Physical exercise during adjuvant chemotherapy
van Waart, H.

Citation for published version (APA):
Chapter 1

General Introduction
With improved treatments and earlier and better diagnosis, survival rates of cancer have improved,\(^1\) while minimizing damage to healthy tissues.\(^2,3\) Nevertheless, patients may experience several short-term and long-term side effects due to cancer and its treatment. Frequently reported side effects include fatigue, nausea, vomiting, bone marrow suppression leading to infections, hair loss, ovarian function suppression, reduced cardiac function and reduced physical fitness (cardiorespiratory fitness and muscle strength), all of which may have a large impact on health-related quality of life and activities of daily life.\(^4,5\)

**PHYSICAL EXERCISE AND CANCER**

Although historically rest and outright inactivity was often recommended, research has shown that being physically active might be the better option for patients with cancer.\(^6\) Inactivity itself has a direct effect on loss of physical fitness,\(^7\) but inactivity could also contribute to higher risk of cancer development and cancer recurrence.\(^8,9\) Several studies have shown that being physically active reduces the risk of cancer development,\(^10,11\) and can have salutary effects on the experienced problems due to cancer and its treatment.

Since the first research in 1986 showing that exercise for cancer patients is feasible,\(^12\) we have come a very long way in this relatively new research field of exercise oncology. Especially in the last years an explosion of new research and reviews show evidence of the beneficial effects of exercise for patients with cancer.

A systematic review of the effect of exercise in patients undergoing adjuvant treatment following surgery was performed in 2015.\(^13\) The review included mainly patients with breast cancer and 17% other cancer diagnosis. The review showed that exercise has beneficial outcomes on physical fitness, health-related quality of life and fatigue. The authors concluded that because of the lack of adequately powered randomized controlled trials, it remains unclear what would be the optimal timing to initiate an exercise program and what kind of program would be effective in improving clinically important outcome measures.

A systematic review performed in 2015, focusing on the effect of exercise during chemotherapy on muscle strength and endurance capacity showed improvements in both outcome measures.\(^14\) With 2% - 38% improvement in muscle strength and 8% - 31% improvement in endurance capacity in the exercise groups, while the usual care groups showed very limited increase in muscle strength (1% - 7%) and a decrease in endurance capacity (1% - 32%).\(^14\) The quality of the studies included in this review was rated as poor, with considerable variations in study populations and heterogeneous training programs. The authors recommended more research to unravel the best intensity, frequency and duration of exercise programs.

Another systematic review and meta-analysis performed in 2015 studied the effect of resistance training on muscle strength and body composition in patients with breast or prostate cancer undergoing active adjuvant or neoadjuvant systemic treatment.\(^15\) The meta-analysis showed that muscle strength of the lower extremities improved, together with improved lean body mass, while body fat reduced.\(^15\) This is in line with another review
assessing the effect of physical exercise on muscle mass and strength in cancer patients during treatment performed in 2012. The authors concluded that cancer patients and survivors should consider undertaking resistance exercise. Yet, they also pointed out that there was only a limited number of studies available for meta-analysis, requiring more and better evidence in future studies.

A meta-analysis performed in 2014 on the effects of exercise during and after treatment for patients with breast cancer showed that exercise interventions resulted in better physical functioning and reduced fatigue. It was recommended to prolong the follow-up period to at least five years. More research into the optimal and preferred frequency, intensity and timing of exercise was deemed necessary. Future studies should also unravel how to obtain long-term behavior changes.

A systematic review performed in 2015, reviewed the effect of physical self-management programs on quality of life in patients with breast cancer during and after active treatment. Different self-management techniques were identified, such as a booklet, brochure, multimedia and recommendations. These self-management programs had a positive effect on quality of life, fatigue, physical functioning, emotional well being and social well being. The effects during active treatment represented stabilization or a slower decrease, compared to effects after treatment. They recommended prolonging follow-up durations. They concluded that multiple methods could be offered to the patient to engage in self-management by physical activities.

The total prescribed length of chemotherapy will last between 12 to 24 weeks. Side effects can lead to adjustments in the chemotherapy, either delay administrations, adjustment of the prescribed dose, or stopping the chemotherapy all together, which in turn might influence the survival. It is hypothesized that exercise during chemotherapy may reduce these side effects, thus, allowing for the complete chemotherapy dose to be received. An exploratory follow-up of this exercise trial lends preliminary support to this hypothesis. Although evidence is still preliminary, randomized controlled trials of exercise that included biomarker endpoints suggest that exercise may result in beneficial changes in inflammation, and, possibly, immunity.

In conclusion, exercise during active treatment can have positive effects on fatigue, cardiorespiratory fitness, muscle strength, health-related quality of life, and possibly on immune function and chemotherapy completion rates. However, there remains debate about the optimal mode, type, intensity, and timing of physical activity for different patient groups.

As resources are scarce, policy makers are not only interested in the effectiveness of interventions, but also in their costs in relation to these effects. While supervised interventions may be more effective, they involve additional costs. Economic evaluations compare alternative courses of action in terms of both their costs and consequences.
Various kinds of economic evaluations are possible. A cost-utility analysis provides insight into the additional cost per quality-adjusted life year (QALY) gained. A cost-effectiveness analysis provides insight into the additional cost per unit of effect gained in terms of a clinical outcome. Such analyses give guidance to reimbursement of physical activity programs by health care decision makers. Currently, exercise programs are not reimbursed by the basic insurance, which limits access for patients with cancer.

The effectiveness of physical activity will depend on whether patients are able to adhere to physical activity programs following cancer diagnosis. This requires understanding of the factors associated with adherence. As described by the Theory of Planned Behavior, motivational factors, including attitudes, subjective norms, self-efficacy, and perceived benefits and barriers can help in understanding and explaining exercise behavior in patients with cancer. Also, sociodemographic and clinical variables, physical fitness, and psychosocial factors such as health related quality of life may play a role in adherence to exercise programs. Additionally, satisfaction with physical activity and exercise programs can also provide leads to improve these programs.

In many cases, only a small percentage of eligible patients participate in exercise trials. It is likely that patients who participate in an exercise trial are not entirely representative of the larger target population. Depending on the reasons for non-participation, the observed effects may overestimate or underestimate the true effect in the target population.

There is a range of reasons why patients may not wish to participate in exercise-oncology trials. Previous studies among varied other patient groups have identified logistic barriers (e.g., difficulty fitting exercise into one’s daily schedule), health-related barriers (e.g., side effects of treatment), and attitudinal barriers (e.g., aversion to or low perceived benefit of exercising) or trial-specific reasons (e.g., not wanting to risk assignment to a control group).

Insight in the characteristics of (non)-participants in exercise-oncology trials helps us to evaluate the generalizability of such trials. This may also be of relevance for implementation of exercise interventions in clinical practice, since different approaches may be needed to reach those patients who, for whatever reason, are initially reluctant or unwilling to participate.

To address some of these questions, the Alpe d’HuZes Cancer Rehabilitation (A-CaRe) consortium was formed. The A-CaRe consortium is a collaboration between five (university) hospitals in the Netherlands. The primary objective of A-CaRe Clinical Research was to evaluate the effectiveness and cost-effectiveness of exercise interventions on physical fitness and fatigue and on health related quality of life in specific cancer patient and survivor groups. The design of the A-CaRe trials is based on a conceptual model, where exercise improves physical fitness (cardiorespiratory fitness and muscle strength), which improves fatigue and subsequently also physical function and health related quality of life.
to this model, physical fitness may also directly influence physical function and health related quality of life (Figure 1).

The A-CaRe trials were: 1) REACT: exercise after chemotherapy, 2) PACES: exercise during chemotherapy, 3) EXIST: exercise after stem cell transplantation and 4) QLIM: exercise during childhood cancer. The exercise interventions were compared with either a waiting list control group or usual care. To uniformly research different modes, types, intensities and timings for different groups of patients, similar methods were used in the four A-CaRe randomized controlled trials.

**OBJECTIVE OF THE THESIS AND RESEARCH QUESTIONS**

In this thesis, we will focus on one of the A-CaRe trials, the Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES), researching 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 1

OUTLINE OF THIS THESIS

Chapter 2 describes the study design of the Physical exercise during Adjuvant Chemotherapy Study (PACES), in which rationale and study methods are described. Chapter 3 presents the effects of the randomized controlled trial evaluating a home-based, low-intensity physical activity program and a supervised, moderate-to-high intensity, combined resistance and aerobic exercise program on physical fitness, fatigue, chemotherapy completion rates and other psychosocial outcomes in patients undergoing chemotherapy for their breast cancer. Chapter 4 describes the cost-effectiveness of both interventions in the PACES trial in patients with breast cancer. Chapter 5 presents the effect of adherence on the primary outcome measures, adherence to, factors associated with, and satisfaction with both physical activity programs. Chapter 6 compares psychosocial health and attitudes towards physical activity between participants in the PACES trial and non-participants. Chapter 7 reports the recruitment of participants with colon cancer in the PACES trial, provides insight in the non-participants and shares the outcome measures of the pilot randomized controlled trial in patients with colon cancer on physical fitness, fatigue, chemotherapy completion rates and other psychosocial outcome measures. This thesis ends with a general discussion of the research of this thesis and its context in Chapter 8, and an overall summary in Chapter 9.
REFERENCES


