Physical exercise during adjuvant chemotherapy
van Waart, H.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 8

General discussion
In the previous chapters we described the Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES), a randomized controlled trial in patients undergoing adjuvant chemotherapy. We gained insight into the effectiveness, cost-effectiveness, participation and adherence to a home-based, low-intensity physical activity program (Onco-Move) and a supervised, moderate-to-high intensity, combined resistance and aerobic exercise program (OnTrack). Different aspects of health were studied; physical fitness, fatigue, psychosocial well-being, side effects and treatment efficacy. This chapter discusses the study results, some methodological considerations and implications for further research.

MAIN FINDINGS

During treatment with chemotherapy for breast cancer, Onco-Move and OnTrack resulted in less decline in cardiorespiratory fitness, better physical functioning, less nausea and vomiting and less pain compared with Usual Care. OnTrack also resulted in better outcomes for muscle strength and physical fatigue. At the 6-month follow-up, most outcomes returned to baseline levels for all three groups (Chapter 3). The effects of both programs on physical fitness were significantly larger in patients who were adherent (Chapter 5). Fewer participants in OnTrack required chemotherapy dose adjustments compared to those in the Usual Care or Onco-Move groups. Participants in Onco-Move and OnTrack returned to work earlier, as well as for more hours per week, than participants in Usual Care (Chapter 3).

Due to the very small groups, the effectiveness of Onco-Move and OnTrack could not be established for patients with colon cancer (Chapter 7). However, both programs are safe and feasible in these patients as well.

Onco-Move is not likely to be cost-effective due to the relatively high willingness-to-pay necessary to reach reasonable probabilities of cost-effectiveness. Depending on the decision-makers’ willingness-to-pay, OnTrack could be considered cost-effective for QALY, and general and physical fatigue in comparison with Usual Care. The probability of cost-effectiveness for both Onco-Move and OnTrack was greater among adherent participants (Chapter 4).

Adherence to the home-based exercise components was 64% (Onco-Move) and 62% (OnTrack) and 71% to the supervised OnTrack sessions for patients with breast cancer. Higher baseline endurance time was associated with higher adherence to home-based exercise components of Onco-Move and OnTrack. Participants with a higher disease stage, a partner, and higher global quality of life were better able to adhere to the supervised sessions. Overall satisfaction with the exercise programs was high, although the encouragement as provided as part of the program was rated less highly in terms of usefulness and quality (Chapter 5).

The trial non-participants could be divided into two groups: those who wanted to exercise on their own and those who did not wish to exercise (in the context of a trial). Those who preferred to exercise on their own were relatively similar to trial participants, but were more likely to be in the maintenance exercise stage. Those non-participants who did not wish to exercise had a significantly lower level of education, were less likely to be working, reported more fatigue and lower health-related quality of life, had a lower sense of self-
efficacy, more negative attitudes towards exercise, less social support, and perceived fewer benefits and more barriers to exercising during treatment than trial participants (Chapter 6). A similar division of non-participant groups could be made for patients with colon cancer, albeit with weaker associations (Chapter 7).

Effectiveness

During chemotherapy the body is exposed to toxic agents with the intent of eradicating potential circulating microscopic metastases.\(^1\) Although improved targeted treatments minimize damage to healthy tissues,\(^2\) agents such as trastuzumab also impact on healthy cells, resulting in possible side-effects.\(^3,4\) In this light it is not surprising that participants with breast cancer in Usual Care experienced a decline in physical fitness and an increase in fatigue (Chapter 3). Participants with breast cancer in the Onco-Move group also declined in physical fitness, although less so than participants in the Usual Care group. Participants with breast cancer in the OnTrack group were able to maintain their physical fitness levels throughout the entire study period. Their level of fatigue increased slightly from baseline, but significantly less compared to participants in Usual Care. Other exercise trials in patients with breast cancer undergoing active treatment also report a less steep decline or a stable situation rather than improvement,\(^5–8\) with only one trial reporting improvement at the end of the intervention in muscle strength.\(^5\)

After six months follow-up, all groups with breast cancer had increased their physical fitness and decreased their fatigue levels to approximately their baseline (i.e., pre-chemotherapy) levels (Chapter 3). This does not necessarily imply that the patients had returned to their pre-illness fitness levels. Our baseline assessments took place after patients had undergone surgery and, in most cases, radiotherapy. Previous studies have reported a decline in physical fitness and functioning levels after surgery and/or radiotherapy.\(^9\) Thus, it is likely that participants in our study had not returned to their pre-illness levels of physical health. There are several possible ways of bridging this gap. A structured physical exercise program after treatment completion could help to further improve physical fitness levels.\(^10\) Another option could be to prevent this drop from pre-illness levels, similar to the PACES trial during chemotherapy, by starting a physical activity program earlier in the cancer treatment trajectory.\(^11,12\) However, the PACT trial, in patients with breast cancer who started a physical activity program within six weeks after diagnosis,\(^11\) was less effective compared to the PACES trial. Contamination by the active control group may have led to an underestimation of the effect of this trial. However, the trials also differed in program duration. The PACT trial used a fixed program of 18 weeks, after which most patients had not finished their chemotherapy regimen. Since being physically active is more difficult with each subsequent chemotherapy cycle,\(^13\) this may leave patients without an exercise program when they most need it. A potential pitfall of introducing exercise even earlier in the disease and treatment process is that it may be overwhelming for the patient around the time of diagnosis. Studies are needed that investigate the willingness of patients to begin exercise interventions soon after diagnosis, and to identify and attempt to resolve reported barriers to such an approach.

Lastly, we found that participants with breast cancer who adhered to the exercise
programs not only had better physical fitness levels at the end of chemotherapy, but also after six months follow-up (Chapter 5). Improving adherence to the exercise programs could help shift these participants to a state where being physically active is incorporated into their daily lives. Higher baseline physical fitness was associated with adherence to the home-based components, but not with adherence to the OnTrack sessions (Chapter 5). We hypothesized that higher baseline physical fitness might reflect exercise history, which is a well-known predictor of adherence.\textsuperscript{14} This suggests that patients with low levels of physical fitness at program entry might benefit more from the extra motivation and structure of a supervised program, while having higher levels of physical fitness could make it easier to start and maintain a largely unsupervised home-based physical activity program.

The home-based programs could be improved by increasing the amount and quality of the encouragement provided by the health care providers (nurses and physical therapists), both of which were rated as insufficient by participants in the Onco-Move and OnTrack programs (Chapter 5). The lack of encouragement could be due to time-constraints or lack of expertise. Even with available funds for the encouragement sessions by the nurses, we observed that it was not always given priority in the busy day-to-day schedule. Although physical therapists seemed to be well prepared for the supervised sessions, this was less so for the home-based component. It may be that our half-day training session was too short to give nurses and physical therapists enough information and experience with physical activity counseling techniques. Based on this evaluation, the training sessions have been transformed to a one and a half day course that also provide extra attention to counseling techniques.

Another approach to resolving the problems associated with both time constraints of health professionals and the quality of their encouragement could be the use of online encouragement and online diaries.\textsuperscript{15,16} A feasibility study of the eHealth intervention ‘MijnAVL’ included the principles of the home-based components of Onco-Move and OnTrack. This showed that median vigorous physical activity improved over time and that the burden for professionals was limited.\textsuperscript{17}

**Effect on chemotherapy completion rates**

Breast cancer patients who participated in OnTrack reported less side effects and were less likely to require dose adjustment of the prescribed chemotherapy regimen (12%) than participants in either Usual Care (34%) or Onco-Move (34%). The average dose reduction among those who required chemotherapy adjustment in OnTrack and Onco-Move was significantly lower (10%), compared with Usual Care (25%) (Chapter 3). A similar trend was observed for colon cancer patients (Chapter 7). The most frequently reported reason for chemotherapy adjustment for participants with breast cancer was neuropathy (31%), followed by (the effects of) myelosuppression (22%), and nausea and vomiting (11%) (Chapter 3). In OnTrack these side effects were reported less frequently, which may explain, at least in part, the lower frequency of required dose adjustment, since chemotherapy is typically adjusted based on the physical condition of the patient and the experienced side effects.\textsuperscript{1}
A proposed working mechanism between exercise and a reduction in such side effects as neuropathy is through an anti-inflammatory effect. During exercise the muscle fibers produce IL-6, a cytokine stimulating other anti-inflammatory cytokines. A recent study in patients with breast cancer receiving neoadjuvant chemotherapy supports this hypothesis, with lower levels of inflammation observed in an exercise group compared to a control group.

Higher chemotherapy completion rates may improve disease-free and overall survival. An exploratory follow-up of the first exercise trial to report higher chemotherapy completion rates, has yielded some preliminary support for positive effects on both disease-free and overall survival.

Exercise, in and of itself, may also have a salutary effect on survival rates. In a laboratory study, exercise significantly reduced breast cancer tumor growth in mice and was associated with an increase in apoptosis. Exercise increased the chemotherapy effectiveness compared to chemotherapy alone. This suggests the added value of prescribing exercise in combination with chemotherapy as an adjuvant treatment.

Another potential mechanism for improved disease-free and overall survival could be the resulting increase in physical activity levels. Large epidemiological studies have demonstrated a relationship between being physically active and a lower risk of developing cancer or experiencing disease recurrence. Large trials with survival as the primary outcome measure are necessary to gain further insight into these mechanisms. The ongoing international Colon Health and Life-Long Exercise Change (CHALLENGE) trial, investigating the effects of regular exercise on recurrence and overall survival in patients with colorectal cancer, is an example of such a trial.

Lastly endurance exercise may prevent anthracycline-induced cardiac injury. This protective effect of exercise against cardiotoxicity, may also explain the trend observed in the OnTrack group toward less delay or discontinuation of trastuzumab treatment. The first study in humans with breast cancer studying the effects of acute exercise prior to doxorubicin on cardiac function, observed that 30 minutes of vigorous-intensity exercise 24 hours prior to the first doxorubicin treatment has a protective effect on cardiac function compared to a control group. It has been hypothesized that the mechanism for this protective effect could be improved antioxidant capacity in the heart and vasculature, and subsequent reduction of treatment-related oxidative stress in these structures. Replication of these findings is needed.

**Return to work**

Directly after chemotherapy, significantly more patients in OnTrack (34%) and Onco-Move (40%) were working than in the Usual Care group (15%). After six months follow-up, not only had more participants returned to work (83% and 79% versus 61%), but they also worked a significantly higher percentage of the pre-illness hours than participants in Usual Care (59% and 60% versus 42%) (Chapter 3). In a qualitative study, breast cancer survivors have reported that physical or psychological side effects hampered their work resumption. In another qualitative study, most participants believed that physical exercise had most likely
contributed to their ability to return to work, primarily by increasing energy levels.\textsuperscript{29} Our study provides preliminary support for this notion. Physical health limitations were reported more frequently as the reason for not returning to work by participants in the Usual Care group compared to the intervention groups. This could be a direct effect of the higher level of physical fitness. Return to work not only has financial implications, but also has meaning in terms of quality of life and a sense of return to normalcy.\textsuperscript{30}

**Cost-effectiveness**

Depending on the decision-makers' willingness-to-pay, in comparison to Usual Care, OnTrack could be considered cost-effective in terms of QALYs, and general and physical fatigue. Onco-Move, in its current form, is not likely to be cost-effective due to the relatively high willingness-to-pay necessary to reach reasonable probabilities of cost-effectiveness (Chapter 4). However, the potential benefit of chemotherapy completion was not incorporated in our analyses, while the extra costs of receiving more chemotherapy sessions were. We intend to conduct additional analyses in which the potential effect of increased chemotherapy completion rates on survival are modeled and incorporated into the cost-utility estimates.

**METHODOLOGICAL CONSIDERATIONS**

The PACES study had a number of methodological strengths, including a randomized comparison of home-based, low-intensity and supervised, moderate- to high-intensity exercise programs versus Usual Care, a large sample size, multicenter participation, limited loss to follow-up, the use of both objective and self-reported outcomes, extensive data on reasons for non-participation and detailed information on sociodemographic, clinical, attitudinal, and behavioral factors potentially associated with non-participation. However, there are also a number of methodological limitations or considerations relating to the design of the study, the nature and quality of the assessments, and the external validity or generalizability of the results that merit discussion.

**Intervention content**

The two interventions that we investigated differed in mode, type, and intensity. Due to the nature of the two exercise interventions in our trial, we cannot determine which components of the interventions are essential, and which may be less important. To increase muscle strength, it is necessary to add resistance training,\textsuperscript{5,6} while cardiorespiratory fitness mandates aerobic training.\textsuperscript{6} A recent study after chemotherapy completion showed that higher intensity aerobic training is more beneficial than lower intensity.\textsuperscript{10} In the POLARIS study, a meta-analysis of individual patient data from 34 RCTs found that the effects of exercise programs on quality of life and physical function were significantly larger for supervised than unsupervised programs.\textsuperscript{31} The larger effects of supervised exercise may be explained by the amount of attention (in the PACES trial, biweekly versus once every three weeks in the home-based program), better tailoring (in the PACES trial, adjustment of the program during each chemotherapy cycle) and/or by better adherence to the prescribed exercise protocol.
Since it is more difficult to monitor and adjust muscle strength exercises and higher intensity protocols for safety, these are usually excluded from home-based programs. These factors could also contribute to observed differences in supervised versus unsupervised programs. With the current popularity of short exercise routines, including muscle strength exercise, provided through an app, it would be interesting to study whether such home-based programs (for example as part of the eHealth intervention ‘MijnAVL’) could be enhanced and/or equally effective as a supervised program.

**Potential biases in study design**

In an ideal research setting, all factors can be controlled and accounted for. In research with patients, life happens and with it variation and interaction is introduced.

**Contamination**

All participants were informed about the general aim of the study, which may have led to an increased awareness in the Usual Care group that exercise during chemotherapy might be beneficial. This may have led to the uptake of exercise regimes or the decision to follow an exercise program even when allocated to the Usual Care group. We refrained from assessing physical activity levels during chemotherapy by means of an exercise diary in the Usual Care group, since this could be viewed as an intervention in and of itself. Unfortunately, we did not systematically assess the uptake of exercise regimes in the Usual Care group during follow-up. Future trials should do so in order to better estimate the possible contamination in the Usual Care group. The uptake of exercise by Usual Care groups is frequently reported in other trials. Any significant increase in physical activity in a Usual Care group could mask or suppress real differences in outcome between the interventions under investigation and the control group.

**Measurements types and recall**

Although peak oxygen uptake is considered the gold standard in aerobic exercise testing, we were unable to determine this as a result of limited testing facilities and the small time-window between referral to the trial and start of chemotherapy. Instead, we used the maximal short exercise capacity on the steep ramp test to evaluate changes in cardiorespiratory fitness. The steep ramp test has been shown to be reliable (intraclass correlation coefficient, 0.996) and valid in detecting changes in maximal short exercise capacity. We also added an endurance test, which may be more clinically relevant than maximal short exercise capacity, given that activities in daily living are not performed at peak levels.

Upper and lower muscle strength were assessed using a handheld dynamometer, which directly assessed the strength of the trained muscle groups. Although a very valid and user-friendly measurement tool, for a break test, as used in our study, it is important that the person taking the measurement is stronger than the patient being measured. The person taking the measurement could also use her weight and gravity to her
advantage. Nevertheless, some patients may have been stronger than the person taking the measurement, resulting in a measurement of the strength not of the patient, but of the person taking the measurement. We have no reason to suspect that this was a significant problem in our trial, since the difference over time in hand-grip dynamometer\textsuperscript{37} is of a similar magnitude.

A large battery of questionnaires was used in this study. The Impact on Participation and Autonomy is a particularly lengthy questionnaire.\textsuperscript{38} In an earlier study, this questionnaire was shown to detect within-person improvement over time in patients suffering from traumatic hand injury or neuromuscular disease.\textsuperscript{38} However, this questionnaire may be of limited use in patients with cancer. In the A-Care REACT,\textsuperscript{10} PACES,\textsuperscript{39} and EXIST\textsuperscript{40} trials, its responsiveness to change over time was found to be extremely limited. Based on these results, and considering the respondent burden in completing this lengthy questionnaire, we would not recommend its use in future research such as ours.

For our cost-effectiveness and cost-utility analyses, cost data on number of visits to health care providers and loss of productivity were based on self-report with a 3-month recall period, which is advised in order to balance loss in precision with increase in research costs and participant burden.\textsuperscript{41} Although we have no reason to suspect that there were systematic differences in recall and/or social desirability bias between the study groups,\textsuperscript{42} we would recommend administering the cost diaries at the beginning of the 3-month assessment period to facilitate prospective cost registration. It may be more accurate and less stressful for participants to recall all the visits to health care providers and loss of productivity for the last three months than over a longer time period.

**External validity and generalizability**

The results of this study are applicable to patients with breast cancer who receive adjuvant chemotherapy. Although we intended to recruit both patients with breast cancer and colon cancer into our trial, we experienced significant problems in recruiting the latter group. First, more patients than anticipated were receiving palliative rather than adjuvant chemotherapy, resulting in a much smaller source population. Second, clinicians seemed hesitant to refer patients with colon cancer to our study. Recently, Courneya et al.\textsuperscript{43} described this phenomenon, in which staff labeled patients as “does not look like an exerciser”, as “too old” or as “unable to exercise”. This could also reflect the fact that colon cancer patients can have more significant postsurgical complaints (e.g., prolonged wound healing, stomas and bowel problems) than do patients with breast cancer.\textsuperscript{44} In any case, this suggests the need to explain more clearly to both clinicians and patients that the physical exercise program will be tailored to the functional status and capacity of each individual patient. Lastly, because of differences in the way in which the adjuvant treatment care planning was organized for the colon versus breast cancer patients in the participating hospitals, it was more difficult to screen colon cancer patients for eligibility and to inform the treating physician in a timely manner.

The trial non-participants differed from trial participants in distinct ways. The first group of non-participants, those who preferred to exercise on their own, should, at least in theory, not be of too great concern to us. However, it is important to note that this was their self-
The reported reason for non-participation. Objective data on actual physical fitness levels prior and after chemotherapy are needed to confirm their self-report data and the notion that they might not need extra support.

The second group of non-participants did not wish to exercise at all during treatment or not in the context of a trial. These non-participants deserve additional attention. Future research is needed to better understand how those patients with compromised health status, with attitudes and beliefs that are not conducive to exercising, or with social networks that do not encourage them to be physically active can nevertheless be motivated to participate in formal, supervised exercise during treatment. Patient education materials adapted to lower stages of readiness to be physically active could help change the perception of benefits and barriers to be physically active. It is important to include both informal and formal caregivers in these education materials, so that they can provide appropriate encouragement and support. Starting with a lower exercise intensity and/or volume could help build confidence in physical activity, and thereby lead to gradually increasing activity levels that at least match public health guidelines for physical activity. That being said, some of the patients who did not wish to exercise in the context of a trial reported barriers that were specific to the trial itself. Without the stringent requirements of timing and the burden of questionnaires, uptake in clinical practice might be larger.

The primary cost-effectiveness analyses are based on the Dutch health care system and values for return to work. Therefore, we added sensitivity analyses to evaluate potential differences in healthcare systems and different approaches to account for return to work. Although our results are primarily applicable to the Dutch healthcare system, the similar results of the sensitivity analyses for different healthcare systems and different approaches to account for return to work allow the results to be generalized outside the Netherlands.

**IMPLICATIONS FOR FUTURE RESEARCH**

Although some investigators consider a 6-month follow-up period as long, a longer follow-up to measure actual changes in physical activity behavior and potential differences in disease-free and overall survival would be of interest. However, to obtain enough power to measure a potential difference in disease-free or overall survival due to an exercise regime, very large multi-national trials are warranted, such as the ongoing CHALLENGE trial. Insight into the working mechanisms of the hypothesized effect of exercise on disease-free and overall survival is also needed, as is replication of and insight into the working mechanism of the proposed cardioprotective effect of exercise against the cardiac toxicity of anthracyclines and trastuzumab.

Any given randomized control trial performed in the exercise and cancer field can answer only a small portion of the questions about what works for whom, how and when. To tailor the interventions to each patient’s needs, more insight into the moderators of intervention effects is necessary. A single randomized controlled trial is insufficiently powered to answer such questions. Use of pooled data from numerous studies represents a powerful means of addressing a range of research questions difficult to investigate in single studies. The
POLARIS consortium\textsuperscript{48} is an example of such an approach, in which individual patient data from RCTs evaluating the effects of physical activity and/or psychosocial interventions are pooled to identify moderators of intervention effects, to predicting optimal cancer rehabilitation and supportive care.\textsuperscript{31}

**CONCLUSION**

OnTrack is feasible, effective and cost-effective for patients with breast cancer undergoing adjuvant chemotherapy, and we would recommend that it be implemented in daily clinical practice. A project of the Dutch Comprehensive Cancer Centre (IKNL), supported by the Dutch Cancer Society, is currently investigating how best to translate the results of the PACES trial (and of other behavioral and psychosocial oncology research) into clinical practice. Specific to the OnTrack program, to minimize practical barriers like distance to a physical therapy practice, it is crucial to have trained physical therapists throughout the Netherlands. This is currently available and is being expanded via the Onconet Network of physical therapists especially trained in providing this program to cancer patients. Financial barriers to implementing OnTrack on a large scale can best be addressed by ensuring that all health insurance providers reimburse the program. Attitudinal barriers to implementation can be lowered by insuring that all involved healthcare providers receive information about the effectiveness of the program, and particularly that the program is suitable for every patient, as it can be adapted to the functional level of each individual patient.

Finally, we recognize that, even in the best-case scenario, not all patients will be able or willing to follow such an intensive program as OnTrack. For these patients, our trial results indicate that Onco-Move represents a viable alternative, particularly if it is enhanced by the use of more encouragement strategies.
REFERENCES


