Wiel, H.J. van de, Groen, W.G., Kampshoff, C.S., Buffart, L.M., Mechelen, W. van, Schep, G., Sonke, G.S., Huijsmans, R., Harten, W.H. van, Aaronson, N.K., Stuiver, M.M.The construct validity of the Steep Ramp Test for assessing cardiorespiratory fitness in patients with breast cancer, and the impact of chemotherapy-related symptom burden. Archives of Physical Medicine and Rehabilitation: 2022, 103(12), p. 2362-2367

Postprint version	:	2.0
Journal website	:	https://www.archives-pmr.org/
Pubmed link	:	https://pubmed.ncbi.nlm.nih.gov/35732249/
DOI	:	10.1016/j.apmr.2022.05.014

This is a Nivel certified Post Print, more info at nivel.nl

The construct validity of the Steep Ramp Test for assessing cardiorespiratory fitness in patients with breast cancer, and the impact of chemotherapy-related symptom burden

Hester J. Van de Wiel,[1] Wim G. Groen[1], Caroline S. Kampshoff[2], Laurien M. Buffart[3,4], Willem van Mechelen[5,6,7,8], Goof Schep[9], Gabe S. Sonke[10], Rosalie Huijsmans [11], Wim H. van Harten[1,12,13], Neil K. Aaronson[1], Martijn M. Stuiver[1,14,15,*]

1 Division of Psychosocial Research and Epidemiology, The Netherlands cancer Institute, Amsterdam, The Netherlands
2 Department of Primary Care, NIVEL, Utrecht, The Netherlands.
3 Department of Physiology, Radboudumc, Radboud Institute for Health Sciences, Nijmegen, The Netherlands
4 Exercise Medicine Research Institute, Edith Cowan University, Joondalup, Western Australia
5 Department of Public and Occupational Health and Amsterdam Public Health Research Insitute, Amsterdam University Medical Centres, location VUmc
6 School of Human Movement and Nutrition Sciences, Faculty of Health and Behavioural Sciences, University of Queensland, Brisbane, Australia
7 Division of Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, South Africa

[*] Corresponding author:
Martijn Stuiver, PhD
Division of Psychosocial Research and Epidemiology
The Netherlands Cancer Institute- Antoni van Leeuwenhoek
Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Phone: 31 205122861, Fax: 31 206601449
Email: m.stuiver@nki.nl

[8] School of Public Health, Physiotherapy and Population Sciences, University College Dublin, Dublin, Ireland
[9] Department of Physiotherapy, The Netherlands cancer Institute, Amsterdam, The Netherlands
[10] Department of Medical Oncology, The Netherlands cancer Institute, Amsterdam, The Netherlands
[11] Department of Rehabilitation Medicine, Amsterdam University Medical Centre, Amsterdam, The Netherlands
[12] Rijnstate Hospital, Arnhem, The Netherlands
[13] Department of Health Technology and Services Research, University of Twente, Enschede, the Netherlands
[14] Center for Quality of Life, The Netherlands cancer Institute, Amsterdam, The Netherlands
[15] Center of Expertise Urban Vitality, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, the Netherlands

Abstract

Objective To investigate the construct validity of the Steep Ramp Test by longitudinally comparing the correlation between Maximum Short Exercise Capacity (MSEC) of the Steep Ramp Test (SRT) and direct measurements of VO_2peak during or shortly after treatment in patients with breast cancer and the potential impact of chemotherapy-induced symptom burden

Design Cross-sectional

Setting Multicenter

Participants We used data from two studies that included women with breast cancer treated with chemotherapy, resulting in 274 observations. 161 patients performed the Cardiopulmonary Exercise Test (CPET) and the Steep Ramp Test in two test sessions on different time points around chemotherapy treatment.

Interventions Not Applicable

Main Outcome Measures Fatigue was assessed with the Multidimensional Fatigue Inventory, and nausea and vomiting and pain by the EORTC Quality of Life Questionnaire -Core 30. The longitudinal correlation between the Maximum Short Exercise Capacity and VO_2peak was investigated using a linear mixed model. Interaction terms were added to the model, to investigate whether the correlation varied by symptom burden.

Results We found a statistically significant moderate correlation between VO_2peak and Maximum Short Exercise Capacity (.61, 95% CI; .51– .70, $p < .01$) over time. This correlation was slightly attenuated (-.07, 95% CI; -.13 – .00, $p = .04$) in patients' with chemotherapy-related nausea and vomiting, indicating smaller correlations of VO_2peak with the Maximum Short Exercise Capacity with increasing symptom burden. Pain and fatigue did not significantly modify the correlation.

Conclusion The Steep Ramp Test can only be used as a proxy for changes in aerobic capacity with great caution and with attention for the level of nausea and vomiting.

Abbreviations

CPET – Cardiopulmonary Exercise Test
ECG- Electro Cardio Gram
EORTC QLQ- C30 - European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire – Core30
HR – Heart rate

MFI - Multidimensional Fatigue Inventory
MSEC – Maximum Short Exercise Capacity
NKI – Netherlands Cancer Institute
RPM – Revolutions per minute
SRT – Steep Ramp Test
VO_2peak – Peak Oxygen uptake
WR - Work Rate
W - Watt
min. – minute

Introduction

It has been demonstrated that physical exercise during and shortly after cancer treatment has beneficial effects on a range of outcomes, including physical fitness, fatigue, and quality of life (1, 2). Exercise programs are increasingly offered to patients with cancer. Supervised exercise programs are generally more effective than unsupervised programs in managing treatment side effects (1, 2). Although the reasons for this differential effect are not entirely understood, it is likely related, in part, to higher treatment fidelity, and more challenging (progressive) training (1). To ensure an adequate and effective training stimulus, repeated exercise testing is essential to prescribe the adequate training load, taking into account patient characteristics, including possible physical limitations (3, 4). Several exercise tests can be used for this purpose, with the Cardiopulmonary Exercise Test (CPET) being the gold standard test for cardiorespiratory fitness (5, 6). The CPET has its main purpose as a diagnostic test enabling to identify the exercise limitation and detect potential pathology. However, there are clear drawbacks to using a CPET for repeated measurement of cardiorespiratory fitness for monitoring and aerobic exercise intensity prescription. The CPET requires expensive equipment, trained personnel and maximal effort of patients (7, 8). Therefore, alternative tests are often used in clinical practice. The Steep Ramp Test (SRT) is one of those tests (9) that has been advocated in the context of cancer rehabilitation, due to its high reliability (6), ease of use, and high correlation with peak oxygen uptake (4).

Although the SRT and the CPET measure different aspects of exercise capacity, they are highly correlated (4). The SRT was originally developed for patients with cardiac disease (9) as an alternative to a maximal exercise test, without the need for expensive breathing gas analysis equipment or electrocardiogram (ECG) monitoring, and minimizing cardiac stress. The main outcome of the SRT is the Maximum Short Exercise Capacity (MSEC), which is defined as the highest workload attained. The MSEC is limited by peripheral muscle endurance, and maximal cardiopulmonary load is not achieved during the test. Yet it is assumed that the MSEC reflects patient's cardiorespiratory fitness. Previous studies have shown strong construct validity at the group level between the VO_2peak estimated during the SRT and the VO_2peak measured with the CPET. However, at the level of the individual patient, there is also substantial misclassification of measured VO_2peak (4, 6). Nevertheless, the SRT remains popular in clinical practice as a practical surrogate for the CPET, both for monitoring cardiorespiratory fitness and for exercise prescription.

Given the high test-retest reliability of the SRT (4), it is assumed that, over time, the correlation between VO_2peak and the SRT remains unaltered and concurs with observed cross-sectional correlation. This is important when using the SRT for monitoring of cardiorespiratory fitness over time. This longitudinal relationship has, however, never been investigated empirically. Another issue is that the MSEC may be sensitive to the patients' motivation, due to the short duration, steep increments applied, the assumed higher reliance on anaerobic metabolism, and the lack of an objective criterion to confirm maximal effort (6). This is in contrast to the CPET, where the outcome

is determined by maximal exercise test criteria that lie outside the patient's influence (e.g. attained % of predicted age-specific maximum heart rate; respiratory exchange ratio exceeding a predefined thresholds). The sensitivity to the patients' motivation of the SRT is of particular importance in the context of exercise program prescriptions during and shortly after cancer treatment, since cancer treatment is not only associated with changes in cardiorespiratory fitness, but also with symptoms such as fatigue, nausea and vomiting and pain (10-12).

It is conceivable that the MSEC is affected by symptom burden, which may affect its association with VO_2peak. In clinical practice, this could result in inadequate training for patients. Increased understanding of the impact of symptom burden is important to optimize the monitoring of physical fitness and the subsequent rehabilitation programs during chemotherapy.
Therefore, the first aim of this study was to investigate the correlation of VO_2peak with the SRT outcomes over time in patients with breast cancer during and shortly after treatment. Secondly, we investigated the influence of patients' symptom burden (fatigue, pain and nausea and vomiting) of chemotherapy on this correlation.

Methods

Participants

We combined data from a prospective, clinimetric study among patients with breast cancer (the START study) and data from patients with breast cancer who participated in a randomized controlled exercise trial following cancer treatment (the REACT study). Both studies were approved by the review boards of the hospitals. Data was already collected, so no additional permission needed to be sought. Figure 1 presented an overview of the inclusion criteria and the timing of measurements of the included studies.

[Figure 1]

Sample size consideration

With an expected multiple R2 (assuming 4 linear predictors) of at least 0.25, a sample of 52 unique observations would already suffice to achieve 90% power at an alpha level of 0.05 [G*Power 3.6.1, computer program]. In addition, simulation studies have shown that the number of observations per variable in an (ordinary) linear regression model can be as low as 2 without biasing the regression coefficients and while correctly estimating the confidence intervals (13). This study used already collected repeated measurements from two other studies, in which a total of 166 patients had been included. Thus, the sample size far exceeded the minimum requirements for adequate estimation of the regression coefficients.

Procedure of the REACT study

For the REACT study, patients were recruited from nine Dutch hospitals between 2011 and 2013 (14, 15). Participants were randomized to either a 12-week, high intensity or low- to moderate-intensity exercise program, or a waiting list control group. The Medical Ethics Committee of the Máxima Medical Center approved the study. Full details of the REACT study have been reported elsewhere (14). For the current study, we used VO_2peak values of patients allocated to the 12-week exercise intervention groups obtained during the baseline assessments which took place shortly after completion of primary cancer treatment (T0); and the follow-up data obtained 12 weeks later (T1). The SRT data was collected as part of the exercise intervention during the first and last training session. Consequently, this information was not available for the waitlist control group.

Wiel, H.J. van de, Groen, W.G., Kampshoff, C.S., Buffart, L.M., Mechelen, W. van, Schep, G., Sonke, G.S., Huijsmans, R., Harten, W.H. van, Aaronson, N.K., Stuiver, M.M.The construct validity of the Steep Ramp Test for assessing cardiorespiratory fitness in patients with breast cancer, and the impact of chemotherapy-related symptom burden. Archives of Physical Medicine and Rehabilitation: 2022

Procedure of the START study

For the START study, patients were recruited between December 2013 and May 2016 from the Antoni van Leeuwenhoek (AVL). Patients who were scheduled for (neo)-adjuvant chemotherapy were approached by their treating medical oncologist who provided them with written study information. Procedures were approved by the institutional review board of the NKI (NL44287.031.13 - PTC13.0407/M13SRT), and all patients provided written consent before entering the study. A research assistant contacted interested patients by phone to confirm their eligibility and willingness to participate. For included patients, two testing sessions were planned. Baseline measures (T0) were planned at the beginning of chemotherapy (i.e. before the third cycle of chemotherapy) and at follow-up (T1) around the time of the last cycle of chemotherapy. Each session started with the SRT, as recovery (T1) around the time of the last cycle of chemotherapy. from the SRT is faster compared to the CPET. After at least 20 minutes recovery from the SRT, and verbal confirmation of being fully recovered, participants performed the CPET. The SRT and the CPET were always supervised by two assessors who were thus blinded for the result of the other tests. Participants were instructed not to communicate SRT test results with the supervisor of the CPET. Participants performed the SRT on a calibrated, electronically-braked cycle ergometer (Lode Corival, ProCare, Groningen, The Netherlands). The height of the seat was adjusted to the length of the legs, such that there was a slight bend in the knee when the leg was extended. The participants started with a warm-up phase of three minutes of cycling at 10 Watts (W). After the warm-up phase, they were instructed to maintain a pedaling frequency of between 70 and 80 revolutions per minute^{-1} (RPM), starting at 25 W, after which the load was increased by 2.5 W every second (16). The protocol continued until pedaling cadence dropped below 60 RPM despite strong verbal encouragement. MSEC was defined as the highest attained workload at the point where cadence dropped below 60 RPM.

VO_2peak was measured by a CPET on the same electronically-braked cycle ergometer as the SRT, as attained during an incremental test until maximal volitional exhaustion. The test was supervised by an exercise physiologist. The health status of the participants was carefully checked by a medical oncologist in advance of every test session by a screening list to confirm that the patient could safely participate in maximal exercise testing. Expired gas was analyzed breath-by-breath from a mouthpiece for oxygen (VO_2), carbon dioxide (VCO_2) and volume by the Jaeger Masterscreen CPX (CareFusion, San Diego, United States of America). Electrocardiographic (ECG) activity was continuously monitored with a 12-lead electrocardiogram. The height of the seat was adjusted corresponding to the seat height used during the CPET. Workloads were increased 10, 15 or 20 W/min (depending on the estimated fitness level) until volitional exhaustion, or until a symptom-limitation was achieved. The participants were instructed to cycle at a pedaling frequency between 60 and 80 RPM and were verbally encouraged to continue exercise until exhaustion. The highest oxygen uptake obtained during a 30 second period was defined as the VO_2peak (mL·kg^{-1}·min^{-1}).

Symptom burden

Both studies used a questionnaire to assess the three most common chemotherapy-related physical symptoms in patients with breast cancer that might affect performance on the SRT; general fatigue, pain, and nausea and vomiting (12). Self-reported general fatigue was assessed with a subscale of the Multidimensional Fatigue Inventory (MFI)(17), consisting of 4 items scale range from 4 to 20, with higher scores indicating more fatigue) (17). Self-reported pain and nausea and vomiting were assessed with scales of the European Organization for Research and Treatment of Cancer (EORTC) Questionnaire Quality of Life Questionnaire – Core 30 (QLQ-C30). Both subscales consist of 2

items (18). Scores were linearly converted to a 0 to 100 scale, following the EORTC scoring manual (19). Higher scores indicate a higher symptom burden.

Statistical analyses

Data preparation

Descriptive statistics for the sample were calculated, using means and standard deviation, medians and interquartile ranges, or frequencies and percentages, as appropriate, based on data type and distribution. Data cleaning and analyses were performed in the R statistical package (3.3.1, (20)) using the Rstudio interface (Version 1.1453, 2009-2018, Rstudio Inc., Boston, USA).

Prior to the analyses, we standardized the variables by subtracting the mean and dividing by the standard deviation, to obtain regression coefficients similar to a Pearson correlation coefficient. Linear mixed models were used to investigate the correlation over time between the MSEC as obtained by the SRT and the VO_2peak as assessed by the CPET, using all available observations. All models included a random slope for time since start of chemotherapy (in weeks) per participants, to account for the repeated observations. Furthermore, participants were nested in one of the two studies (i.e., START or REACT) to account for possible clustering effects. Several different models were fitted. Model 1 included the fixed effect for MSEC. In the next step, in different models, the symptom score and an interaction term for MSEC with the symptom score were added for general fatigue (model 2), pain (model 3) or nausea and vomiting (model 4), respectively. In these models, the main effect of the MSEC indicates the correlation of the MSEC with the VO_2peak over time, and the interaction term between MSEC and the symptom score indicates how strongly this correlation is affected by symptom burden. According to Munro, we considered correlations for the main effect between 0.26 to 0.49 to be small, 0.50 to 0.69 moderate, 0.70 to 0.89 high, and 0.90 to 1.00 very high (21). A p-value of <0.05 for the interaction term was considered to indicate a statistically significant effect by symptom burden. A sensitivity analysis per study was performed to investigate the effect of the timing of the measurements.

Results

From the 42 patients who participated in the START study, 27 (60%) patients completed both measurements and 10 (22%) completed one measurement. From 124 participants of the REACT study, 93 (75%) completed both measurements and 31 (25%) a single measurement. Single measurements were the result of participants missing follow-up measurements or not completing a test procedure. Thus, a total of 274 observations was available for analysis. Descriptive statistics of the participants in this merged sample are presented in Table 1.

Without taking symptom burden into account, there was a significant but moderate correlation between VO_2peak and MSEC over time (β= .61; 95% CI= .51 – .70, P < .01), adjusted for study and time since start of chemotherapy. In the subsequent models, nausea and vomiting showed significant but small modification of the correlation of VO_2peak with MSEC (β interaction = -.07, -.13 – .00, P = .04). The other symptoms did not significantly modify the correlation between VO_2peak and MSEC (Table 2). A sensitivity analysis per study showed a stronger effect of fatigue (β interaction = -.11 (.30 : .08) and pain (β interaction = -.10 (-.13 : -.09) during treatment (START) than after treatment (REACT) (β interaction = -.02 (-.12 : .08) and -.02 (-.33 : .12), respectively), although none of the interaction terms were significant.

Discussion

In this study, we observed a significant moderate longitudinal correlation of VO_2peak assessed by a CPET with MSEC assessed by an SRT, in patients with breast cancer who were during or shortly after treatment. This correlation was slightly attenuated in patients with chemotherapy-related nausea and vomiting. While patients with higher levels of fatigue had lower physical fitness, neither fatigue nor pain modified the correlation between VO_2peak and MSEC.

The correlation with VO_2peak observed in our study (0.61) was similar to a previous study from our group (ICC = 0.61)(6) and slightly lower than reported by de Backer et al., who found a correlation of 0.82 (4). While we observed a small effect of nausea and vomiting on the correlation, our hypothesis that pain and fatigue might affect the relationship between MSEC and VO_2peak was not confirmed. This suggests that the impact of symptom burden on exercise testing may not be specific for the SRT, despite its steep increments and emphasis on muscle endurance. As such, this result supports the proposed use of the SRT for monitoring exercise capacity in patients with breast cancer during or shortly after treatment, who may suffer from treatment side effects. However, given the moderate correlation, evaluation of cardiorespiratory fitness should rather be based directly on the MSEC instead of the VO_2peak estimated from the SRT. The MSEC can also be used directly for exercise prescription, for example in high-intensity interval exercise protocols (22). When the MSEC is used to prescribe endurance bouts based on estimated VO_2peak, additional parameters such as the Borg score for perceived exertion could be used to fine-tune the training load (9, 10).

Given the disadvantages of the CPET, in terms of the cost of equipment and trained personnel, and the maximal cardiopulmonary effort required of patients, its applicability for repeated testing in, for example, physical therapy practices is limited. Based on the results of the current study, the dilemma of repeated exercise testing in such clinical settings remains, and further research on other alternative tests is therefore needed. A fixed load endurance test could be a viable alternative to evaluate endurance capacity, as it has been shown to be responsive in an RCT on the effect of training during chemotherapy (10). However, such a test cannot be used easily to guide training load. Previous studies on alternatives for a maximal test have reported that changes in heart rate, at a fixed submaximal workload that requires a heart rate greater than 140 bpm (23), and short protocol submaximal treadmill tests may be feasible alternatives to a CPET in cancer rehabilitation (24) . Recently, submaximal lactate and ventilatory thresholds have also been investigated as potentially useful alternatives for VO_2peak for intensity prescription in breast and prostate cancer survivors after primary treatment (25). However, while this latter approach is more patient-friendly due to its submaximal nature, it still requires specialized equipment. The best approach to evaluate and monitor cardiorespiratory fitness during cancer treatment in clinical practice thus remains a continuing discussion.

Study Limitations

This study has some limitations that should be noted. First, we combined data from two studies. While this enabled us to increase the available sample size, it also introduced heterogeneity with regard to timing of the assessments. START study participants performed the exercise tests at the beginning and end of their chemotherapy, while REACT participants performed them shortly after completion of primary cancer treatment and 12 weeks later. While this enabled us to generalize our findings over a longer period of the treatment continuum, the data at each time points were derived from different participants. We attempted to correct for this by adjusting all of the analyses for study. Second, the time between the two exercise tests was different in both studies. In the REACT study, participants did not complete the two exercise tests on the same day, while participants in START did. However, the time between assessments were generally short (approximately one week),

and a previous study showed that this shortly time difference between assessments did not influence the correlation between VO_2peak and MSEC (9). Third, the small effect of symptom burden may partly be related to the limited variance observed in the symptom scales. Also, approximately 30% of the participants did not have a second assessment. It is possible that these data were not missing at random, but rather due to missed appointments because of high symptom burden. In that case, the results could have been an underestimation. Finally, our study population is limited to patients with breast cancer (26). In terms of generalizability, future research is needed to investigate longitudinal exercise testing in other cancer patient populations as well.

Our study also has several strengths. First, due to the data pooling, we obtained a large sample size with repeated measurements to allow for analysis of longitudinal relationships. Second, to the best of our knowledge, this is the first study to investigate the influence on symptom burden during chemotherapy on the correlation between VO_2peak and the SRT. This is particularly important for clinical practice.

Conclusion

In conclusion, the moderate longitudinal correlation observed between VO_2peak assessed by CPET and MSEC assessed by the SRT measures suggests that changes in MSEC should not be used as proxy for changes in aerobic capacity without great caution and with attention for the level of nausea and vomiting. Additionally, experienced nausea and vomiting, due to chemotherapy treatment in patients with breast cancer appears to affect the correlation, albeit slightly. If physical therapists use the SRT as monitoring test, we would recommend the direct use of the MSEC instead of the VO_2peak estimated from the SRT. During and after chemotherapy, the SRT could still be a useful test to monitor changes in other aspects of physical exercise capacity (e.g. muscle endurance, maximum short workload).

Funding

The START study was financially supported by “Stichting Achmea Gezondheidszorg”.
REACT study was part of the A-CaRe Program, funded by Alpe d’HuZes/ Dutch Cancer Society [Grant number ALPE 2009-4619]

Acknowledgements

We would like to thank Marieke ten Tusscher, Carla Agasi-Idenburg for assisting with the CPETs, and Lisa Vliegendhart and Ilse van Wees for their contributions to study logistics and data collection of the START study.
We wish to thank Karen van der Weiden, Charlotte de Kruif, Joep van Kesteren, Michiel Greidanus, and Julie Heeren for their support in data collection as well as assembly of data of the REACT study.

Disclosers

Dr. van Mechelen reports and For the avoidance of doubt I would like to report that I am:Ñ. Nonexecutive board member of Arbo Unie B.V. (B.V. is Dutch for Ltd.: www.arbounie.nl);Ò. director of Evalua Nederland B.V. (www.evalua.nl)Ûoth companies operate in the Dutch occupational health care market (I am a licensed occupational physician).
Dr. Sonke reports Institutional research support from Astra-Zeneca, Merck, Novartis and Roche outside the submitted work.

Wiel, H.J. van de, Groen, W.G., Kampshoff, C.S., Buffart, L.M., Mechelen, W. van, Schep, G., Sonke, G.S., Huijsmans, R., Harten, W.H. van, Aaronson, N.K., Stuiver, M.M.The construct validity of the Steep Ramp Test for assessing cardiorespiratory fitness in patients with breast cancer, and the impact of chemotherapy-related symptom burden. Archives of Physical Medicine and Rehabilitation: 2022

References

1. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer treatment reviews. 2017;52:91-104. Epub 2016/12/23. doi: 10.1016/j.ctrv.2016.11.010. PubMed PMID: 28006694.
2. Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A Systematic Review of Exercise Systematic Reviews in the Cancer Literature (2005-2017). PM & R : the journal of injury, function, and rehabilitation. 2017;9(9s2):S347-s84. Epub 2017/09/26. doi: 10.1016/j.pmrj.2017.07.074. PubMed PMID: 28942909; PubMed Central PMCID: PMCPMC5679711.
3. Irwin ML, Ainsworth BE. Physical activity interventions following cancer diagnosis: methodologic challenges to delivery and assessment. Cancer investigation. 2004;22(1):30-50. Epub 2004/04/09. doi:10.1081/cnv-120027579. PubMed PMID: 15069762.
4. De Backer IC, Schep G, Hoogeveen A, Vreugdenhil G, Kester AD, van Breda E. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. Archives of physical medicine and rehabilitation. 2007;88(5):610-6. Epub 2007/05/01. doi:10.1016/j.apmr.2007.02.013. PubMed PMID: 17466730.
5. Tran D. Cardiopulmonary Exercise Testing. Methods Mol Biol. 2018;1735:285-95. Epub 2018/01/31. doi: 10.1007/978-1-4939-7614-0_18. PubMed PMID: 29380321.
6. Stuiver MM, Kampshoff CS, Persoon S, Groen W, van Mechelen W, Chinapaw MJM, et al. Validation and Refinement of Prediction Models to Estimate Exercise Capacity in Cancer Survivors Using the Steep Ramp Test. Archives of physical medicine and rehabilitation. 2017;98(11):2167-73. Epub 2017/03/23. doi: 10.1016/j.apmr.2017.02.013. PubMed PMID: 28322759.
7. Vanhees L, Lefevre J, Philippaerts R, Martens M, Huygens W, Troosters T, et al. How to assess physical activity? How to assess physical fitness? European Journal of Cardiovascular Prevention and Rehabilitation. 2005;12(2):102-14.
8. Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. Physical therapy. 2000;80(8):782-807.
9. Meyer K, Samek L, Schwaibold M, Westbrook S, Hajric R, Beneke R, et al. Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. Med Sci Sports Exerc. 1997;29(3):306-12. Epub 1997/03/01. doi: 10.1097/00005768-199703000-00004. PubMed PMID: 9139168.
10. van Waart H, Stuiver MM, van Harten WH, Geleijn E, Kieffer JM, Buffart LM, et al. Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(17):1918-27. Epub 2015/04/29. doi: 10.1200/jco.2014.59.1081. PubMed PMID: 25918291.
11. Courneya KS. Exercise in cancer survivors: an overview of research. Medicine and science in sports and exercise. 2003;35(11):1846-52. Epub 2003/11/06. doi: 10.1249/01.mss.0000093622.41587.b6. PubMed PMID: 14600549.
12. Browall M, Brandberg Y, Nasic S, Rydberg P, Bergh J, Ryden A, et al. A prospective exploration of symptom burden clusters in women with breast cancer during chemotherapy treatment. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2017;25(5):1423-9. Epub 2016/12/17. doi: 10.1007/s00520-016-3527-1. PubMed PMID: 27981366; PubMed Central PMCID: PMCPMC5378737.

13. Austin PC, Steyerberg EW. The number of subjects per variable required in linear regression analyses. J Clin Epidemiol. 2015;68(6):627-36. Epub 2015/02/24. doi: 10.1016/j.jclinepi.2014.12.014. PubMed PMID: 25704724.
14. Kampshoff CS, Buffart LM, Schep G, van Mechelen W, Brug J, Chinapaw MJ. Design of the Resistance and Endurance exercise After ChemoTherapy (REACT) study: a randomized controlled trial to evaluate the effectiveness and cost-effectiveness of exercise interventions after chemotherapy on physical fitness and fatigue. BMC cancer. 2010;10:658. Epub 2010/12/02. doi: 10.1186/1471-2407-10-658. PubMed PMID: 21118564; PubMed Central PMCID: PMCPMC3009679.
15. Kampshoff CS, Chinapaw MJ, Brug J, Twisk JW, Schep G, Nijziel MR, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance exercise After ChemoTherapy (REACT) study. BMC medicine. 2015;13:275. Epub 2015/10/31. doi: 10.1186/s12916-015-0513-2. PubMed PMID: 26515383; PubMed Central PMCID: PMCPMC4625937.
16. Meyer K, Samek L, Schwaibold M, Westbrook S, Hajric R, Lehmann M, et al. Physical responses to different modes of interval exercise in patients with chronic heart failure--application to exercise training. European heart journal. 1996;17(7):1040-7. Epub 1996/07/01. doi: 10.1093/oxfordjournals.eurheartj.a015000. PubMed PMID: 8809522.
17. Smets EMA, Garssen B, Bonke B, De Haes JCJM. The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. Journal of Psychosomatic Research. 1995;39(3):315-25. doi: https://doi.org/10.1016/0022-3999(94)00125-O.
18. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI: Journal of the National Cancer Institute. 1993;85(5):365-76. doi: 10.1093/jnci/85.5.365 %J JNCI: Journal of the National Cancer Institute.
19. Fayers PM AN, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). European Organisation for Research and Treatment of Cancer, Brussels. 2001.
20. RstudioTeam. RStudio: Integrated Development for R. RStudio, Inc, Boston, MA. 2018;http://www.rstudio.com/.
21. Munro BH. Statistical Methods for Health Care Research: Lippincott Williams & Wilkins; 2005.
22. De Backer IC, Van Breda E, Vreugdenhil A, Nijziel MR, Kester AD, Schep G. High-intensity strength training improves quality of life in cancer survivors. Acta Oncol. 2007;46(8):1143-51. Epub 2007/09/14. doi: 10.1080/02841860701418838. PubMed PMID: 17851864.
23. May AM, van Weert E, Korstjens I, Hoekstra-Weebers JE, van der Schans CP, Zonderland ML, et al. Monitoring training progress during exercise training in cancer survivors: a submaximal exercise test as an alternative for a maximal exercise test? Archives of physical medicine and rehabilitation. 2010;91(3):351-7. Epub 2010/03/20. doi: 10.1016/j.apmr.2009.11.018. PubMed PMID: 20298823.
24. Kirkham AA, Neil-Sztramko SE, Morgan J, Hodson S, Weller S, McRae T, et al. Health-related physical fitness assessment in a community-based cancer rehabilitation setting. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2015;23(9):2525-33. Epub 2015/01/27. doi: 10.1007/s00520-014-2599-z. PubMed PMID: 25617069.
25. Schneider J, Schlüter K, Sprave T, Wiskemann J, Rosenberger F. Exercise intensity prescription in cancer survivors: ventilatory and lactate thresholds are useful submaximal alternatives to VO(2peak). Supportive care in cancer : official journal of the Multinational Association of

Supportive Care in Cancer. 2020;28(11):5521-8. Epub 2020/03/16. doi: 10.1007/s00520-020-05407-y. PubMed PMID: 32173766.

26. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2012;37(5):390-2. Epub 2012/11/21. doi: 10.1111/coa.12015. PubMed PMID: 23164265.z

Tables and figures

Figure 1 Inclusion criteria and the timing of measurements of the included studies

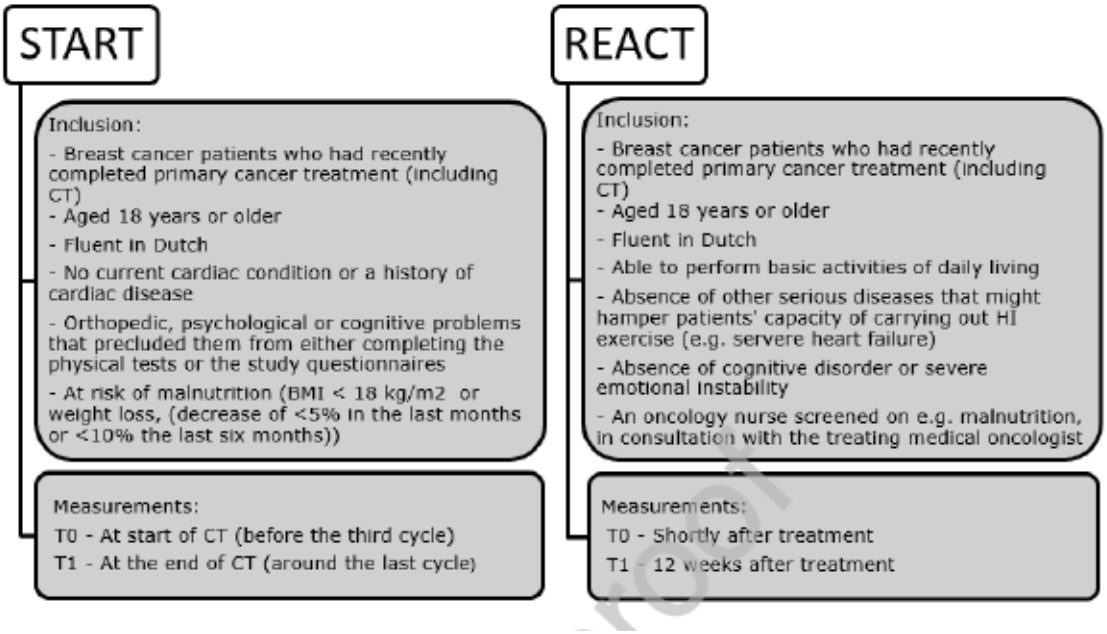

Table 1 Descriptive statistics

	At start of chemotherapy *START T0 N= 37*	***Shortly after treatment*** *START T1 + REACT T0 N= 161*	***12 weeks after treatment*** *REACT T1 N= 124*
Age *(years) (mean, SD)*	45.9 (9.8)	50.5 (10.1)	51.7 (9.9)
Time since start chemotherapy, in weeks *(median, IQR)*	2.5 (1 – 5)	24.5 (19 – 31)	40 (34 – 47)
MSEC *(median, IQR)*	258.5 (234.2 – 282.2)	225.0 (195.8 – 255.0)	235.0 (202 – 270)
VO_2peak, ml/min *(median, IQR)*	1811.0 (1581.0 – 1972.5)	1719 (1475.0 – 1920.0)	1755 (1615.0 – 1997.5)
VO_2peak, ml/kg/min *(median, IQR)*	24.2 (20.9 – 27.8)	20.7 (17.5 – 23.7)	21.4 (18.8 – 25.4)
General Fatigue* *(median, IQR)*	12 (9 – 15)	13 (10 – 16)	12 (9 – 14)
Pain *(median, IQR)*	0 (0 – 33)	16.7 (0 – 33.3)	16.67 (0 – 33.3)
Nausea and Vomiting *(median, IQR)*	0 (0 – 17)	0 (0 - 0)	0 (0 – 0)

*** scores range from 4 to 20. ** scores range from 0 to 100.**

Table 2 Models on Symptom Burden

Variable	***Beta***	***95% CI for Beta***	***P- value***
	VO_2peak		
Model 1 – Crude			
MSEC (W)	.61	.51 – .70	**< .01**
Model 2 – Pain			
MSEC (W)	.59	.50 – .69	**< .01**
Pain	-.09	-.18 – .00	.04
Time	.00	-.01 – .02	.09
*MSEC * Pain*	-.01	-.10 – .07	.76
Model 3 – Fatigue			
MSEC (W)	.56	.46 – .67	**< .01**
Fatigue	-.11	-.20 – -.02	.02
Time	.00	-.01 – .01	1.0
*MSEC * Fatigue*	-.01	-.09 – .07	.79
Model 4 – Nausea and Vomiting			
MSEC (W)	.61	.51 – .71	**< .01**
Nausea and Vomiting	-.04	-.14 – .07	.48
Time	.00	-.01 – .02	.96
*MSEC * Nausea and Vomiting*	-.07	-.13 – .00	**.04**