High intensity or low-to-moderate intensity exercise after chemotherapy:

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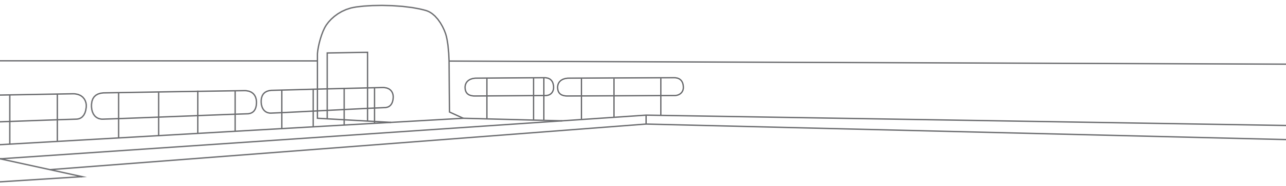
CHAPTER 9

General discussion



GENERAL DISCUSSION

The first and main research objective of this thesis was to evaluate the effectiveness and cost-effectiveness of a 12-week high intensity (HI) and low-to-moderate intensity (LMI) exercise intervention in cancer survivors who completed primary cancer treatment including chemotherapy. Furthermore, we tested the underlying hypothesis that exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and consequently improving global quality of life (QoL) and physical function. Finally, to facilitate implementation, we studied demographic, clinical, psychosocial and environmental factors associated with participation in and adherence to exercise programs in cancer survivors, and with daily physical activity (PA), aiming to identify intervention targets as well as subgroups at highest need for improving exercise and PA. This general discussion will start with a summary of the main findings of this thesis. Furthermore, methodological issues related to the studies will be discussed, as well as the clinical implications and suggestions for future research.

MAIN FINDINGS

Effectiveness and cost-effectiveness of exercise after completion of primary cancer treatment

Compared to a waiting list control (WLC) group, both HI and LMI exercise resulted in significant and clinically meaningful improvements in cardiorespiratory fitness, reductions in fatigue and improved health-related quality of life (HRQoL) in cancer survivors who completed cancer treatments including chemotherapy (Chapter 3). Moreover, a head-to-head comparison between HI and LMI exercise showed a potential dose-response relationship regarding exercise intensity for cardiorespiratory fitness (i.e., peak oxygen uptake (peakVO_2)), favoring HI over LMI exercise, but not for fatigue. Furthermore, compared to WLC, improved physical function was found after HI and LMI exercise, improved global QoL and reduced anxiety after HI exercise, and less problems at work after LMI exercise. Chapter 4 found support for the hypothesis that a 12-week resistance and endurance exercise program improved cardiorespiratory fitness, leading to lower physical fatigue, and consequently to higher global QoL and physical function, illustrating the importance of improving cardiorespiratory fitness.

At 64 weeks follow-up (Chapter 5), gain in cardiorespiratory fitness after the 12-week intervention was successfully maintained, but there was no significant difference between HI and LMI exercise. Furthermore, in both HI and LMI exercise, general and physical fatigue returned to their baseline levels, and differences between exercise groups were statistically not significant. Finally, at 64 weeks follow-up, improvements in global QoL and physical function tended to be larger for HI than for LMI exercise.

In the Netherlands, the informal societal willingness-to-pay threshold ranges from €20,000 per Quality Adjusted Life Years (QALY) to €80,000 per QALY depending on the severity of a disease. The probability that HI exercise was cost-effective compared to LMI exercise analyzed from a Dutch societal perspective ranged from 0.91 at €20,000 per QALY to 0.95 at €52,000 per QALY, and therefore, HI exercise should be considered as being cost-effective compared to LMI exercise (Chapter 5). However, the willingness-to-pay thresholds were not reached for cardiorespiratory fitness, hand-grip strength and general fatigue.

Adherence to and participation in exercise

The systematic literature review presented in Chapter 6 showed that exercise history was significantly associated with adherence to exercise interventions. Other important demographic, clinical, psychosocial and environmental correlates of exercise adherence could not be distinguished due to the limited number of studies, the inconsistency of findings across the studies, and variations in the definition of adherence. In the study described in Chapter 7 we found that psychosocial factors, such as lower psychological distress and higher self-efficacy were significantly associated with better exercise adherence in HI exercise, but not in LMI exercise. Furthermore, cancer survivors who attained a higher level of education were non-smokers, perceived less psychological distress, had higher outcome expectations regarding exercise participation and perceived more exercise barriers. They were also more likely to participate in a randomized controlled trial (RCT) evaluating effects of a combined resistance and endurance exercise program. The research described in Chapter 8 showed that female breast cancer survivors who were younger, reported lower body mass index scores, higher self-efficacy scores or higher social support from family and friends were more likely to be physically active.

METHODOLOGICAL CONSIDERATIONS

In this thesis, various study designs were used to answer our study questions. Each chapter contains a discussion of the methodological issues related to the specific study design in that particular chapter. Here, we will discuss some general methodological considerations of this thesis.

Study population, participation rate and generalizability

The Resistance and Endurance exercise After ChemoTherapy (REACT) study was a prospective multicenter RCT in which participants were recruited from nine hospitals in the Netherlands. The eligibility criteria included as many as six cancer diagnoses (primary breast, colon, ovarian, cervix and testis cancer, or lymphomas). Although a mixed group of cancer survivors were recruited, breast cancer survivors represented 65% of the study population, while 1-18% participants represented the other cancer types. As a consequence, there was not sufficient statistical power to explore whether patients with other cancer types responded different to exercise.

The participation rate in the REACT study was 37%, which is in line with previous RCTs evaluating the effects of exercise interventions in cancer survivors [1,2]. The most frequently reported reason for non-participation was having too many things on one's mind (Chapter 7), which is a common finding in cancer survivors shortly after completion of primary cancer treatments [3]. Perhaps cancer survivors who lack a history of sports or exercise might become overwhelmed with a schedule of twice per week supervised exercise sessions shortly after cancer treatments. However, sport history and current PA level did not differ between the participants and non-participants of the REACT study. Yet, assessments of sport history and current PA level relied on self-report measures, which are prone to either over- or under-estimation due to inaccurate recall, social desirability and misinterpretation of the survey questions [4].

The low response rates may hamper the generalizability of the study findings. However, no significant differences in age, gender and cancer type were found between participants and non-participants, supporting generalizability. Though, cancer survivors who attained a lower or intermediate level of education, were smokers, perceived more psychological distress, had lower outcome expectations or perceived less exercise barriers were less likely to participate in the REACT study. Therefore, one should be cautious to generalize the results from the REACT study to all cancer survivors treated with chemotherapy.

Study designs and statistical power

Different study designs were conducted to address the three primary research objectives of this thesis. First, a RCT was conducted to evaluate the (cost-) effectiveness of HI and LMI exercise compared with WLC group on physical fitness, fatigue and HRQoL. An RCT is considered the most rigorous study design to evaluate the effectiveness of interventions, as it controls for selection bias and confounding [5]. While setting up the REACT study (Chapter 2), the availability of cancer rehabilitation groups in clinical practices increased rapidly in the

Netherlands, and the Dutch guideline for cancer rehabilitation [6] and the international PA guidelines for cancer survivors [7] were developed. Both emphasize the importance of exercise during and after cancer treatments. To limit non-participation and minimize the possibility of contamination (i.e., undertaking supervised exercise on a person's own initiative) whilst allowing optimal care for all participants, a WLC group was included, instead of a 'true' non-exercising control group. Despite these advantages, the WLC group hampered the evaluation of longer-term effectiveness, because all participants had received the 12-week intervention at 64 weeks follow-up. In addition, patients may have been disappointed when they were assignment to a WLC group, which may have caused patients to belief that they would not improve as quickly as possible, and thereby slowing down natural recovery or increase the risk for contamination [8]. Yet, in the REACT study, the WLC group showed natural recovery on most outcomes (Chapter 3, Table 4), and contamination rates were low (8%). Therefore, it seems unlikely that the intervention effects were either overestimated or underestimated as a result of the choice for a WLC group.

A priori power calculations based on a previous uncontrolled trial evaluating the effectiveness of a HI resistance and endurance exercise program in 119 cancer survivors post-treatment [9], estimated a total sample size of 280 participants on peakVO_2 as primary outcome measure. Although statistically powered to show a main intervention effect on peakVO_2 (Chapter 3 and 5), the between-group differences on peakVO_2 for HI and LMI exercise were smaller than anticipated and therefore we may have failed to show statistical significance.

Second, mediation analyses were conducted to identify which exercise intervention components (e.g., muscle strength, cardiorespiratory fitness) were most relevant for reducing fatigue and consequently improving HRQoL (Chapter 4). Studying causal mechanisms underlying intervention effects requires data from a well-designed RCT, including a relatively large sample size. Despite using a RCT design, the mediator variables and the outcome variables were assessed at the same time-points, and therefore, inferences about causality between mediators and outcome variables could not be made.

Third, a cross-sectional study design was used to identify correlates of participation in a combined resistance and endurance exercise program and daily PA, however, this type of study design is limited in its ability to draw conclusions about causality. Nevertheless, studying associations in cross-sectional studies may help to generate hypotheses for future research [10] which are useful in the development of targeted interventions to improve exercise participation and PA levels, and consequently improving outcomes.

Primary outcome measures

The REACT study is one of four RCTs included in the Alpe d'HuZes Cancer Rehabilitation (A-CaRe) clinical research program [11]. All RCTs within A-CaRe were based on a similar conceptual model in which increasing physical fitness and reducing fatigue were both expected to improve HRQoL. The primary and secondary outcome measures were carefully chosen, based on the International Classification of Functioning, Disability and Health (ICF), and the validity and reliability of the instrumentation was established [11].

PeakVO$_2$ was measured during a maximal exercise test, including a continuous gas exchange analysis and electrocardiography monitoring. Such a test is widely acknowledged as the gold standard for assessing cardiorespiratory fitness [12]. Furthermore, a maximum exercise test in cancer survivors provides important diagnostic information before the start of an exercise program [13] and could detect cardiac or pulmonary toxicities resulting from chest irradiation or chemotherapeutic agents, such as anthracyclines [14] and bleomycin [15]. However, there might be a difference in responsiveness between maximal and submaximal exercise testing. Because submaximal exercise testing assesses functional capacity more directly, larger improvements may be detected following training, representing a lower physical strain during the same absolute level of daily activities and decreased dependence on anaerobic metabolism [16]. Nonetheless, the international guidelines on cardiopulmonary testing recommend that clinical studies in exercise oncology should aim to include a maximum exercise test when possible, particularly given the wealth of clinical information it can obtain [17].

Upper body muscle strength and lower body function were assessed using a hand-grip dynamometer and the 30-seconds chair-stand test, both established as valid outcome measures [18,19]. Whereas the indirect 1-RM tests, conducted by the physiotherapists to evaluate training progress, showed 37% improvements on the leg press and 34% improvements on the vertical row, no significant intervention effects were found on hand-grip strength or lower body function. Perhaps the hand-grip strength and 30-seconds chair-stand test might have been limited to detect changes [20,21]. Therefore, in future studies, it would be worthwhile to consider using outcome measures that more directly assess the strength of targeted muscle groups, and therefore are more likely to detect changes. For example, a handheld dynamometer is a user-friendly tool for clinical practice, and is able to measure muscle strength of various upper and lower body muscles [1].

Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI), specially designed for use in clinical trials focusing on cancer survivors and the psychometric properties are well documented [22]. Although, both exercise interventions achieved significant and clinically meaningful reductions in general and physical fatigue at 12 weeks follow-up, the exercise-induced benefits were not maintained at 64 weeks follow-up. The lack of longer-term effects may suggest that cancer survivors gain more confidence in managing cancer and treatment-related problems during supervised exercise program. However, when chores of everyday life resume and supervision and support from a physiotherapist is finished, one may struggle to remain confident, particularly in the self-management of fatigue [23]. On the other hand, while evaluating fatigue in a longitudinal study design, the possibility of a "response shift", defined as a recalibration of a participant's internal standard used to judge one's current fatigue experience, should also be taken into account [24]. Fatigue is a subjective outcome based on self-report, and the internal standard of fatigue perception may change throughout the cancer trajectory [24]. To gain a better understanding how exercise-induced benefits on fatigue can successfully be maintained on the longer term, future studies are warranted to identify mediators of the exercise intervention effects on fatigue.

CLINICAL IMPLICATIONS

Supervised HI and LMI exercise shortly after completion of cancer treatment is safe and superior to natural recovery on cardiorespiratory fitness, fatigue and HRQoL. We therefore recommend implementation of exercise as part of standard cancer care. HI exercise may be preferred to LMI exercise when aiming to improve peakVO_2 levels in cancer survivors, because some indication for a dose-response relationship was found. Improving cardiorespiratory fitness of cancer survivors is particularly important because, compared to reference values of healthy adults, their peakVO_2 levels were "very poor", which increases the risk of reduced ability to carry out activities of daily living [25]. Therefore, a 5-10% gain in peakVO_2 from supervised exercise can be of great clinical importance for the individual patient. Moreover, results from observational studies showed a positive association between peakVO_2 and survival [26], but causality needs to be established.

Further, HI exercise may also be preferred over LMI exercise when aiming to improve HRQoL. Yet, decisions about implementation of exercise programs as standard and reimbursed cancer care are not only guided by their effectiveness on health outcomes, but also by their additional costs in relation to these effects (i.e., cost-effectiveness) [27]. In line with the results on HRQoL, HI exercise was cost-effective in terms of QALY compared to LMI exercise, mostly due to lower medical costs.

Studying correlates of adherence may identify intervention targets to further improve adherence. The finding that higher self-efficacy was significantly associated with high session attendance and high compliance with endurance exercises, and lower psychological distress was significantly associated with high compliance with resistance exercises in HI exercise, but not in LMI exercise, suggests that an individual's self-efficacy and distress levels are important characteristics while accomplishing a HI exercise program. Therefore, for improving adherence rates, additional programs may be required for patients with low self-efficacy and/or high distress. Cognitive behavioral techniques, such as motivational interviewing [28] and goal setting [29], could be included to improve self-efficacy and may support cancer survivors in achieving their exercise goals. Hence, patients with lower self-efficacy or higher psychological distress could also be recommended to start with LMI exercise, and -after gaining further confidence in exercise- the exercise intensity could gradually increase over time [30].

The Dutch evidence-based guideline "Cancer rehabilitation" published in 2011 [31], underlined the recommendations of the international exercise guidelines for cancer survivors (i.e., being as physically active as their abilities and conditions allow and avoid being physically inactivity [7]) and included a structured action plan for all disciplines involved in cancer care. Health care professionals (i.e., medical specialist, (specialized) nurse, and/or general practitioner) are appointed to screen cancer survivors on cancer and treatment-related problems, such as fatigue, psychological distress and reduced physical function. Furthermore, the guideline differentiates between single and multiple or complex cancer and treatment-related problems, and informs health care professionals whether survivors should be referred to either monodisciplinary or multidisciplinary care. Most likely, the majority of the cancer survivors with a request for assistance report a single problem suggesting monodisciplinary care, such as supervised exercise to be sufficient. Based on the results of the REACT study, HI and LMI exercise should be considered as effective monodisciplinary strategy to improve cardiorespiratory fitness, fatigue and HRQoL in cancer survivors after completing primary treatments.

FUTURE RESEARCH

To further optimize effectiveness and efficiency of exercise programs for cancer survivors, it is necessary to move away from current one-size fits all approaches and to develop targeted interventions that meet the capabilities, characteristics and needs of cancer survivors. This requires more insight into optimal exercise prescriptions, as well as moderators and mediators of intervention effects.

Optimal exercise prescription

Exercise prescriptions should include specific guidelines on four main parameters; frequency, intensity, type and duration of exercise (i.e., exercise FITT parameters). However, at present, exercise prescriptions for cancer survivors are rather generic. The REACT study was the largest RCT to date that primarily evaluated the effects of different exercise intensities after completion of primary cancer treatments. Two previous RCTs evaluated the effects of different exercise types [32] and doses [2] in breast cancer survivors during chemotherapy and reported that the effect of aerobic exercises on peakVO_2 was superior to a resistance exercises, whereas, the effect of the resistance exercises on upper and lower body muscle strength was superior to the aerobic exercises [32]. Further, higher exercise doses (3 times 60 minutes per week at moderate-to-high intensity) resulted in significantly better physical function and less symptoms, compared to standard doses (3 times 30 minutes per week at moderate-to-high intensity) [2]. In order to define the optimal exercise prescription for cancer survivors, additional head-to-head comparisons on the FITT parameters are needed to further detangle their effects on a given outcome, for a given cancer type, in a particular phase of the cancer trajectory (e.g., during treatment, after treatment, end of life [33]).

Moderators of exercise intervention effects

Furthermore, to maximize benefits of interventions for the individual, it is important to determine which exercise program works, for whom, and under what circumstances (i.e., moderators of intervention effects [34]). Moderators identify subgroups of cancer survivors that are most responsive to certain exercise programs, and those that are less responsive [35]. In the REACT study, larger intervention effects on peakVO_2 of both interventions were found for younger participants (Chapter 3). Additionally, the intervention effects of HI exercise on global QoL were larger for younger participants and for participants with breast cancer, compared to other types of cancer, and women showed larger improvements after HI exercise in global QoL and physical function than men (Chapter 3). Few previous studies found that demographic (e.g., age [36], marital status [36,37]) and clinical variables (e.g., treatment type [37,38]) moderate the physical exercise effects on HRQoL in cancer survivors. Hence, none of the forgoing studies (including the REACT study) were designed or powered to analyze moderating effects and to conduct subsequent stratified analyses. Aiming to overcome these limitations, the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study [39] was launched in which individual patient data from RCTs evaluating the effects of PA and/or psychosocial interventions exercise on HRQoL in cancer survivors are pooled to identify moderators of intervention effects. Identifying patient subgroups at highest need for improving exercise and PA, enables health care professionals to target subgroups in the cancer population more efficiently.

Mediators of exercise intervention effects

Finally, conducting targeted interventions requires a good understanding of the mediators (i.e., working mechanisms) underlying the exercise intervention effects on fatigue and HRQoL in cancer survivors. The REACT study found support for the hypothesis that a 12-week resistance and endurance exercise program improves cardiorespiratory fitness, leading to lower physical fatigue, and consequently to higher global QoL and physical function (Chapter 4). However, cardiorespiratory fitness did not mediate the intervention effect on general fatigue, which was in line with previous studies [40,41]. Because general fatigue comprises physical as well as mental aspects, only improving cardiorespiratory fitness might not be sufficient and concepts other than or additional to cardiorespiratory fitness should be taken into account when aiming to reduce general fatigue. Forgoing research in cancer survivors reported that the exercise effects on fatigue may be mediated by psychosocial factors, such as reduced sleep quality, psychological distress and self-efficacy [40,42]. The importance of self-efficacy in relation to fatigue has been acknowledged in earlier reports among cancer survivors [42,43] and may suggest a role for behavior change theories, such as social cognitive theory in developing interventions for cancer survivors. In addition to psychosocial working mechanisms, biological factors (e.g., function of immune and metabolic systems) and physiological factors (e.g., neuromuscular function) may mediate the effect of PA and exercise on relevant health outcomes, including fatigue and HRQoL [44]. Future studies that further investigate the mediating role of psychosocial, biological and physiological factors on exercise intervention effects of health outcomes may successfully identify the critical intervention components, and therefore, be a support in building and refining (cost-)effective exercise programs for cancer survivors.

Physical activity assessments

In addition to the ultimate aim to optimize the effectiveness and efficiency of exercise programs and provide targeted interventions, PA assessments in cancer survivors require further investigation as well. The outcome measures for PA in the REACT study included self-reported PA using the Physical Activity Scale for the Elderly questionnaire (PASE) and objectively measured PA using accelerometers. Although, self-reported measures of PA are widely used, these instruments are prone to to either over or under-estimation due to inaccurate recall, social desirability and misinterpretation of the survey questions [4]. Objective PA monitoring using accelerometers overcomes these limitations and provides a more valid estimate of PA. An accelerometer measures vertical accelerations that are converted into activity counts per minute (cpm; sum of counts for y-axis, divided by valid wear time). Based on the continuous data derived from the accelerometers, multivariable linear regression analyses were conducted to evaluate the effectiveness of HI and LMI exercise compared to WLC group (Chapter 3 and 5) on PA, and to identify possible correlates of PA (Chapter 8). However, more often, count cut-points are applied in objective PA monitoring, categorizing the counts into sedentary time, and light, moderate and vigorous intensity PA [45]. These cut-points have been validated in the general population [45], which generally have a higher fitness level, and may therefore be less appropriate for cancer survivors. Future research should explore the validity of these accelerometer cut-points in cancer survivors. A more accurate estimate of PA provides more precise estimates of intervention effects as well as associations with potential determinants.

CONCLUSION

This thesis showed that exercise interventions can improve cardiorespiratory fitness, reduce fatigue and enhance HRQoL in cancer survivors who recently completed treatment with curative intent, including chemotherapy. Our results advocate the implementation of exercise as part of standard cancer care for cancer survivors. Moreover, the current thesis provides several directions to optimize exercise programs. First, when offering exercise programs aiming to improve peakVO_2 and HRQoL among cancer survivors, HI exercise may be preferred. Second, cancer survivors who attained a higher level of education were non-smokers, perceived less psychological distress, had higher outcome expectations and perceived more exercise barriers; they were also more likely to participate in a combined resistance and endurance exercise trial. This finding is worth acknowledging when promoting exercise participation as part of cancer care. Third, several demographic, clinical and psychosocial factors were found to be significantly associated with exercise adherence in which psychosocial factors, such as psychological distress and self-efficacy, were more strongly associated with HI than LMI exercise. When offering HI exercise, it may therefore be recommended to screen these variables and if needed, include additional behavioral motivational strategies or consider starting at a lower training intensity.

REFERENCES

1. 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. J Clin Oncol 2015, 33: 1918-1927.
2. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Friedenreich CM, Yasui Y et al.: Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. J Natl Cancer Inst 2013, 105: 1821-1832.
3. van Waart H, van Harten WH, Buffart LM, Sonke GS, Stuiver MM, Aaronson NK: Why do patients choose (not) to participate in an exercise trial during adjuvant chemotherapy for breast cancer? Psychooncology 2015.
4. Harris TJ, Owen CG, Victor CR, Adams R, Ekelund U, Cook DG: A comparison of questionnaire, accelerometer, and pedometer: measures in older people. Med Sci Sports Exerc 2009, 41: 1392-1402.
5. Akobeng AK: Understanding randomised controlled trials. Arch Dis Child 2005, 90: 840-844.
6. Integraal Kankercentrum Nederland: Richtlijn Oncologische revalidatie. www oncoline nl/oncologische-revalidatie 2011.
7. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM et al.: American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010, 42: 1409-1426.
8. Mohr DC, Spring B, Freedland KE, Beckner V, Arean P, Hollon SD et al.: The selection and design of control conditions for randomized controlled trials of psychological interventions. Psychother Psychosom 2009, 78: 275-284.
9. Buffart LM, De Backer IC, Schep G, Vreugdenhil A, Brug J, Chinapaw MJ: Fatigue mediates the relationship between physical fitness and quality of life in cancer survivors. J Sci Med Sport 2013, 16: 99-104.
10. Mann CJ: Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J 2003, 20: 54-60.
11. Chinapaw MJ, Buffart LM, van Mechelen W, Schep G, Aaronson NK, van Harten WH et al.: Alpe d'HuZes Cancer Rehabilitation (A-CaRe) Research: Four Randomized Controlled Exercise Trials and Economic Evaluations in Cancer Patients and Survivors. Int J Behav Med 2012, 19: 143-156.
12. Steins Bisschop CN, Velthuis MJ, Wittink HM, Kuiper K, Takken T, van der Meulen WJTM et al.: Cardiopulmonary exercise testing in cancer rehabilitation. A systematic review. Sports Med 2012, 42: 367-379.
13. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF et al.: Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010, 122: 191-225.
14. Truong J, Yan AT, Cramarossa G, Chan KK: Chemotherapy-induced cardiotoxicity: detection, prevention, and management. Can J Cardiol 2014, 30: 869-878.
15. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. Eur Respir J 1997, 10: 2662-2689.
16. Larsen AI, Aarsland T, Kristiansen M, Haugland A, Dickstein K: Assessing the effect of exercise training in men with heart failure; comparison of maximal, submaximal and endurance exercise protocols. Eur Heart J 2001, 22: 684-692.
17. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS: Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncol 2008, 9: 757-765.
18. Bohannon RW: Hand-grip dynamometry provides a valid indication of upper extremity strength impairment in home care patients. J Hand Ther 1998, 11: 258-260.

19. Rikli RE, Jones CJ: Development and validation of a functional fitness test for community-residing older adults. J Aging Phys Activity 1999, 7: 129-161.

20. Lamers I, Kelchtermans S, Baert I, Feys P: Upper limb assessment in multiple sclerosis: a systematic review of outcome measures and their psychometric properties. Arch Phys Med Rehabil 2014, 95: 1184-1200.

21. Baruth M, Wilcox S, Wegley S, Buchner DM, Ory MG, Phillips A et al.: Changes in physical functioning in the Active Living Every Day program of the Active for Life Initiative(R). Int J Behav Med 2011, 18: 199-208.

22. Smets EM, Garssen B, Bonke B, de Haes JC: The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995, 39: 315-325.

23. Foster C, Breckons M, Cotterell P, Barbosa D, Calman L, Corner J et al.: Cancer survivors' self-efficacy to self-manage in the year following primary treatment. J Cancer Surviv 2015, 9: 11-19.

24. Andrykowski MA, Donovan KA, Jacobsen PB: Magnitude and correlates of response shift in fatigue ratings in women undergoing adjuvant therapy for breast cancer. J Pain Symptom Manage 2009, 37: 341-351.

25. Paterson DH, Cunningham DA, Koval JJ, St Croix CM: Aerobic fitness in a population of independently living men and women aged 55-86 years. Med Sci Sports Exerc 1999, 31: 1813-1820.

26. Schmid D, Leitzmann MF: Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. Ann Oncol 2014.

27. van Dongen JM, van Wier MF, Tompa E, Bongers PM, van der Beek AJ, Van Tulder MW et al.: Trial-based economic evaluations in occupational health: principles, methods, and recommendations. J Occup Environ Med 2014, 56: 563-572.

28. Bennett JA, Lyons KS, Winters-Stone K, Nail LM, Scherer J: Motivational interviewing to increase physical activity in long-term cancer survivors: a randomized controlled trial. Nurs Res 2007, 56: 18-27.

29. Michie S, Abraham C, Whittington C, McAteer J, Gupta S: Effective techniques in healthy eating and physical activity interventions: a meta-regression. Health Psychol 2009, 28: 690-701.

30. May AM, van Weert E, Korstjens I, Hoekstra-Weebers JE, van der Schans CP, Zonderland ML 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: 825-834.

31. van den Berg JP, Velthuis MJ, Gijssen BCM, Lindeman E, van der Pol MA, Hillen HFP: Richtlijn 'Oncologische revalidatie' [Guideline cancer rehabilitation]. Ned Tijdschr Geneeskd 2011, 155.

32. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM 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: 4396-4404.

33. Courneya KS: Physical activity in cancer survivors: a field in motion. Psychooncology 2009, 18: 337-342.

34. Buffart LM, Galvao DA, Brug J, Chinapaw MJ, Newton RU: Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. Cancer Treat Rev 2014, 40: 327-340.

35. Bauman AE, Sallis JF, Dzewaltowski DA, Owen N: Toward a better understanding of the influences on physical activity: the role of determinants, correlates, causal variables, mediators, moderators, and confounders. Am J Prev Med 2002, 23: 5-14.

36. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Reid RD, Friedenreich CM et al.: Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy: a randomized controlled trial. Cancer 2008, 112: 1845-1853.

37. Buffart LM, Newton RU, Chinapaw MJ, Taaffe DR, Spry NA, Denham JW et al.: The effect, moderators, and mediators of resistance and aerobic exercise on health-related quality of life in older long-term survivors of prostate cancer. Cancer 2015, 121: 2821-2830.

38. Kalter J, Buffart LM, Korstjens I, van Weert E, Brug J, Verdonck-de Leeuw IM et al.: Moderators of the effects of group-based physical exercise on cancer survivors' quality of life. Support Care Cancer 2015, 23: 2623-2631.

39. Buffart LM, Kalter J, Chinapaw MJ, Heymans MW, Aaronson NK, Courneya KS et al.: Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS): rationale and design for meta-analyses of individual patient data of randomized controlled trials that evaluate the effect of physical activity and psychosocial interventions on health-related quality of life in cancer survivors. Syst Rev 2013, 2: 75.

40. Rogers LQ, Vicari S, Trammell R, Hopkins-Price P, Fogleman A, Spenner A et al.: Biobehavioral factors mediate exercise effects on fatigue in breast cancer survivors. Med Sci Sports Exerc 2014, 46: 1077-1088.

41. Buffart LM, Galvao DA, Chinapaw MJ, Brug J, Taaffe DR, Spry N et al.: Mediators of the resistance and aerobic exercise intervention effect on physical and general health in men undergoing androgen deprivation therapy for prostate cancer. Cancer 2014, 120: 294-301.

42. Buffart LM, Ros WJ, Chinapaw MJ, Brug J, Knol DL, Korstjens I et al.: Mediators of physical exercise for improvement in cancer survivors' quality of life. Psychooncology 2014, 23: 330-338.

43. Foster C, Breckons M, Cotterell P, Barbosa D, Calman L, Corner J et al.: Cancer survivors' self-efficacy to self-manage in the year following primary treatment. J Cancer Surviv 2015, 9: 11-19.

44. Buffart LM, Galvao DA, Brug J, Chinapaw MJ, Newton RU: Evidence-based physical activity guidelines for cancer survivors: Current guidelines, knowledge gaps and future research directions. Cancer Treat Rev 2013.

45. Matthew CE: Calibration of accelerometer output for adults. Med Sci Sports Exerc 2005, 37: S512-S522.