Physical Exercise during Adjuvant Chemotherapy.
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PHYSICAL EXERCISE DURING ADJUVANT CHEMOTHERAPY

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Summary
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Survival rates of cancer have improved, thanks to improved treatments and earlier and better diagnosis. During and even long after cessation of treatment, patients can experience a wide range of side effects due to the disease and its treatment. This includes fatigue, reduced cardiorespiratory fitness and muscle strength, which may have a large impact on health-related quality of life. **Chapter 1** of this thesis introduces exercise during active treatment as a promising strategy to mitigate these effects. While previous reviews have reported on the beneficial effects of exercise during and after cancer treatment, there are still questions about the optimal mode, type, intensity, and timing of physical activity for different patient groups. To address some of these questions, we conducted the Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES). This study evaluated the effectiveness of a home-based, low-intensity physical activity program (Onco-Move) and a supervised, moderate-to-high intensity, combined resistance and aerobic exercise program (OnTrack) in patients undergoing adjuvant chemotherapy. In this thesis, we posed the following research questions:

1. What is the effectiveness of Onco-Move and OnTrack in maintaining or enhancing physical fitness, minimizing fatigue, chemotherapy completion rates and other psychosocial outcomes in patients undergoing adjuvant chemotherapy?
2. What is the cost-effectiveness of Onco-Move and OnTrack?
3. What is the adherence to and satisfaction with Onco-Move and OnTrack, and which factors are associated with adherence?
4. What is the rate and scope of patient participation in the PACES trial, and thus its generalizability to the larger patient population of interest?

**Chapter 2** describes the design of the PACES randomized controlled trial, evaluating the effectiveness and cost-effectiveness of exercise during adjuvant chemotherapy on maintaining or enhancing cardiorespiratory fitness and muscle strength, minimizing fatigue, improving psychosocial outcomes, and on chemotherapy completion rates. We compared a home-based, low-intensity physical activity program (Onco-Move) and a supervised, moderate-to-high intensity, combined resistance and aerobic exercise program (OnTrack) with Usual Care. In Onco-Move, participants received encouragement by specially trained nurses at each chemotherapy cycle to engage in at least 30 minutes of physical activity per day, five days per week and to keep an activity diary. Participants in OnTrack attended two supervised training sessions per week for muscle strength and cardiorespiratory fitness. OnTrack participants were also encouraged to be physically active five days a week for 30 minutes per session and to keep an activity diary. Both interventions started with the first cycle of chemotherapy and continued until three weeks after the last cycle. Usual Care varied according to hospital guidelines and preferences, but did not involve routine exercise. Performance-based and self-reported outcomes were assessed at baseline, at the end of chemotherapy and at 6-month follow-up.
Chapter 3 presents the results pertaining to the effectiveness of Onco-Move and OnTrack in terms of physical fitness, fatigue, chemotherapy completion rates and other psychosocial outcomes in patients undergoing chemotherapy for their breast cancer. Participants in Onco-Move and OnTrack had a longer mean endurance time than the Usual Care group (4 and 8 minutes longer; ES, 0.45 and 0.90, respectively). Participants in OnTrack also had a higher maximal short exercise capacity, and muscle strength of the arms and legs than those in Onco-Move or Usual Care. Compared to Usual Care, participants in OnTrack experienced less physical and general fatigue, and perceived this fatigue as less frustrating and frightening and more pleasant. Participants in OnTrack also experienced less physical fatigue and experienced this as less frightening than participants in Onco-Move. Participants in both OnTrack and Onco-Move reported better physical functioning, less nausea and vomiting, and less pain than those in the Usual Care group. In addition, OnTrack participants reported better cognitive functioning and less constipation compared with Usual Care. In general, physical fitness and fatigue levels were maintained immediately after completion of chemotherapy in the OnTrack group, but declined and increased in the Usual Care and Onco-Move groups, respectively. At the 6-month follow-up, the Onco-Move and Usual Care groups had increased their physical fitness and decreased their fatigue levels to baseline levels (i.e. pre-chemotherapy). A smaller percentage of participants in OnTrack (12%) required chemotherapy dose adjustments than those in the Usual Care (34%) or Onco-Move (34%) groups. The average dose reduction among those who required chemotherapy adjustment in OnTrack and Onco-Move was significantly lower (10% versus 25% in Usual Care). Participants in both Onco-Move and OnTrack returned to work earlier, and also worked more hours per week than participants to Usual Care.

Chapter 4 describes the cost-effectiveness of both of the PACES trial interventions in patients with breast cancer. 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 Quality Adjusted Life Year (QALY), and general and physical fatigue in comparison with Usual Care. Incremental cost-effectiveness ratios for OnTrack compared to Usual Care were €26,916 per QALY, €788 per 1-point decrease in general fatigue and €1,402 per 1-point decrease in physical fatigue. The probability of OnTrack being cost-effective ranged from 31% to 95% for QALYs, 31% to 97% for general fatigue, and 31% to 86% for physical fatigue. The probability of cost-effectiveness for both Onco-Move and OnTrack was greater among compliant participants.

Chapter 5 presents the results pertaining to the effect of adherence on the primary outcome measures, factors associated with adherence, and satisfaction with both physical activity programs. Adherence to the home-based components of the program was 64% (Onco-Move) and 62% (OnTrack). Adherence to the supervised OnTrack sessions was 71%. Effects of both interventions on physical fitness were significantly larger in patients who were adherent. Higher baseline endurance time was associated with higher adherence to the
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 provided by health care professionals as part of the programs was rated as less useful and of lower quality. Providing additional time for and training in motivational counseling techniques could improve the quality and hopefully the effectiveness of the interventions. The use of online diaries and smartphone apps may also provide additional encouragement to participants, leading to higher levels of adherence and better outcomes. Finally, allowing greater flexibility in the planning and availability of supervised exercise training in order to accommodate the variability in cancer treatment schedules and the (acute) side effects of the treatments could also enhance program adherence.

Chapter 6 compares the psychosocial health and attitudes towards physical activity between participants in the PACES trial and non-participants. Of the eligible patients with breast cancer, 56% declined to participate in the trial. The non-participants indicated either that they wanted to exercise on their own or that they 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 (in the context of a trial) 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. Minimizing practical barriers to participation, providing educational materials on the potential benefits of exercise, and giving adequate professional and social network encouragement may increase the number of patients willing to exercise during treatment and to participate in such studies.

Chapter 7 reports on the recruitment and pilot results of participants with colon cancer in the PACES trial. Only 23 of 63 referred patients with colon cancer agreed to participate in the trial. Due to the very small groups, the effectiveness of Onco-Move and OnTrack could not be established for patients with colon cancer. We did observe a trend toward higher chemotherapy doses in the intervention groups than in the Usual Care group. Compliance to both programs was high and no adverse events occurred, suggesting that both programs are safe and feasible for patients with colon cancer. However, program effectiveness needs to be established in a larger trial. Those non-participants who did not want to exercise had higher fatigue scores at baseline and a more negative attitude towards exercise. In summary, recruitment of patients with colon cancer to a physical exercise trial during adjuvant chemotherapy proved to be difficult, underscoring the need to develop more effective strategies to increase participation rates.
Chapter 8 discusses the main findings of this thesis, including methodological considerations relating to the design of the study, the nature and quality of the assessments, and the external validity or generalizability of the results.

In conclusion, our results indicate that OnTrack is feasible, effective and cost-effective for patients with breast cancer undergoing chemotherapy, and we recommend that it be implemented in clinical practice. However, 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 Onco-Move represents a viable alternative, particularly if it is enhanced by the use of more encouragement strategies. To further tailor the interventions to each patient’s needs, future analysis using pooled data from numerous studies could help answer the question about what works for whom, how and when. Future research into a nationwide implementation strategy should address practical and financial barriers, and knowledge of the programs.

Future trials in exercise oncology are needed to provide insight into the working mechanisms of the hypothesized effect of exercise on disease-free and overall survival, and the proposed cardioprotective effect of exercise against the cardiotoxicity of anthracyclines and trastuzumab. Such trials require longer follow-up to assess the putative effect of exercise on disease-free and overall survival.