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SHORT COMMUNICATION

# Are patient-reported outcomes of physical function a valid substitute for objective measurements?

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## ABSTRACT

**Background** Physical function is important for defining treatment strategies in patients with cancer and can be estimated using patient-reported outcomes (PROs). Although PROs are subjective, physical activity and fitness can be tested objectively with adequate, but more labour-intensive methods that are rarely used in daily clinical practice. To determine whether PROs for physical function (PRO-PF) accurately predict physical function, we studied their interrelationships with objective measures of physical activity and fitness in patients with cancer who had completed cancer treatment, including adjuvant or neoadjuvant chemotherapy or autologous stem-cell transplantation.

**Methods** Baseline data from the REACT (Resistance and Endurance Exercise After Chemotherapy) and EXIST (Exercise Intervention After Stem-Cell Transplantation) studies were evaluated. In those studies, the effects of an exercise intervention on physical fitness, fatigue, and health-related quality of life in patients with cancer shortly after completion of chemotherapy or stem-cell transplantation were studied. Interrelationships between PRO-PF (physical function subscale of the European Organisation for Research and Treatment of Cancer 30-question core Quality of Life Questionnaire), physical activity (accelerometer), and cardiorespiratory fitness (peak oxygen uptake) were assessed using univariable and multivariable multilevel linear mixed-model analyses.

**Results** After adjustment for age, sex, and body mass index, the PRO-PF was significantly associated with physical activity ($\beta = 1.75$; 95% confidence interval: 1.08 to 2.42) and cardiorespiratory fitness ($\beta = 0.10$; 95% confidence interval: 0.06 to 0.13). Standardized coefficients were 0.28 and 0.26 respectively, indicating a weak association.

**Conclusions** The PRO-PF is only weakly associated with objective physical activity and fitness evaluation in patients after curative treatment for cancer. The PRO-PF cannot, therefore, be used in clinical practice as a substitute for objective measures of physical function.

**Key Words** Physical functioning, patient-reported outcomes, objective measurements, physical activity, cardiorespiratory fitness

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## INTRODUCTION

Optimal selection of a systemic treatment strategy is essential for patients with cancer in both the curative and palliative settings. Premature discontinuation of an initiated treatment does not benefit treatment outcomes and quality of life for patients[1]. The selection and initiation of a treatment depends heavily on an estimation of the patient's physical function, conceptualized as the ability to perform physical activities necessary for daily living and for maintaining functional independence[2].

Physical activity and fitness can be assessed objectively, providing an estimate of a patient's physical function. Physical activity is defined as any bodily movement caused by muscle contractions and resulting in energy expenditure[3]; it can be objectively assessed with an accelerometer. Physical fitness is defined as "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and

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with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies”[3]. Cardiorespiratory fitness is one of the main components of physical fitness. Cardiorespiratory fitness (peak$VO_2$) assessed during a maximal exercise test is the “gold standard” for assessing cardiorespiratory fitness[4].

Although (self-reported) physical activity and fitness are prognostic for survival[5,6], their prognostic value for treatment tolerance is unclear. Earlier randomized controlled trials showed fewer chemotherapy dose adjustments, fewer toxicities, and higher rates of chemotherapy completion in patients participating in an exercise program compared with those receiving usual care[7–9]. Measurements of physical activity and fitness are time-consuming and costly, making them difficult to implement in clinical practice[4].

The 5-item patient-reported outcome of physical function [PRO-PF, part of the 30-question core Quality of Life Questionnaire (QLQ-C30) from the European Organisation for Research and Treatment of Cancer (EORTC)] has often been used to assess a patient’s physical function. Recent studies have shown that, in patients with colorectal cancer, the PRO-PF is more strongly associated with survival than the widely used Eastern Cooperative Oncology Group performance status or World Health Organization performance status[10], and in patients with breast cancer, it is associated with therapy discontinuation for toxicity[11]. In clinical practice, PROs are easy to implement because they are inexpensive and easy for a patient to complete.

To judge whether the PRO-PF sufficiently reflects a patient’s physical function, it should be compared with objective measurements of physical activity and fitness. If agreement is sufficient, the PRO-PF could be used instead of time-consuming and expensive objective measurements of physical activity (with accelerometers, for instance) and fitness (with the maximal exercise test). Earlier studies showed that the association between the PRO-PF and physical activity[12,13] and between the PRO-PF and cardiorespiratory fitness (assessed using the submaximal 6-minute walk test)[12,14] was weak to moderate (Pearson correlation coefficients: 0.33–0.55). However, those studies did not investigate the interrelationships of the PRO-PF and physical activity and cardiorespiratory fitness in the same sample, hampering a direct comparison. Moreover, earlier studies did not compare the PRO-PF with the “gold standard” of cardiorespiratory fitness, peak$VO_2$.

In the present study, we investigated whether the PRO-PF is a valid substitute for objectively assessed physical activity or fitness by studying the relationships between those variables in patients with cancer after adjuvant or neoadjuvant chemotherapy or autologous stem-cell transplantation.

## METHODS

### Study Design and Population

This study used baseline data from two Dutch multicentre randomized controlled trials, REACT[15] (Resistance and Endurance Exercise After Chemotherapy) and EXIST[16] (Exercise Intervention After Stem-Cell Transplantation). The REACT study evaluated the effects of a 12-week high-intensity or low- to moderate-intensity supervised resistance and endurance interval exercise intervention on physical fitness, fatigue, and health-related quality of life in participants compared with a wait-list control group of patients with cancer who had completed cancer treatment for breast, colon, ovarian, testicular, or cervical cancer, or lymphoma ($n$ = 277 total)[15]. The EXIST study investigated the effects on the same outcomes of a supervised 18-week individualized high-intensity resistance and endurance interval exercise intervention compared with usual care in 109 patients with multiple myeloma or lymphoma[16].

### Measures

In the REACT study, baseline assessment took place 4–6 weeks after completion of cancer treatment (adjuvant or neoadjuvant chemotherapy), and in the EXIST study, the assessment took place 6–14 weeks after autologous stem-cell transplantation[15,16]. In both studies, an accelerometer was used to assess physical activity for, respectively, 7 or 5 consecutive days. Vertical accelerations were converted into activity counts per minute (total counts for the $y$ axis, divided by the number of measurement days)[15,16]. Cardiorespiratory fitness was measured during a maximum exercise test on a cycle ergometer according to a ramp protocol, aiming to achieve peak$VO_2$ within 8–12 minutes (expressed in millilitres per kilogram per minute)[15,16]. Peak$VO_2$ was defined as the highest oxygen consumption value averaged over a 15-second interval within the last minute of exercise. A suggested threshold for functional independence is 15 $mL \cdot kg^{-1} \cdot min^{-1}$ for women and 18 $mL \cdot kg^{-1} \cdot min^{-1}$ for men[17]. The PRO-PF was measured using the EORTC QLQ-C30 physical functioning subscale, which consists of 5 questions. A score below 66.7 was considered to be poor physical function[10].

### Statistical Analysis

To investigate whether the PRO-PF is associated with, respectively, physical activity and fitness, univariable and multivariable multilevel linear mixed models were constructed in which clustering of patients within studies was taken into account by a random intercept on the study level. In the multivariable models, adjustments were made for age, sex, and body mass index. Regression coefficients (βs) and corresponding 95% confidence intervals (CIs) are presented. The standardized regression coefficient was determined to facilitate clinical interpretation, with a value less than 0.20 being considered very weak association; 0.20–0.39, a weak association; 0.40–0.59, a moderate association; 0.60–0.79, a strong association; and 0.80–1.0, a very strong association. In addition, sensitivity analyses were performed in which associations were studied separately within each study and only in patients with breast cancer. A $p$ value less than 0.05 was considered statistically significant. All analyses were conducted using the IBM SPSS Statistics software application (version 22: IBM, Armonk, NY, U.S.A.).

## RESULTS

Mean age of all participants was 53 ± 11 years, with 68% being women, and 47% having been diagnosed with breast cancer (Table I). The mean peak$VO_2$ was 21.7 ± 5.7 $mL \cdot kg^{-1} \cdot min^{-1}$, and in 13% of participants, the value was below the threshold for independent living. Mean physical activity was 230 ± 98 counts per minute. The mean score on the PRO-PF was 79.1 ± 15.6, and 26.9% of respondents were rated as having poor physical function.

After adjustment for age, sex, and body mass index, the PRO-PF was significantly associated with physical activity (β = 1.75; 95% CI: 1.09 to 2.42; Table II). The standardized regression coefficient was 0.28, indicating a weak association. The association between the PRO-PF and peak$VO_2$ was also significant (β = 0.10; 95% CI: 0.06 to 0.13), but weak (standardized regression coefficient: 0.26). Of 50 patients with a peak$VO_2$ value below the threshold of functional independence, 24 (48%) were rated on the PRO-PF as having poor physical function.

## DISCUSSION

In the present study, the PRO-PF portion of the EORTC QLQ-30 was evaluated as a potential substitute for objectively measured physical activity and fitness. Results indicated that the PRO-PF had a significant but weak association with physical activity and fitness. Furthermore, just fewer than half the 50 patients with cardiorespiratory fitness below the threshold for independent living were identified by the PRO-PF as having poor physical function. In clinical practice, the use of the PRO-PF as a substitute for objective assessments of physical function is therefore unreliable in patients after curative treatment for cancer.

The weak association between the PRO-PF and cardiorespiratory fitness is in line with results of two earlier studies that showed a weakly-to-moderately significant positive correlation between the PRO-PF and the 6-minute walk test in patients with cancer[12,14]. The association between the PRO-PF and objectively measured physical activity in patients with cancer has also been investigated in three previous studies, two of which found a weakly-to-moderately significant association[12,13]; another study found no significant association[18].

**TABLE I** Characteristics of the study participants

| Characteristic | Patient group | | |
|---|---|---|---|
| | **Overall** | **REACT study** | **EXIST study** |
| Patients *(n)* | 386 | 277 | 109 |
| Mean age (years) | 53±11 | 54±11 | 52±11 |
| Sex [*n* (%) men] | 124 (32) | 55 (20) | 69 (63) |
| Cancer type [*n* (%)] | | | |
| Breast cancer | 181 (47) | 181 (65) | |
| Colon cancer | 49 (13) | 49 (18) | |
| Lymphoma | 77 (20) | 26 (9) | 51 (47) |
| Ovarian cancer | 12 (3) | 12 (4) | |
| Testicular cancer | 5 (1) | 5 (2) | |
| Cervical cancer | 4 (1) | 4 (1) | |
| Multiple myeloma | 58 (15) | | 58 (53) |
| Education [*n* (%) low or intermediate] | 239 (62) | 169 (62) | 70 (64) |
| Mean body mass index ($kg/m^2$) | 26.5±4.5 | 26.9±4.4 | 25.4±4.5 |
| Patient-reported physical function score[a] | | | |
| Mean | 79.1±15.6 | 81.0±14.2 | 74.0±17.7 |
| Minimum–maximum | 20–100 | 40–100 | 20–100 |
| Score < 66.7 [*n* (%)] | 104 (27.1) | 60 (21.7) | 44 (40.7) |
| Cardiorespiratory fitness[b] ($mL \cdot kg^{-1} \cdot min^{-1}$) | | | |
| Mean | 21.7±5.7 | 21.8±5.8 | 21.6±5.4 |
| Minimum–maximum | 10.1–45.6 | 10.1–45.6 | 11.4–40.0 |
| Below threshold of functional independence [*n* (%)] | 50 (13.7) | 34 (12.4) | 16 (18.0) |
| Physical activity (counts per minute) | | | |
| Mean | 230±98 | 245±96 | 194±94 |
| Minimum–maximum | 35–555 | 44–555 | 35–493 |

[a] Using the European Organisation for Research and Treatment of Cancer 30-question core Quality of Life Questionnaire, physical function subscale. (5 items: Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? Do you have any trouble taking a long walk? Do you have any trouble taking a short walk outside of the house? Do you need to stay in bed or a chair during the day? Do you need help with eating, dressing, washing yourself, or using the toilet?)

[b] As peak oxygen uptake.

REACT = Resistance and Endurance Exercise After Chemotherapy; EXIST = Exercise Intervention After Stem-Cell Transplantation.

**TABLE II** Associations of patient-reported physical functioning with objectively assessed physical activity and fitness

| Participant population and variable | Physical activity (counts per minute) | | Cardiorespiratory fitness[a] ($mL \cdot kg^{-1} \cdot min^{-1}$) | |
|---|---|---|---|---|
| | Crude | Adjusted[b] | Crude | Adjusted[b] |
| Overall | | | | |
| Regression coefficient | 1.88 | 1.75 | 0.14 | 0.1 |
| 95% CL | 1.21, 2.54[c] | 1.09, 2.42[c] | 0.10, 0.17[c] | 0.06, 0.13[c] |
| Standardized regression coefficient | 0.30[c] | 0.28[c] | 0.37[c] | 0.26[c] |
| REACT study | | | | |
| Regression coefficient | 1.56 | 1.41 | 0.15 | 0.09 |
| 95% CL | 0.72, 2.40[c] | 0.57, 2.25[c] | 0.10, 0.19[c] | 0.05, 0.13[c] |
| Standardized regression coefficient | 0.23[c] | 0.21[c] | 0.36[c] | 0.22[c] |
| EXIST study | | | | |
| Regression coefficient | 2.41 | 2.35 | 0.12 | 0.08 |
| 95% CL | 1.33, 3.50[c] | 1.16, 3.54[c] | 0.07, 0.18[c] | 0.03, 0.14[c] |
| Standardized regression coefficient | 0.42[c] | 0.41[c] | 0.42[c] | 0.29[c] |
| Breast cancer patients only | | | | |
| Regression coefficient | 1.78 | 1.58 | 0.13 | 0.09 |
| 95% CL | 0.80, 2.77[c] | 0.55, 2.95[c] | 0.08, 0.17[c] | 0.05, 0.13[c] |
| Standardized regression coefficient | 0.28[c] | 0.25[c] | 0.40[c] | 0.29[c] |

a As peak oxygen uptake.
b Adjusted for age, sex, and body mass index.
c $p < 0.05$.
REACT = Resistance and Endurance Exercise After Chemotherapy; EXIST = Exercise Intervention After Stem-Cell Transplantation; CL = confidence limits.

The strength of our study lies in its evaluation of both associations in the same large population of patients with cancer and the use of "gold standard" objective assessments.

One limitation of the study is that the population consisted of participants in exercise trials, who might therefore be more interested in physical activity and fitness[19]. In combination with the curative-treatment intention, that factor could have led to higher levels of physical activity and fitness in our study population than in a general population of patients with cancer. Nevertheless, fitness levels were low, and the mean peak$VO_2$ of 21.7 $mL \cdot kg^{-1} \cdot min^{-1}$ was far below age- and sex-adjusted reference standards, but comparable with the peak$VO_2$ measured in other patients who had just finished chemotherapy treatment[20]. In patients with cancer, peak$VO_2$ might reflect recent treatment in addition to daily physical activity levels. However, regardless of cause, low physical activity and fitness levels should be detected by the PRO-PF. Additionally, the physical activity and fitness results in our study population showed ample variation.

Our study demonstrates that the PRO-PF portion of the EORTC QLQ-C30 is not a valid reflection of objectively assessed physical activity and fitness in patients after curative treatment for cancer. The lack of a strong association is most likely attributable to the subjective nature of the measurement. However, whether our results could be generalized to all PROs assessing physical function is unclear. Whether our findings are generalizable to patients with cancer receiving palliative treatment and whether objective measurements could be of added value in the selection of patients eligible for systemic therapy or participation in clinical trials is also unknown.

It is troublesome that objective measures of physical activity and fitness are so time-consuming and costly. New and more sophisticated objective assessments are needed, possibly with a major role in the future for assessments that are obtained with electronic devices. We recently initiated a validation study and a subsequent prospective study that will investigate whether objective physical activity or fitness assessments by smartphone can be used clinically to predict trial feasibility without early discontinuation. We foresee that this approach could optimize treatment selection for patients with cancer in both the curative and palliative settings.

## CONCLUSIONS

The PRO-PF of the EORTC QLQ-C30 is only weakly associated with objectively measured physical activity and fitness in patients after curative treatment for cancer. It therefore has limited value in clinical practice as a substitute for objective measurements that assess physical function in this patient population.

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## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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