Physical activity for cancer survivors: meta-analysis of randomised controlled trials

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OBJECTIVE To systematically evaluate the effects of physical activity in adult patients after completion of main treatment related to cancer.

DESIGN Meta-analysis of randomised controlled trials with data extraction and quality assessment performed independently by two researchers.

DATA SOURCES PUBMED, CINAHL, and Google Scholar from the earliest possible year to September 2011. References from meta-analyses and reviews.

STUDY selection Randomised controlled trials that assessed the effects of physical activity in adults who had completed their main cancer treatment, except hormonal treatment.

RESULTS There were 34 randomised controlled trials, of which 22 (65%) focused on patients with breast cancer, and 48 outcomes in our meta-analysis. Twenty two studies assessed aerobic exercise, and four also included resistance or strength training. The median duration of physical activity was 13 weeks (range 3-60 weeks). Most control groups were considered sedentary or were assigned no exercise. Based on studies on patients with breast cancer, physical activity was associated with improvements in insulin-like growth factor-I, bench press, leg press, fatigue, depression, and quality of life. When we combined studies on different types of cancer, we found significant improvements in body mass index (BMI), body weight, peak oxygen consumption, peak power output, distance walked in six minutes, right handgrip strength, and quality of life. Sources of study heterogeneity included age, study quality, study size, and type and duration of physical activity. Publication bias did not alter our conclusions.

CONCLUSIONS Physical activity has positive effects on physiology, body composition, physical functions, psychological outcomes, and quality of life in patients after treatment for breast cancer. When patients with cancer other than breast cancer were also included, physical activity was associated with reduced BMI and body weight, increased peak oxygen consumption and peak power output, and improved quality of life.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Current meta-analyses of the efficacy of physical activity in patients who had completed cancer related treatment might feature increased study heterogeneity because of the mixing of studies with outcomes measured under distinct domains or using different instruments

New randomised controlled trials for assessing the efficacy of physical activity in cancer survivors have been published

WHAT THIS STUDY ADDS

Physical activity was associated with important positive effects on physical functions and quality of life, which included physical and social functioning domains, in patients who had completed their treatment for cancer

Efficacy of physical activity could be higher in studies with lower methodological quality, smaller study size, or older patients or that assess a physical activity programme involving both aerobic and resistance training

Introduction

Cancer survivors who have successfully completed their primary cancer treatment often expect to resume their work or daily life at a level similar to that before the cancer diagnosis. While cancer treatment has been shown to be effective in prolonging survival, it can be intensive and can lead to increased fatigue, decreased physical activity, and a reduction in quality of life.[1-3] In addition, these unwanted effects of treatment can be prolonged and hinder the patients' return to normal life.[4-6]

Physical activity is a potentially appealing intervention that could alleviate sequelae related to cancer and assist patients in returning to the health status they had before treatment. A systematic review published in 2005 summarised the evidence supporting the recommendation of physical activity during and after treatment related to cancer[7]; and a meta-analysis published in 2006 reported more favourable outcomes when physical activity was carried out after treatment.[8] In a recent study published in 2011, starting an exercise programme after the completion of treatment was shown to be acceptable to over three quarters of patients.[9] Several randomised controlled trials have assessed the efficacy of physical activity on indicators of physical and mental health in patients after cancer treatment,[8] and these trials reported significant improvement after physical activity.

The effects of physical activity on cancer have been examined in nine meta-analyses, with three focusing on breast cancer[10-12] and six on any type of cancer.[8 13-17] The six meta-analyses on any cancer type did not uniformly examine sources of study heterogeneity,[14-16] assess publication bias,[14-17] or limit inclusion of randomised controlled trials to those with physical activity intervention only after cancer treatment.[8 13 17] Moreover, more randomised controlled trials have been published since the publication of the last meta-analysis in 2011.[18] We updated the most recent meta-analysis by including studies published more recently and included only randomised controlled trials. Using data from randomised controlled trials, we evaluated the best current evidence for the effects of physical activity on physical functions, physiological parameters, body composition, psychosocial outcomes, and quality of life in adult patients after they had completed their main treatment related to cancer.

Methods

Search strategy for identification of relevant studies

We identified relevant studies by systematically searching PubMed, which included Medline, CINAHL, and Google Scholar with the last search being in September 2011. The search terms used were (cancer OR tumour OR tumor OR neoplasm OR carcinoma OR chemotherapy OR radiotherapy OR bone marrow transplant) AND (physical activity OR exertion

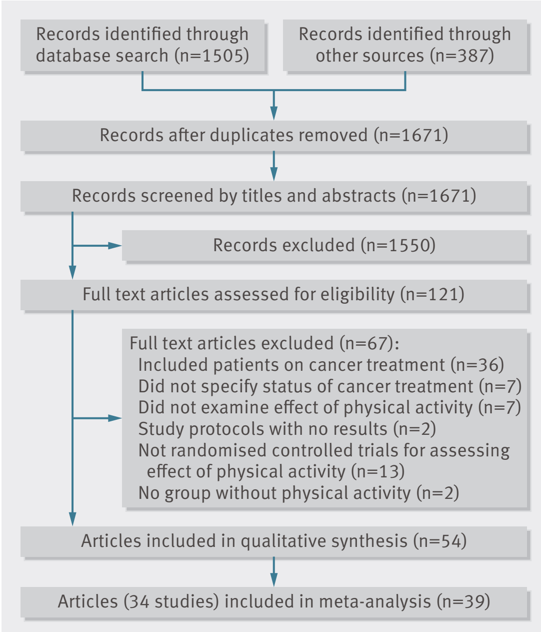

Fig 1 | Selection process of eligible randomised controlled studies

OR exercise therapy OR physical education OR physical training OR physical fitness OR walking) AND (intervention OR trial OR adherence OR compliance OR patient compliance OR patient education OR health promotion OR health education OR health behavior OR health behaviour OR behavioral therapy OR behavioural therapy OR behavioral change OR behavioural change OR positive reinforcement OR cognitive therapy) AND (controlled clinical trial OR randomised OR randomized OR placebo OR randomly OR group). We also searched the Cochrane Library for systematic reviews and meta-analyses on the effects of physical activity in cancer survivors. The reference lists of all selected studies, systematic reviews, and meta-analyses were then examined for relevant studies. We obtained the full papers of studies identified as potentially eligible based on the titles and abstracts, and two of the authors (JWCH and BPHH), who served as raters, independently confirmed their eligibility.

Selection criteria

The studies included were those that adopted a randomised controlled trial design, included adult patients (aged ≥18), included patients diagnosed with cancer, involved patients who had completed their main treatment for cancer but might be still undergoing hormonal treatment, and assessed the effect of physical activity on health indicators.

Data extraction and methodological quality assessment

JWCH and BPHH independently extracted relevant data using a standardised Excel template. From each study, they extracted general study information, details of intervention and control groups, means and standard deviations of outcomes after the intervention, side effects, and compliance/adherence rates. The summary statistics, when not reported, were calculated when sufficient data were available. Any discrepancies between data extracted by the two raters were discussed and consensus was achieved. A biostatistician (DYTF) also checked all extracted statistics.

Two authors (JWCH and DYTF) independently assessed the methodological rigour of the selected studies using a quality assessment checklist developed by the Scottish Intercollegiate Guidelines Network.[19] They assessed the internal validity of each selected study using 10 criteria and rated the overall quality on a scale according to the likelihood that each unmet criterion would alter the study conclusions: ++ (very unlikely), + (unlikely), and – (likely). The two reviewers met to compare their quality assessment results for each study; all discrepancies were discussed and resolved.

Statistical analysis

We planned to assess the effects of physical activity on cancer outcomes (that is, rates of survival and recurrence), psychological outcomes, and physical outcomes. None of the eligible studies provided data on cancer outcomes, and some of the other outcomes were not assessed by multiple studies. We therefore performed a meta-analysis on an outcome if it was assessed in at least two studies. For each outcome, we first assessed study heterogeneity with Cochrane's χ^2 test, with P<0.10 indicating evidence of heterogeneity. The degree of heterogeneity was measured by the I^2 statistic, with I^2 ≥50% indicating substantial heterogeneity.[20] In the presence of heterogeneity, we searched for its sources by random effects meta-regression. We considered the following study characteristics for heterogeneity: study quality (++, +, and –), publication year, percentage of female participants, mean age of participants, number of subjects analysed, duration of intervention, type of physical activity, and percentage of patients with breast cancer. Pooled estimates and their 95% confidence intervals were obtained with the random effects method.[21] Publication bias was also examined with Egger's linear regression method, with P<0.10 taken as an indication of publication bias.[22]

A random effects meta-regression was performed in the SAS version 9.2 (SAS, NC) and the other meta-analyses were conducted in Stata version 11 for Windows (StatCorp, TX). The nominal level of significance was 5% in all tests unless otherwise specified.

Results

We identified 1505 records from the database search and 387 additional records from other sources (fig 1). After screening, 54 articles met our inclusion criteria and we assessed their methodological quality. Of these, 39 articles from 34 studies had at least one common outcome, and there were sufficient data for inclusion in the meta-analysis. Seven studies (21%) and two articles from another two studies had not been included in previous meta-analyses (table 1).[23-31] Twenty two studies (65%) included only patients with breast cancer, three (9%) included only patients with colorectal cancer, one (3%) included only patients with endometrial cancer, and the eight (27%) remaining included patients with different types of cancer. Three studies had more than one intervention group and thus contributed more than one comparison with their control groups to the meta-analysis. Another two studies published both the full and subgroup analyses. Among 43 intervention-control comparisons, the median number of patients analysed was 93 (range 14-641) with a mean age of 55 (39-74). We used 27 (63%) intervention-control comparisons to assess the

Study	Intervention No	Intervention Mean (SD)	Control No	Control Mean (SD)	Difference (95% CI)
Fairey 2003[33]	25	62.5 (23.9)	28	72.6 (24.8)	-10.1 (-23.2 to 3.0)
Schmitz 2005[34]	39	181.2 (72.1)	40	190.3 (72.2)	-9.1 (-40.9 to 22.7)
Irwin 2009[32]	36	207.1 (67.2)	32	243.7 (104.5)	-36.6 (-78.9 to 5.7)
Janelsins 2011[30]	9	—	10	—	-10.7 (-61.3 to 40.0)
Pooled estimate (random effect)					-11.9 (-23.3 to -0.5)

Test for heterogeneity: P=0.703, I^2=0%

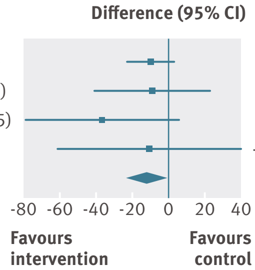

Fig 2 | Association between physical activity and insulin-like growth factor-I (ng/mL) in patients with breast cancer

Study	% with breast cancer	Intervention No	Intervention Mean (SD)	Control No	Control Mean (SD)	Difference (95% CI)
BMI						
Courneya 2003[55]	100	24	29.4 (7.4)	28	29.3 (6.0)	0.1 (-3.6 to 3.8)
Courneya 2003[56]	0	62	28.2 (5.7)	31	28.6 (5.1)	-0.4 (-2.7 to 1.9)
Pinto 2005[58]	100	43	27.7 (5.0)	43	29.0 (5.6)	-1.4 (-3.6 to 0.9)
Schmitz 2005[34]	100	39	26.0 (4.6)	40	25.8 (4.6)	0.2 (-1.9 to 2.2)
Demark-Wahnefried 2007[66]	56	253	27.1 (5.0)	266	27.8 (5.3)	-0.7 (-1.6 to 0.2)
Daley 2007[65]	100	34	—	38	—	2.9 (0.8 to 5.0)
Ligibel 2008[71]	100	40	30.3 (6.3)	42	31.5 (6.8)	-1.2 (-4.0 to 1.6)
Mulero-Portela 2008[23]	100	12	30.5 (4.4)	9	34.7 (15.0)	-4.2 (-14.3 to 5.9)
Mulero-Portela 2008[23]	100	13	27.8 (6.3)	9	34.7 (15.0)	-6.9 (-17.3 to 3.5)
Morey 2009[40]	45	319	—	322	—	-0.4 (-0.6 to -0.2)
Rogers 2009[79]	100	20	30.6 (7.6)	19	30.4 (8.3)	0.2 (-4.8 to 5.2)
Schmitz 2009[77]	100	65	30.0 (5.7)	65	29.9 (6.5)	0.1 (-2.0 to 2.2)
Irwin 2009[75]	100	36	30.5 (6.0)	32	29.9 (7.6)	0.6 (-2.7 to 3.8)
Schmitz 2010[25]	100	66	26.9 (5.0)	68	28.0 (6.0)	-1.1 (-2.9 to 0.8)
Bourke 2011[31]	0	8	26.5 (3.3)	9	26.8 (3.6)	-0.3 (-3.6 to 3.0)
Janelsins 2011[30]	100	9	24.5 (5.5)	10	25.3 (4.8)	-0.8 (-5.4 to 3.9)
Pooled estimate (random effect)						-0.4 (-0.6 to -0.2)
Test for heterogeneity: P=0.498, I^2=0%						
Body weight						
Burnham 2002[54]	83	12	78.2 (24.3)	6	63.7 (19.1)	14.5 (-6.1 to 35.1)
Courneya2003[55]	100	24	78.2 (20.5)	28	80.1 (16.2)	-1.9 (-12.1 to 8.3)
Schmitz 2005[14]	100	39	69.5 (13.9)	40	69.2 (13.9)	0.4 (-5.7 to 6.5)
Culos-Reed 2006[63]	85	18	76.6 (13.5)	18	69.3 (12.5)	7.4 (-1.1 to 15.8)
Herrero 2006[64]	100	8	65.6 (8.7)	8	67.3 (8.9)	-1.7 (-10.3 to 6.9)
Matthews 2007[67]	100	22	74.9 (15.2)	14	78.9 (20.3)	-4.0 (-16.4 to 8.4)
Ligibel 2008[71]	100	40	80.0 (17.5)	42	83.3 (18.7)	-3.3 (-11.1 to 4.5)
von Gruenigen 2008[74]	0	23	112.1 (30.4)	22	106.3 (27.0)	5.8 (-11.0 to 22.6)
Morey 2009[40]	45	319	—	322	—	-1.1 (-1.7 to -0.6)
Schmitz 2009[77]	100	65	80.0 (15.6)	65	79.0 (16.9)	1.0 (-4.6 to 6.6)
Irwin 2009[75]	100	36	80.7 (16.9)	32	78.5 (20.6)	2.2 (-6.8 to 11.3)
Schmitz 2010[25]	100	66	72.4 (14.9)	68	75.5 (17.1)	-3.1 (-8.5 to 2.3)
Bourke 2011[31]	0	8	76.0 (9.9)	9	76.8 (11.8)	-0.8 (-11.1 to 9.5)
Janelsins 2011[30]	100	9	66.4 (14.7)	10	67.3 (10.3)	-0.9 (-12.4 to 10.6)
Pooled estimate (random effect)						-1.1 (-1.6 to -0.6)
Test for heterogeneity: P=0.768, I^2=0%						
Waist:hip ratio						
Ligibel 2008[71]	100	40	0.80 (0.10)	42	0.80 (0.10)	0.00 (-0.04 to 0.04)
Rogers 2009[76]	100	20	0.82 (0.06)	19	0.82 (0.07)	0.00 (-0.04 to 0.04)
Bourke 2011[31]	0	8	—	9	—	-0.06 (-0.14 to 0.02)
Pooled estimate (random effect)						-0.01 (-0.04 to 0.02)
Test for heterogeneity: P=0.366, I^2=0.5%						

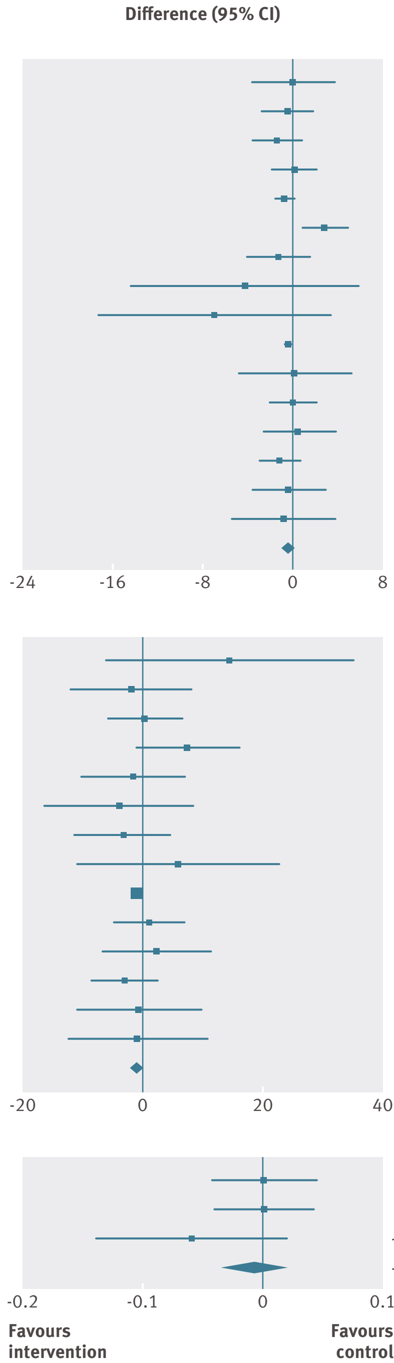

Fig 3 | Association between physical activity and BMI, body weight, and waist:hip ratio in patients with cancer

Table 1 | Characteristics of 34 randomised controlled trials included in meta-analysis of effect of physical activity in patients after treatment for cancer

Study	Cancer type	No of subjects analysed/ randomised	Mean (SD) age (years)	No (%) of women*	Type
Segar,[53] 1998	Breast	24/24	48.9 (7.6)	24 (100)	Aerobic
Burnham,[54] 2002	Breast (83%), colon (17%)	18/21	53.6 (8.6)	15 (83)†	Aerobic
Courneya,[55] 2003a	Breast	52/53	58.5 (5.5)	53 (100)	Aerobic
Courneya,[56] 2003b	Colorectal	93/102	60.3 (10.4)	39 (42)†	Aerobic
Fairey,[33] 2003	Breast	53/53	59 (6)	53 (100)	Aerobic
Dimeo,[57] 2004	Lung (39%), gastric (17%), colorectal (45%)	72/72	57.6 (10.0)	19 (26)	Aerobic
Pinto,[58] 2005	Breast	86/86	53.1 (9.7)	86 (100)	Aerobic
Sandel,[59] 2005	Breast	38/38	59.6 (11.5)	38 (100)	Aerobic
Thorsen,[60] 2005	Breast (42%), gynaecological (22%), lymphoma (23%), testicular (18%)	111/139	39.1 (8.4)	75 (68)†	Individualised, depends on individual preference
Schmitz,[34] 2005	Breast	81/85	53.0 (8.1)	85 (100)	Weight/strength
Ahmed,[61] 2006	Breast cancer related lymphoedema	45/85	52.0 (7.5)	85 (100)	Weight/strength
Basen-Engquist,[62] 2006	Breast	51/60	55.2 (11.3)	60 (100)	Aerobic
Culos-Reed,[63] 2006	Breast (85%), others (15%)	36/38	51.2 (10.3)	36 (95)	Yoga/stretching
Herrero,[64] 2006	Breast	16/20	50.5 (7.7)	20 (100)	Aerobic + resistance training
Daley,[65] 2007	Breast	72/72	51.3 (8.6)	72 (100)	Aerobic
Demark-Wahnefried,[66] 2007	Breast (56%), prostate (44%)	519/543	56.9 (10.8)	291 (56)†	Aerobic, by an effective programme using social cognitive theory
Matthews,[67] 2007	Breast	36/36	53.5 (10.6)	36 (100)	Aerobic
Vallance,[68] 2007	Breast	169/190	57 (NR)	190 (100)	Aerobic, by printed materials
		173/190	57.5 (NR)	190 (100)	Aerobic, by step pedometer
		166/189	57.5 (NR)	189 (100)	Aerobic, by printed materials + step pedometer
Yuen,[69] 2007	Breast	15/15	54.0 (13.0)	15 (100)	Aerobic
		14/14	54.3 (11.9)	14 (100)	Weight/Strength
Bennett,[70] 2007	Breast (75%) others (25%)	56/56	57.8 (10.2)	50 (89)	Aerobic
Ligibel,[71] 2008	Breast	82/101	52.5 (9.0)	101 (100)	Aerobic + Strength
Milne,[72] 2008	Breast	58/58	55.1 (8.2)	58 (100)	Aerobic + resistance training
Fillion,[73] 2008	Breast	87/94	52.5 (9.9)	94 (100)	Aerobic
Mulero Portela,[23] 2008‡	Breast	21/25	54.0 (12.7)	25 (100)	Aerobic + resistance training, in Gymnasium
		22/28	54.6 (12.4)	28 (100)	Aerobic + resistance training, at home
Von Gruenigen,[74] 2008, Von Gruenigen,[24] 2009‡	Endometrial	45/45	54.7 (8.6)	45 (100)	Aerobic
Irwin,[32] 2009 Irwin,[75] 2009	Breast	68/75	56.0 (8.6)	75 (100)	Aerobic
Morey,[40] 2009	Breast (45%), prostate (41%), colorectal (14%)	641/641	73.1 (5.0)	349 (54)	Endurance/strength
Rogers,[76] 2009	Breast	39/41	53 (9)	41 (100)	Aerobic
Schmitz,[77] 2009	Breast cancer related lymphoedema	139/141	56.5 (8.3)	141 (100)	Weight/strength
Speck,[78] 2010	Breast cancer with or at risk for lymphoedema	234/295	56.5 (8.3)	295 (100)	
Schmitz,[25] 2010‡	Breast cancer at risk of lymphoedema	134/154	55.0 (8.0)	154 (100)	
Mehnert,[26] 2011‡	Breast	58/63	51.9 (8.5)	63 (100)	Aerobic
LaStayo,[27] 2011‡	Breast (55%), prostate (27.5%), colorectal (17.5%), lung (7.5%), lymphoma (2.5%)	40/49	74.0 (6.1)	25 (63)†	Resistance
Kaltsatou,[28] 2011‡	Breast	27/27	56.8 (4.1)	27 (100)	Aerobic
Pinto,[29] 2011‡	Colorectal	42/46	57.3 (9.7)	26 (57)	Aerobic
Janelsins,[30] 2011‡	Breast	19/31	53.5 (8.6)	31 (100)	Aerobic
Bourke,[31] 2011‡	Colon	17/18	69.1 (7.2)	6 (33)	Aerobic + resistance training

NR=not reported. *Percentages of women based on number of patients randomised unless stated otherwise. †Percentages of women based on number of analysed patients. ‡Studies not included in previous meta-analyses.

Total duration (weeks)	Physical activity: Minutes/session/ week)	Frequency each week	Intensity	Control group	Study quality
10	30 (120)	4	›60% age predicted maximum heart rate	Maintain sedentary lifestyle	–
10	14-32 (42-96)	3	Low (25-35% heart rate reserve); moderate (40-50% heart rate reserve)	No exercise	–
15	15-35 (45-105)	3	70-75% maximum oxygen consumption	No exercise	+
16	20-30 (60-150)	3-5	65-75% age predicted maximum heart rate	No exercise	+
15	15-35 (45-105)	3	70-75% peak oxygen consumption	No exercise	++
3	30 (150)	5	80% age predicted maximum heart rate	Relaxation training	+
12	10-20 (20-100)	2-5	Moderate	Maintain usual exercise style	+
12	Dance movement: 25-30 (25-60); core exercise: NR	1-2	Not stated	Maintain usual exercise style	+
14	›30 (›60)	›2	Slightly strenuous to strenuous (Borg perceived exertion scale 13-15 (60-70% age predicted maximum heart rate))	Maintain usual exercise style	+
24	60 (120)	2	NR	No exercise	+
24	60 (120)	2	NR	No exercise	–
24	NR	NR	NR	Standard written materials for exercise	–
7	75 (NR)	NR	NR	No exercise	–
8	90 (270)	3	Cycle: 80% age predicted maximum heart rate; resistance: progressively increased intensity	Maintain sedentary lifestyle	–
8	50 (150)	3	Moderate (65-85% age predicted maximum heart rate)	Maintain usual exercise style	+
40	NR	NR	NR	Aerobic, by printed materials only	–
12	20-40 (60-200)	3-5	Moderate (Borg perceived exertion scale 11-13)	Maintain usual exercise style	–
12	30 (150)	5	Moderate/vigorous	Aerobic, by standard recommendation	–
12	20-40 (60-120)	3	Fairly light to somewhat hard (Borg perceived exertion scale 10-13)	Maintain usual exercise style	–
12	NR				
24	30 (210)	7	Moderate	Maintain usual exercise style	++
16	Aerobic: 90 (90); strength: 50 (100)	Aerobic: 1; strength: 2	NR	Maintain usual exercise style	+
12	Aerobic: 20 (60); resistance: NR	3	NR	Maintain usual exercise style	+
4	Supervised: (60); home based: NR	NR	NR	No exercise	+
26	Walking: 30 (90); resistance: NR	Walking: 3; Resistance: 2	Walking: 60-80% age predicted maximum heart rate; resistance: Borg perceived exertion scale 13-15	No exercise	–
26	Walking: 30 (90); resistance: NR	Walking: 3; resistance: 2	Walking: somewhat hard to hard (Borg perceived exertion scale 12-16); resistance: Borg perceived exertion scale 13-15	No exercise	–
24	› 45 (›225)	5	NR	Written information on the benefits of physical activity	+
24	Gymnasium: 30 (90); home: 30 (60)	Gymnasium: 3 home: 2	Moderate	Maintain usual exercise style	+
60	Endurance: 30 (210); strength: 15 (45)	Endurance: 7; strength: 3	Not stated	No exercise	+
12	(150)	NR	Moderate	No exercise	+
					++
52	90 (180)	2	Individualised; upper limb exercise, limited by onset of lymphoedema (stop exercise and then restart)	Maintain usual exercise style	+
					++
10	90 (180)	2	Moderate: 60% VO_2 max	Maintain usual exercise style	+
12	3-20 (9-60)	3	Fairly light to somewhat hard (Borg perceived exertion scale 11-13)	Maintain usual exercise style	+
12	60 (180)	3	Moderate (65-80% age predicted maximum heart rate)	Maintain usual lifestyle	–
12	30 (›150)	›5	Moderate (64-76% age predicted maximum heart rate)	Maintain usual lifestyle	+
12	60 (180)	3	Moderate	Psychosocial therapy	–
12	Aerobic: 30 (90); resistance: NR	Aerobic: 3 Resistance: 3	Aerobic: 55-85% age predicted maximum heart rate. Resistance: NR	Maintain usual lifestyle	–

Table 2 | Study heterogeneity and sources of heterogeneity by meta-regression analysis* of effect of physical activity in patients after treatment for cancer. Meta-regression performed for all outcomes but source of heterogeneity identified only for leg press and left and right handgrip

Outcomes(units or plausible ranges)	No of comparisons	Common characteristics (level)	Heterogeneity	
			I^2 (%)	P value
Physiological markers				
Insulin-like growth factor-I (ng/mL)	4[30 32-34]	Cancer type (breast)	0	0.70
Insulin (pmol/L)	4[30 33 34 71]	Cancer type (breast)	18	0.30
Glucose (mmol/L)	3[33 34 71]	Cancer type (breast)	28	0.25
Homeostatic model assessment	2[34 71]	Cancer type (breast)	0	0.67
Body composition				
% Body fat	11[25 34 54 58 64 65 67 71 75-77]	—	0	0.74
Body fat (kg)	6[25 30 34 64 67 77]	Cancer type (breast)	0	0.77
BMI	16[23 25 30 31 34 40 55 56 58 65 66 71 75-77]	—	0	0.50
Waist circumference (cm)	3[34 71 75]	Quality (+); cancer type (breast)	0	0.58
Waist:hip ratio	3[31 71 76]	—	0.5	0.37
Lean mass (kg)	7[25 30 34 64 67 75 77]	Cancer type (breast)	0	0.97
Weight (kg)	14[25 30 31 34 40 54 55 63 64 67 71 74 75 77]	—	0	0.77
Physical functions				
Peak heart rate (beats/min)	3[55 63 64]	—	24	0.27
Peak oxygen consumption (mL/kg/min)	7[26 29 54 55 60 64 73]	—	18	0.29
Peak power output (W)	3[55 57 64]	—	0	0.56
Six minute walk (m)	5[27 28 62 69]	—	20	0.29
Bench press (kg, 1 repetition maximum)	3[25 61 78]	Cancer type (breast)	54	0.12
Leg press (kg, 1 repetition maximum)	3[25 61 78]	Cancer type (breast)	71	0.03
Left handgrip (kg)	3[28 63 76]	—	71	0.03
Right handgrip (kg)	5[23 28 63 76]	—	56	0.06
Sit and reach (cm)	2[54 63]	Quality (−)	0	0.32

*Multivariable meta-regression. Source of heterogeneity for leg press: quality −20.4 (95% CI −36.2 to −4.6), P=0.01 (confounder: one grade increase); source of heterogeneity for left handgrip: age 2.3 (0.6 to 4.0), P=0.01 (confounder year 2.1 (0.3 to 3.8), P=0.02); source of heterogeneity for right handgrip: year 1.8 (0.4 to 3.2), P=0.01 (confounder age 1.4 (0.2 to 2.7), P=0.03).

effects of an aerobic exercise programme, and six (14%) studies had patients who additionally underwent resistance or strength training. The other comparisons were made for strength or tailored training based on preference of patients. The median duration of the physical activity intervention was 13 weeks (range 3-60). Only 13 studies stated the intensity level of physical activity; 11 were of moderate intensity and two were of vigorous intensity. Most control groups were considered sedentary or were assigned no exercise. We assessed 48 outcomes at least twice in the 43 intervention-control comparisons (tables 2 and 3).

Meta-analysis of physiological markers

Physiological markers were assessed only in breast cancer studies. Four physiological markers were included in the meta-analysis: insulin-like growth factor-I, insulin, glucose, and homeostatic model assessment. There was no study heterogeneity in these physiological markers, with I^2 being 28% at most, and there was no evidence of publication bias (P≥0.47). In three studies, of which two assessed aerobic exercise and the third assessed weight/strength training, physical activity was associated with significantly reduced insulin-like growth factor-I (−12.0 ng/mL, 95% confidence interval −23.3 to −0.5; P=0.04; fig 2) more than the controls) (table 4). No effect was shown for the other physiological markers. Forest plots for all physiological markers can be found on bmj.com.

Meta-analysis of body composition

There was no study heterogeneity for any of the six body parameters assessed. Physical activity was associated with slightly reduced body mass index (BMI) (−0.4, −0.6 to −0.2; P<0.01) and body weight (−1.1 kg, −1.6 to −0.6 kg; P<0.001) (fig 3) than the control condition (table 4). Publication bias was evident only for the waist:hip ratio (P=0.06) because of one of the three studies reporting a more substantial reduction than the other two. The effect on waist:hip ratio, however, remained insignificant after we removed this study from the meta-analysis. Forest plots for all markers of body composition can be found on bmj.com.

Meta-analysis of physical functions

Except for bench press and leg press, which were assessed only in patients with breast cancer, all other physical functions were assessed in studies on several types of cancer. Substantial heterogeneity was found for leg press, left handgrip, and right handgrip (table 2). The higher quality study reported a smaller increase in leg press, whereas the studies involving older patients or published in recent years reported larger increases in left handgrip and right handgrip. Otherwise, neither heterogeneity nor publication bias was detected (P≥0.12). Physical activity was associated with significantly increased peak oxygen consumption (2.2 mL/kg/min, 1.0 to 3.4; P<0.01), peak power output (21.0 W, 13.0 to 29.1; P<0.01), the distance walked in six minutes (29 m, 4 to 55; P=0.03; fig 4), bench press

Table 3 | Study heterogeneity and sources of heterogeneity by meta-regression analysis of effect of physical activity in patients after treatment for cancer

Outcomes(units or plausible ranges)	No of comparisons	Common characteristics (level)	Heterogeneity		Multivariable meta-regression*		
			I^2 (%)	P value	Source of heterogeneity [confounder]	Estimate (95% CI)	P value
Psychological outcomes							
FACT-fatigue (0-52)	8[24 29 31 55 56 68]	—	0	0.86	—	—	—
PFS-fatigue (0-10)	3[65 69]	Publication year (2007); cancer type (breast)	0	0.64	—	—	—
EORTC-fatigue (0-100)	2[57 60]	Quality (+)	75	0.05	Any one of sources except quality†	—	—
BDI (0-63)	4[24 28 53 65]	Physical activity (aerobic); sex (female)	47	0.13	—	—	—
HADS-depression (0-21)	2[26 60]	Quality (+)	76	0.04	Any one of sources except quality†	—	—
HADS-anxiety (0-21)	2[26 60]	Quality (+)	78	0.03	Any one of sources except quality†	—	—
POMS-total mood disturbance	2[58 63]	—	53	0.15	—	—	—
Quality of life outcomes							
EORTC:							
Physical function (0-100)	2[57 60]	Quality (+)	0	0.49	—	—	—
Emotional function (0-100)	3[57 60 63]	—	77	0.01	Quality: + *v* – [study size]	−17.4 (−28.9 to −5.8) [−0.22 (−0.37 to −0.06)]	0.003 [0.006]
Total (0-100)	3[57 60 63]	—	70	0.04	Quality: + *v* – [study size]	−16.5 (−29.2 to −3.8) [−0.18 (−0.34 to −0.08)]	0.01 [0.03]
FACT:							
Physical wellbeing (0-28)	6[24 55 56 65 72 76]	Quality (+)	92	<0.001	Aerobic + resistance *v* aerobic	8.4 (6.3 to 10.5)	<0.001
Emotional wellbeing (0-24)	6[24 55 56 65 72 76]	Quality (+)	61	0.03	Aerobic + resistance *v* aerobic	2.8 (0.9 to 4.7)	0.01
Social/family wellbeing (0-28)	6[24 55 56 65 72 76]	Quality (+)	15	0.32	—	—	—
Functional wellbeing (0-28)	6[24 55 56 65 72 76]	Quality (+)	93	<0.001	Aerobic + resistance *v* aerobic	9.6 (7.1 to 12.1)	<0.001
Breast (0-36)	4[55 65 72 76]	Quality (+); cancer type (breast)	78	0.003	Aerobic + resistance *v* aerobic	5.3 (1.9 to 8.7)	0.002
					Treatment duration [age]	−0.8 (−1.4 to −0.1) [−0.7 (−1.3 to −0.1)]	0.02 [0.03]
Breast total (0-140)	10[23 55 59 65 68 72 76]	Cancer type (breast)	86	<0.001	Aerobic + resistance *v* aerobic	24.4 (17.9 to 30.9)	<0.001
Colorectal total (0-136)	3[29 31 56]	Cancer type (colorectal)	0	0.72	—	—	—
General total (0-108)	7[24 55 56 65 66 72 76]	—	92	<0.001	Aerobic + resistance *v* aerobic	22.1 (16.7 to 27.4)	<0.001
SF-36:							
Physical function (0-100)	2[40 62]	—	0.0	0.51	—	—	—
Role physical (0-100)	2[40 62]	—	56	0.13	—	—	—
Bodily pain (0-100)	2[40 62]	—	54	0.14	—	—	—
General health (0-100)	2[40 62]	—	76	0.04	Any one of sources†	—	—
Vitality (0-100)	2[40 62]	—	0	0.82	—	—	—
Social function (0-100)	2[40 62]	—	0	0.45	—	—	—
Role emotion (0-100)	2[40 62]	—	0	0.82	—	—	—
Mental health (0-100)	2[40,62]	—	0	0.64	—	—	—
SF physical component scale (0-100)‡	4[59 73 78]	—	55	0.09	Age	−0.9 (−1.8 to −0.04)	0.04
SF mental component scale (0-100)†‡	4[59 73 78]	—	39	0.18	—	—	—

BDI=Beck depression inventory; EORTC=European Organization for Research and Treatment of Cancer; FACT=functional assessment of cancer therapy; HADS=hospital anxiety and depression scale; PFS=revised Piper fatigue scale; POMS=profile of mood states; SF-36=short form-36.
*Values in square brackets correspond to those confounders.
†As there were only two studies.
‡Two studies used SF-36 and one used SF-12.

weight (6 kg, 4 to 8; P<0.01), leg press weight (19 kg, 9 to 28; P<0.01), and right handgrip strength by 3.5 kg, 0.3 to 6.7; P=0.03) (table 4). Forest plots for all markers of physical function can be found on bmj.com.

Meta-analysis of psychological outcomes

There was no heterogeneity in any of the psychological outcomes except for fatigue measured by the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire and the two hospital anxiety and depression scales (table 3). Measured by the revised Piper fatigue scale, physical activity was associated with slightly reduced fatigue (−1.0, −1.8 to −0.1; P=0.03; fig 5) in three comparisons from two studies on breast cancer compared with the control (table 5). Measured by the Beck depression inventory, physical activity was associated with reduced depression (−4.1, −6.5 to −1.8; P<0.01) in survivors of mixed types of cancer, which was of near clinical

Study	% with breast cancer	Intervention No	Intervention Mean (SD)	Control No	Control Mean (SD)	Difference (95% CI)
Basen-Engquist 2006[62]	100	28	501 (33)	23	471 (37)	30 (10 to 49)
Yuen 2007[69]	100	8	582 (119)	7	567 (53)	15 (-76 to 106)
Yuen 2007[69]	100	7	545 (83)	7	567 (53)	-22 (-95 to 50)
Kaltsatou 2011[28]	100	14	483 (86)	13	403 (72)	80 (21 to 140)
LaStayo 2011[27]	55	20	467 (125)	20	453 (122)	13 (-63 to 90)
Pooled estimate (random effect)						29 (3 to 55)
Test for heterogeneity: P=0.288, I^2=20%						

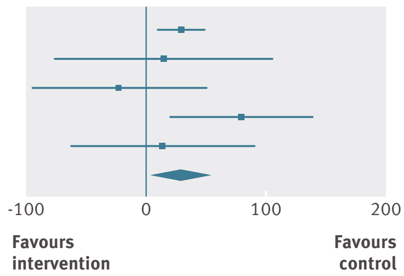

Fig 4| Association between physical activity and distance (m) walked in six minutes in patients with cancer

Study	% with breast cancer	Intervention No	Intervention Mean (SD)	Control No	Control Mean (SD)	Difference (95% CI)
Piper fatigue scale						
Yuen 2007[69]	100	8	3.9 (1.7)	7	4.2 (1.7)	-0.3 (-2.0 to 1.5)
Yuen 2007[69]	100	7	2.8 (1.9)	7	4.2 (1.7)	-1.4 (-3.2 to 0.5)
Daley 2007[65]	100	34	—	38	—	-1.1 (-2.4 to 0.1)
Pooled estimate (random effect)						-1.0 (-1.8 to -0.1)
Test for heterogeneity: P=0.636, I^2=0%						
Beck depression inventory						
Segar 1998[53]	100	16	5.5 (2.1)	8	10.0 (2.0)	-4.5 (-6.2 to -2.8)
Daley 2007[65]	100	34	—	38	—	-6.0 (-10.2 to -1.8)
Von Gruenigen 2009[24]	0	23	8.6 (7.2)	22	8.3 (7.4)	0.3 (-4.0 to 4.6)
Kaltsatou 2011[28]	100	14	16.5 (1.7)	13	22.3 (7.7)	-5.8 (-10.1 to -1.5)
Pooled estimate (random effect)						-4.1 (-6.5 to -1.8)
Test for heterogeneity: P=0.132, I^2=47%						

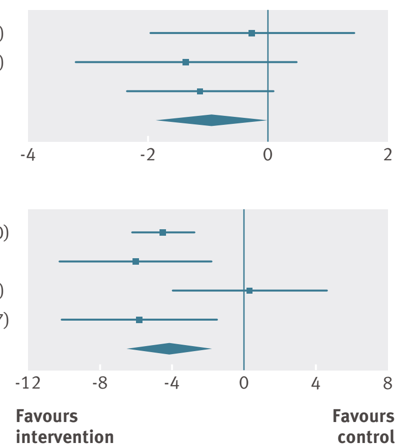

Fig 5| Association between physical activity and fatigue and depression in patients with cancer

Study	% with breast cancer	Intervention No	Intervention Mean (SD)	Control No	Control Mean (SD)	Difference (95% CI)
Mental health						
Basen-Engquist 2006[62]	100	28	78.2 (10.6)	23	77.2 (12.0)	1.0 (-5.3 to 7.3)
Morey 2009[40]	45	319	—	322	—	2.5 (0.8 to 4.3)
Pooled estimate (random effect)						2.4 (0.7 to 4.1)
Test for heterogeneity: P=0.644, I^2=0%						
Physical function						
Basen-Engquist 2006[62]	100	28	82.5 (12.7)	23	77.4 (11.5)	5.1 (-1.6 to 11.8)
Morey 2009[40]	45	319	—	322	—	2.7 (0.2 to 5.2)
Pooled estimate (random effect)						3.0 (0.7 to 5.3)
Test for heterogeneity: P=0.506, I^2=0%						
Social function						
Basen-Engquist 2006[62]	100	28	84.6 (16.9)	23	84.9 (19.2)	-0.3 (-10.3 to 9.7)
Morey 2009[40]	45	319	—	322	—	3.8 (0.6 to 6.9)
Pooled estimate (random effect)						3.4 (0.4 to 6.4)
Test for heterogeneity: P=0.449, I^2=0%						

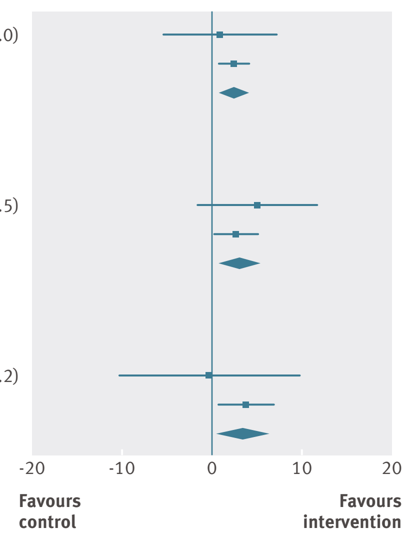

Fig 6| Association between physical activity and markers of quality of life (measured by SF-36) in patients with cancer

Table 4 | Pooled effects of physical activity in patients after treatment for cancer

Outcomes (units or plausible ranges)	Pooled estimate (95% CI)	P value	Minimal clinically important difference
Physiological markers			
Insulin-like growth factor-I (ng/mL)	−12.0 (−23.3 to −0.5)	0.04	NA
Insulin (pmol/L)	0.72 (−12.0 to 13.5)	0.91	NA
Glucose (mmol/L)	−0.04 (−0.32 to 0.24)	0.77	NA
Homeostatic model assessment	−0.08 (−0.50 to 0.34)	0.71	NA
Body composition			
% Body fat	−0.8 (−1.7 to 0.02)	0.06	NA
Body fat (kg)	−1.5 (−3.3 to 0.3)	0.10	NA
BMI	−0.4 (−0.6 to −0.2)	<0.01	NA
Waist circumference (cm)	−0.7 (−4.2 to 2.8)	0.69	NA
Waist:hip ratio	−0.01 (−0.04 to 0.02)	0.59	NA
Lean mass (kg)	0.6 (−0.5 to 1.7)	0.26	NA
Weight (kg)	−1.1 (−1.6 to −0.6)	<0.01	NA
Physical functions			
Peak heart rate (beats/min)	−0.5 (−9.5 to 8.5)	0.91	NA
Peak oxygen consumption (mL/kg/min)	2.2 (1.0 to 3.4)	<0.01	NA
Peak power output (W)	21.0 (13.0 to 29.1)	<0.01	4[79]
Six minute walk (m)	29 (4 to 55)	0.03	25[80]
Bench press (kg, 1 repetition maximum)	6 (4 to 8)	<0.01	NA
Leg press (kg, 1 repetition maximum)	19 (9 to 28)	<0.01	NA
Left handgrip (kg)	4.3 (−1.5 to 10.2)	0.15	6.2[81]
Right handgrip (kg)	3.5 (0.3 to 6.7)	0.03	6.2[81]
Sit and reach (cm)	2 (−3 to 8)	0.36	NA

NA=not available.

importance. No publication bias was found in any of the psychological outcomes (P≥0.82). Forest plots for all markers of psychological outcome can be found on bmj.com.

Meta-analysis of quality of life outcomes

There were 21 quality of life domains included in the meta-analysis and 10 of them exhibited heterogeneity (table 3). Identified sources of heterogeneity were study quality, sample size, type and duration of physical activity, and age. Study quality was strongly and positively associated with sample size, with smaller studies being associated with larger effects of physical activity on emotional function and total domains of the European Organization for Research and Treatment of Cancer. One study in patients with breast cancer found that aerobic plus resistance training was significantly more effective than aerobic training alone on physical, emotional, and functional wellbeing, breast concerns, breast total, and general total scores on the functional assessment of cancer therapy. In addition, the effect of physical activity on breast concerns was significantly greater in younger patients. The age effect, however, was confounded by the duration of physical activity.

In mixed types of cancer survivors, physical activity improved the SF-36 physical function scores by 3.0 points (0.6 to 5.3; P=0.01), social function by 3.4 points (0.4 to 6.4; P=0.03) and mental health by 2.4 points (0.7 to 4.1; P=0.01) (fig 6) compared with the control group (table 5). No publication bias was found in any of the quality of life domains (P=0.21). Forest plots for all markers of quality of life can be found on bmj.com.

Discussion

Effects of physical activity

In patients who have completed treatment for cancer, physical activity is associated with significantly reduced insulin-like growth factor-I, BMI, body weight, fatigue, and depression; it is also associated with increased peak oxygen consumption, peak power output, distance walked in six minutes, bench and leg press weight, right handgrip strength, and quality of life in the physical function, social function, and mental health domains. Our meta-analysis featured both exploration of sources of heterogeneity and assessment of publication bias that assesses the efficacy of physical activity on health indicators in patients with any type of cancer after completion of their primary cancer treatment. We reviewed 48 outcomes reported from 34 randomised controlled trials in patients with cancer. The effects were clinically important to physical functions and quality of life. We found substantial study heterogeneity, which was attributed to study quality and size, patients' age, and type and duration of physical activity.

Based on data from four randomised controlled trials in breast cancer,[30 32-34] physical activity was associated with significantly reduced serum concentration of insulin-like growth factor-I, despite insignificant results being reported in the primary studies. This was because of the increased precision resulting from combining different studies. A recent meta-analysis that pooled three of the studies we included also reported a small reduction in insulin-like growth factor-I.[16] Another meta-analysis that examined physiological changes after exercise reported that the effect of physical activity was insignificant.[14] That meta-analysis, however, combined different physiological parameters and might have included non-randomised studies. Raised concentration of insulin-like growth factor-I is known to be associated with an increased risk of colorectal cancer.[35] Thus, a significant reduction in insulin-like growth factor-I by aerobic or weight/strength training could potentially imply a reduced risk of cancer recurrence. However, there was no clear trend of an effect of physical activity on blood

Table 5 | Pooled effects of physical activity in patients after treatment for cancer

Outcomes(units or plausible ranges)	Pooled estimate (95% CI)	P value	Minimal clinically important difference
Psychological outcomes			
FACT-fatigue (0-52)	0.4 (−0.8 to 1.6)	0.50	3-4[82]
PFS-fatigue (0-10)	−1.0 (−1.8 to −0.1)	0.03	NA
EORTC-fatigue (0-100)	17.1 (−0.7 to 34.9)	0.06	5[83]
BDI (0-63)	−4.1 (−6.5 to −1.8)	<0.01	5[84]
HADS-depression (0-21)	−0.5 (−2.8 to 1.7)	0.64	1.40[85]
HADS-anxiety (0-21)	−0.7 (−3.4 to 2.1)	0.63	1.32[85]
POMS-total mood disturbance	−7.5 (−16.0 to 1.0)	0.09	7.4[86]
Quality of life outcomes			
EORTC-physical function (0-100):			
All	−1.2 (−5.1 to 2.6)	0.54	5[83]
EORTC-emotional function (0-100):			
All	1.5 (−9.8 to 12.7)	0.80	4.3[86]
Study quality +	−4.4 (−9.9 to 1.1)	0.12	—
Study quality –	13.0 (2.8 to 23.2)	—	—
EORTC-total (0-100):			
All	3.7 (−5.2 to 12.6)	0.41	4[83]
Study quality +	−0.8 (−5.4 to 3.9)	0.75	—
Study quality –	15.7 (4.0 to 27.5)	—	—
FACT-physical wellbeing (0-28):			
All	1.4 (−1.7 to 4.5)	0.39	2-3[82]
Assessed aerobic exercise	0.0 (−1.1 to 1.1)	1.00	—
Assessed aerobic+resistance	8.4 (6.5 to 10.3)	—	—
FACT-emotional wellbeing (0-24):			
All	0.7 (−0.6 to 1.9)	0.31	2-3[82]
Assessed aerobic exercise	0.1 (−0.8 to 1.1)	0.80	—
Assessed aerobic+resistance	2.9 (1.2 to 4.6)	—	—
FACT-social/family wellbeing (0-28):			
All	0.7 (−0.2 to 1.6)	0.14	2-3[82]
FACT-functional wellbeing (0-28):			
All	1.9 (−1.9 to 5.8)	0.33	2-3[82]
Assessed aerobic exercise	0.2 (−1.5 to 1.9)	0.82	—
Assessed aerobic+resistance	9.7 (7.6 to 11.8)	—	—
FACT-breast (0-36):			
All	1.9 (−1.6 to 5.4)	0.28	2-3[87]
Assessed aerobic exercise	0.6 (−2.6 to 3.8)	0.73	—
Assessed aerobic+resistance	5.6 (2.8 to 8.4)	—	—
FACT-breast total (0-140):			
All	7.6 (0.6 to 14.5)	0.03	5-6[87]
Assessed aerobic exercise	2.5 (−0.9 to 6.0)	0.15	—
Assessed aerobic+resistance	27.9 (21.5 to 34.3)	—	—
FACT-colorectal total (0-136):			
All	−1.6 (−6.2 to 2.9)	0.48	5-8[88]
FACT-general total (0-108):			
All	4.2 (−3.1 to 11.5)	0.26	3-7[87]
Assessed aerobic exercise	0.7 (−2.4 to 3.8)	0.65	—
Assessed aerobic+resistance	22.3 (17.3 to 27.3)	—	—
SF-36 (all 0-100):			
Physical function	3.0 (0.7 to 5.3)	0.01	3[89]
Role physical	6.1 (−4.1 to 16.2)	0.24	3[89]
Bodily pain	4.3 (−0.6 to 9.2)	0.08	3[89]
General health	5.8 (−1.2 to 13.)	0.12	3[89]
Vitality	2.1 (−0.4 to 4.5)	0.10	3[89]
Social function	3.4 (0.4 to 6.4)	0.03	3[89]
Role emotion	−0.01 (−3.7 to 3.6)	1.00	3[89]
Mental health	2.4 (0.7 to 4.1)	0.01	3[89]
SF Physical component scale (0-100)†	1.2 (−1.9 to 4.4)	0.44	3[89]
SF Mental component scale (0-100)†	0.4 (−2.3 to 3.2)	0.76	3[89]

BDI=Beck depression inventory; EORTC=European Organization for Research and Treatment of Cancer; FACT=functional assessment of cancer therapy; HADS=hospital anxiety and depression scale; NA=not available; PFS=revised Piper fatigue scale; POMS=profile of mood states; SF-36=short form 36.
†Two studies used SF-36 and one used SF-12.

insulin, glucose, and homeostatic model assessment levels.

BMI and body weight were found to be slightly but significantly reduced after physical activity intervention in studies that included patients with any cancer or breast cancer. The same result was found in the most recent meta-analysis, which also reported significant but not clinically important effects.[16] None of the other body parameters was significantly improved by physical activity. This finding is consistent with the literature, although previous meta-analyses have shown that percentage of body fat and lean body mass were significantly improved.[11 12 16] These meta-analyses, however, also included studies assessing physical activity during cancer treatment or did not show a clinically important effect.

Physical activity after completion of cancer treatment had clear benefits for many physical functions, including peak oxygen consumption, peak power output, distance walked in six minutes, and bench and leg press weights. Except for those of bench and leg presses, these findings have also been consistently reported in all other meta-analyses.[8 10-14] The only meta-analysis that reported unstandardised effects showed a slightly larger effect than ours on peak oxygen consumption (3.39 mL/kg/min, 1.67 to 5.10 mL/kg/min) and distance walked in six minutes (35 m, 13 to 58 m).[11] That meta-analysis, however, included only studies on patients with breast cancer, who might carry out physical activity during and after treatment.

A significant but small reduction in fatigue was observed in breast cancer studies using the revised Piper fatigue scale but not in studies on any cancer using either of the other two fatigue scales. Both the revised Piper fatigue scale and functional assessment of cancer therapy-fatigue have been shown to perform satisfactorily in measuring cancer related fatigue.[36 37] The fatigue scale by the European Organization for Research and Treatment of Cancer has also been shown to have satisfactory psychometric performance but it is not specific to cancer related fatigue.[38] The revised Piper fatigue scale, however, was primarily used in patients with breast cancer and thus has limited generalisability to patients with other cancers.[39] Nevertheless, it measures the current, rather than recalled, fatigue level of patients and so could be more sensitive in assessing the acute short term effects of physical activity. Only three meta-analyses have concluded that physical activity had significant effects on relieving fatigue.[15-17] They reported at least small to moderate effects of physical activity. Although the two studies that used the fatigue scale from the European Organization for Research and Treatment of Cancer showed significant improvement, their reported effects were largely different. This led to a large variation that resulted in an insignificant pooled random effects estimate. The same phenomenon was also observed for the total mood scale of the profile of mood states. Depression measured by the Beck depression inventory, however, was significantly reduced at a level of near clinical importance. This finding has not been reported in other meta-analyses.

Quality of life in patients with cancer has been assessed in the physical, mental, social, and overall quality of life domains by using four common instruments. For the physical domain, only the SF-36 survey showed a significant improvement of marginal clinical importance. The study of aerobic plus resistance exercise, however, found significantly larger improvements on both the physical and functional wellbeing scales of the functional assessment of cancer therapy than studies that examined aerobic exercise alone. The effect of the type of physical activity was not examined for the European Organization for Research and Treatment of Cancer and SF-36 scales because they were not measured in studies that used aerobic plus resistance training. The significant improvement shown in the physical function scale of the SF-36 survey is probably because of the inclusion of a recent large study.[28] For the mental domain, there was a significant improvement in the emotional wellbeing scale of the functional assessment of cancer therapy and the mental health scale of the SF-36 survey in studies of breast cancer survivors. The European Organization for Research and Treatment of Cancer also has a scale for emotional function, but no significant effect was found except in one study with the smallest sample size. For the social domain, clinically important improvement was found only in the social function scale of the SF 36 survey but not in the social/family wellbeing scale of the functional assessment of cancer therapy. This could be because of the inclusion of a large study.[40] These findings have not been reported in other meta-analyses.

Limitations of selected studies and previous meta-analyses

The intensity of physical activity could play an important role in its effects.[41 42] The intensity levels in interventions in the selected studies, however, were not consistently reported, which made it difficult to assess their influence on study heterogeneity. Nevertheless, the significantly larger effects of aerobic plus resistance training than aerobic training alone might indicate a potential benefit of higher intensity. Standardisation of reporting of exercise intensity, perhaps with a new method of considering both the gas exchange threshold and the conventional maximal oxygen uptake,[43] in future randomised controlled trials of physical activity in patients with cancer is desirable.

The standardised effect sizes of the outcomes across studies were measured by different methods or measurement scales in all but one meta-analysis. This resulted in previously unidentified important effects of physical activity on quality of life. Four meta-analyses that assessed the effects of physical activity in patients of any cancer type included both randomised and non-randomised controlled trials.[8 13 14 16] This might have increased study heterogeneity or publication bias. In addition, although these meta-analyses reported that physical activity improved physical function or cardiorespiratory fitness, the measures used to define these two health indicators were unclear. Only one meta-analysis clearly described physical function as a set of aerobic capacity or timed walking distance.[13] Although these meta-analyses standardised the mean difference between groups before pooling the estimates, the estimates represented a combination of different outcomes, such as peak oxygen consumption and distance walked in six minutes, which measured distinct domains of physical performance. The same concern applies to other health outcomes, such as fatigue, which might have been measured with different scales. In the sequel, although the other two meta-analyses included randomised controlled trials only, they also pooled different measures of fatigue.[15 17] Mixing studies with outcomes measured with different instruments

has long been known to potentially pose a threat to the validity of the resulting conclusions, although researchers might still statistically combine diverse study outcomes.[44] Importantly, it is difficult to interpret the resulting pooled estimate because it represents a mixture of outcomes under distinct domains.[45] Indeed, the Cochrane Handbook has generally emphasised the importance of due consideration when combining different variables, and researchers should not combine outcomes that are too diverse.[46] These suboptimal meta-analytic protocols were probably used because of the limited number of relevant randomised controlled trials in the literature. Thus, this meta-analysis included only randomised controlled trials and pooled studies for each outcome measured on the same scale.

Limitations

We included only published randomised controlled trials in our meta-analysis, which could have increased the risk of publication bias by not including non-randomised studies or unpublished studies. 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. Non-randomised studies had been included in previous meta-analyses because of the lack of published randomised controlled trials.[8 13 14 16] Non-randomised studies, however, can overestimate treatment effects by 30-41%[47]; thus, their inclusion in our study might have yielded overly optimistic effects of physical activity. In addition, unpublished studies, such as abstracts or reports, often report smaller treatment effects,[48] are often of poor quality, and do not provide sufficient data for statistical synthesis. Furthermore, we carefully examined all relevant meta-analyses, including the most recent three published in 2010 and 2011. We were not aware of any relevant unpublished studies when this study was conducted. Moreover, most outcomes did not exhibit publication bias; when it was found, it did not influence the conclusions.

Although we did not impose any language restriction in our systematic search, we eventually included only studies published in English. Although the exclusion of non-English language studies might result in smaller intervention effects, the language bias is generally small.[49] In addition, there might also be bias from not blinding the abstractors and reviewers to authors, institutions, and journals. There has been considerable debate on whether these details should be blinded. One empirical study did not advocate blinding as there is only a small risk of bias, but masking the details requires a large amount of administration time.[50]

Substantial study heterogeneity was found in several outcomes. This can limit the interpretability of the pooled estimates. Subgroup analyses by the identified sources of study heterogeneity, however, largely reduced the degree of heterogeneity, which became statistically insignificant.

The median duration of physical activity interventions in the included studies was only 13 weeks (range 3-60 weeks). Most mainstream studies of such interventions often conclude that physical activity needs to become integrated into everyday life to have long term benefits on health and fitness.[51 52] The generally short duration of interventions in our selected studies would limit assessment of the long term benefits of physical activity.

Implications for research and practice

Future research should focus on cancers other than breast cancer. Moreover, a standardised use of outcome measures and assessment of the intensity of physical activity are desirable and important in future randomised controlled trials to facilitate more reliable and valid synthesis of results from different studies.

Conclusions

Based on our review of 48 outcomes reported from 34 randomised controlled trials in patients with cancer, physical activity was shown to be associated with clinically important positive effects on physical functions and quality of life in patients who had completed their treatment for cancer. All of these benefits were applicable to patients with breast cancer. When we included studies of other types such as prostate, gynaecological, colorectal, gastric, and lung cancers, there was evidence of clinically important benefits on peak oxygen consumption, peak power output, and quality of life, which included physical and social functioning domains. Further randomised controlled trials on patients with cancers other than of the breast are needed to further assess the efficacy of physical activity on other health outcomes.

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