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

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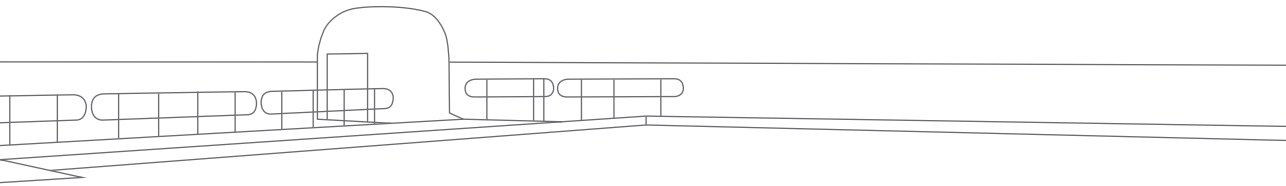
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# CHAPTER 1

General introduction





## GENERAL INTRODUCTION

### **Cancer**

According to current estimates in developed countries more than one in three people will be affected directly by cancer at some point in their lifetime [1]. The most prevalent cancer diagnoses in adults are breast, colon, prostate and lung cancer, representing 43% of all new cases worldwide [2]. Over the past few decades, major milestones have been achieved in early detection, diagnosis, and effective treatment regimens of cancer. As a result, the 5-year relative survival rates improved significantly, and currently rates are 68% for all cancers combined [1]. Given the increased incidence and survival rates, cancer survivors represent a growing population, reflecting anyone who has been diagnosed with cancer, from the time since diagnosis through the rest of life [3].

### **Physical and psychosocial problems**

Surviving cancer, however, is associated with long-term disease- and treatment-related problems including decreased cardiorespiratory fitness and muscle strength, increased risk of anxiety and depression, and/or severe feelings of fatigue [4,5]. These physical and psychosocial problems may persist for years after completing active treatments and reduce a person's health-related quality of life (HRQoL) [6]. Fatigue, in particular, has been identified as one of the most distressing problems reported by cancer survivors affecting more than 70% of the population [7]. Moreover, fatigue becomes a chronic condition in 30% of the cancer survivors [8]. Traditionally, cancer survivors were advised to rest and avoid exercise when they feel fatigued [4]. However, reducing daily physical activity may further reduce the compromised levels of cardiorespiratory fitness and muscle mass following cancer treatments, resulting in a self-perpetuating cycle of physical inactivity, contributing to poorer physical fitness and long term persistence of fatigue [4].

### **Physical activity and exercise programs**

Physical activity (i.e., any bodily movement that results in energy expenditure from muscle contraction) and exercise (i.e., form of physical activity that is planned, structured, and repetitive and that aims to improve or maintain physical fitness, performance or health) [9] have been increasingly recognized as promising interventions to break the self-perpetuating cycle of daily physical inactivity [4]. This, in turn, may assist cancer survivors to cope with and recover from the cancer- and treatment-related problems and contribute to a better quality of life [10,11]. Over the past few decades, the field of exercise oncology has

evolved rapidly and the impact of exercise on specific health outcomes - including HRQoL - has been studied extensively [12]. Aiming to organize research on exercise and cancer survivorship, Courneya et al. proposed the Physical Activity and Cancer Control framework (PACC), distinguishing four time periods following cancer diagnosis (i.e., pre-treatment, treatment, survivorship, and end of life) [13]. A limited number of studies have examined the effects of exercise pre-treatment and at the end-of-life phases [14], while most research to date has investigated the effectiveness of exercise during and post treatment. Generally, during primary cancer treatment, exercise showed beneficial effects in minimizing decline in cardiorespiratory fitness [15] and muscle strength [16], limiting fatigue and improving quality of life [10]. After completion of primary cancer, exercise may reverse losses in physical fitness that have occurred during treatment and may prevent, manage or reduce long-term psychosocial problems. Moreover, observational studies have found that higher levels of physical activity after diagnosis might improve survival.

### **Optimal exercise prescriptions**

Current systematic literature reviews have underlined the positive physical and psychosocial benefits of exercise programs among cancer survivors, but also have highlighted the importance to firmly establish the magnitude of positive effects in high-quality randomized controlled trials (RCT)s [10,11,17,18]. Furthermore, additional research is needed to move away from one-size fits all exercise programs and to define specific exercise prescriptions in terms of frequency, intensity, type and time (i.e., FITT factors) of exercise [19,20]. Studying exercise prescriptions for cancer survivors may facilitate the development of targeted interventions, which in turn is likely to contribute to more effective exercise programs [19]. The first RCTs evaluating the effects of different exercise doses and modes in breast cancer survivors during chemotherapy on physical functioning and HRQoL [21,22] have indicated that higher exercise doses (3 times 60 minutes per week at moderate-to-high intensity) resulted in significantly better physical functioning and less symptoms, compared to standard doses (3 times 30 minutes per week at moderate-to-high intensity) [22]. Furthermore, resistance exercises had superior effects on lower and upper body muscle strength compared to aerobic exercises and usual care, while, aerobic exercises had larger effects on peak oxygen uptake compared to resistance exercises and usual care [21]. Neither exercise modes prevented weight gain, but compared to usual care both, i.e., resistance and aerobic exercises, showed beneficial effects on body composition and self-esteem [21].

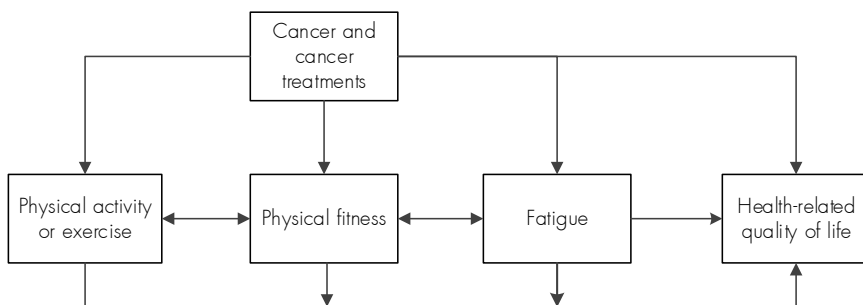
To date, only two relatively small RCTs examined the effects of different exercise intensities after completion of primary cancer treatment [23,24]. Burnham et al. have compared

moderate versus low intensity aerobic exercise in breast cancer survivors (n=18) and have reported that both exercise programs improved cardiorespiratory fitness compared to usual care, with no differences in effects between the interventions [23], whereas Gibbs et al. reported larger improvements in cardiorespiratory fitness in breast cancer survivors (n=73) after high intensity resistance exercise compared to low intensity resistance exercise and usual care [24]. Due to the scarcity of studies, small sample sizes and a predominant focus on breast cancer survivors, future research is needed to define the optimal exercise intensity among cancer survivors.

### REACT study

The Resistance and Endurance exercise After ChemoTherapy (REACT) study was developed to evaluate a 12-week high intensity (HI) and low-to-moderate intensity (LMI) resistance and endurance exercise program compared to a waiting list control (WLC) group in cancer survivors who had completed primary cancer treatment including chemotherapy [25]. The REACT study is one of the four RCTs of the Alpe d’HuZes Cancer Rehabilitation clinical research program (A-CaRe). Primarily, A-CaRe Clinical Research aimed to develop, evaluate and implement state-of-the-art exercise programs among four different subgroups of cancer survivors [26]. A-CaRe clinical research program hypothesized that exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and consequently improving HRQoL among cancer survivors (Figure 1).

FIGURE 1 Conceptual model of the A-CaRe program



Further, implementation of exercise programs might be facilitated by a better understanding about the demographic, clinical, psychosocial, physical and environmental factors that influence participation and exercise adherence among cancer survivors [20]. More

specifically, knowledge of demographic and clinical factors will identify subgroups that are at most risk for declining participation or withdrawing from an exercise program. Knowledge of psychosocial factors may identify relevant targets for additional strategies to support the improvement of participation and adherence rates.

### **Objectives and outline of this thesis**

The overall objective of the current thesis is to evaluate (cost-)effectiveness and facilitate implementation of exercise programs in a mixed group of cancer survivors who had completed primary cancer treatment, including chemotherapy. In particular, this thesis addresses three primary objectives:

- I. To evaluate the (cost-)effectiveness of a HI and LMI resistance and endurance exercise intervention on physical fitness and fatigue;
- II. To test the hypothesis that resistance and endurance exercises improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and consequently improve global quality of life and physical function;
- III. To identify demographic, clinical, psychosocial, physical and environmental factors that are associated with exercise participation and exercise adherence.

Chapter 2 describes the design of the REACT study, a randomized controlled trial evaluating the effectiveness and cost-effectiveness of exercise interventions in a large group of cancer survivors (n=277) who had recently completed treatment with curative intent, including chemotherapy. Chapter 3 presents the results of the REACT study at 12 weeks follow-up by reporting on the effectiveness of HI exercise and LMI exercise compared to a WLC group, with cardiorespiratory fitness, muscle strength, and fatigue as primary outcomes. Secondary outcomes included HRQoL, physical activity, daily functioning, body composition, mood, and sleep disturbances. Chapter 4 evaluates the hypothesis that resistance and endurance exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and consequently improving global quality of life and physical function. Chapter 5 describes the effectiveness and cost-effectiveness of HI versus LMI exercise programs in the REACT study at 64 weeks follow-up. Chapter 6 presents a systematic review that summarized evidence on demographic, clinical, psychological, physical and environmental correlates of exercise intervention adherence and exercise maintenance after completion of an intervention. In this review, a distinction is made between correlates of exercise adherence before, during and after primary cancer treatment according to the PACC framework [13]. Chapter 7 explores correlates of participation in and adherence to exercise programs in cancer survivors. The

differences between participants and non-participants of the REACT study were studied to identify subgroups of cancer survivors who are most likely to participate in exercise programs. Furthermore, this chapter studies the demographic, clinical, psychosocial, physical and environmental correlates of exercise intervention adherence, in which a distinction was made between correlates of session attendance and correlates of compliance to the prescribed protocol for HI exercise and LMI exercise. Chapter 8 examines demographic, clinical, psychosocial, and environmental correlates of objectively assessed physical activity among breast cancer survivors that participated in one of three RCTs, in order to facilitate the development of effective and targeted interventions aiming to improve physical activity. Chapter 9 describes the main findings of the current thesis, discusses the strengths and limitations of the work that is presented, as well as clinical implications and directions for future research.



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