity. Metaregression revealed that low/moderate-intensity RT (≤75% 1RM) was associated with greater improvement than moderate/high-intensity RT (>75% 1RM). These data beg the question, how low can the RT intensity be and still produce a physiological adaptation and functional benefit? A recent study in healthy young adults showed that low-load high-volume leg RT to failure (30% 1RM) was more effective at increasing muscle protein synthesis than high-load low-volume RT to failure (90% 1RM) (7). Thus, RT-induced muscle protein synthesis may not necessarily be intensity dependent but may instead be determined by exercise volume. This would be important news for cancer patients who may be unable to sustain lifting weights at a relative high intensity due to sarcopenic comorbidities, such as connective tissue complications.

Although our metaregression suggests that moderate-intensity RT may be more effective than high-intensity for body fat loss, it is important to remember that the scientific evidence suggest only a modest effect of RT on body fatness and this may be influenced by whether the resistance exercise is accompanied by a concurrent reduction in energy intake (19). RT without energy restriction does not show clinically significant decreases in body weight; however, data show that RT may be an effective alternative to improve body composition in the short-term and long-term (1–2 kg loss of body fat with 1–2 kg increase in lean body mass) (18).

On the basis of our review, an RT intervention resulted in a significant improvement in FACT-Fatigue in studies reporting muscle strength or body composition as primary outcome measure. However, there was no evidence for associations between total exercise volume or mean intensity and beneficial effects on cancer-related fatigue. Although a recent meta-analysis conducted by Brown et al. demonstrated the superiority of higher intensity RT for fatigue reduction (6), no study has examined RT interventions greater than 80%1RM. It remains unknown whether more vigorous-intensity RT would provide greater or lesser reductions in cancer-related fatigue. For the current analysis, it is conceivable that the limited number of study groups and the overall lack of substantial variability in training regimens across intervention trials may have limited our analyses. Thus, further research is required to determine the optimal type and intensity of an exercise intervention on fatigue.

Strengths and limitations. Our study has several strengths. To our knowledge, this is the first systematic review to assess the association between dose of RT with changes in muscle strength, body composition, and fatigue both during and after cancer treatment. We included only published RCT in our meta-analysis. This is important because nonrandomized studies can overestimate treatment effects by 30%–41% (53). We used the random-effects model to estimate WMD with 95% CI to consider heterogeneity. We excluded studies with a cointervention and where the RT was not either directly supervised or well documented.

Limitations of the present review include the limited number of studies and the heterogeneity in study design. Heterogeneity may be explained by the range of different RT intervention used (and protocols used) across studies (64). Intervention differences included duration, frequency, intensity, and dose of exercise; diversity in the initial strength; and clinical status of participating individuals. The studies included had a broad array of populations: men and/or women; adults of any age; cancer survivors of any tumor type, tumor stage, and type of cancer treatment; and participants during treatment (radiotherapy, chemotherapy, and androgen deprivation therapy) or in long-term follow-up. Further, although the studies are expected to have internal validity, there may be limited generalizability because of differences between study participants and all cancer patients. Some studies did not provide information on the quality of the intervention such as randomization method, allocation concealment, and blinding of the study assignments to the persons performing the outcome measurements. However, the median quality score of 4 reflects high methodological quality of included trials.

Inspection of funnel plots suggests that publication bias cannot be excluded (see Figures, Supplemental Digital Content 3, http://links.lww.com/MSS/A279 and 4, http://links.lww.com/MSS/A280, which illustrate funnel plots showing study precision against the WMD effect estimate with 95% CI for lower- and upper-limb muscle strength, respectively). It appears that smaller studies with null results and larger SE may have been not published. The risk of publication bias might have been further increased by searching only three electronic databases and not contacting other experts for possible inclusion of more relevant studies as well as limiting this review to English-language publications.

CONCLUSIONS

The optimal exercise program for adult cancer survivors has not yet been established. Current exercise guidelines for cancer survivors emphasize the importance of participating in aerobic exercise, complemented with resistance and flexibility exercises and often make no or minimal mention of RT (20,52). Although some recent reviews (10,15,16) analyzed the effectiveness of RT in cancer survivors and suggested some positive effects of RT programs on muscle function and quality of life, this is the first investigation of the pooled effects of RT using meta-analysis. Because the dose–response relationship of RT for cancer patients has not yet been clarified, we lack clear recommendations for optimal RT. Findings from this meta-analysis support whole body RT as an appropriate training modality 1) to increase muscle strength in cancer patients and 2) to improve body composition in the short and long-term. However, whole-body RT is essential for correcting muscular deficiencies seen in the cancer patients, the use of weights for upper body RT is strongly recommended to improve pain, disability, and range of shoulder movements in patients treated for breast or head and neck cancer. Overall, chronic RT is well tolerated in adult cancer patients. None of the included studies reported significant adverse effects. Only one patient with head and neck cancer experienced increased pain as a result of soft-tissue injury to the scapular region due to RT (35). The optimal frequency for RT appears to be 2 $d{\cdot}wk^{-1}$. The intensity of RT could play an important role in its effects. Our analysis suggests that low- to moderate-intensity RT (≤75%1RM) be performed to fatigue may promote equivalent gains in lean body mass and strength as moderate to high-intensity RT. Furthermore, there is now good evidence that low- to moderate-intensity RT is equally or even more effective at lowering percentage of body fat than is high-intensity RT. The intensity should be such that fatigue results after 12–17 repetitions, corresponding to 60%–70% 1RM (72). A minimum of two sets per muscle group per week should be performed at the beginning of the program and be increased progressively to a maximum of six sets per muscle group per week. On the basis of this analysis of dose–response evidence, there is little to suggest that a greater number of RT sets will yield greater improvements in muscle function, body composition, and fatigue in cancer survivors.

In conclusion, on the basis of our review of 11 RCT in adult cancer patients, RT was associated with clinically important positive effects on muscular function and body composition in patients during treatment or in long-term follow-up without causing significant adverse events. These benefits were observed among patients with breast cancer, prostate cancer, and head and neck cancer. Additional RCT among patients with other cancer types such as gynecological, colorectal, gastric, and lung cancer are needed to further assess the efficacy of RT on health-related outcomes. The implications of these results on cancer recurrence or survival may become more evident with physical activity intervention trials of longer duration among cancer survivors.

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REFERENCES

1. Abe T, DeHoyos DV, Pollock ML, Garzarella L. Time course of strength and muscle thickness changes following upper and lower body resistance training in men and women. *Eur J Appl Physiol*. 2000;81:174–80.

2. Ahmed RL, Thomas W, Yee D, Schmitz KH. Randomized controlled trial of weight training and lymphedema in breast cancer survivors. *J Clin Oncol*. 2006;24:2765–72.
3. Atlantis E, Martin SA, Haren MT, Taylor AW, Wittert GA; Members of the Florey Adelaide Male Ageing Study. Inverse associations between muscle mass, strength, and the metabolic syndrome. *Metabolism*. 2009;58:1013–22.
4. Battaglini C, Bottaro M, Dennehy C, et al. The effects of resistance training on muscle strength and fatigue in breast cancer patients. *Rev Bras Med Esporte*. 2007;12:139e–44e.
5. Battaglini C, Bottaro M, Dennehy C, et al. The effects of an individualized exercise intervention on body composition in breast cancer patients undergoing treatment. *Sao Paulo Med J*. 2007;125:22–8.
6. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2011;20:123–33.
7. Burd NA, West DW, Staples AW, et al. Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. *PLoS One*. 2010;5:e12033.
8. Carrillo AE, Flynn MG, Pinkston C, et al. Impact of vitamin D supplementation during a resistance training intervention on body composition, muscle function, and glucose tolerance in overweight and obese adults. *Clin Nutr*. 2013;32:375–81.
9. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage*. 2002;24:547–61.
10. Cheema B, Gaul CA, Lane K, Fiatarone Singh MA. Progressive resistance training in breast cancer: a sytematic review of clinical trials. *Breast Cancer Res Treat*. 2008;109:9–26.
11. Cheville AL, Girardi J, Clark MM, et al. Therapeutic exercise during outpatient radiation therapy for advanced cancer. *Am J Phys Med Rehabil*. 2010;89:611–19.
12. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*. 2007;25:4396–404.
13. Cramp F, Byron D. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev*. 2012;11:CD006145.
14. Cramp F, Daniel J. Exercise for the management for cancer-related fatigue in adults. *Cochrane Database Syst Rev*. 2008;2:CD006145.
15. Cramp F, James A, Lambert J. The effects of resistance training on quality of life in cancer: a systematic literature review and meta-analysis. *Support Care Cancer*. 2010;18:1367–76.
16. De Backer IC, Schep G, Backx FJ, Vreugdenhil G, Kuipers H. Resistance training in cancer survivors: a systematic review. *Int J Sports Med*. 2009;30:703–12.
17. Dimeo F. Effects of exercise on cancer-related fatigue. *Cancer*. 2001;92:1689–93.
18. Donnelly E, Jakicic M, Pronk NP. Is resistance exercise effective for weight management? *Evid Based Prev Med*. 2004;1:21–9.
19. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK; American College of Sports Medicine. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc*. 2009;41(2):459–71.
20. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin*. 2006;56:323–53.
21. Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High intensity strength training in nonagenarians. Effects on skeletal muscle. *JAMA*. 1990;263:3029–34
22. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ*. 2012;344:e70.
23. Frontera WR, Meredith CN, O'Reilly KP, Evans WJ. Strength training and determinants of $\dot{V}O_{2max}$ in older men. *J Appl Physiol*. 1990;68:329–33.
24. Galvao DA, Nosaka K, Taaffe DR, et al. Resistance training and reduction of treatment side effects in prostate cancer patients. *Med Sci Sports Exerc*. 2006;38(12):2045–52.
25. Henwood TR, Taaffe DR. Improved physical performance in older adults undertaking a short-term programme of high-velocity resistance training. *Gerontology*. 2005;51:108–15.
26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–60.
27. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarker Prev*. 2008;17:379–86.
28. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005;293:1479–86.
29. Jackson AW, Lee DC, Sui X, et al. Muscular strength is inversely related to prevalence and incidence of obesity in adult men. *Obesity*. 2010;18:1988–95.
30. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12.
31. Kraemer WJ, Adams K, Cafarelli E, et al.; American College of Sports Medicine. American College of Sports Medicine Position Stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc*. 2002;34(3):364–80.
32. Larew K, Hunter GR, Larson-Meyer DE, Newcomer BR, McCarthy JP, Weinsier RL. Muscle metabolic function, exercise performance, and weight gain. *Med Sci Sports Exerc*. 2003;35(2):230–6.
33. Marcell TJ. Sarcopenia: causes, consequences, and prevention. *J Gerontol A Biol Sci Med Sci*. 2003;58:M911–6.
34. McNeely ML, Parliament M, Courneya KS, et al. A pilot study of a randomized controlled trial to evaluate the effects of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors. *Head Neck*. 2004;26:518–30.
35. McNeely ML, Parliament MB, Seikaly H, et al. Effect of exercise on upper extremity pain and dysfunction in head and neck cancer survivors. A randomized controlled trial. *Cancer*. 2008;113:214–22.
36. Narici MV, Hoppeler H, Kayser B, et al. Human quadriceps cross-sectional area, torque and neural activation during 6 months strength training. *Acta Physiol Scand*. 1996;157:175–86.
37. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Cancer-related fatigue version 1 [Internet]. 2010 [cited 2010 August 10]. Available from: http://www.nccn.org.
38. Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ. Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. *JAMA*. 1994;272:1909–14.
39. Newman AB, Kupelian V, Visser M, et al. Strength but not muscle mass, is associated with mortality in the health aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci*. 2006;61:72–7.
40. Ohira T, Schmitz KH, Ahmed RL, Yee D. Effects of weight training on quality of life in recent breast cancer survivors. *Cancer*. 2006;106:2076–83.
41. Peddle-McIntyre CJ, Bell G, Fenton D, McCargar L, Courneya KS. Feasibility and preliminary efficacy of progressive resistance exercise training in lung cancer survivors. *Lung Cancer*. 2012;75:126–32.

42. Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. *Ageing Res Rev*. 2010;9:226–37.
43. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. *Med Sci Sports Exerc*. 2011;43(2):249–58.
44. Phillips MD, Flynn MG, McFarlin BK, Stewart LK, Timmerman KL. Resistance training at eight-repetition maximum reduces the inflammatory milieu in elderly women. *Med Sci Sports Exerc*. 2010;42(2):314–25.
45. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. *Am J Physiol*. 1997;273:E99–107.
46. Ruiz JR, Sui X, Lobelo F, et al. Muscular strength and adiposity as predictors of adulthood cancer mortality in men. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1468–76.
47. Ryan JL, Carroll JK, Ryan EP, Mustian KM, Fiscella K, Morrow GR. Mechanisms of cancer related fatigue. *Oncologist*. 2007;12:22–34.
48. Schmidt T, Weisser B, Jonat W, Baumann FT, Mundhenke C. Gentle strength training in rehabilitation of breast cancer patients compared to conventional therapy. *Anticancer Res*. 2012;32:3229–34.
49. Schmitz KH, Ahmed R, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. *Cancer Epidemiol Biomarkers Prev*. 2005;14:1672–80.
50. Schmitz KH, Ahmed RL, Troxel AB, et al. Weight lifting for women at risk for breast cancer-related lymphedema. *JAMA*. 2010;304:2699–705.
51. Schmitz KH, Ahmed RL, Troxel AB, et al. Weight lifting in women with breast cancer-related lymphedema. *N Engl J Med*. 2009;361:664–73.
52. Schmitz KH, Courneya KS, Matthews C, et al.; American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409–26.
53. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–12.
54. Schwartz AL, Winters-Stone K, Gallucci B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. *Oncol Nurs Forum*. 2007;34:627–33.
55. Schwartz AL, Winters-Stone KM. Effects of a 12-month randomized controlled trial of aerobic or resistance exercise during and following cancer treatment in women. *Phys Sportsmed*. 2009;37:62–7
56. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2003;21:1653–59.
57. Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*. 2009;27:344–51.
58. Skipworth RJ, Stewart GD, Dejong CH, Preston T, Fearon KC. Pathophysiology of cancer cachexia: much more than host-tumor interaction? *Clin Nutr*. 2007;26:667–76.
59. Speck RM, Courneya KS, Mâsse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv*. 2010;4:87–100.
60. Speck RM, Gross CR, Hormes JM, et al. Changes in the body image and relationship scale following a one-year strength training trial for breast cancer survivors with or at risk for lymphedema. *Breast Cancer Res Treat*. 2010;121:421–30.
61. Strasser B, Keinrad M, Haber P, Schobersberger W. Efficacy of systematic endurance and resistance training on muscle strength and endurance performance in elderly adults—a randomized controlled trial. *Wien Klin Wochenschr*. 2009;121:757–64.
62. Strasser B, Leeb G, Strehblow C, Schobersberger W, Haber P, Cauza E. The effects of strength and endurance training in patients with rheumatoid arthritis. *Clin Rheumatol*. 2011;30:623–32.
63. Strasser B, Siebert U, Schobersberger W. Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. *Sports Med*. 2010;40:397–415.
64. Thompson SG. Why and how sources of heterogeneity should be investigated. In: Egger M, Smith GD, Altman DG, editors. *Systematic Reviews in Health Care: Meta-Analysis in Context*. London: BMJ Publishing Group; 2001. p. 157–75.
65. Tisdale MJ. Cachexia in cancer patients. *Nat Rev Cancer*. 2002;2:862–71.
66. US Cancer Statistics Working Group. *United States Cancer Statistics: 2004 Incidence and Mortality*. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2007. p. 1–22.
67. Vance V, Mourtzakis M, McCargar L, Hanning R. Weight gain in breast cancer survivors: prevalence, pattern and Health consequences. *Obes Rev*. 2011;12:282–94.
68. Vincent HK, Bourguignon C, Vincent KR. Resistance training lowers exercise-induced oxidative stress and homocysteine levels in overweight and obese older adults. *Obesity*. 2006;14:1921–30.
69. Waltman NL, Twiss JJ, Ott CD, et al. The effect of weight training on bone mineral density and bone turnover in postmenopausal breast cancer survivors with bone loss: a 24-month randomized controlled trial. *Osteoporos Int*. 2010;21:1361–69.
70. Wernbom M, Augustsson J, Thomeé R. The influence of frequency, intensity, volume and mode of strength training on whole muscle cross-sectional area in humans. *Sports Med*. 2007;37:225–64.
71. Westcott W. Strength training for frail older adults. *J Active Aging*. 2009;8:52–9.
72. Williams MA, Haskell WL, Ades PA, et al.; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2007;166:572–84.
73. Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. *J Cancer Surviv*. 2012;6:189–99.
74. Winters-Stone KM, Dobek J, Nail L, et al. Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors. A randomized, controlled trial. *Breast Cancer Res Treat*. 2011;127:447–56.
75. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy measurement system. *J Pain Symptom Manage*. 1997;13:63–74.
76. Yuen HK, Sword D. Home-based exercise to alleviate fatigue and improve functional capacity among breast cancer survivors. *J Allied Health*. 2007;36:e257–75.