REVIEW ARTICLE

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Cardiopulmonary Exercise Testing in Cancer Rehabilitation

A Systematic Review

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Abstract

This systematic review aims to get insight into the feasibility of cardiopulmonary exercise testing (CPET) in patients with cancer prior to a physical exercise programme. We will focus on quality (defined as the adherence to international guidelines for methods of CPET) and safety of CPET. Furthermore, we compare the peak oxygen uptake ($\dot{V}O_{2peak}$) values of patients with cancer with reference values for healthy persons to put these values into a clinical perspective. A computer aided search with 'cardiopulmonary exercise testing' and 'cancer' using MEDLINE, EMBASE, Pedro, CINAHL® and SPORTDiscus™ was carried out. We included studies in which CPET with continuous gas exchange analysis has been performed prior to a physical exercise programme in adults with cancer. Twenty studies describing 1158 patients were eligible. Reported adherence to international recommendations for CPET varied per item. In most studies, the methods of CPET were not reported in detail. Adverse events occurred in 1% of patients. The percentage $\dot{V}O_{2peak}$ of reference values for healthy persons varied between 65% and 89% for tests before treatment, between 74% and 96% for tests during treatment and between 52% and 117% for tests after treatment. Our results suggest that CPET is feasible and seems to be safe for patients with cancer prior to a physical exercise programme. We recommend that standard reporting and quality guidelines should be followed for CPET methods. The decreased $\dot{V}O_{2peak}$ values of patients with cancer indicate that physical exercise should be implemented in their standard care.

1. Introduction

Early detection and improved treatments for cancer have resulted in an increasing number of cancer survivors, which will further increase due to ageing of the population.[1,2]

Historically, clinicians advised patients with cancer to rest and to minimize physical exercise. However, emerging research on physical exercise has challenged this recommendation; over the past decade there is growing evidence for the beneficial effects of physical exercise in patients with cancer in terms of improved physical fitness, quality of life and reduced cancer-related fatigue.[3]

Physical exercise programmes offered during, as well as following, cancer treatment, are becoming more common in the usual care of patients with cancer.[4] Both the roundtable convened by the American College of Sports Medicine (ACSM), as well as the newly developed Dutch evidence-based guideline *Cancer Rehabilitation* concluded that physical exercise should be recommended to all patients with cancer.[5,6]

The Dutch guideline *Cancer Rehabilitation* recommends tailoring physical exercise programmes to the patients' individual cardiopulmonary fitness levels to obtain optimal training effects.[6] Individual cardiopulmonary fitness levels can be assessed by measuring peak oxygen uptake ($\dot{V}O_{2peak}$).[5] $\dot{V}O_{2peak}$ reflects the integrative ability of the cardiopulmonary system to deliver oxygen to skeletal muscles and the efficiency of muscles to utilize oxygen.[5] Cardiopulmonary exercise testing (CPET) with continuous gas exchange analysis during incremental exercise is the only test that measures $\dot{V}O_{2peak}$ directly, and is therefore considered as the gold-standard assessment of $\dot{V}O_{2peak}$. This makes CPET an excellent exercise test to determine and to monitor individual cardiopulmonary fitness levels in patients with cancer.[7,8] Furthermore, CPET allows tailoring physical exercise programmes to the individual cardiopulmonary fitness level of the patient by using either a percentage of $\dot{V}O_{2peak}$, a percentage of the peak heart rate or the heart rate at the anaerobic threshold as individual measurements of exercise intensity.[9] In addition, CPET with gas exchange analysis and electrocardiography monitoring can be used as a diagnostic tool before the start of the physical exercise programme to detect cardiac or pulmonary limitations, and muscular limitations can become manifest during the test as well.[10]

Despite this, CPET is not routine in rehabilitation programmes for patients with cancer. This is partly due to logistic problems (costs, lack of appropriate equipment, lack of experienced healthcare professionals) but there also is a general uncertainty about exposing patients with cancer to additional physical stressful burdens like CPET.[11]

In a previous review, Jones et al.[7] summarized the quality of methods in different types of exercise tests for patients with cancer. They concluded that exercise testing in clinical oncology does not always comply with (inter)national quality guidelines.

This systematic review aims to provide insight into the feasibility of CPET in patients with cancer prior to a physical exercise programme. We will describe (i) the characteristics of patients with cancer who underwent CPET; (ii) the quality of CPET (defined as adherence to international recommendations for methods of CPET); and (iii) the safety of CPET. Furthermore, we will compare the $\dot{V}O_{2peak}$ values of patients with cancer with reference values for healthy persons to put these values into a clinical perspective.

2. Methods

2.1 Search Strategy

A computer aided search using MEDLINE, EMBASE, Pedro, CINAHL® and SPORTDiscus™ was carried out. The following search terms were used: 'cardiopulmonary exercise testing' (with synonyms) and 'cancer' (with synonyms) [see Appendix 1 in the Supplemental Digital Content (SDC) http://links.adisonline.com/SMZ/A8]. The reference lists of identified studies were searched for additional relevant studies.

2.2 Inclusion Criteria

We included studies in which CPET had been performed in adults who were older than 18 years of age and were diagnosed with cancer, regardless of type or stage. CPET had to be performed prior to a physical exercise intervention because our study is focused on the feasibility of CPET in patients with cancer prior to a physical exercise programme. Patients with cancer performed physical exercise before, during or after cancer treatment. Cardiopulmonary fitness had to be assessed using CPET with continuous gas exchange analysis during incremental or ramped exercise. We excluded review articles and case reports. No language restrictions were used.

2.3 Selection of Studies

Two independent reviewers (CS, MV) screened the titles and abstracts of identified studies for eligibility. Papers that seemed to be relevant were obtained, and the full-text articles were read by two reviewers (CS, MV) for inclusion. Disagreement between the reviewers was resolved by discussion.

2.4 Data Extraction and Analysis

The included studies were described according to the following items: (i) the characteristics of patients with cancer who underwent CPET; (ii) the adherence to international guidelines for methods of CPET;[7,8] (iii) the safety of CPET (defined as the reported adverse events); and (iv) the mean $\dot{V}O_{2peak}$ (mL/kg/min) values and percentages of $\dot{V}O_{2peak}$ of healthy controls taking sex, age and body mass index (BMI) into account.

Adherence to international guidelines was defined as adherence to the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) recommendations for CPET,[8] as previously used by Jones et al.[7,8] (table I). Additionally, we reported if the respiratory exchange ratio (RER) was above 1.1 and if a scale for the rating of perceived exertion (RPE) was used to evaluate the test, because these are important items to evaluate how the test was performed.

We made a distinction between patients with breast cancer, lung cancer, lymphoma, haematological cancer, prostate cancer and patients with mixed cancer types (see supplemental tables 1–6 in the SDC).

For tests on a treadmill, median reference $\dot{V}O_{2peak}$ values for healthy persons were derived from the percentile tables of the ACSM guidelines.[12] In these guidelines,[12] the reference values were described as normative with specific reference to age and sex. Median reference $\dot{V}O_{2peak}$ values for healthy persons were calculated from the equation from the Study of Health in Pomerania (SHIP) for tests performed on a cycle ergometer.[13] In the SHIP study[13] the study popula-

Table I. Item adherence to American Thoracic Society/American College of Chest Physicians recommendations

Characteristics	Protocol
Pre-test procedures	Abstain from exercise on day of test
	Abstain from eating/drinking coffee 2–3 hours before test
	Others
Conduct of exercise test	Measurements at rest (heart rate, blood pressure, 12-lead ECG, physician monitored)
	Measurements during exercise (continuous 12-lead ECG, continuous heart rate, continuous pulse oximetry, blood pressure)
Exercise test	Before test equipment calibration, after test equipment calibration check
Exercise modality	Treadmill, cycle ergometer
Exercise protocol	Incremental, ramp, Bruce, Balke
RER >1.1	
Scale for RPE	

ECG = electrocardiography; **RER** = respiratory exchange ratio; **RPE** = rating of perceived exertion.

tion was described as volunteers representative for a healthy population, and the following equation was given: 47.7565 (–0.9880 × age) (–0.2356 × age^2) (–8.8697 × sex) (2.3597 × BMI) (–2.0308 × age × BMI) (–3.7405 × sex × BMI) (0.2512 × age × sex) (1.3797 × age × sex × BMI). Sex was coded as 1 for males and 2 for females. BMI was coded as 0 for BMI ≤25 kg/m^2 and 1 for BMI >25 kg/m^2. There were five age groups: 25–34, 35–44, 45–34, 55–64 and ≥64 years of age, coded as 1–5, respectively. We assumed, for studies reporting mean age and BMI only for the total population, that mean age and BMI for the total study population was comparable with the mean of men and women separately. Since studies in our review reported mean values of $\dot{V}O_{2peak}$ instead of median values, we compared mean $\dot{V}O_{2peak}$ values of patients with cancer, with median $\dot{V}O_{2peak}$ values of healthy persons. Assuming that $\dot{V}O_{2peak}$ follows a normal distribution, mean and median values of $\dot{V}O_{2peak}$ will essentially be identical.

Two independent reviewers (CS, MV) extracted and analysed the data. Authors were contacted when relevant data were missing.

3. Results

We identified 4714 articles of which 122 were potentially relevant after screening the title and abstract (figure 1). Applying our inclusion criteria led to the inclusion of 28 articles describing

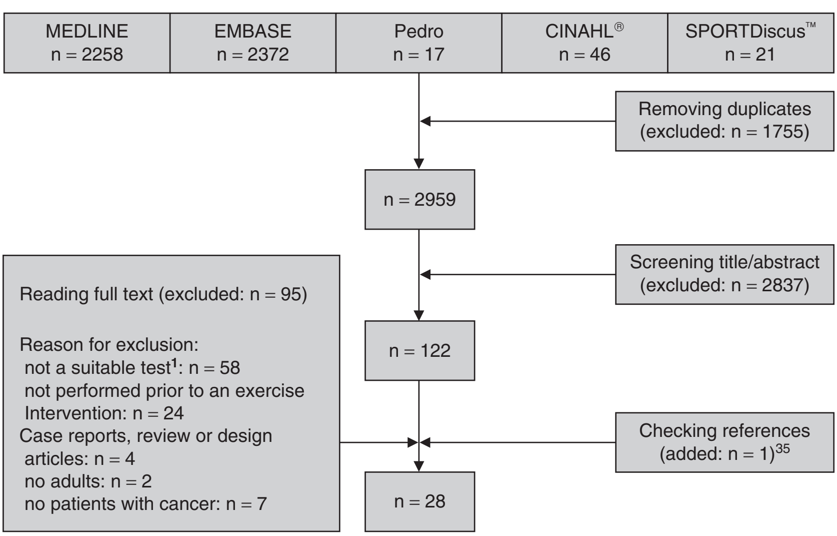

Fig. 1. Literature search updated on 6 April 2011. Results of some studies were published in several articles.[10,14-26] **1** A suitable test was defined as a cardiopulmonary exercise test with continuous gas exchange analysis.

20 studies, including 1158 patients. Most studies (n = 58) were excluded because they did not use a cardiopulmonary exercise test with continuous gas exchange analysis.

3.1 Patients with Cancer Who Underwent Cardiopulmonary Exercise Testing (CPET)

Studies of patients who underwent CPET included patients with breast cancer (six studies[14-18,27-30]), lung cancer (four studies[19-23,31,32]), lymphoma (one study[24,25]), haematological cancer (two studies[33,34]), prostate cancer (one study[35]) and mixed cancer types (six studies[10,26,36-40]) [table II]. Mean age of the patients was between 35 and 74 years. Mean BMI was ≤25 in five studies (25%), >25 kg/m^2 in nine studies (45%) and not reported in six studies (30%). More than 50% of all studies excluded patients with cardiovascular co-morbidity.

3.2 Adherence to Recommendations for CPET

As described in table III, pre-test procedures were reported in three (15%) studies. Reporting the conduct of the exercise tests varied per item as follows: 6 studies (30%) reported a physician-monitored test, 11 studies (55%) reported the use of continuous 12-lead electrocardiography (ECG) during CPET, 13 studies (65%) reported continuous heart rate monitoring, 3 studies (15%) reported continuous pulse oximetry and 8 studies (40%) reported blood pressure measurement during exercise. Five studies (25%) described that system calibration was performed before CPET. All studies reported the exercise modality, i.e. half of the tests (50%) were performed on a treadmill and the other half on a cycle ergometer. Fifteen studies (75%) described the exercise protocol; in ten of these studies, workload during testing was increased incrementally. Nine studies (45%) reported an RER above 1.1 during CPET, and six studies (30%) reported that they used a scale for the RPE to evaluate the test.

3.3 Adverse Events during CPET

Whether adverse events occurred during CPET was described in 11 studies (11/20 [55%]) including 843 patients (843/1158 [73%]) [table IV]. Adverse events occurred in six patients (6/843 [1%]) and were described as follows: asymptomatic ECG abnormalities (n = 2), low blood oxygen saturation (n = 1), syncope (n = 1), light headedness (n = 2) and dizziness (n = 1).

3.4 Peak Oxygen Uptake ($\dot{V}O_{2peak}$)

Lowest mean $\dot{V}O_{2peak}$ values (<15 mL/min/kg) were reported in the studies including patients with lung cancer (table V). The majority of the studies reported mean $\dot{V}O_{2peak}$ values between 16 mL/min/kg and 25 mL/min/kg. The percentage $\dot{V}O_{2peak}$ of reference values for healthy persons varied between 65% and 89% for tests before cancer treatment, between 74% and 96% for tests during cancer treatment and between 52% and 117% for tests after cancer treatment. Eleven studies (55%) did not describe the methods of determination of $\dot{V}O_{2peak}$; in the remaining studies the methods of determination differed.

4. Discussion

The advantages of performing CPET in patients with cancer prior to an exercise programme are an objective determination of individual cardiopulmonary fitness levels and parameters for training intensities, and accurate screening for cardiac, pulmonary or muscular limitations.

This review shows that CPET has been used for exercise programmes before, during and after cancer treatment in 1158 patients diagnosed with breast cancer, lung cancer, lymphoma, haematological cancer, prostate cancer and mixed cancer types. Reported adherence to the ATS/ACCP recommendations[7,8] varied: reporting of the pre-test procedures was lacking in most studies, reporting of the conduct of the exercise tests varied per item, calibration of gas exchange analysis was reported in 25%, exercise modality was reported in all studies and the exercise protocol was reported in 75% of the studies. Adverse events occurred in only 1% of CPET. The percentage $\dot{V}O_{2peak}$ of reference values for healthy persons varied between 65% and 89% for tests before cancer treatment, between 74% and 96% for tests during

Table II. Study characteristics

Characteristics	Breast cancer [14-18,27-30]	Lung cancer[19-23,31,32]	Lymphoma[24,25]	Haematological cancer[33,34]	Prostate cancer[35]	Mixed cancer[10,26,36-40]	All studies [n (%)]
No. of studies	6	4	1	2	1	6	20 (100)
Sex							
Men	–	–	–	–	1	–	1 (5)
Women	6	–	–	–	–	–	6 (30)
Men and women	–	4	1	2	–	6	13 (65)
Mean age (years)							
35–44	–	–	–	1	–	–	1 (5)
45–54	5	–	1	1	–	5	12 (60)
55–64	1	1	–	–	–	1	3 (15)
65–74	–	3	–	–	1	–	4 (20)
Mean BMI							
≤25 kg/m	–	1	–	1	–	3	5 (25)
>25 kg/m	4	3	1	–	1	–	9 (45)
NR	2	–	–	1	–	3	6 (30)
Disease stage							
II	1	–	–	–	–	–	1 (5)
I-II	1	–	–	–	–	–	1 (5)
II-III	–	–	–	–	–	–	0
I-III	2	3	–	–	–	–	5 (25)
All stages	2	–	–	–	–	–	2 (10)
NR/NA	–	1	1	2	1	6	11 (55)
Treatment							
Radiotherapy	–	–	–	–	1	–	1 (5)
Radio- and/or chemotherapy	–	–	1	–	–	–	1 (5)
Radio- and/or chemotherapy and/or surgery	6	4	–	–	–	6	16 (80)
Chemotherapy and/or SCT	–	–	–	2	–	–	2 (10)
Excluded co-morbidity							
Cardiovascular diseases	5	1	1	1	1	2	11 (55)
Orthopaedic exercise limitations	1	–	–	–	–	–	1 (5)
Metastasis (skeletal)	1	–	–	–	–	2	3 (15)
Endocrine diseases[a]	1	–	–	1	–	–	2 (10)

Continued next page

Table II. Contd

Characteristics	Breast cancer [14-18,27-30]	Lung cancer[19-23,31,32]	Lymphoma[24,25]	Haematological cancer[33,34]	Prostate cancer[35]	Mixed cancer[10,26,36-40]	All studies [n (%)]
Infection/immune abnormality	1	–	–	1	–	1	3 (15)
Graft vs host disease	–	–	–	1	–	–	1 (5)
Chronic or uncontrolled pain	1	–	–	1	1	0	3 (15)
Psychiatric illness	3	–	–	1	1	2	7 (35)
Cognitive disturbances	–	–	–	–	–	3	3 (15)
Timing CPET							
Before lung surgery	–	2	–	–	–	–	2 (10)
Before radiotherapy	1	–	–	–	1	–	2 (10)
During chemotherapy	1	–	1	–	–	–	2 (10)
After lung surgery	–	2	–	–	–	–	2 (10)
After treatment	2	–	–	2	–	5	9 (45)
NR	2	–	–	–	–	1	3 (15)

a Endocrine diseases included: endocrine abnormalities, thyroid disease and diabetes mellitus.

BMI = body mass index; **CPET** = cardiopulmonary exercise testing; **NA** = not applicable; **NR** = not reported; **SCT** = stem cell transplantation; – indicates not assessable.

cancer treatment and between 52% and 117% for tests after cancer treatment.

4.1 Patients with Cancer Who Underwent CPET

This review demonstrates that CPET can be performed in patients with different cancer types prior to a physical exercise programme. Although most studies report results for breast cancer and excluded patients with cardiovascular disease, this review also suggests that the use of CPET can be recommended for other cancer types prior to a physical exercise programme. Cardiovascular diseases are no contraindication for CPET because ECG monitoring is recommended and, furthermore, CPET is frequently used in the evaluation of patients with cardiovascular diseases.[7,8]

4.2 Adherence to Recommendations for CPET

Whether the reported adherence represents the real adherence to the recommendations for CPET, is unknown. Some items of the recommendations for CPET might be performed but not reported in the published article.[7,8] In a previous systematic review, Jones et al.[7,8] concluded that exercise testing in patients with cancer does not always comply with quality guidelines, such as the ATS/ACCP recommendations.[7,8] However, methods of exercise testing might be useful to report to ensure that the tests are valid, reproducible and safe.[7,8] We agree with Jones et al.[7,8] that developing recommendations for the clinical use of CPET for patients with cancer might be useful.

4.3 Adverse Events during CPET

Adverse events occurred in only 1% of CPET. However, whether adverse events occurred was described in only 55% of studies. Moreover, only 55% of studies were monitored with an ECG, and monitoring adverse events was not the aim of these studies. Therefore, in the other studies, ECG abnormalities could have been missed. Finally, all studies were among patients enrolled in an exercise programme, so the current findings cannot be generalized to the wider cancer population. On

Table III. Reported adherence to American Thoracic Society/American College of Chest Physicians recommendations

Characteristics	Breast cancer[14-18,27-30]	Lung cancer[19-23,31,32]	Lymphoma[24,25]	Haematological cancer[33,34]	Prostate cancer[35]	Mixed cancer[10,26,36-40]	All studies [n (%)]
No. of studies	6	4	1	2	1	6	20
Pre-test procedures							
Abstain from exercise on day of test	1	–	–	–	–	–	1 (5)
Abstain from eating/drinking coffee 2–3 hours before test	–	–	–	–	–	1	1 (5)
Other[a]	1	–	–	–	–	–	1 (5)
Conduct of exercise test							
Measurements at rest							
Heart rate	1	–	–	–	–	–	1 (5)
Blood pressure	1	–	–	–	–	1	2 (10)
12-lead ECG	1	–	–	–	–	–	1 (5)
Physician-monitored	2	2	1	1	–	–	6 (30)
Measurements during exercise							
Continuous 12-lead ECG	3	2	1	1	–	4	11 (55)
Continuous heart rate	3	2	1	2	–	5	13 (65)
Continuous pulse oximetry	–	2	1	–	–	–	3 (15)
Blood pressure	4	2	1	1	–	–	8 (40)
Exercise test							
Before test equipment calibration	1	1	–	1	–	2	5 (25)
Before and after test equipment calibration check	1[b]	1[b]	–	1[b]	–	–	3 (15)
Exercise modality							
Treadmill	3	–	–	2	1	4	10 (50)
Cycle ergometer	3	4	1	–	–	2	10 (50)
Exercise Protocol							
Incremental	3	4	1	–	–	2	10 (50)
Ramp	–	–	–	–	–	1	1 (5)
Bruce	2	–	–	–	–	–	2 (10)
Balke	–	–	–	–	–	2	2 (10)
NR	1	–	–	2	1	1	5 (25)
RER >1.1	2	2	–	1	–	4	9 (45)
Scale for RPE	1	2	–	1	–	2	6 (30)

a Patients were asked to follow the same diet for 3 days before CPET.

b Same study as the study with before test equipment calibration.[22,23]

CPET = cardiopulmonary exercise testing; **ECG** = electrocardiography; **NR** = not reported; **RER** = respiratory exchange ratio; **RPE** = rating of perceived exertion; – indicates not assessable.

Table IV. Adverse events during cardiopulmonary exercise testing

Characteristics	Breast cancer[14-18,27-30]	Lung cancer[19-23,31,32]	Lymphoma[24,25]	Haematological cancer[33,34]	Prostate cancer[35]	Mixed cancer[10,26,36-40]	All pts [n (%)]
No. of pts	416	61	122	24	121	414	1158
Reported AEs (n = 843)							
On a treadmill							
Before treatment	–	–	–	–	1/121	–	1/121 (1)
During treatment	2/242	–	–	–	–	–	2/242 (1)
After treatment	–	–	–	–	–	3/104	3/104 (3)
On a cycle ergometer							
Before treatment	–	0/20	–	–	–	–	0/20 (0)
During treatment	–	–	0/122	–	–	–	0/122 (0)
After treatment	0/68	0/19	–	–	–	0/147	0/234 (1)
Total occurred AEs	2/310 (1%)	0/39 (0%)	0/122 (0%)	–	1/121 (1%)	3/251 (1%)	6/843 (1)
Missing (n = 315)[a]	106/416 (25%)	22/61 (36%)	0/122 (0%)	24/24 (100%)	0/121 (0%)	163/414 (39%)	315/1158 (27)

a These studies did not report whether AEs occurred.

AEs = adverse events; **pts** = patients; – indicates not assessable.

the other hand, our results do not suggest that CPET is unsafe for patients with cancer prior to an exercise programme. Our findings agree with Jones et al.[41] who described a comparable adverse event rate in a meta-analysis. According to the ACSM guidelines for exercise testing, the risk of cardiac events in a mixed population during exercise testing is low, with approximately six cardiac events per 10 000 tests.[42] Furthermore, Knutsen et al.[11] qualitatively investigated the experiences of patients with cancer with CPET while undergoing chemotherapy, and they concluded that patients felt safe.

4.4 $\dot{V}O_{2peak}$

We found lower $\dot{V}O_{2peak}$ values in patients with cancer compared with the healthy population indicating decreased physical fitness levels and, consequently, an indication for physical training. Accurate determination of individual cardiopulmonary fitness levels and aerobic training intensity is then important to not only prevent overtraining but also undertraining. Several explanations for low $\dot{V}O_{2peak}$ values in patients with cancer have been described. Direct results of cancer such as anaemia, result in a decreased oxygen carrying capacity of the blood.[43] In addition, cancer systematic therapy might cause cardiac limitations, e.g. anthracyclines could lead to atrial and ventricular arrhythmias, pericarditis/myocarditis, a reduced ejection fraction and cardiomyopathy; and alkylating agents, such as cisplatin, may result in myocardial ischaemia/infarction, hypertension, heart failure and arrhythmias.[44] Furthermore, radiotherapy might cause cardiac or pulmonary limitations, such as angina, dyspnoea, heart failure, pericardial constriction, atherosclerosis and mediastinal fibrosis.[44] Finally, the reduction of physical activity after cancer diagnosis also contributes to low cardiopulmonary fitness levels. Physical inactivity could result in a reduction in cardiac output, oxidative capacity and muscle cross-sectional area.[45-47]

The following limitations have to be considered. For calculating the percentage $\dot{V}O_{2peak}$ of reference values for healthy persons we used the mean $\dot{V}O_{2peak}$ value of the total study population.

Table V. Values and methods of determination of peak aerobic capacity in patients with cancer

Characteristics	Breast cancer[14-18,27-30]	Lung cancer[19-23,31,32]	Lymphoma[24,25]	Haematological cancer[33,34]	Prostate cancer[35]	Mixed cancer[10,26,36-40]	All studies[a]
No. of studies	6	4	1	2	1	6	20
Mean $\dot{V}O_{2peak}$ (mL/min/kg)							
≤15	–	3	–	–	–	–	3 (15)
16–20	2	–	–	–	–	2	4 (20)
21–25	2	–	1	–	–	–	3 (15)
>25	2	1	–	1	–	3	3 (15)
NR							7 (35)
%$\dot{V}O_{2peak}$ of reference values for healthy persons (min-max)[b]							
Before cancer treatment	65	69–73	–	–	85–89	–	65–89
During cancer treatment	74–77	–	82–96[c]	–	–	–	74–96
After cancer treatment	82–101	55–70	–	–	–	52–117	52–117
Total	65–101	55–73	82–96	–	85–89	52–117	52–117
Methods of determination of $\dot{V}O_{2peak}$							
Mean 15 sec period[d]	2	–	–	–	–	–	2 (10)
Mean last 2 min[e]	1	–	–	–	–	–	1 (5)
Mean 20 sec period[f]	1	–	–	–	–	–	1 (5)
Mean highest 30 sec period	–	1	–	–	–	–	1 (5)
Highest value during a 15 sec period	–	–	–	–	1	–	1 (5)
Mean last 30 sec period	–	–	–	–	–	2	2 (10)
Highest value	–	–	–	–	–	1	1 (5)
NR	2	3	1	2	–	3	11 (55)

a Data for all studies are presented in [n (%)] values or %$\dot{V}O_{2peak}$ min-max, where stated.

b Median reference $\dot{V}O_{2peak}$ values for healthy persons were derived from the SHIP study for tests on a cycle ergometer and the ACSM guidelines for tests on a treadmill.

c This study included patients without treatment for lymphoma as well.

d Mean of four consecutive 15 sec values at the end of the power output.

e Mean of the three highest values of $\dot{V}O_{2peak}$ during the last 2 min.

f Highest mean values obtained for any continuous 20 sec period.

ACSM = American College of Sports Medicine; **min-max** = minimum-maximum; **NR** = not reported; **SHIP** = Study of Health in Pomerania; $\dot{V}O_{2peak}$ = peak oxygen uptake; – indicates not assessable.

Ideally, the percentage $\dot{V}O_{2peak}$ should be calculated with individual data to realize a more accurate estimation. However, our results are in agreement with others presenting the percentage $\dot{V}O_{2peak}$ of reference values for healthy persons calculated with individual data; they also report lower $\dot{V}O_{2peak}$ values in patients with cancer.[10,19,22] Furthermore, we used the mean age and mean BMI for the total study population instead of individual data. This might result in an underestimation of the percentage $\dot{V}O_{2peak}$ for younger patients with a BMI of ≤25 kg/m^2, and in an overestimation for older patients with a BMI of >25 kg/m^2. Moreover, for CPET on a cycle-ergometer, reference values for healthy persons are based on the SHIP study.[13] Because the SHIP study includes healthy persons who were not obese or currently non-smokers these reference values do not represent those for cancer patients (most cancer patients were obese). Therefore, percentage $\dot{V}O_{2peak}$ for cancer patients tested on a cycle ergometer might be underestimated.

Another possible flaw is that we included studies that determined $\dot{V}O_{2peak}$ and not the maximal oxygen uptake ($\dot{V}O_{2max}$). $\dot{V}O_{2max}$ is often defined as the point at which oxygen uptake ($\dot{V}O_2$) reaches a plateau, despite a further increase in work rate during CPET. In patients, such a plateau in $\dot{V}O_2$ is rarely seen, suggesting that patients do not always attain a maximal exercise level during CPET because of premature (muscular) exhaustion and discomfort.[48] Consequently, the highest attainable $\dot{V}O_2$ at the end of a CPET is often referred to as $\dot{V}O_{2peak}$ rather than $\dot{V}O_{2max}$ and, for practical purposes, $\dot{V}O_{2max}$ and $\dot{V}O_{2peak}$ are frequently used interchangeably.[7,8]

Furthermore, only the minority of the studies assessed the so-called secondary maximal criteria during CPET (e.g. RER >1.1). Therefore, the level of $\dot{V}O_{2peak}$ values may vary between the studies due to different testing procedures, and the true $\dot{V}O_{2peak}$ might not always be achieved due to symptom limitations. Moreover, this makes it difficult to judge whether patients were tested maximally. In addition, reporting the secondary maximal criteria during CPET, such as the RER, might also be interesting for assessing the effect of physical training.

5. Conclusion

Our results suggest that CPET is feasible and seems to be safe for patients with cancer prior to a physical exercise programme. CPET can be used as a diagnostic tool and for tailoring the exercise programmes to individual cardiopulmonary fitness levels for precisely defining exercise intensities in order to prevent over- and undertraining, and to obtain optimal training effects. We recommend that standard reporting and quality guidelines should be followed for methods of CPET, secondary maximal criteria and adverse events. The decreased $\dot{V}O_{2peak}$ values of patients with cancer further highlight the importance of close monitoring of physical cardiopulmonary fitness levels and indicate that physical exercise should be implemented in the standard care of cancer patients.

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References

1. Kanker in Nederland. Report of the Dutch Cancer Society. Trends prognoses en implicaties voor zorgvraag: signaleringscommissie Kanker van KWF Kankerbestrijding. Amsterdam: KWF Kankerbestrijding, 2009
2. Siesling S, Visser O, Luth TK, et al. Adult cancer patients are surviving longer in the Netherlands: 5-year survival rate increased by 12% between the periods 1989-1993 and 2004-2008. Ned Tijdschr Geneeskd 2011; 155: A3169
3. Scientific Program Committee. Physical activity across the cancer continuum: report of a workshop. Review of existing knowledge and innovative designs for future research. Cancer 2002; 95 (5): 1134-43
4. Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev 2006 Oct 18; (4): CD005001
5. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010; 42: 1409-26
6. Comprehensive Cancer Center the Netherlands. Guideline Cancer Rehabilitation. 2011 [online]. Available from URL: http://www.oncoline.nl/uploaded/docs/onco%20rev/richtlijn%20onc%20rev%20versie%20150311%20voor%20autorisatie.pdf [Accessed 2012 Feb 24]

7. Jones LW, Eves ND, Haykowsky M, et al. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncol 2008; 9: 757-65
8. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211-77
9. Astrand P, Rodahl K. Evaluation of physical performance on the basis of tests. In: Bahrke MS, Schrag M, Bernard K, et al. Textbook of work physiology: physiological bases of exercise. Champaign (IL): Human Kinetics, 2011: 421-446B
10. May AM, van WE, Korstjens I, et al. Improved physical fitness of cancer survivors: a randomised controlled trial comparing physical training with physical and cognitive-behavioural training. Acta Oncol 2008; 47: 825-34
11. Knutsen L, Quist M, Midtgaard J, et al. Maximum physical capacity testing in cancer patients undergoing chemotherapy: qualitative findings from an exercise program. Scand J Med Sci Sports 2006; 16: 403-11
12. American College of Sports Medicine. Health-Related Physical Fitness testing and interpretation: ACSM guidelines for exercise testing and prescription (8th ed.), 2010 [online]. Available from URL: http://www.ebook3000.com/Sports/ACSM-s-Guidelines-for-Exercise-Testing-and-Prescription–8th-Edition-_36089.html [Accessed 2012 Feb 24]
13. Koch B, Schaper C, Ittermann T, et al. Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study. Eur Respir J 2009; 33: 389-97
14. Herrero F, San Juan AF, Fleck SJ, et al. Combined aerobic and resistance training in breast cancer survivors: a randomized, controlled pilot trial. Int J Sports Med 2006; 27: 573-80
15. Herrero F, San Juan AF, Fleck SJ, et al. Effects of detraining on the functional capacity of previously trained breast cancer survivors. Int J Sports Med 2007; 28: 257-64
16. Dolan LB, Gelmon K, Courneya KS, et al. Hemoglobin and aerobic fitness changes with supervised exercise training in breast cancer patients receiving chemotherapy. Cancer Epidemiol Biomarkers Prev 2010; 19: 2826-32
17. Courneya KS, McKenzie DC, Mackey JR, et al. Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy: a randomized controlled trial. Cancer 2008; 112: 1845-53
18. 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
19. Jones LW, Peddle CJ, Eves ND, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer 2007; 110: 590-8
20. Jones LW, Eves ND, Peddle CJ, et al. Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. Appl Physiol Nutr Metab 2009; 34: 197-202
21. Peddle CJ, Jones LW, Eves ND, et al. Effects of presurgical exercise training on quality of life in patients undergoing lung resection for suspected malignancy: a pilot study. Cancer Nurs 2009; 32: 158-65
22. Jones LW, Eves ND, Peterson BL, et al. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. Cancer 2008; 113: 3430-9
23. Jones LW, Eves ND, Spasojevic I, et al. Effects of aerobic training on oxidative status in postsurgical non-small cell lung cancer patients: a pilot study. Lung Cancer 2011 Apr; 72 (1): 45-51
24. Courneya KS, Sellar CM, Stevinson C, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. J Clin Oncol 2009; 27: 4605-12
25. Courneya KS, Sellar CM, Stevinson C, et al. Moderator effects in a randomized controlled trial of exercise training in lymphoma patients. Cancer Epidemiol Biomarkers Prev 2009; 18: 2600-7
26. May AM, van WE, Korstjens I, et al. Monitoring training progress during exercise training in cancer survivors: a submaximal exercise test as an alternative for a maximal exercise test? Arch Phys Med Rehabil 2010; 91: 351-7
27. MacVicar MG, Winningham ML, Nickel JL. Effects of aerobic interval training on cancer patients' functional capacity. Nurs Res 1989; 38: 348-51
28. Courneya KS, Mackey JR, Bell GJ, et al. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 2003; 21: 1660-8
29. Drouin JS, Young TJ, Beeler J, et al. Random control clinical trial on the effects of aerobic exercise training on erythrocyte levels during radiation treatment for breast cancer. Cancer 2006; 107: 2490-5
30. Kim CJ, Kang DH, Smith BA, et al. Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy. Cancer Nurs 2006; 29: 156-65
31. Bobbio A, Chetta A, Ampollini L, et al. Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. Eur J Cardiothorac Surg 2008; 33: 95-8
32. Spruit MA, Janssen PP, Willemsen SC, et al. Exercise capacity before and after an 8-week multidisciplinary inpatient rehabilitation program in lung cancer patients: a pilot study. Lung Cancer 2006; 52: 257-60
33. Hayes SC, Davies PS, Parker TW, et al. Role of a mixed type, moderate intensity exercise programme after peripheral blood stem cell transplantation. Br J Sports Med 2004; 38: 304-9
34. Carlson LE, Smith D, Russell J, et al. Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study. Bone Marrow Transplant 2006; 37: 945-54
35. 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
36. De Backer IC, Schep G, Hoogeveen A, et al. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. Arch Phys Med Rehabil 2007; 88: 610-6
37. Dimeo F, Schwartz S, Wesel N, et al. Effects of an endurance and resistance exercise program on persistent cancer-related fatigue after treatment. Ann Oncol 2008; 19: 1495-9

38. Burnham TR, Wilcox A. Effects of exercise on physiological and psychological variables in cancer survivors. Med Sci Sports Exerc 2002; 34: 1863-7
39. Klika RJ, Callahan KE, Drum SN. Individualized 12-week exercise training programs enhance aerobic capacity of cancer survivors. Phys Sportsmed 2009; 37: 68-77
40. Griffith K, Wenzel J, Shang J, et al. Impact of a walking intervention on cardiorespiratory fitness, self-reported physical function, and pain in patients undergoing treatment for solid tumors. Cancer 2009; 115: 4874-84
41. Jones LW, Liang Y, Pituskin EN, et al. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. Oncologist 2011; 16: 112-20
42. American College of Sports Medicine. ACSM guidelines for exercise testing and prescription. pp 12; 8th ed. 2011 [online]. Available from URL: www.acsm.org [Accessed 2012 Mar 1]
43. Harrison LB, Shasha D, Homel P. Prevalence of anemia in cancer patients undergoing radiotherapy: prognostic significance and treatment. Oncology 2002; 63 Suppl. 2: 11-8
44. Jones LW, Haykowsky MJ, Swartz JJ, et al. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol 2007; 50: 1435-41
45. McGuire DK, Levine BD, Williamson JW, et al. A 30-year follow-up of the Dallas Bedrest and Training Study: I. Effect of age on the cardiovascular response to exercise. Circulation 2001; 104: 1350-7
46. McGuire DK, Levine BD, Williamson JW, et al. A 30-year follow-up of the Dallas Bedrest and Training Study: II. Effect of age on cardiovascular adaptation to exercise training. Circulation 2001; 104: 1358-66
47. Jones LW, Eves ND, Haykowsky M, et al. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. Lancet Oncol 2009; 10: 598-605
48. Wasserman K, Hansen JE, Sue DY, et al. editors. Principles of exercise testing and interpretation: physiology of exercise. Philadelphia (PA): Lippincott Williams & Wilkins, 2011; 65-7

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