Chapter 1

General introduction
Cancer, treatment, and treatment-related symptoms

Cancer counts for 14 million new cases worldwide every year, and the number of new cases is expected to rise by 70% over the next two decades due to aging and growth of the population [1]. Lung, prostate and colorectal cancer are the most commonly diagnosed types of cancer among men worldwide, accounting for 17%, 15% and 10% of the total cancer diagnosis, respectively. Breast (25%), colorectal (9%) and lung cancer (9%) are the most commonly diagnosed cancers among women worldwide [1]. In the Netherlands, the number of people diagnosed with cancer increased from 64,604 in 1995 to 105,844 in 2015 [2], and it is expected that the number of patients with cancer will increase up to 666,000 in 2020 [3]. The most prevalent cancer types in the Netherlands are breast, skin, and prostate cancer, representing 56% of all new cases [2].

In the last decades, cancer survival rates have increased substantially, but differs greatly between cancer types. In the Netherlands, the overall 5-year cancer survival rate has increased from 47% in 1989-1993 to 64% in 2011-2015 [2]. These improvements in survival rates are caused by advances in early cancer detection (i.e. diagnosis and screening) and more effective treatments [4]. Advances in radiation, chemotherapy, immunotherapy, and targeted treatments have improved survival, especially for cancer of the breast, prostate, lung, liver, melanoma, and colon or rectum [5, 6]. The type of treatment(s) used depends on the location and size of the tumor, the presence of metastases, and the general health status of the patient [1].

Unfortunately, many patients with cancer are confronted with physical and psychosocial problems that may persist years after treatment [7, 8]. For example, cancer-related fatigue is reported in up to 90% of the patients during treatment [9, 10], and in one-quarter of patients with breast cancer, it may persists for up to 5 years after completion of treatment [10]. It has also been shown that cardiorespiratory fitness of patients with breast cancer is 31% lower during adjuvant therapy and 22% lower after adjuvant therapy compared to age-matched healthy sedentary women [11]. In addition, androgen deprivation therapy, commonly used in the treatment of patients with prostate cancer, may decrease muscle mass by 2% to 4% within 3 to 12 months of initiation of treatment [12-14]. Also, muscle mass decreased during chemotherapy by 6.1% in patients with metastatic colorectal cancer [15]. Loss of muscle mass is associated with reduced muscle strength [16], poorer physical
function [17] and fitness [18], and poorer survival [15]. Furthermore, depression and anxiety disorder, as measured by a diagnostic interview is prevalent in 14% and 10% of patients with cancer during treatment, respectively [19, 20]. Prevalence of symptoms of depression and anxiety (based on patient reported outcome measures) is estimated to be much higher (27% [20] and 26% [21], respectively). In patients with cancer who were at least 2 years after diagnosis, the prevalence of depression and anxiety disorder is estimated to be 8% and 18%, respectively [22]. These physical and psychosocial problems are associated with reduced health-related quality of life (QoL) [23, 24]. QoL is a subjective multidimensional health outcome, encompassing physical, emotional and social functioning, symptom burden and perceived health status [25, 26]. With the increasing number of patients with cancer in the coming decades, the demand for developing intervention strategies that not only focus on treating the cancer itself, but also on preventing or reducing physical problems, and maintaining or improving QoL will rise as well [27-33].

**Exercise and psychosocial interventions**

Previous studies showed that physical activity (i.e. any bodily movement that results in energy expenditure [34]), exercise (i.e. a form of physical activity that is planned, structured and repetitive and aims to improve fitness, performance or health [34]) and/or psychosocial interventions improve physical and/or psychosocial function and QoL in patients with cancer [27-33]. It is hypothesized that physical inactivity induces muscle catabolism and causes further detraining, which may result in a self-perpetuating detraining state with easily induced cancer-related fatigue [24, 35]. Physical activity and exercise may interfere this self-perpetuating cycle by improved physical fitness, and consequently reduced cancer-related fatigue and improved QoL [24, 35]. Furthermore, psychosocial interventions may help to reduce psychological distress, depression, anxiety, and fatigue, and to reduce sleep problems, and subsequently improve the patient’s QoL [30-33].

Exercise interventions may have different dimensions with respect to the mode of intervention delivery (e.g. supervised or unsupervised), intervention duration and timing, or exercise frequency (e.g. number of exercise sessions per week), intensity (e.g. low, moderate, or high intensity), type (e.g. aerobic, resistance, or impact training) and time (i.e. session duration) [36]. Psychosocial interventions
for patients with cancer can be categorized into different types. Cunningham’s hierarchic classification distinguishes five types of heterogenetic psychosocial interventions based on the degree of psychological change the different interventions seek to promote in patients with cancer: (I) information provision, i.e. interventions aimed at increasing the patient’s knowledge of cancer, its treatments, side effects and consequences; (II) support, i.e. interventions intended to help patients to cope with the implications of cancer and its treatment, e.g. express associated emotions, diminish a sense of isolation, identify unmet needs, take some control over events, deal with family members and health care personnel and accept losses and changed roles; (III) coping skills training, i.e. interventions targeted at attaining new cognitive-behavioral skills such as relaxation, mental imaging, thought and affect management and activity planning; (IV) psychotherapy, i.e. interventions delivered by a well-trained professional that aim to achieve a more fundamental psychological change to increase self-understanding via, for example, psychodynamic therapy and supportive-therapeutic approaches; and (V) spiritual or existential therapy, i.e. interventions promoting experiential awareness of a transcendent order or power, some sense of belonging to a meaningful universe including mediation and prayer (where meaningful to the patient), appropriate reading, discussion and reflection around spiritual topics [37]. In addition, psychosocial interventions may exist in different durations, formats (e.g. individual, group, or couple therapy), methods (e.g. face-to-face, telephone, or web-based), and can be delivered by different professions (e.g. psychologist or nurse) and at different moments (e.g. during or after primary cancer treatment).

Optimizing QoL with exercise and psychosocial interventions

Previous meta-analyses have evaluated the effectiveness of exercise and psychosocial interventions on QoL in patients with cancer [27-33]. In most studies, significant and positive effects on QoL were observed, although the mean effect sizes were small-to-moderate [27-33]. One possible explanation for the small effect sizes of exercise and psychosocial interventions is that these interventions are often evaluated in a heterogeneous group of patients with cancer and are not sufficiently targeted to specific cancer populations with the highest needs [38], or tailored to specific characteristics of patient groups. The development of targeted interventions can
contribute to more effective intervention programs [39]. It is therefore important to identify subgroups of patients that respond best to the intervention, by conducting moderation analysis [38]. Moderators are variables that affect the direction and/or strength of the relation between the intervention and outcome [40, 41]. This will inform clinical practice such that some interventions may only be used for a particular subgroup of patients with cancer, ensuring optimal use of limited resources [42].

Few previous studies have found that demographic, clinical and personal factors may moderate the effects of exercise and psychosocial interventions on QoL [43-47]. However, as these single studies have insufficient power to conduct stratified analyses by the moderator subgroup, the moderator effects found in previous single studies should be interpreted as exploratory analyses [38]. Thus, to study the moderators of exercise and psychosocial interventions on QoL, and to conduct subsequently stratified analyses by the moderator subgroup, a study with a much larger sample size is needed [38].

To further improve the effectiveness of exercise and psychosocial interventions on QoL among patients with cancer, insights in the working mechanisms of an intervention (i.e. insight into the mediators of the effect of an intervention) are needed [38, 48, 49]. Intervention mediators are intermediate variables that explain how or why an intervention influences an outcome [38].

Identification of mediators may help identify effective intervention components. By keeping effective intervention components and by removing ineffective ones, the cost-effectiveness and participant burden of the interventions can be improved [50]. Furthermore, identification of mediators may support in the building and refining of intervention theory [51]. For example, previous studies have shown that fatigue and psychological distress may mediate the relationship between physical activity and QoL [52, 53]. In addition, exercise effect on QoL may be mediated by physical activity, self-efficacy, mastery, fatigue, and distress [54]. However, studies investigating mediators of exercise and psychosocial intervention effects on QoL are scarce.
Predicting Optimal Cancer Rehabilitation and Supportive care (POLARIS) study

Meta-analyses that synthesize results of different individual studies inform health professionals about the best available treatment and are an integral part of evidence-based medicine [55, 56]. An important aspect of a meta-analysis is the ability to explore whether intervention effects vary or are moderated by study characteristics (e.g., type or duration of intervention) [57]. Subgroup analyses or meta-regression, in which the change in overall intervention effect in relation to study-level characteristics is investigated, are used to compare intervention effects across different modes of intervention or across different patient populations [57]. Summary data can be used to investigate these sorts of study-level interactions. However, to investigate interactions between the intervention and patient-level characteristics (e.g., age or stage of cancer), a meta-regression relies on summary data, such as the mean age of the patients [56, 57]. In contrast, a meta-analysis that uses individual patient data (IPD) is not limited to using summary data. It obtains and harmonizes the raw IPD from multiple related studies [56], and has the advantage to test interactions between interventions and patient-level characteristics using the large number of raw data points, conducting subsequent stratified analyses, and standardized analytic techniques across the included studies [58, 59]. IPD meta-analysis is therefore considered the ‘gold-standard’ to evaluate moderators of intervention effects with sufficient power [56, 60, 61], and it will help to ensure that clinical practice and research is informed by robust evidence about the effect of interventions [57].

To study moderator effects of exercise and psychosocial interventions on QoL, the Predicting Optimal Cancer Rehabilitation and Supportive care (POLARIS) study has been set up. For POLARIS, an international consortium and a database of IPD from multiple randomized controlled trials was created to (I) conduct an IPD meta-analysis to evaluate the effects of exercise and psychosocial interventions on the QoL in patients with cancer compared to a wait-list, usual care or attention control group, and to (II) identify demographic, clinical and personal characteristics, and intervention-related characteristics that moderate the effects of exercise and psychosocial interventions on QoL.

One of main challenges of an IPD meta-analysis is to harmonize raw data of
single studies. Harmonizing IPD from single studies is a timely endeavor, particularly when many eligible studies are available [62]. Difficulties may arise with harmonizing IPD as different studies often use different coding schemes or constructs [63]. A platform that enables harmonizing as soon as IPD from the first studies has been received is more time-efficient, especially when the number of variables and datasets are large. Thus, a flexible data harmonization platform that enables harmonizing data during data collection is therefore useful. To our knowledge, a platform allowing this flexible approach has not yet been developed.

**Aims and outline of this thesis**

This thesis aims to (I) investigate the effects of exercise and psychosocial interventions on QoL in patients with cancer during and after treatment and to assess the possible moderators of these intervention effects; (II) investigate the mechanisms of exercise interventions on QoL; and (III) build a flexible data harmonization platform that facilitates harmonizing data starting already during data collection.

Chapter 2 explores demographic, clinical and psychological moderators of the effect of a group-based physical exercise intervention on global QoL in patients with cancer who completed treatment. In this chapter, the moderator effects of age, gender, education level, marital status, employment status, type of treatment, time since treatment, the presence of comorbidities, fatigue, general self-efficacy, depression and anxiety are studied. Chapter 3 explores physical and psychological mediators of a combined resistance and endurance exercise intervention effect on QoL and physical function. This chapter investigates the hypothesis that combined resistance and endurance exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and improving global QoL and physical function among patients with cancer who completed curative treatment including chemotherapy. Chapter 4 describes the design of the POLARIS study which was set up to evaluate the effects of exercise and psychosocial interventions on the QoL of patients with cancer, and to identify demographic, clinical, and intervention-related moderators of these intervention effects. Chapter 5 contains the description of the development and use of a flexible data harmonization platform that facilitates harmonization of IPD for meta-analyses as used in the POLARIS study. Chapter 6 and 7 present the results of the POLARIS study, evaluating the effects of exercise
and psychosocial interventions, respectively, on QoL in patients with cancer, and studying demographic, clinical and intervention-related moderators of intervention effects. Finally, Chapter 8 summarizes and discusses the main findings of this thesis, methodological issues, clinical implications, and provides suggestions for future research.
References


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