Exercise Training in Cancer Control and Treatment

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ABSTRACT

Exercise training is playing an increasing role in cancer care, as accumulating evidence demonstrates that exercise may prevent cancer, control disease progression, interact with anti-cancer therapies, and improve physical functioning and psychosocial outcomes. In this overview article, we present the current state of the field of exercise oncology, which currently comprises of nearly 700 unique exercise intervention trials with more than 50,000 cancer patients. First, we summarize the range of these interventions with regard to diagnoses, clinical setting, timing, and type of intervention. Next, we provide a detailed discussion of the 292 trials, which have delivered structured exercise programs, outlining the impact of exercise training on cancer-specific, physiological, and psychosocial outcomes in the light of the challenges and physiological limitations cancer patients may experience. In summary, the safety and feasibility of exercise training is firmly established across the cancer continuum, and a wide range of beneficial effects on psychosocial and physiological outcomes are well documented. Many of these beneficial effects are linked to the general health-promoting properties of exercise. However, it is becoming increasing evident that exercise training can have direct effects on cancer and its treatment. This calls for future exercise oncology initiatives, which aim to target cancer-specific outcomes, and which are integrated into the concurrent cancer trajectory. Here, the field must bridge extensive knowledge of integrative exercise physiology with clinical oncology and cancer biology to provide a basis of individualized targeted approaches, which may place exercise training as an integrated component of standard cancer care. © 2019 American Physiological Society. *Compr Physiol* 9:165-205, 2019.

Didactic Synopsis

Major teaching points

- Of the almost 700 exercise intervention studies in cancer patients, the vast majority has been performed in early stage breast cancer
- Exercise training is safe and feasible across the cancer continuum
- Exercise training can improve physical functioning and psychosocial outcomes; however, adaptations in physiological outcomes may be hampered be adverse effects of concurrent anti-cancer treatment
- Exercise training may reduce chemotherapy-induced toxicities and improve treatment completion rates
- Early evidence indicates that exercise training may delay disease progression and improve survival
- Preclinical evidence points to rationales for an enhanced efficacy of anti-cancer therapy by exercise training
- Exercise training in cancer patients represents a continuum of stimuli, which may be adjusted according to the physical limitations cancer patients experience

Introduction

Cancer is one of the most deadly and debilitating diseases worldwide. More than 14 million people are diagnosed with cancer every year, and this number is expected to increase by 70% across the next two decades (170). It is estimated that two thirds of all cancers are caused by random errors during DNA replication (175, 176), although this fraction varies across organs and shows the highest fraction in organs with high rates of cell division, that is, immune cells, GI tract, and germ cell cancers. In contrast, some cancer diagnoses are highly linked to smoking and virus infections, making these factors major causes of cancers such as lung cancer, HPV

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positive head and neck cancer, and HCV positive hepatocarcinoma. Finally, lifestyle related factors such as smoking, diet, alcohol consumption, and physical inactivity can play a role in promoting cancer development and disease progression (15). These modifiable lifestyle factors are targets of large scale national and international cancer prevention campaigns (185), but with the exception of smoking cessation, changes in these lifestyle related risk factors may only prevent up to 25% of all new cancer cases (15). Fortunately, major progressions have been made across most cancer diagnoses in cancer management with improved detection and development of new therapies and treatment modalities (11). In modern cancer management, the majority of cancer patients received a battery of curative or palliative treatments, which have markedly increased both the number of cancer survivors living without detectable cancer disease, as well as the years, cancer patients may live with their cancer disease. Despite this, cancer is still plagued by high mortality, and heavy deconditioning and toxicities during anti-cancer treatment, calling for strategies, which together with the administered anti-cancer treatment, may improve treatment responses and lower toxicity burden. To this end, exercise training is gaining increasing ground as exercise interventions tailored to cancer patients are increasingly being developed and implemented in cancer care.

In this overview, we aim to provide a comprehensive overview of the field of exercise oncology. First, we provide a historical overview of the development of the research field, followed by a summary of all exercise intervention studies performed with regard to cancer diagnoses, clinical setting, and type of intervention. Next, we provide a detailed discussion of endpoints and outcomes included in published exercise intervention studies, according to three overall outcome categories: (i) cancer- and disease-specific outcomes, (ii) physiological outcomes, and (3) psychosocial outcomes. We discuss these outcomes in light of the current mechanistic and biological insight of exercise physiology in cancer patients. Lastly, we offer our views on the clinical and research perspectives of the field of exercise oncology.

History of Exercise Interventions in Patients with Cancer

Historically, patients with cancer were recommended to rest and avoid strenuous activity following their diagnosis, but this dogma has changed markedly over the last 20 years as exercise intervention studies and physical activity initiatives have gained widespread acceptance and popularity. While recommendations on physical activity to cancer patients only recently started to change, the notion that voluntary exercise could inhibit tumor growth in experimental rodent models dates back to the mid-1940s and the early work of Rusch and colleagues [(148), see Table 1]. In the aftermath of these early preclinical studies, focus on the relevance of exercise behavior was exclusively linked to cancer prevention, whereas studies examining the application of exercise interventions in populations with a cancer diagnosis remained nonexisting for more than four decades. Indeed, it was not until the mid-to-late 1980s that Mary MacVicar and Maryl Winningham conducted the pioneering work comprising the first randomized trial in patients with breast cancer exploring exercise training as a supportive care strategy during chemotherapy (189), and this work is today considered the origin of the modern exercise oncology research field. In the first decade after this seminal study, exercise intervention studies were heavily focused on utilizing exercise interventions as supportive care strategies with specific emphasis on the capacity of exercise training to counteract cancer-related fatigue and health-related quality-of-life (39). These early exercise trials demonstrated that the prior dogma of prolonged bedrest as the principle management of physical and mental fatigue in individuals with cancer was ineffective at best and inflammatory at worst.

Since these early studies, the number of clinical trials has increased exponentially, but perhaps more notably, the field has segregated with regard to the scientific scopes and related disciplines involved in exercise oncology research. In 1997, Dimeo and colleagues conducted a landmark study, demonstrating that hospital-based aerobic exercise was associated with lower risk of common chemotherapy-related complications including neutropenia, thrombopenia, severe diarrhea, pain, and length of hospital stay in patients undergoing high-dose chemotherapy before autologous blood stem cell transplantation (49). In addition to these clinically relevant outcomes, the authors reported significant improvements in physical performance as a direct consequence of exercise training. This study indicated that exercise training can have immediate beneficial impact on important clinical outcomes when integrated into the clinical setting, in this case during

Table 1 Early Animal Studies with Exercise and Cancer

As early as in 1911 was, the first medical record describing a relationship between exercise and cancer published (162), and in 1938, the first experimental study in animals demonstrated that physical activity could alter the course of tumor growth. Here, both exercise and caloric restriction proved to reduce tumor onset and progression in both transplantable and genetic tumor models (162). In particular, the focus on energy regulation went well with the contemporary and seminal discovery by Otto Warburg that tumors obtain most of their energy from anaerobic glycolysis (183, 184). In 1943, Rusch and Kline placed Swiss Albino mice in slowly rotating cylindrical wire-mesh cages for 16 hours daily and showed that this nonexhaustive physical activity significantly reduced the growth of mouse fibrosarcomas (148). In 1952, Rashkis subjected Swiss Albino mice to swimming for 1.5 to 4.25 h per day in glass jars, and found that this strenuous exercise training significantly reduced the growth of ascites tumors, as well as chemically induced epithelial tumors (141). From the 1980s and onward, investigations into the role of exercise in tumor control gained moment, in particular with interventions using running wheels placed in the home cages of the rodents and later treadmill running. Collectively, the bulk of exercise intervention studies in rodents indicated that exercise training inhibits tumor incidence, progression, and metastasis (138).

hospitalization for high-dose chemotherapy and stem cell transplantation.

In parallel, a plethora of studies has emerged focusing on ameliorating more indirect symptoms of cancer treatment. This line of studies was initiated with a landmark study by Segal and colleagues who showed that self-directed exercise or supervised exercise improved physical functioning and reduced body weight in 123 breast cancer survivors (156). This study was the first exercise intervention study to be published in the prestigious *Journal of Clinical Oncology (JCO)*, the official journal of American Society of Clinical Oncology. This paper was put in perspective by another JCO publication by Wahnefried and colleagues showing that excess body weight, specifically fat mass, was associated with reduced physical activity in women with breast cancer undergoing chemotherapy (43), highlighting that a main part of the weight gain experienced by women with breast cancer was due to physical inactivity.

In continuation of these early intervention studies, the attention toward the role of physical activity and exercise behavior on prognosis and secondary risk of cancer emerged from the millennium and onward with solid epidemiological studies demonstrating a tight correlation between physical activity and survival in cancer survivors. It has long been recognized that exercise behavior, evaluated as self-reported physical activity level, is associated with lower risk of cancer, and constitutes an independent predictor of overall and cancer-specific mortality in healthy subjects (14, 118). In 2005, Holmes and colleagues published findings from the "Nurses' Health Study," an epidemiological cohort study of more than 100,000 healthy women who were followed longitudinally for health behavioral factors (73). From the background cohort, Holmes and colleagues identified 4484 women who were diagnosed with breast cancer up till 2002, and included 2987 women with nonmetastatic breast cancer who had provided data for physical activity at least 2 years after their diagnosis in the final analyses. The study showed that for women, who engaged in more than 9 MET h/week of physical activity, the relative risk of breast cancer specific death was 0.63 (95% CI, 0.48-0.81), suggesting that behavior after a cancer diagnosis is inversely associated with breast cancer-specific mortality risk. This association has since been demonstrated across several other malignancies, including prostate and colorectal cancer (89, 114, 182).

Along these observational reports, pointing directly to a prognostic importance of physical exercise after cancer diagnoses, were initiatives aimed at elucidating the underlying biological mechanisms undertaken. These initiatives have been heavily influenced by prior studies demonstrating that metabolic and inflammatory disturbances were associated with weight gain following a cancer diagnosis, particularly in long-term survivors of breast, prostate, and colon cancer. As a result, it became a dominating view that obesity-driven physiological changes such as increases in circulating sex hormone and metabolic hormone levels, and poor immune function, were principle candidates for the risk of disease recurrence and mortality. It was therefore proposed that the effect of exercise training on cancer mortality was driven by weight control and associated lowering of the adiposity-related risk factors, as summarized in the seminal review by McTiernan (111).

With the emerging evidence on the beneficial effect of exercise training on cancer outcomes, arose the question of which type of training, cancer patients should perform. To this end, Courneya and colleagues published another seminal paper, reporting on the results of the START trial, which was the first large-scale RCT to compare the effects of different exercise modalities in a three parallel-group design, randomizing patients to either aerobic exercise, resistance training, or usual care in women with breast cancer receiving adjuvant chemotherapy. The study showed—not surprisingly—that different training modalities led to different adaptations with resistance training improving muscle strength and lean body mass, while aerobic training was superior in improving fitness levels and fat percentage. While these finding may have been expected, the study demonstrated that "normal" exercise adaptations can be achieved in breast cancer patients during concurrent treatment, emphasizing that the physiologically response to exercise training largely resembles that of non-cancer populations. Furthermore, the study provided another highly interesting finding, as it was observed that women with breast cancer in the resistance-training group had higher compliance to their adjuvant chemotherapy, indicating that exercise training improved treatment tolerance. These findings expand on the original findings by Dimeo and colleagues in 1997 (49).

With emerging evidence pointing toward a potential synergetic effect of exercise and chemotherapy when delivered in conjunction, clinical interest developed toward the application of exercise training as a cancer-treatment moderator. However, despite promising data from epidemiological studies and experimental models, the field of exercise oncology still has limited evidence to demonstrate that structured exercise training may improve hard clinical endpoints, that is, mortality or disease progression in large randomized controlled trials. In 2014, Courneya and colleagues published a paper with 8-year follow-up data from the aforementioned START trial and found, encouragingly, a 25% reduction in the risk of death for the two training groups compared with the usual care group. However, the study did not have sufficient power to demonstrate statistically significant difference (36). In direct continuation, two large RCT studies have been initiated to explore the definitive effect of exercise training on survival, including the ongoing CHALLENGE trial in colon cancer survivors and the INTERVAL study in metastatic prostate cancer patients (33, 124).

This historical tour de force through the field of exercise oncology highlights that the field has evolved extensively over three decades from the early work specifically aimed at improving cancer-related symptom burden, toward modern research initiatives now addressing every conceivable outcome in cancer patients (Fig. 1). In parallel, preclinical studies have explored the biological interactions between

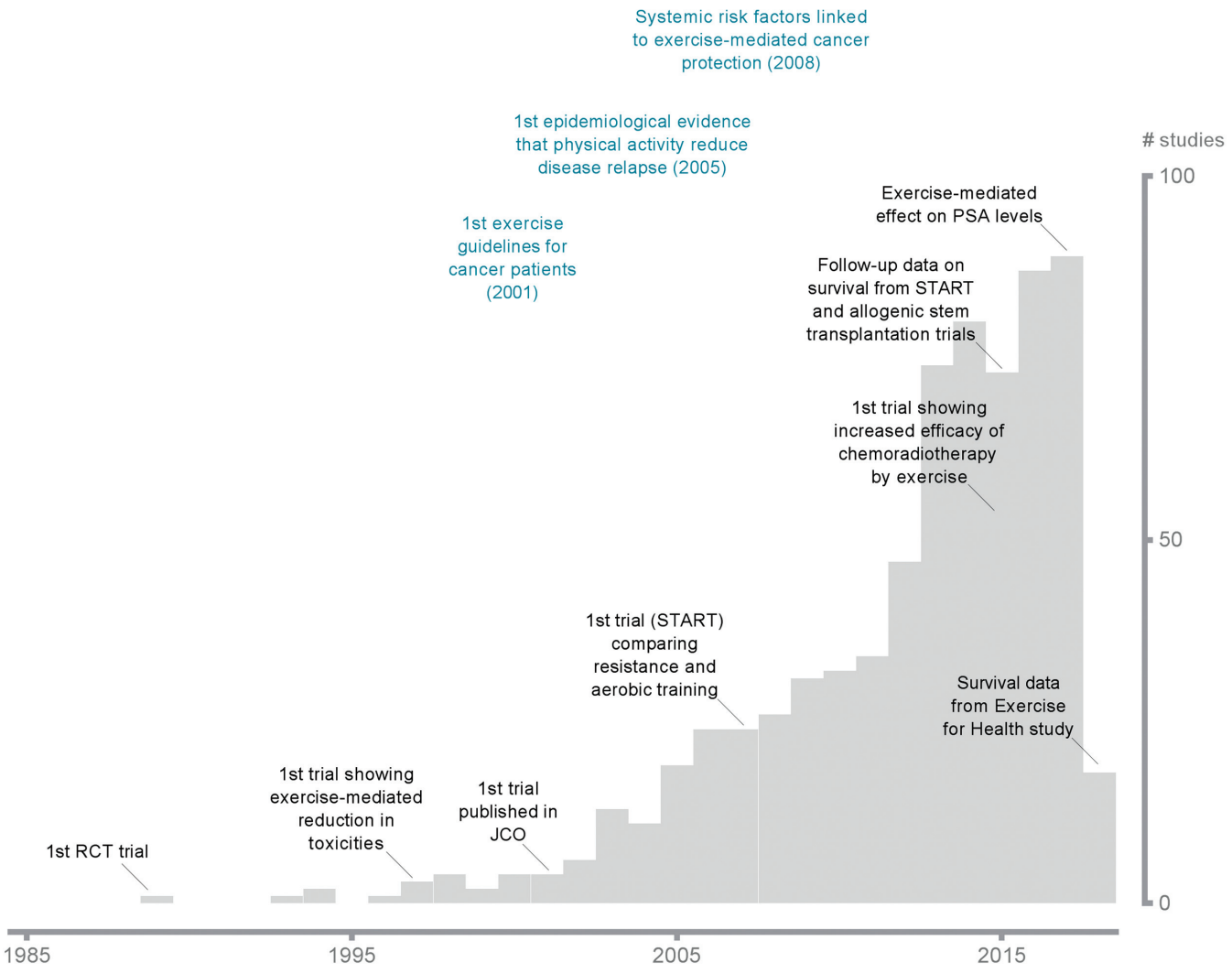


Figure 1 Historic overview of exercise intervention studies in cancer patients. Here, the time course of the number of published exercise intervention studies in cancer patients is presented. Seminal clinical exercise intervention trials are highlighted in black at the time of publication. Other important contributions to the field are inserted in blue, including the first publication of exercise guidelines in cancer patients, the first epidemiological evidence for a protective effect of exercise on relapse and mortality in cancer patients, and the first major review to summarize the role of exercise-dependent regulation of systemic cancer risk factors.

exercise and cancer, and recent results from a number of cell culture, animal, and translational human studies have demonstrated direct inhibitory effects of exercise factors on cancer. These exercise factors are released during acute bouts of exercise and include catecholamines (e.g., epinephrine and norepinephrine), myokines (e.g., SPARC and OSM), and immune cells [as reviewed in (47)]. Essentially, the field of exercise oncology is currently at a stage where methodological approaches span the entire scale from experimental laboratory work to real-life evidence-based epidemiology, examining applications of exercise interventions and behavior at multiple levels. This comprehensive evidence base provides clinicians and physiologists with a unique, but also highly complex scientific discipline. To devise a comprehensive overview of the field of exercise oncology, we focus our discussion on the cancer-specific, physiological and psychosocial outcomes that exercise training have been proposed to target. This approach highlights that exercise training may play distinct and diverse roles dependent on where in the cancer trajectory patients are introduced to exercise training.

Summary of Exercise and Physical Activity Intervention Studies in Cancer Patients

The state of the exercise oncology field was assessed through a comprehensive literature search for all PubMed indexed exercise and physical activity intervention studies performed in cancer patients from 1986 until today (Fig. 2). We defined exercise and physical activity interventions as physical

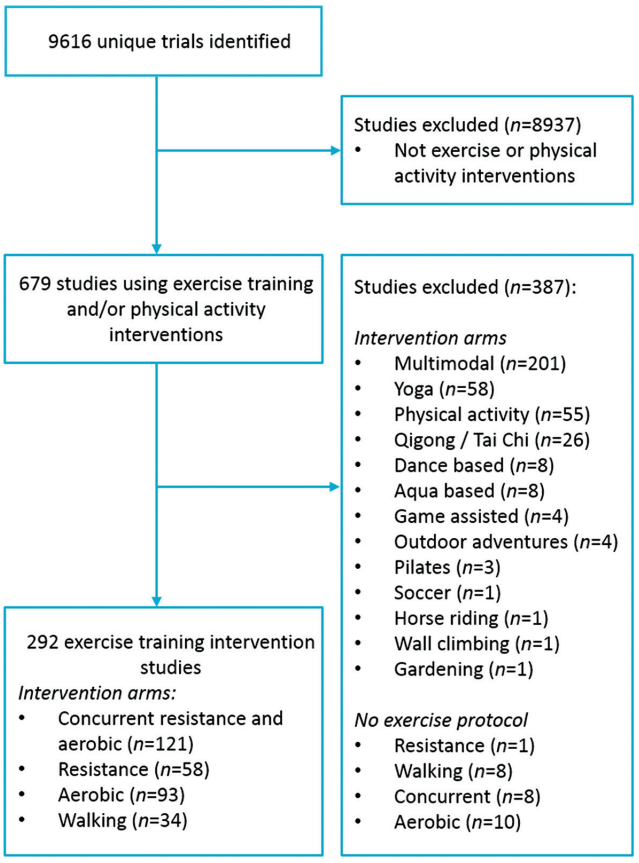


Figure 2 Flowchart of the screening process for exercise intervention studies. The figure provides an overview of the screening process for exercise intervention studies. Presented first is the total number of PubMed indexed studies ($n=9616$) identified using our search string. The total number of studies were screened on title and abstract for studies utilizing exercise and physical activity interventions, which resulted in 679 studies. Next, we differentiated between studies applying structured exercise interventions and physical activity interventions. Exercise interventions were defined as structured, planned, and repetitive interventions aiming to maintain or improve physical fitness. Thus, studies, which did not provide a description of the exercise protocol, were excluded. Furthermore, we excluded studies applying multimodal interventions (e.g., combined exercise and diet interventions), counseling-based physical activity studies, holistic training including yoga or tai chi and other preference-based interventions. Based on these inclusion criteria, 292 unique exercise intervention studies were identified. For both exercise training intervention studies ($n=292$), and the excluded studies ($n=387$), we determined the number of specific intervention arms evaluated (note: the number of intervention arms do not add up to the total number of studies as some studies included more than one intervention arm).

interventions, which include any component of metabolic challenge on the whole-body physiological system. Thus, structured aerobic and resistance training programs, as well as free-living walking, promotion of physical activity and sports activities were included as exercise and physical activity interventions in this overview, but specific supportive care interventions, for example, pelvic floor exercises, inspiratory muscle training/breathing exercises and swallowing exercises were excluded.

Literature search terms

We searched for all PubMed indexed exercise studies published until February 22, 2018. The search was performed using two blocks of keywords related to cancer and exercise. The keywords were searched in title, abstract, and MeSH terms. A full overview of the search strategy is available in *Supplementary material 1,* and the full list of identified studies is available in *Supplementary material 2*, found at https://onlinelibrary.wiley.com/doi/full/10.1002/cphy.c180016.

Cancer diagnoses and disease stages

Cancer covers more than 100 different diagnoses based on cancer site and with most primary diagnoses further subcategorized based on gen-mutational profile and/or anatomical position. We identified 679 unique exercise and physical activity intervention studies in which 50,112 patients were enrolled (Table 2). Of the studies only including patients of a single cancer diagnosis, studies with women with breast cancer comprised the vast majority namely 292 studies (59.6%) including 20,808 patients (65.7%), almost 2/3 of all cancer patients enrolled in training studies. Of these studies with women with breast cancer, 49 studies included more than 100 patients, 149 studies included 30 to 100 patients, while 94 studies included less than 30 patients, highlighting that most studies are small- to medium-sized intervention studies. The three other large patient populations, that is, prostate, lung and colorectal cancer, comprise the second most studied patient groups with respectively 51 studies (9.8%) in prostate cancer, 48 studies (9.3%) in lung cancer, and 35 studies (6.8%) in colorectal cancer. Besides these large groups, exercise and physical activity intervention studies have been performed across a wide range of smaller diagnoses, but with less than a handful of studies within each group (Table 2). In addition to the diagnosis specific studies, 189 studies (27.8%) with 18,387 patients have enrolled patients with mixed diagnoses. Within these studies of mixed populations, the distribution between the different diagnoses follows the overall picture with a large majority of women with breast cancer participating.

The majority, 645 studies (95%), included adult participants, while 32 studies were performed in childhood cancers, that is, hematological diseases, bone cancer and brain cancer. Moreover, two studies intervened for survivors of childhood cancer in the adult years. The vast majority of the studies (559 studies, 82.3%) included patients with early stage disease (39,195 patients, 78.2%), while 40 studies included patients with advanced stage cancer (1,737 patients) and 80 studies included patients with early and advanced stage disease (9,180 patients).

Cancer setting

From the point of diagnosis, cancer patients move through a treatment trajectory, which comprise a window of preoperative optimization, which may include neoadjuvant therapy,

Table 2 Exercise Intervention Studies According to Cancer Diagnosis

Diagnosis	# studies	% studies	# patients	% patients
Breast cancer	292	59.6	20,808	65.6
Prostate cancer	45	9.2	3,881	12.2
Lung cancer	44	9.0	2,022	6.4
Colorectal cancer	32	6.5	1,806	5.7
Head and neck cancer	15	3.1	533	1.7
Hematological cancers				
Blood cancers, diverse	11	2.2	487	1.5
Acute lymphoblastic leukemia	8	1.6	247	0.8
Multiple myeloma	3	0.6	248	0.8
Acute myeloid leukemia	2	0.4	93	0.3
Lymphoma	2	0.4	161	0.5
Gynecological cancers				
Ovarian cancer	7	1.4	111	0.3
Endometrial cancer	3	0.6	336	1.1
Div. gynecological caner	3	0.6	150	0.5
Brain cancers	5	1.0	155	0.5
Gastric cancer	2	0.4	105	0.3
Germ cell cancer	3	0.6	105	0.3
Esophageal cancer	2	0.4	71	0.2
Bone cancer	2	0.4	52	0.2
Bladder cancer	2	0.4	125	0.4
Thyroid cancer	2	0.4	76	0.2
Colorectal liver metastases	1	0.2	38	0.1
Liver cancer	1	0.2	51	0.2
Pancreatic cancer	1	0.2	20	0.1
Kidney cancer	1	0.2	32	0.1
Melanoma	1	0.2	12	0.0
TOTAL	**490**	**100**	**31,725**	**100**
Mixed diagnoses	189		18,387	
TOTAL	**679**		**50.112**	

surgical tumor resection, adjuvant therapy including chemo- and/or radiotherapy, and after this curative intended treatment return to normal life in the survivor phase (Fig. 3). This trajectory varies in extend and form across different cancer diagnoses, but is typically characterized by acute symptom burden, including hospitalization, treatment toxicities, mental distress, as well as long-term complications, which can influence the capability to exercise. Accordingly, we stratified the available exercise and physical activity studies based on the clinical setting, (i) preoperative optimization, (ii) during treatment, (iii) after complication of primary treatment, and (iv) advanced stage cancers (Fig. 3).

We identified 33 studies, which were conducted prior to cancer surgery. These studies have primarily been conducted in patients with lung cancer [11 studies (33%) and gastrointestinal cancers, i.e., colorectal cancer (7 studies), gastric cancer (1 study), esophageal cancer (1 study), colorectal liver metastases (1 study), and pancreatic cancer (1 study)].

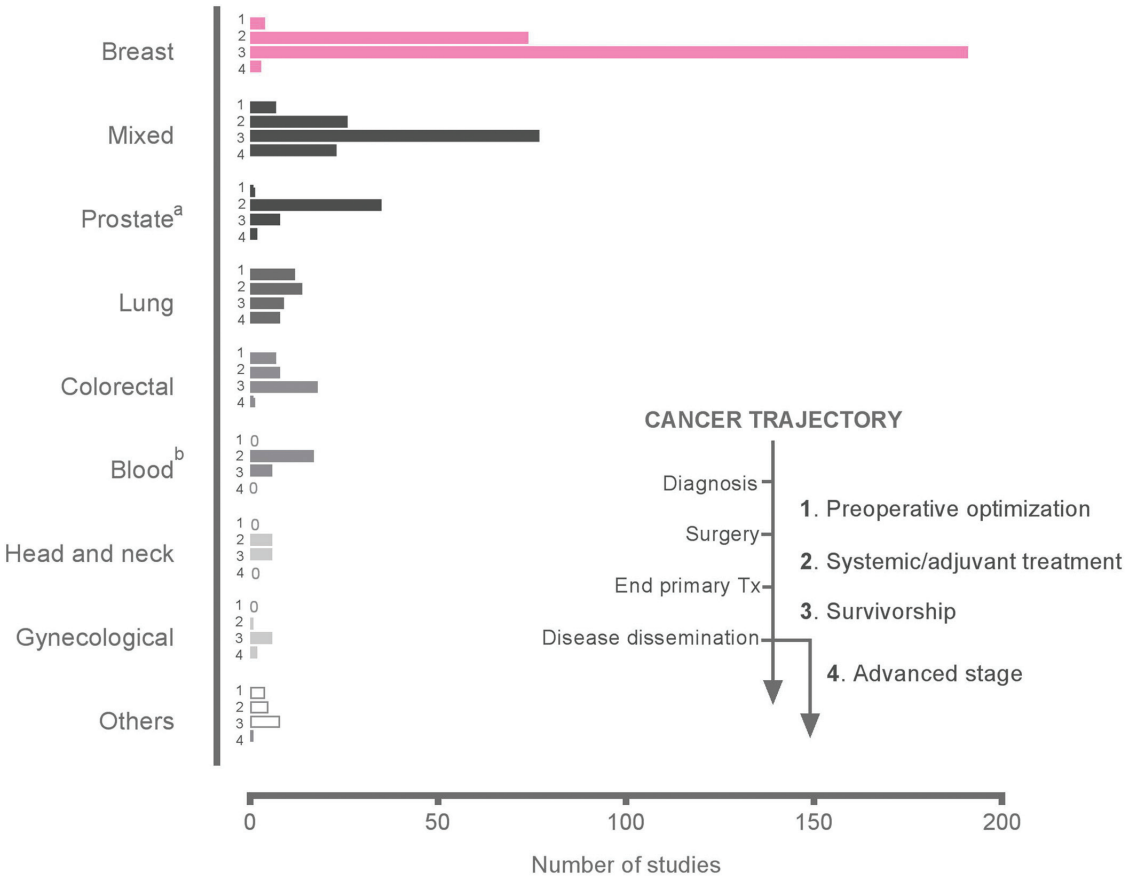


Figure 3 Overview of exercise intervention studies across the cancer trajectory. The figure illustrates the number of exercise intervention trials performed according to diagnosis. Further, trials are subcategorized by timing relative to primary treatments. We distinguish between four overall clinical settings: (i) exercise interventions prescribed before surgery as preoperative optimization, (ii) exercise interventions prescribed during systemic adjuvant therapies for patients treated with curative intend, (iii) exercise interventions prescribed after completion of curative and/or adjuvant therapy, and (iv) exercise interventions prescribed for patients with metastatic cancer with or without concurrent palliative treatment. [a]For studies in prostate cancer, systemic/adjuvant treatment includes radiotherapy and androgen deprivation therapy without surgery in patient with local or locally advanced stage disease.[b]For blood cancers, adjuvant/systemic treatment includes high dose chemotherapy prior to or during inpatient chemotherapy after allogenic stem cell transplantation in the vast majority of studies.

Moreover, four studies have been conducted in breast cancer during neoadjuvant chemotherapy, one in prostate cancer, and six in mixed cancer diagnoses.

After radical tumor resection, the majority of cancer patients undergo adjuvant treatments with, for example, chemo-, chemo-radio-, or hormonal therapy, and exercise interventions are thus administered either during or after this course of primary treatment. For the largest group namely the breast cancer patient, 25.6% of the studies were conducted concurrent with adjuvant chemotherapy, while 66.1% of studies were performed after completion of primary treatment. The same pattern was found in studies, which included populations of mixed diagnoses, and given the large majority of studies in breast cancer and mixed population, the overall picture is that 5.4% of all studies have been performed prior to tumor resection, 25.2% of all studies during adjuvant treatment, 52.9% of all studies after completion of primary treatment, and 16.4% of all studies at various stages of the treatment trajectory. Of the 40 studies enrolling advanced stage cancer patients, more than half (23 studies) enrolled patients with mixed diagnoses, while 8 studies enrolled patients with lung cancer. The remaining studies were performed in breast cancer (three studies), ovarian cancer (two studies), prostate cancer (two studies), colorectal cancer (one study), and germ cell cancer (one study).

Lastly, prostate cancer differs somewhat from other diagnoses with regard to staging, treatments, and follow-up. Early stage prostate cancer patients may be followed in active surveillance, where the disease is monitored the routine PSA assessments, but with no concurrent treatment. In this early stage of the prostate cancer trajectory, one exercise intervention study has been performed. At disease progression, prostate cancer patients may undergo tumor resection, radiotherapy, and/or androgen deprivation therapy (ADT). In

Table 3 Type of Interventions in Exercise Intervention Studies in Cancer Patients

Intervention	# studies
Concurrent aerobic and resistance training	129
Aerobic training	95
Resistance training	59
Yoga	58
Counseling	49
Walking	42
Qigong	14
Tai chi	12
Aqua-based training	9
Dance	7
Games (TV, computer, etc.)	4
Dragon boat racing	4
Outdoor adventure	3
Pilates	3
Football/Soccer	1
Horse riding	1
Whole body vibration	1
Triathlon training	1
Wall climbing	1
Gardening	1
Multimodal interventions	201

particular, ADT therapy is associated with large metabolic disturbances, and thus most exercise intervention studies [25 studies (56.8%)] have been conducted during ADT. In addition, five studies (11.4%) were performed concurrent with adjuvant treatment and five studies (11.4%) after completion of treatment (Fig. 3).

Type of intervention

A wide range of different training interventions has been explored in the identified studies (Table 3). One hundred twenty-nine studies (19.0%) have prescribed concurrent aerobic and resistance training, 95 studies (14.0%) have prescribed aerobic training alone, and 59 studies (8.7%) studies have prescribed resistance training alone. Of these, 10 studies have compared the effect of aerobic and resistance training in different intervention arms in the same study. Structured walking interventions have been explored in 42 studies with breast, prostate, lung, and ovarian cancer patients. In addition to these traditional exercise designs, studies have applied more holistic training forms, that is, yoga (58 studies), qigong (14 studies), tai chi (12 studies), and pilates (3 studies).

Smaller studies have explored interventions, which may speak to more personal preferences, that is, aqua-based training (eight studies), dance classes (eight studies), game-assisted training (e.g., Wii fit) (four studies), dragon boat racing (four studies), outdoor adventures (four studies), team-based soccer practice (one study), horse riding (one study), triathlon training (one study), wall climbing (one study), and gardening (one study).

We also identified 55 studies, which in some form, utilized counseling to enhance physical activity levels. These interventions used anything from structured motivation interviews and telephone counseling, to IT-supported counseling through smartphone applications, video-based material, social media groups, and traditional written pamphlets and materials. Also included in this group are interventions with recommendations from the treating physician and single consultations with a nurse or physiotherapist.

The largest number of studies, 201 studies (29.6% of all studies), explored multimodal interventions, in which training interventions were combined with other initiatives in particular diet interventions and other health promoting activities to improve lifestyle behaviors. A cancer diagnoses has been described as an "open window of opportunity" where many patients are motivated for lifestyle changes, which in psychological terms has been labeled a teachable moment and thus represent an optimal timing for targeted interventions aimed at smoking cessation, diminishing of alcohol intake, weight loss, and promotion of physical activity. Such interventions clearly have relevance for individual patients, but for the purpose of this overview, we will only present and discuss exercise-specific interventions, and therefore exclude reports where any exercise-dependent impact cannot be teased out from other health interventional components.

In summary, the overwhelming majority of exercise and physical activity intervention studies have been performed in breast cancer patients, in particular as physical rehabilitation after primary anti-cancer treatment. Experiences from these numerous studies in patients with breast cancer can likely be extrapolated to patients with other cancer diagnoses within the context of cancer rehabilitation. However, high-quality studies in patients with other diagnoses than breast cancer are still warranted, and exercise trials targeting the cancer-specific challenges associated with preoperative optimization and tolerability of intensive anti-cancer treatments are scarce. Also, the current body of evidence in the exercise oncology field involves a myriad of nonspecific interventions, which either does not target physiological, for example, cardiovascular or muscular-skeletal, systems or comprise multimodal components, which does not allow for evaluation of exercise-specific effects. To advance the scientific rationale for exercise training as a clinical cancer treatment strategy, targeted exercise programs designed on the principles on training to improve specific physiological systems need as a minimum to be clearly distinguished from supportive care interventions, which may involve physical activity as a behavioral component or endpoint.

Summary of Trial Outcomes in Exercise Oncology

In the current exercise oncology literature, exercise training has been proposed to address and improve almost every conceivable outcome in patients with cancer. The wide range of outcomes suggested to be improved by exercise range from psychosocial outcomes, for example, quality of life (QoL), depression, cancer-related-fatigue, anxiety, body-image and self-esteem, sleep quality, across direct physiological effects of the exercise training, such as fitness levels, oxygen consumption, muscle mass and strength, and exercise-related functional outcomes such as functional capacity and body composition, to symptom-driven trials for lymphedema, bone health, sexual performance, incontinence, etc. Moreover, exercise interventions have been proposed to help cancer patients return to work earlier and lower sick leave after successful treatment (62, 101, 177) and to improve disease-specific outcomes, including survival, disease progression, treatment tolerability, treatment response, regulation of tumor markers, risk factors, as well as other biological mechanisms, highlighting the wide range of complaints and symptoms that exercise training has been suggested to improve in cancer patients.

While exercise-enthusiasts point to its multifactorial impact as a pleotropic miracle pill, this attitude is difficult to use constructively in the clinical setting. For further development and integration of exercise interventions in clinical oncology, it is critical to adapt an outcome-driven approach, where exercise training is prescribed with the aim of targeting specific and well-defined outcomes. Generally, exercise training is considered to be health promoting for all humans (137), not just patients with cancer, but cancer patients may have specific reasons to engage in physical training. Exercise may ameliorate anti-cancer treatment toxicities, enhance treatment efficacy, or directly affect tumor progression, altogether these effects lead to improved overall survival for the cancer patients (72). Yet, to fully explore the therapeutic potential of exercise training, it is of paramount importance to understand the mechanistic interactions between different modes and intensities of training, the different settings and diagnoses of cancer, as well as any interactions with the prescribed anti-cancer therapy. As evident from the overview above the research field of exercise oncology still has a long way to go to accomplish this.

For the purpose of this overview, we have divided the trial outcomes into three overall categories. First, we present exercise impact on cancer- and disease-specific outcomes, including survival, disease progression, treatment tolerability, treatment response, regulation of tumor markers and risk factors, as well as other biological anti-cancer mechanisms. Second, we outline the direct effects of exercise training on physiological outcomes including aerobic fitness levels/maximum oxygen consumption, muscle mass and strength, functional capacity, and body composition. Finally, we summarize the impact of exercise on important psychosocial outcomes including health-related quality of life (HRQoL), depression, and cancer-related fatigue (Fig. 4). We have narrowed our initial literature search to exercise studies based on the definition of exercise being structured, planned and repetitive interventions with an objective of improving or maintaining physical fitness (19), thus applying structured exercise programs following exercise physiology principles. Therefore, multimodal interventions, counseling-based studies, holistic training modalities, and other preference-based interventions are discarded in this part. This narrowed the number of studies to 292 unique trials with 19,346 patients enrolled.

Cancer and Disease Specific Outcomes

The cancer trajectory is associated with serious acute and long-term adverse reactions to the primary treatment. In recent years, substantial progress has been made for prognostic outlook for early stage cancers, and in parallel, a growing number of cancer patients are living with disseminated disease for several of years, given the progress in anti-cancer treatment. The principle scientific question in the exercise oncology field is whether exercise training has the capacity to impact the course of the disease in this trajectory, and specifically, if exercise training may affect outcomes directly linked to cancer prognosis. In the following section, we discuss the current available evidence describing an impact of exercise training on (i) disease outcomes, including disease progression and disease-free survival, (ii) interaction with primary treatment, including improvement of treatment tolerability and enhancement of treatment efficacy, and (iii) secondary prevention of long-term adverse effect, that is, cardiotoxicities and metabolic disturbances, which may be associated with disease relapse or mortality from other causes (Fig. 5).

Disease outcomes

Disease progression and disease-free survival

Relative survival rate is the principle outcome in clinical oncology, and comprises both cancer and non-cancer specific mortality risk. Of primary importance for the cancer-specific risk of mortality is measures of tumor progression, that is, time to tumor progression and disease-free survival. We identified 10 intervention studies, which have investigated the effect of exercise interventions on survival and two studies reporting on disease progression as key endpoints (22, 36, 37, 77, 80, 103, 127, 143, 190, 191). For instance, Rief and colleagues investigated the effect of supervised resistance training initiated concurrent with radiotherapy in a mixed group of patients ($n = 60$) with bone metastases. The training was continued for 6 months in a home-based setting after 2 weeks of support. No local bone metastasis progression was observed in the exercise group 0% compared with 16.7% in the control ($P = 0.02$), and systemic disease progression

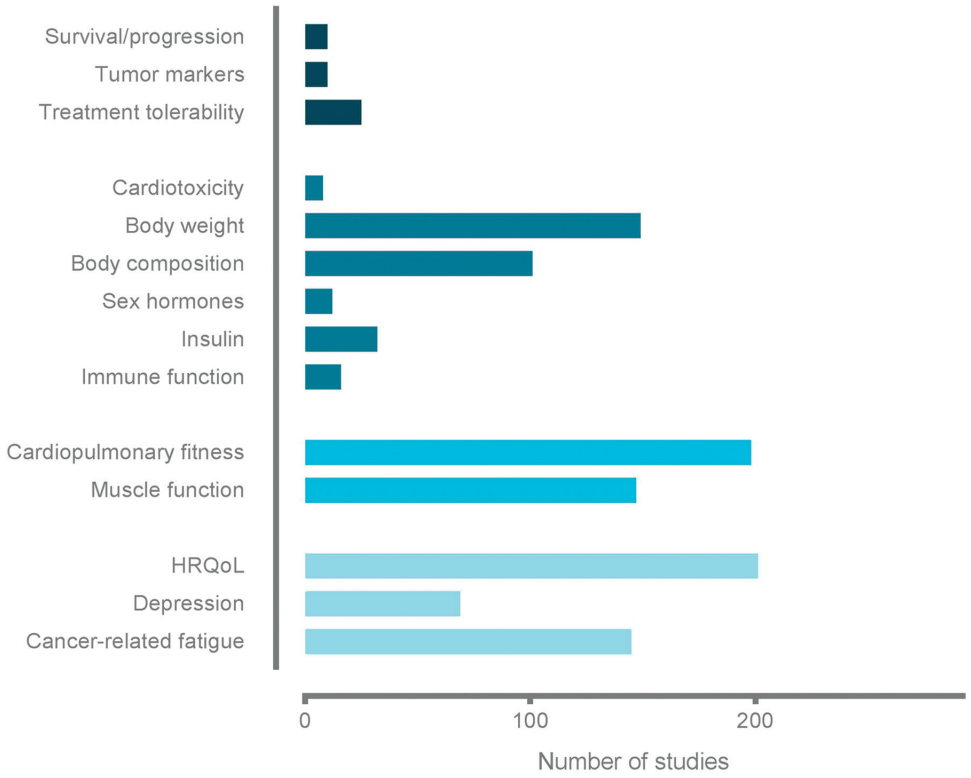


Figure 4 Summary of the outcomes measured in exercise-oncology trials. Here, we present an overview of the number of different outcomes reported in the 292 unique exercise intervention studies, which examined the effects of structured exercise programs identified in our PubMed search. Overall, we divide these outcomes into four different categories: (i) cancer-specific outcomes, that is, survival, disease progression, regulation of tumor markers, and treatment tolerability; (ii) secondary prevention outcomes, that is, cardiotoxicities, body weight, body composition, sex hormone levels, insulin levels, and immune function; (iii) exercise-specific physiological outcomes, that is, cardiopulmonary fitness and muscle function; and (iv) psychosocial outcomes, that is, health-related quality of life (HRQoL), depression, and cancer-related fatigue.

also tended to be lower in the exercise group compared with the control group (73% vs. 90%, $P = 0.095$). There was no effect on overall survival at 12 and 24 months (143); however, it should be noted that there was an uneven distribution of patients with more lung cancer patients in the exercise group and more prostate cancer patients in the control group. Karenovics and colleagues investigated if short-term high-intensity interval training prior to lung cancer surgery could improve long-term postoperative outcomes. Across a waiting time of median 25 days, 151 patients participated in between 7 and 10 exercise sessions prior to lung cancer surgery or usual care. At 1-year follow-up, 93% of the patients in the exercise group were alive compared with 91% in the usual care group ($P = 0.51$) (87). Moreover, both groups declined to similar extend in pulmonary function, suggesting that this short intervention had little effect on long-term outcome. Lastly, Yeo and colleagues randomized 102 patients with resected pancreas or periampullary cancer to a 3 months home-based walking program. The follow-up period was not long enough to reach a median survival, but using cox regression analyses to compare cases of pancreas cancer, the authors found a hazard ratio of 1.3 (95% CI 0.7-2.5) for usual care compared to the home-based walking group (191).

It is difficult to make solid conclusions on disease progression based on these few studies, thus larger-scaled studies with a substantial exercise volume and duration is required to evaluate survival as a primary endpoint. Two such large-scale randomized controlled exercise intervention trials are currently ongoing, namely the CHALLENGE trial, targeting 962 colon cancer patients with disease free survival after 3 years as the primary endpoint; and the INTERVAL trial, targeting 866 metastatic prostate cancer patients with overall survival as the primary endpoint (33,124). The results of these studies are highly anticipated although both studies include close to 1000 subjects and involve 3-year interventions thus require much longer trial periods than previous trials.

In the meantime, initiatives to pool individual patient data in electronic databases from already conducted exercise intervention trials, could allow for secondary analyses on a larger patient material. Such meta-analyses have already been published describing the effect of exercise interventions on physical functioning and psychosocial outcomes, as well as identifying moderators and mediators for these responses (16,85). Thus, there is a considerable potential for such databases to link up with regular patient follow-up and clinical evaluations. Indeed, with the larger exercise intervention trials available,

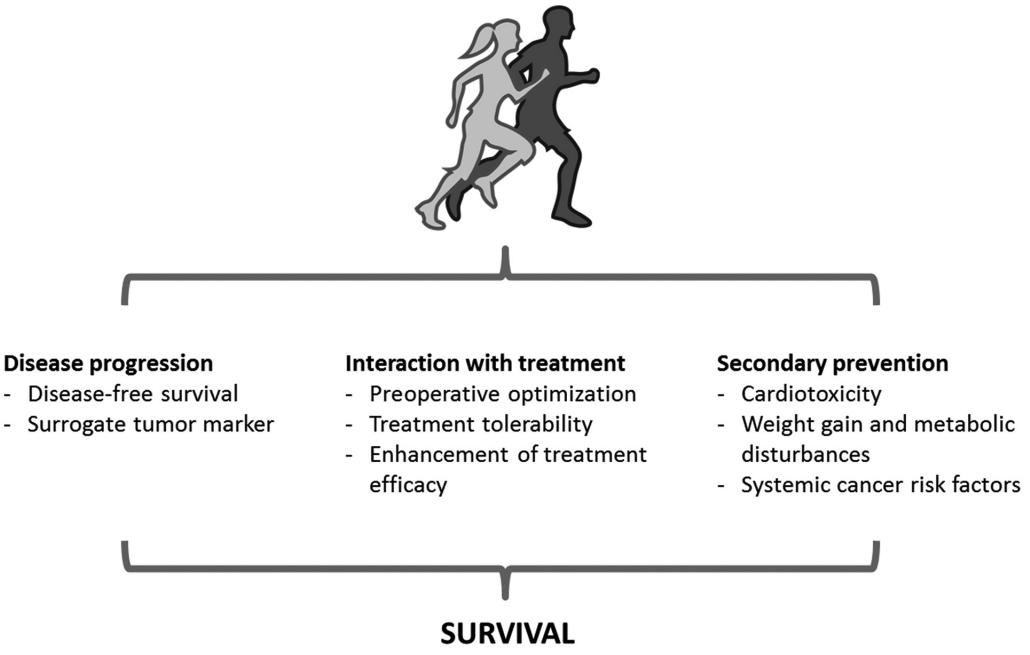


Figure 5 Factors linking exercise training to cancer survival. The association between exercise behavior and cancer prognosis is well established, and this protective role is likely mediated by a wide range of exercise-dependent responses. Here, we outline three interrelated modes-of-action, through which exercise training may directly or indirectly influence the prognostic outlook following a cancer diagnosis. Exercise training may influence the risk of clinical disease progression, evaluated by disease-free survival or surrogate tumor markers, by imposing direct antiproliferative actions on residual tumor cells. In addition, exercise training may interact with the impact of standard treatment in different settings including preoperative optimization, improvement of treatment tolerability and/or enhancement of antineoplastic efficacy. Finally, exercise training can play a critical role in secondary prevention of acute- and late-occurring detrimental health-effects associated with cancer and its' treatments, including protection from cardiotoxicity, weight gain, metabolic disturbances, and dysregulation of systemic cancer risk factors.

pooling of data from existing trials, as well as high-quality observational data from real-world practice and registries, where exercise programs has been implemented, secondary analyses could be important tools for elucidating the effects of exercise on cancer specific survival.

Three individual studies have conducted secondary analyses on disease progression in follow-up reports. Courneya and colleagues re-visited the data from the previous mentioned START trial after 8 years of follow-up in 242 women with breast cancer and found a disease-free survival rate of 82.7% in the training groups and 75.6% in the control group (HR 0.68, 95% CI 0.37-1.24) (36). Similarly, overall survival was 91.2% in the exercise group and 82.7% in the control group (HR 0.60, 95% CI 0.27-1.33). The trial was not powered to detect significant differences in disease-free and overall survival, but sub-group analysis showed that patients, who received more than >85% of the prescribed chemotherapy during the exercise intervention, tended to have improved disease-free survival (HR 0.5, 95% CI 0.25-1.01) (36), indicating a synergetic effect with adjuvant chemotherapy on survival outcomes.

Hayes and colleagues also re-addressed 8-year follow-up data from the Exercise for Health trials, which include trials of women with breast cancer living in either urban or rural Australia, and who were randomized to 8 months of combined aerobic and resistance training after surgery ($n = 337$) (68). The overall survival was 94.7% in the training groups compared with 88.5% in the usual care group (HR 0.45, 95% CI 0.20-0.97), suggesting the randomization to exercise training halved the risk of dying in this follow-up period. For disease-free survival events, 12.1% of the patients in the exercise groups and 17.7% of the patients in the usual care groups experienced an event (HR 0.66, 95% CI 0.38-1.17). Subgroup analyses showed that the benefits of exercise training on overall survival were most pronounced for women younger than 55 years, those with stage II+ disease, as well as those who reported higher compliance to exercise training and who met the national targets of 150 min of weekly physical activity. Moreover, the beneficial effect on disease-free survival was most pronounced in women living in urbans areas who received supervised exercise training.

Wiskemann and colleagues reported survival data from a randomized controlled exercise intervention trial in allogenic stem cell transplant patients ($n = 103$) (190). Patients in the exercise group participated in combined aerobic and resistance training 4 weeks prior to hospitalization, during hospitalization (mean 44 days) and up to 8 weeks after discharge. There was no difference in the number of deaths

during hospitalization between the exercise ($n = 11$) and the control group ($n = 12$). However, after discharge at 2-year follow-up, six patients had died in the exercise group compared with 15 in the control group, resulting in a significantly lower mortality in the exercise group after discharge (12.0% vs. 28.3%, $P = 0.03$). In the entire observation period including the inpatient period and the follow-up period 34.0% of the patients in the exercise group died compared to 50.9% of the patients in the control group ($P = 0.112$). The main reasons of death were infections and graft versus host disease.

These promising findings from the few studies, which have reported data for disease progression and overall survival, indicate that exercise training may affect these critical endpoints. Yet so far, the findings are based exclusively on secondary—and underpowered—analyses. To advance this area, principle studies designed specifically to elucidate the effect of exercise training on disease outcomes are required, concurrent with experimental investigations exploring the potentially underlying mechanisms of exercise on cancer control.

Preclinical evidence There is a long history of animal studies demonstrating that exercise interventions can directly inhibit tumor incidence and growth in rodent models (Table 1). Currently, hundreds of studies in mice and rats have shown that physical activity in the form of voluntary wheel running, forced treadmill running or swimming can reduce the incidence, growth rate, and metastatic potential of cancers across a large range of murine or human tumor models of different cancer type. Results from these studies are discussed in detail in these reviews (5, 138).

Within the recent years, the underlying mechanisms for this protective effect of exercise have also started to be elucidated (Fig. 6). In particular, factors, which change acutely during exercise, have been demonstrated to have either direct inhibitory effects on tumor growth, or to elicit intratumoral adaptations, which contribute to reduced tumor growth (72). During each bout of exercise marked changes occur in the blood, which include mobilization of cytotoxic immune cells, induction of catecholamines and other stress-related hormones, as well as release of muscle-derived factors from the contraction muscles, that is, factors known as myokines. Each of these components has been shown to direct contribute to the tumor inhibitory potential of exercise.

During exercise, the concentration of immune cells, that is, cytotoxic NK and T cells, monocytes, and neutrophils increases dramatically in the circulation (75, 136). In particular, mobilization of the cytotoxic NK cells has been demonstrated to be instrumental in the exercise-mediated control of tumor growth in mice. These NK cells are mobilized during exercise through stress-induced shear stress on the vascular bed and adrenergic signaling, and once mobilized they survey the body for virus-infected or transformed cells as immunological targets (136). Studies in mice have proven that blockade of this epinephrine-dependent mobilization of NK cells diminishes the suppressive effect of exercise on tumor growth (139). Similar, depletion of NK cells completely abolishes the exercise-mediated inhibition of tumor growth, highlighting the importance of this acute mobilization and activation of NK cells in exercise-mediated control of tumor growth (139). NK cells are also mobilized during exercise in cancer patients. A study in breast cancer survivors has demonstrated that these women were able to mobilize NK cells to a similar extent as age-matched healthy control subjects (53). Moreover, we have shown that patients with cancer of the gastro-esophageal junction in neoadjuvant chemotherapy can elicit large increases in NK cell mobilization comparable to increases seen in young and elderly healthy subjects (unpublished data). Thus, regulation of immune cell mobilization is feasible and achievable in cancer patients also during ongoing anti-cancer treatment.

In addition to the changes in the immune cell compartment, marked changes in the plasma composition occur during exercise. Results from translational studies utilizing cancer patient-derived exercise-conditioned serum for cancer cell incubation studies *in vitro*, have demonstrated that the humoral changes occurring during exercise can inhibit cancer cell proliferation and clonogenic expansion of breast, prostate and colon cancer cell lines (46, 97, 147). Noticeable candidates for the observed suppressive effect on cancer cell viability are the exercise hormones, epinephrine, and norepinephrine. Besides contributing to immune cell mobilization, these catecholamines can signal directly to cancer cells, and it was recently shown that the catecholamines could suppress tumorigenesis by inactivating downstream effectors of the Hippo signaling pathway, namely, the oncoproteins YAP/TAZ (192) (Fig. 7). The Hippo signaling pathway is involved in organ formation and tumor development (132). Accordingly, exercise-dependent induction of the catecholamines in serum samples from breast cancer patients participating in structured training has been shown to reduce the incidence of breast cancer with 50% in an experimental metastatic tumor model (45).

Lastly, muscle-derived cytokines, known as myokines, are released from contracting muscles during exercise. This exercise-dependent myokine release has been suggested to contribute to the health beneficial effects of physical activity in most metabolic diseases (10, 135), and a few preclinical studies have linked myokines to a muscle-to-cancer cross talk axis, which can contribute to the regulation of cancer cells during exercise. To this end, a few myokines have been showed to directly inhibit cancer. These include SPARC, which suppresses colon cancer growth (4), and Oncostatin M and Irisin, which inhibits breast cancer cells *in vitro* (58, 70). However, skeletal muscles may be secreting more than 600 different myokines during exercise (188), and very few of these have been thoroughly investigated, in particular in regard to their potential to regulate cancer cell growth.

Regulation of surrogate tumor markers

Tumor detection and disease progression rely on solid confirmation through imaging modalities such as PET, CT, and MR scanning, as well as histological verified tumor biopsies.

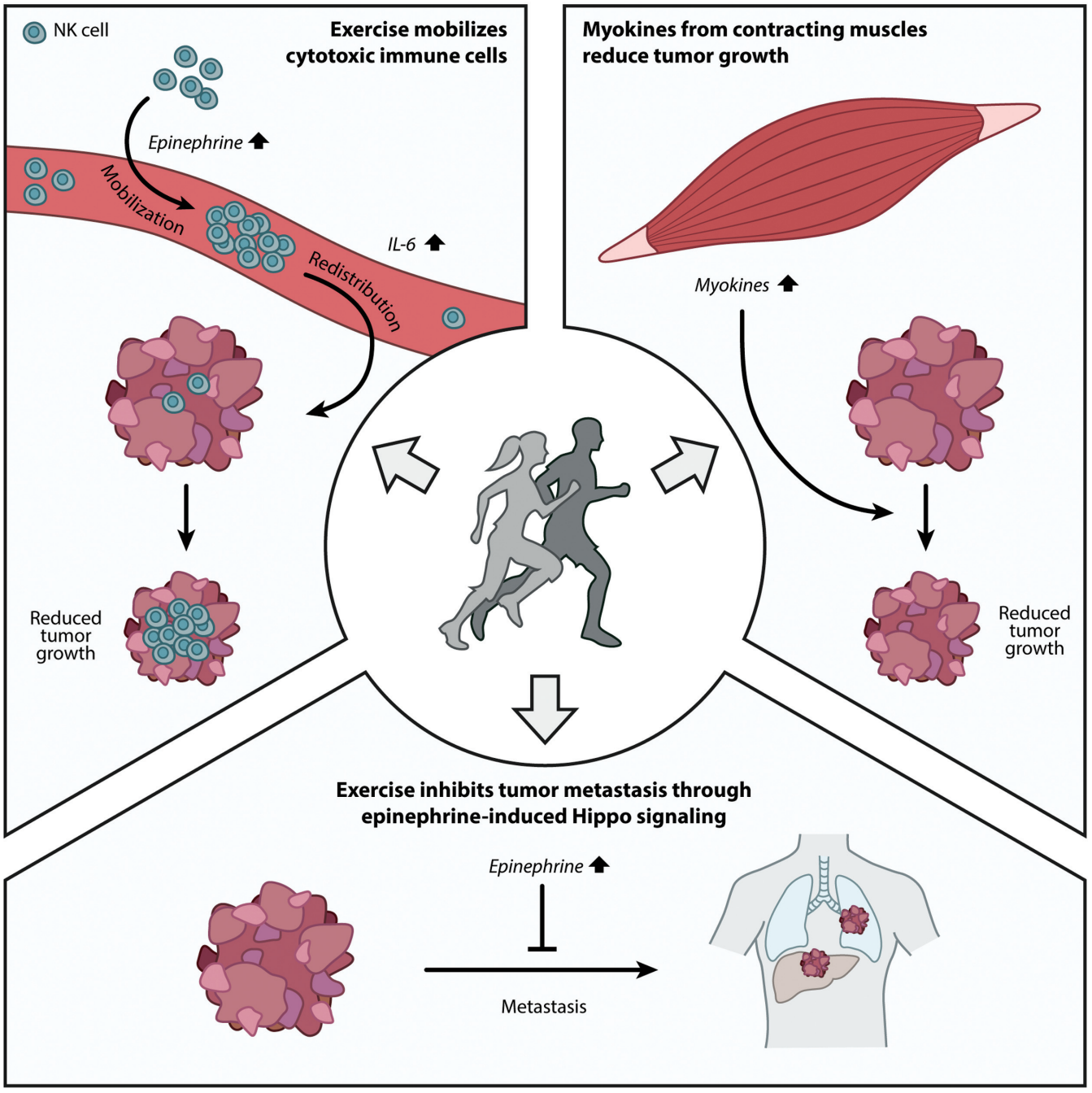


Figure 6 Mechanisms involved in exercise-dependent control of tumor growth. Evidence from preclinical studies indicates that exercise can reduce tumor growth and inhibit metastasis through various mechanistic pathways. Exercise is associated with an acute mobilization and redistribution of cytotoxic immune cells, Natural Killer (NK)-Cells to malignant tumors. Exercise is also associated with the release of antioncogenic myokines from contracting muscles. Finally, exercise-derived increase in epinephrine is shown to activate the 'Hippo Tumor Suppressor' signaling pathway in tumor cells, which in particular has been found to inhibit the formation of new malignant tumors associated with the metastatic process.

In addition, there is a constant quest to identify circulating markers of cancer for easier and faster detection of tumor development and progression. There are a range of established circulating tumor markers, which are routinely used to assess tumor progression and response to treatment for certain cancer diagnoses. These include prostate specific antigen (PSA) for prostate cancer, alpha-fetoprotein (AFP) for liver and germ cell cancers, carcinoembryonic antigen (CEA) for colorectal cancer, chromogranin A (CgA) for neuroendocrine tumors, thyroglobulin for thyroid cancer, as well as several combined protein signatures, which reflect different cancers. While these factors are commonly monitored for the relevant cancers, they have rarely been included as trial outcomes in exercise intervention studies. The main explanation for the

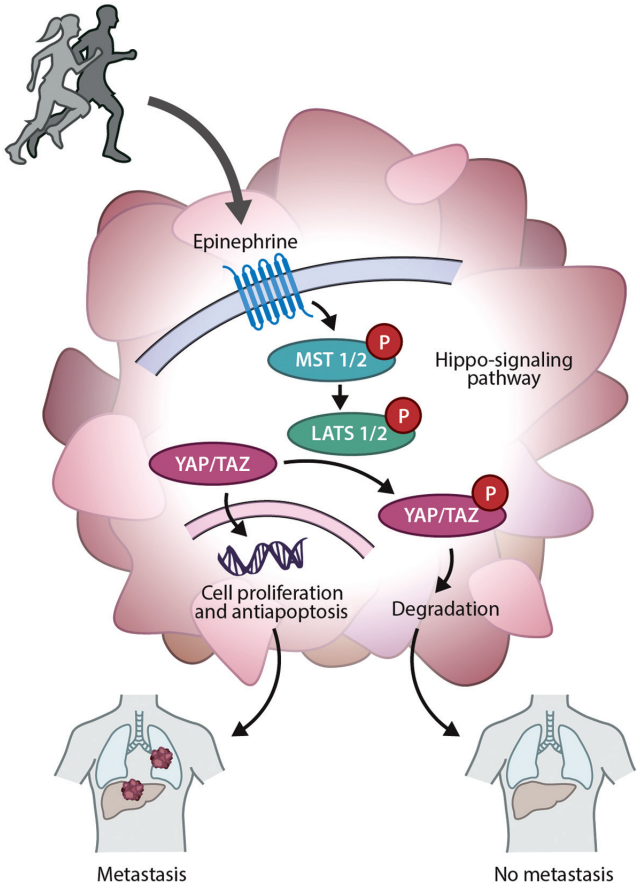


Figure 7 Exercise-dependent regulation of the Hippo signaling pathway. The Hippo signaling pathway is involved in basal processes like cellular growth, differentiation, and apoptosis, and is particularly recognized for its role in tissue development. The Hippo signaling pathway comprise of the oncoproteins Yap and Taz, which in the activated state, will translocate to the nucleus and induce transcription of factors involved in cell proliferation, antiapoptosis, and metastasis. However, upon phosphorylation by Lats1/2, Yap, and Taz are retained in the cytosol and degraded. This inactivation and degradation of Yap and Taz will reduce the rate of tumor metastasis. The Hippo signaling pathway has been shown to be dysregulated in several types of cancer, including breast cancer, where activation of the oncoproteins YAP/TAZ have been associated with a poor prognosis. Exercise can regulate the Hippo signaling pathway, as exercise-induced epinephrine can induce phosphorylation and degradation of Yap and Taz, and this has in mice been shown to reduce tumor formation by 50%.

lack of measurements of these surrogate tumor markers is probably that most of the markers relate to cancers, in which patients have rarely been subjected to exercise intervention studies. However, one exception is prostate cancer where we identified 10 exercise intervention studies measuring PSA.

Assessment of PSA plasma levels and doubling time is a cornerstone of active surveillance, where this surrogate marker for tumor progression is routinely followed, and systemic increases govern clinical decisions to initiated further therapy actions. One study evaluated the effect of a 2-year home-based high-volume exercise intervention on PSA doubling time during active surveillance. In this small study, the exercise group had an increase in PSA doubling time from 28 to 76 months during the first 6 months of exercise training ($P < 0.05$), suggesting that exercise markedly reduced early stage prostate cancer progression since the time to double systemic PSA levels increased by 48 months. In addition, the exercise group experienced improvements in VO_2max and body composition, including an average loss of 3.6 kg fat. Of these physiological adaptations, the increase in PSA doubling time proved to be tightly correlated to improvements in VO_2max ($r^2 = 0.42$, $P < 0.01$), but not to changes in fat or lean body mass, suggesting that exercise training relating to improvements in fitness levels is a stronger mediator for any anti-cancer effect than changes in body composition in prostate cancer patients in active surveillance (74).

PSA levels are also routinely measured after initiation of androgen deprivation treatment and/or radiotherapy. In this setting, Hojan and colleagues performed a one-year intervention study in 72 patients with intermediate to high-risk prostate cancer. During the first 8 weeks of concurrent radiotherapy, patients trained five times per week in supervised sessions, but moved to a home-based training program thrice a week for the remaining 10 months after radiotherapy completion, while the control group received standard recommendations regarding physical activity via printed materials instructing the participants to perform 30 min of moderate physical activity 5 days per week. During the first 8 weeks of radiotherapy, both groups showed declines in plasma PSA levels given the intense treatment, but in the following 10 months of intervention, the exercise group continued to show a decrease in plasma PSA levels (3.08 ng/mL to 2.47 ng/mL), while no further decreases were observed in the control group (3.73 ng/mL to 3.64 ng/mL) with a significant difference between the group ($P < 0.01$) (69). In continuation, we identified several larger exercise intervention studies, where plasma PSA levels were included in the outcome measures. Most of these studies were of shorter duration (12 weeks) and only included PSA measurements at baseline and after the intervention (57). Most of the studies observed a decline in plasma PSA levels both in the control and exercise groups, as the exercise intervention was initiated concurrent with or close to the start of androgen deprivation treatment and/or radiotherapy (32, 157, 158, 180).

Besides studies with the prostate cancer biomarker PSA, we identified one study, which investigated the interaction of nuclear β-catenin staining and exercise training in patients with metastatic colorectal cancer ($n = 19$). This single-arm study provided a once weekly supervised combined aerobic and resistance training program for 3 months concurrent with chemotherapy (22). In addition, the patients were encouraged to perform home-based exercise. Forty-two percent of the patients had tumors, which stained strongly for nuclear β-catenin, and this strong nuclear staining was associated with a lower risk of death (HR = 0.54, 95% CI 0.14-1.96), thus comprising a low-risk group. In the high-risk group of patients with weak nuclear staining for β-catenin, participation in exercise training improved survival with exercise (HR = 0.39, 95% CI 0.025-6.1), while no effect was determined when analyzing the low-risk and high-risk subgroup of patients together (22).

Taken together, the effect of exercise training on disease progression and survival is still poorly elucidated in clinical intervention studies. Three studies have directly addressed disease progression in patients with bone metastases or survival in lung cancer patients after short preoperative training or pancreatic cancer patients after 3 months home-based walking, while two studies have shown that exercise training can delay disease progression when measured by the surrogate tumor marker, PSA. Moreover, numerous preclinical studies have demonstrated that exercise training may elicit physiological responses during exercise, which have direct effect on cancer growth and metastasis. Finally, secondary analyses of two larger studies suggest that patients subjected to exercise training during chemotherapy for breast cancer or allogenic stem cell transplantation may improve long-term prognosis. In these later trials, the clinical evidence suggests that part of the protective effect of exercise training may be due to enhanced treatment tolerability and/or efficacy of the standard adjuvant chemotherapy.

Interaction with anti-cancer treatment

With few exceptions, patients with measurable cancer burden are treated with one or more anti-cancer treatments, that is, surgery, chemotherapy, radiotherapy, immuno- and antihormonal therapy, and it is therefore imperative to consider their concurrent pathophysiological interaction with exercise training.

We identified 188 exercise intervention studies performed prior to tumor resection or during adjuvant cancer treatment (*Supplementary material 2*), which overall demonstrates that exercise training to be safe during ongoing anti-cancer therapy and feasible. However, the therapeutic potential of exercise training is currently hampered by a limited mechanistic understanding of the impact of difference exercise modes and intensities and their molecular interaction with anti-cancer therapies. Emerging evidence suggest that exercise training may lower treatment-related adverse events, and directly or indirectly improve the antineoplastic potency of traditional therapies. Here, we discuss the role of exercise training as a moderator and/or mediator of treatment efficacy in three possible integrated scenarios; preoperative optimization prior to tumor resection; improved treatment tolerability by protection against chemotherapy-induced toxicities; and enhancement of tumor response to chemo-, radio-, and/or immune therapies.

Preoperative optimization

For most solid cancers, radical surgery is first line treatment, and the single most important, curative treatment modality. Over the last two decades, significant advances have been made in surgical techniques including the evolvement of robot-assisted procedures to improve the surgical outcome. Moreover, introduction of "fast-track surgery" or "enhanced recovery after surgery" (ERAS) procedures has sought to optimize patient recovery in the perioperative trajectory, but cancer surgery remains associated with serious risks of postoperative complications and prolonged recovery periods, particularly in frail and/or elderly patients. Thus, it remains a critical challenge to get patients with local stage disease to the operating table while minimizing their risk of serious complications.

To this end, we identified 33 exercise studies performed in the preoperative window of the cancer trajectory. These trials demonstrate that exercise training is safe during this period, although exercise dose, progression, and delivery may need to be closely adapted to the individual patient (169). The most commonly explored group of patients in preoperative setting is patients with lung cancer. A recent Cochrane review (20), showed across 5 studies in 167 patients with nonsmall cell lung cancer that preoperative exercise interventions were associated with a 67% reduction in risk of pulmonary complications (RR 0.33, 95% CI 0.17-0.61). Moreover, preoperative exercise training was associated with 3 days shorter chest drainage, 4 days shorter length of hospital stay, improved 6-min walk distance (18 meters), and 3% better lung function immediately before surgery ($P < 0.01$ for all comparisons).

In addition to patients with lung cancer, preoperative exercise interventions have been a focus point in patients with colorectal cancer, a group where the field of ERAS-research also originated. Work from Gillis and colleagues showed that a 4-week prehabilitation program significantly improved 6-min walking performance 8 weeks after surgery, facilitating a more rapid recovery to presurgical functional levels for the prehabilitation group compared with the rehabilitation group (84% vs. 62%, $P = 0.049$) (61). Another critical population with a high-risk profile is the diverse group of upper gastrointestinal malignancies, including cancers of the esophagus, stomach, pancreas, and liver, as these patients receive some of the most complicated surgical procedures. In one of the largest preoperative exercise trials performed to date, Barberan-Garcia and colleagues examined the effect of a personalized prehabilitation program comprised of supervised high-intensity aerobic exercise along with daily physical activity promotion for an average of 6 weeks prior to major gastrointestinal surgery. Patients were screened for high risk of complications defined by age >70 and/or American Society of Anesthesiologists (ASA)-score of III/IV. The study found that preoperative exercise training reduced the risk of postoperative complications up to 50% (62% vs. 31%, $P < .001$), which was driven by lowering medical complications and especially infection rates (7).

Although the current evidence consists of few relatively small-scaled studies, encouraging preliminary findings suggest that the preoperative setting could be pivotal for exercise oncology research in the future. Preoperative optimization by structured exercise training as part of standard ERAS care may provide clinicians with an effective strategy for lowering postoperative complication risk, shortening hospital length of stay, and facilitating functional recovery. This indicates an immediate benefit of exercise training. However, this acute intervention may provide the patients with long-term benefits, as

studies have shown that patients with serious postoperative complications, especially anastomotic leakages, have increased risks of disease progression following radical surgery (96). Moreover, it has become increasingly clear that various perioperative risk factors, including surgical stress and inflammatory responses, are prominent facilitators of metastatic progression. It is possible that exercise adaptations including improved immune regulation, lowered psychological stress, and increased levels of anti-inflammatory markers in the circulation, may arrest and/or eliminate residual disease during the perioperative period. Finally, the role of preoperative exercise training may be of special relevance in patients receiving neoadjuvant treatment. Neoadjuvant chemo- or chemoradiotherapy improves the chance of achieving a positive surgical outcome, but is not without challenges. Delaying surgery possess risk of disease progression in nonresponders, while physical deterioration and other toxicities can increase the risk of serious peri- or postoperative complications or preclude surgery due to poor performance status. Thus, preoperative exercise training may increase the chance of patients with operable cancer undergoing neoadjuvant treatment to actually reach surgery in a strong physiological condition.

Regulation of chemotherapy toxicity and treatment completion rates

Chemotherapy has been a mainstay in cancer treatment for more than 50 years comprising different classes of cytotoxic or cytostatic drugs, which kill cancer cells or inhibit their growth through direct actions on DNA replication, cell division, inhibition of the synthesis of cellular components, interfering with cellular metabolism or disturbances of the cellular wall. The antineoplastic efficacy of chemotherapy is dose dependent and so are a wide range of the toxic side effects. These toxicities may be so severe that they are direct reasons to terminate, reduce, or postpone planned dosages. Toxicities may involve objectively assessed hematology profile such as neutropenia, leukopenia, thrombopenia, and anemia, or organ damage leading to, for example, cardiomyopathy, or impaired pulmonary or kidney function, but may also include subjectively assessed toxicities such as hearing loss, neuropathies, pain, nausea or diarrhea. Thus, the decision to reduce, postpone, or terminate planned chemotherapy administration can be based on pathophysiological evaluations or individual factors.

We have identified two large exercise trials in breast cancer patients, which have addressed the effect of exercise training on treatment completion rates. The first exercise intervention study to demonstrate that exercise training can improve therapy completion rates was the START trial, which compared usual care to either resistance or endurance training in women undergoing adjuvant chemotherapy. Here, the resistance training group had better therapy completion rates compared with the usual care group (89.8% vs. 84.1%, $P = 0.033$) (35). The authors did not elaborate on these findings, but noted that the usual care group required more granulocyte colony-stimulating treatment than the resistance-training group. In the PACES study (177), the effectiveness of a home-based low-intensity physical activity program, and a supervised moderate- to high-intensity concurrent resistance and aerobic exercise program was compared to usual care for patients with breast cancer undergoing adjuvant chemotherapy. Significantly fewer patients (12%) in the supervised moderate to high-intensity training group required dose adjustments in the prescribed chemotherapy regimen compared with the home-based low-intensity training group (34%) and the usual care group (34%) (OR 0.26, 95% CI 0.11-0.61, for both comparisons). Moreover, the average level of dose reduction was lower with exercise training, as the patients requiring chemotherapy dose reduction in both the supervised training group and the home-based group was reduced by 10% compared with 25% in the usual care group ($P = 0.014$). While neuropathies overall were the main cause of chemotherapy dose reduction across all groups, it was mainly a lack of febrile neutropenia and infections that ensured the higher treatment completion rates in the exercise groups (177).

We also identified several studies within blood cancers, which investigated the effect of exercise training on treatment completion rates and toxicities to chemotherapy. Courneya and colleagues randomized 122 patients with lymphoma to 12 weeks of supervised endurance training or usual care after initiation of chemotherapy (37). The patients in the exercise group, completed 103% of the planned minimum and 94% the planned maximum cycles of chemotherapy, compared with 99% ($P = 0.45$) and 89% ($P = 0.20$), respectively, in the usual care group. The authors also addressed the complete response rate to treatment, which were 46.4% in the exercise group and 30.8% in the usual care group ($P = 0.24$). Given the overall high treatment completion rates, the study was not powered to address whether exercise training may improve these, but the intervention did not seem to worsen the response to chemotherapy.

For patients with blood cancers, infections and fevers are major problems, and several studies have explored the impact of exercise training on these toxicities. Alibhai and colleagues investigated the effect of supervised hospital-based concurrent aerobic and resistance training in 80 patients with newly diagnosed or relapse acute myeloid leukemia during hospital admission for induction chemotherapy. The average length of the intervention was 36 days. In this period, 45.8% of the patients in the control group experienced episodes of sepsis compared with 29.1% in the exercise group ($P = 0.15$). In continuation, 12.5% of the patients in the control group were admitted to the ICU compared with 5.6% in the exercise group ($P = 0.26$) (3). Baumann and colleagues investigated the effect of supervised endurance training in 36 leukemia and lymphoma patients in early stages of high-dose chemotherapy. Here, seven patients in the control group developed pneumonia compared with two in the exercise group ($P = 0.06$). Pneumonia was most prevalent in patients with leukemia, and in these patients exercise participation significantly reduced

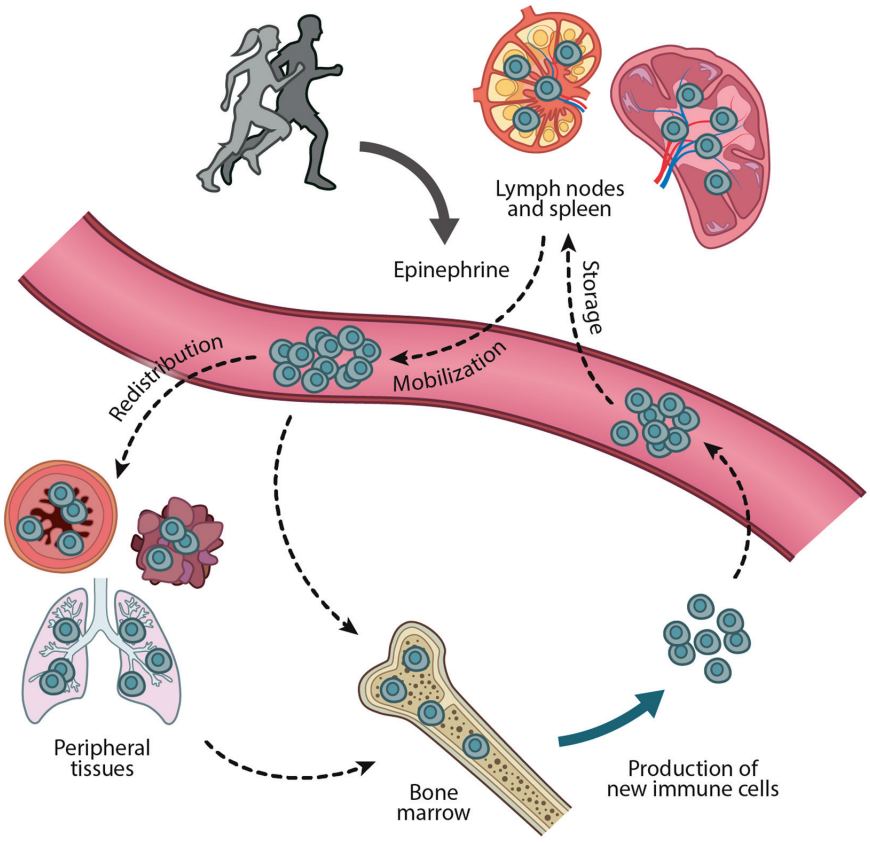


Figure 8 Exercise-dependent regulation of immune cells. Several studies have reported that patients allocated to exercise training were either more likely to receive their planned dosage of chemotherapy or reported fewer toxicities compared with usual care controls. This observation has coincided with maintenance of the patients' immune cells population, that is, the patient experienced lower incidence of neutropenia, trombopenia, and lymphopenia, which are principle causes of chemotherapy dose reduction and/or postponement. During exercise, immune cells are acutely mobilized to the circulation through adrenergic signaling and shear stress on the vascular bed induced by the increased blood flow during exercise. The most responsive immune cells are NK cells and monocytes, followed by T cells and to a lesser extent B cells. Once mobilized, the immune cells will be distributed to the peripheral tissue to survey for malignant transformed or virus infected cells. This exercise-mediated mobilization and redistribution of immune cells will provide yet unidentified signals to the bone marrow to initiate the production of new immune cells, which are released to the circulation and stored in the spleen and lymph nodes. This exercise-mediated feedback loop to the bone marrow may explain why cancer patients can maintain their immune cell population despite receiving bone marrow suppressive anti-cancer treatment.

the risk of pneumonia ($P = 0.04$) (8). These early results highlight the role of maintaining an efficient immune cell function, and thus extend the early findings by Dimeo and colleagues, who demonstrated that patients exercising during high dose chemotherapy before stem cell transplantation, experienced less deteriorations in their blood cell counts (49).

We propose two mechanisms whereby exercise training may counteract chemotherapy related toxicities and protect against toxicity-associated dose-reduction, (i) maintenance and/or stimulation of the immune cells production and (ii) regulation of body composition and thus compartmentalization of the administered chemotherapeutics.

Stimulation of immune cell populations Acute exercise has a dramatic effect on the levels of circulating immune cells (Fig. 8). The frequency of monocytes and lymphocytes in the circulation increases progressively during exercise, followed by a drop below baseline levels after exercise cessation. In contrast, neutrophil concentration increases during exercise, and then continues to increase hours into the recovery period after exercise cessation (75, 136). These mobilized immune cells are recruited from the spleen, lymph nodes, gastrointestinal tract, as well as cells lying immobilized along the vascular walls. Thus, the early increase in immune cells does not derive from newly generated immune cells. Once mobilized, these immune cells will patrol the body, in particular, ending up in peripheral tissues with mucosal surface areas, that is, lungs, GI tract ,and skin, while no data points to that these mobilized immune cells should infiltrate skeletal muscles. After this exercise-mediated immune cell mobilization,

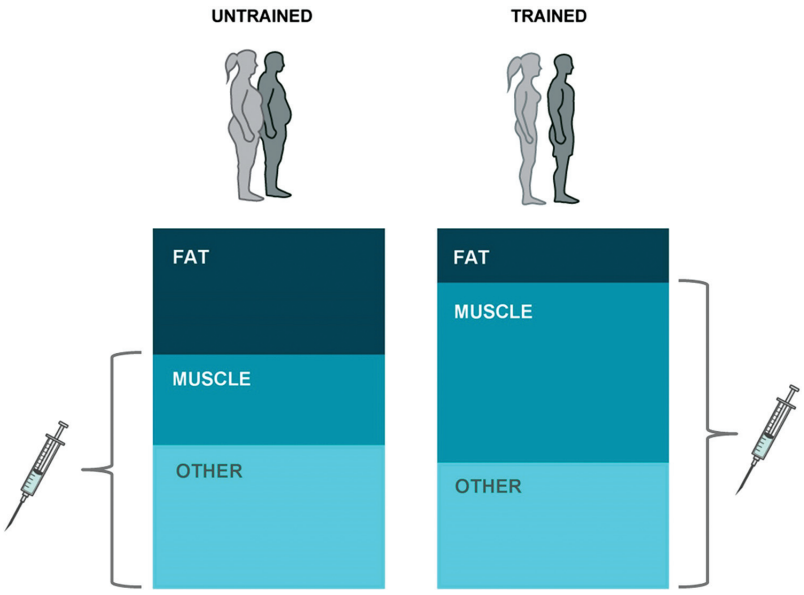


Figure 9 Drug compartmentalization in untrained and trained individuals. Systemic treatments with chemotherapy or immunotherapy are associated with toxicities and organ damage in a dose-dependent manner. Importantly, systemic treatments are administered by anthropometrics, that is, body mass or body surface area, which do not take into account the relative composition of fat and fat-free mass. Since cancer drugs is distributed in metabolically active tissues only, it has been proposed that obesity alone, and in particular in combination with low muscle mass, known as sarcopenic obesity, is associated with higher risk of toxicity induced dose reduction. This figure illustrates the hypothetical distribution of the same absolute dosage, administered to two individuals with the same body mass/surface area, but different distribution of fat and muscle, as often observed in untrained (high fat mass, low muscle mass) and training individuals (low fat mass, high muscle mass). The "relative" dose encountered in thus metabolically (fat free) active tissue is thus higher in the untrained, relative to the trained individual, who are distributing the same dose to a larger fat-free mass.

the efflux of immune cells from the storage organs may provide a feedback response to the bone marrow to initiate *de novo* immune cell generation (18). This *de novo* generation of immune cells may explain why cancer patients engaging in exercise training are less likely to have therapy reductions due to low immune cell numbers (Fig. 8).

Pharmacokinetics and compartmentalization

Chemotherapy is administered based on body weight or body surface area. Yet, the drug distribution may vary considerably in relation to body composition, and this may be linked to the degree of toxicity experienced. Intravenously delivered drugs bypass the stomach and liver before they are distributed around the body. This bodily distribution is uneven due to variations in tissue perfusion, inter-tissue pH, tissue binding, and permeability of cell membrane. In addition, drug absorption and elimination plays important roles for the circulating drug concentration. The most sensitive organs to chemotherapy-induced toxicities are the blood and bone marrow, and highly perfused organs like the heart, lungs, kidneys, and brain. During exercise, blood perfusion in skeletal muscles increases many fold, and thus add to the volume in which the chemotherapy can be distributed. Thus, engaging the muscular compartment both in terms of mass and perfusion, may limit direct treatment toxicities. In contrast, the adipose tissue and skeleton represents poorly perfused organs and act in terms of drug distribution as dead volumes. Thus, a high body fat percentage may therefore limit the volume in which chemotherapy can be distributed and thus increase the risk of therapy toxicities solely by increasing the accumulative dose in the highly perfused organs (Fig. 9).

Enhancement of treatment efficacy

The efficacy of anti-cancer treatment, first and foremost, depends on successful targeting, that is, delivery of drug or radiation to the tumor or residual tumor cells. Secondly, the tumor must be sensitive to the cytotoxic impact of the treatment. The new generation of anti-cancer drugs is highly selective, targeting specific oncogenic pathways or receptors. This lessens toxicities on normal cells, but also requires the proper molecular profile of the tumor to respond to the treatment. In our literature search, we identified 194 exercise intervention studies, which were performed concurrent with ongoing anti-cancer treatment, in particular chemotherapy. These studies have largely focused on the safety and feasibility, as well as ability to improve physical functioning despite presence of

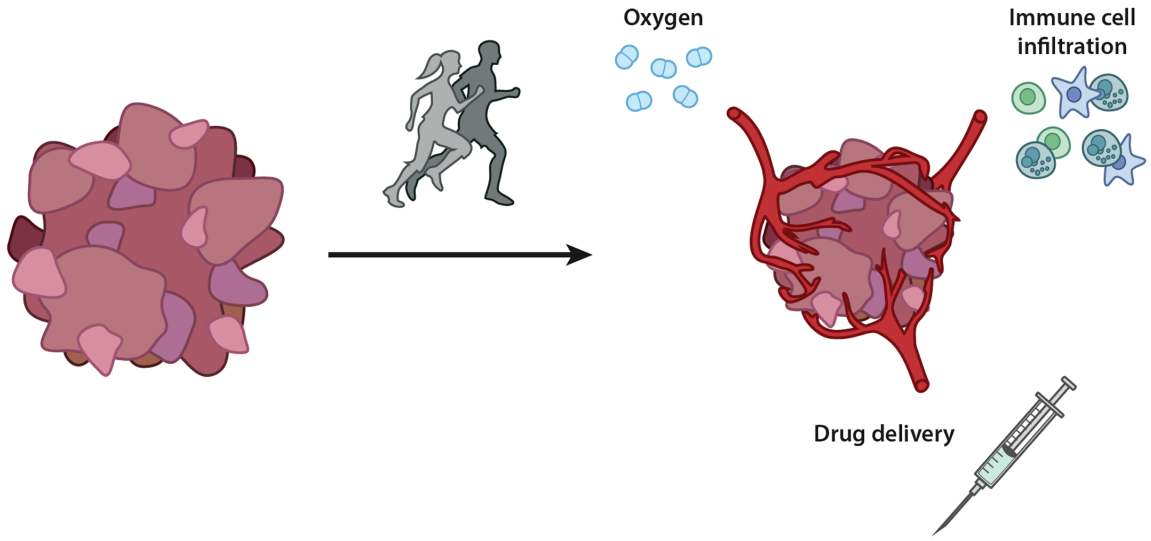


Figure 10 Exercise-mediated enhancement of anti-cancer therapy efficacy. Data from clinical trials and preclinical experiments suggest that exercise training may enhance the antineoplastic efficacy of traditional cancer treatments including radiotherapy, chemotherapy, and immunotherapy. The principle candidate mechanism responsible for this synergistic effect is increased vascularization leading to improved intratumoral blood perfusion. Such increase in blood perfusion by exercise training has been demonstrated in murine studies, where acute exercise directly can blood perfusion, while long-term training has been associated with increased vascularization, normalization of capillary perfusion and reduction in tumor hypoxia. Together, this can improve the anti-cancer efficacy by (i) increasing the delivery capacity of drugs, for example, chemotherapy to the interior of the tumor, (ii) improving oxygenation of the interior of the tumor, which is required for the generation of reactive oxidative species (ROS) in radiotherapy, and (iii) increasing intratumoral immune cell infiltration, which are required for removal of dead cells after cytotoxic treatment, as well as for interaction with immunotherapy.

toxic therapies. Thus, very few studies have formally investigated if there may be any synergistic effect of exercise training and drug or treatment administration. However, strong rationales from preclinical studies suggest that exercise training might enhance the efficacy of anti-cancer drugs or treatments (Fig. 10).

Radiotherapy The efficacy of radiotherapy relies on sufficient oxygen delivery to tumors for generation of the radiation-induced reactive oxidative species, which facilitates the therapeutic effect on cancer cells. Thus, radiotherapy works poorly in hypoxic tumors. Exercise training strongly affects blood circulation and oxygen delivery to peripheral tissues, and while regulation of blood perfusion has not been investigated in human tumors, several interesting animal studies have been conducted. McCullough and colleagues elegantly showed that treadmill running in rodents acutely increased intratumoral blood perfusion and relieved intratumoral hypoxia in models of prostate cancer. The authors furthermore demonstrated that blood perfusion of the noncancerous prostate remain unchanged during exercise, while the underperfused and hypoxic tumor foci within the prostate showed higher blood perfusion and alleviation of hypoxia during exercise performance (109). In general, blood flow regulation during exercise is controlled by the parasympathetic nervous system, driving elevation in heart rate and blood pressure, thus regulating vascular tension, directing the blood to the 'active' organs, while limiting blood flow to 'inactive' organs during exercise. Yet, the data from McCullough and colleagues suggest that the regulation of tumor blood perfusion differ from blood flow regulation in normal organs. In addition to the acute effects on blood flow regulation, repeated bouts of exercise have been shown to lead to biophysical adaptations that over time increase angiogenesis and intratumoral vascularization, and thus counteract intratumoral hypoxia in several murine models of tumors (59, 109, 110).

We have not identified any interventions, which investigated the interaction between exercise training and radiotherapy on its own. However, we did identify one study, which reported on the therapeutic effect of preoperative chemoradiotherapy concurrent with 6 weeks of supervised hospital-based aerobic exercise with three weekly sessions or usual care in patients with locally advanced rectal cancer in a nonrandomized parallel group design (187). Following tumor resection, tumor staging was evaluated by histology, colonoscopy, and thoracic CT and MRI scans. These evaluations showed that all subjects in the aerobic exercise group experienced tumor downstaging in response to neoadjuvant chemoradiotherapy compared with 61% in the control group ($P = 0.006$), suggesting that exercise may potentiate the efficacy of the concurrent treatment. Of note, 3 of 22 (13.6%) patients in the exercise group experienced radiation-induced skin changes compared with 1 of 13 (7.7%) patient in the control group (187), suggesting that radiotherapy has had full access to oxygen for mediated its therapeutic effect on the tissue in the exercise group.

Acute regulation of blood flow occurs very fast within seconds or minutes of exercise initiation. In the study by West

and colleagues (187), the exercise training was not planned in conjunction with radiotherapy, but it may be foreseen that just a very short bout of exercise prior to radiotherapy would enhance tumor blood perfusion and reduce intratumoral hypoxia, promoting the efficacy of radiotherapy. Such short bursts of exercise could also be feasible for fragile and advanced stage cancer patients. We know of several initiatives where stationary bikes have been placed in radiation bunkers to provide access to exercise just prior to radiotherapy. Accordingly, characterizations of any synergistic effects of acute relief of tumor hypoxia by a short bout of exercise with the response to radiotherapy are likely to appear in the near future.

Chemotherapy Chemotherapy can be given as adjuvant therapy, in which setting chemotherapy most often have been combined with exercise training. Here, the aim is to eradicate residual tumor cells, which may have escaped during tumor resection. In the previous mentioned START trial, of the patients who received 85% and more of the prescribed chemotherapy, the long-term disease-free survival was better in the training group, suggest that there may be some kind of interaction, whereby exercise training affect treatment efficacy (36). We can only speculate as to the mechanisms behind, but a good distribution of the drug throughout the body, followed by a strong immunological recognition of the dying tumor cells and induction of memory immune cells, could add to future protection against recurrent nodules.

Chemotherapy may also be given as neoadjuvant or palliative treatment. Here, the goal is to reduce solid tumors or metastases. Here, the efficacy of chemotherapy also relies on adequate intratumoral blood perfusion to deliver the cytotoxic drugs to the interior of the tumors. As for radiotherapy, such enhanced drug delivery has not been investigated in human tumors, but preclinical studies convincingly show that combining chemotherapy with access to running wheels or treadmills improves the treatment response in mouse models (12, 81, 151). For instance, Schadler and colleagues showed that treadmill running normalized tumor vascularization in B16 melanomas and PDAC pancreatic adenocarcinomas as determined by longer and lectin positive vessels, while the overall density of capillaries did not increase with exercise training. This improved tumor vascularization led to intratumoral accumulation of chemotherapeutics, that is, gemcitabine and doxorubicin, and thus enhanced tumor growth inhibition in the exercise group (151). The author attributed the improved tumor vascularization to the mechanical stimuli exerted on endothelial cells by increase in blood flow during treadmill running, which will modulate vascular integrity and remodel blood vessels in both normal and malign tissues (151). Similarly, Betof and colleagues showed normalization of tumor vascularization and improved blood perfusion by functional MRI in 4T1 breast cancer tumors with voluntary wheel running, leading to enhanced tumor inhibition, when chemotherapeutic administration of cyclophosphamide was combined with voluntary wheel running (12).

Immune therapy Immune therapy, in particular in the form of immune checkpoint blockade, has led to important clinical advances and provides a novel weapon against cancer (160). Cytotoxic immune cells play an important role in the regulation of cancer growth, and intratumoral infiltration of cytotoxic immune cells are associated with a positive disease outcome and overall survival in several cancers (174). However, tumors have developed ways of evading immune destruction by expressing inhibitory ligands, known as immune checkpoint molecules, which dampens the cytotoxic immune response (166). This therapy can elicit durable clinical responses in a fraction of patients, but long-term remission requires a high degree of cytotoxic immune cell infiltration and immune checkpoint molecule expression in the responding patients (160). Thus, efforts to obtain this prognostic favorable immunogenic intratumoral environment are warranted.

As mentioned earlier, a recent preclinical study has linked exercise-dependent mobilization of cytotoxic immune cells to control of tumor growth by exercise. In this study, Pedersen and colleagues showed across various genetic and inoculated tumor models more than 50% reduction in tumor growth with voluntary wheel running, and this effect was abolished if the exercising mice were depleted of NK cells. Moreover, the exercise-dependent control of tumor growth was associated with a high degree of cytotoxic immune cell infiltration in the tumors of running mice (139). Follow-up analyses from tumors of these mice demonstrate that the high infiltration of cytotoxic immune cells, were further associated with induction of immune checkpoint ligands (unpublished data), spurring interest into the role of exercise in improving the efficacy of immune checkpoint therapy by enhancing the immunogenic interior of the tumors.

We did not identify any intervention studies, which combined exercise training with immune checkpoint therapy, but given the large expansion in the use of these drugs and the strong rationale for their synergistic effects, such trials may be undertaken in the near future. In contrast, we identified one small exercise intervention study in patients with melanoma ($n = 12$), who were receiving methylphenidate (interferon-alpha) treatment. This study demonstrated that exercise training was feasible with high training adherence rates, and beneficial effects on physical functioning, cancer-related fatigue, and cognitive function. However, the study did not address any treatment-related outcomes, other than four patients stopped taking methylphenidate within the first week, and thus probably independent of any interaction with the exercise intervention (153).

Taken together, preclinical data and preliminary findings from clinical trials point to potential roles of exercise in improving tolerability to anti-cancer treatment and efficacy of systemic treatments. Conceptually, exercise training may influence the classic dose-response curves of anti-cancer treatments shifting the tumor response curves to the left, that is, increasing the tumor response to a given dosage, and/or shifting the toxicity curves to the right, that is, tolerating higher

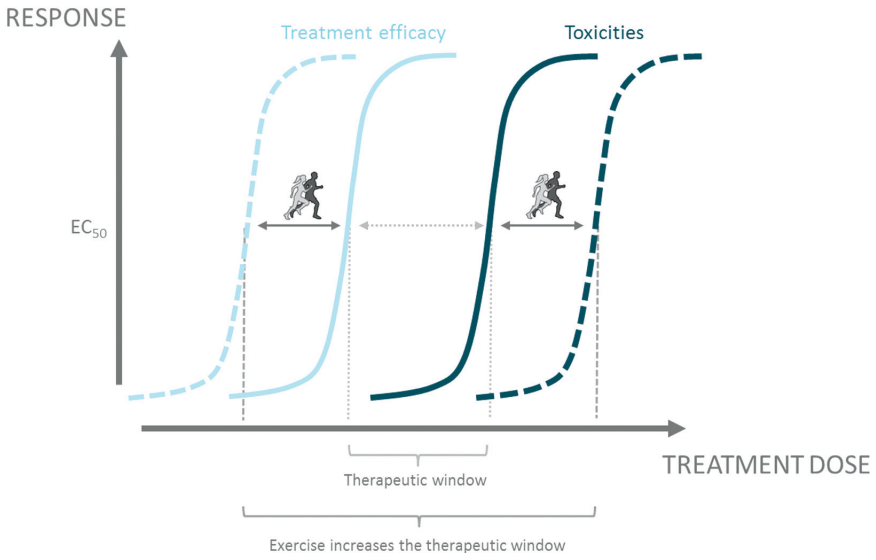


Figure 11 Conceptual model of the possible interaction between exercise training and cancer treatment. In pharmacology, the therapeutic window is determined by the dosage range interval from the "median effective dose" (ED50), defined as the dose achieving a positive response in 50% of the patients, and the "median toxic dose" (TD50) defined as the dose resulting in toxicity (here arbitrarily defined) in 50% of the patients. The lower limit of this therapeutic window is therefore determined by the antineoplastic potency of the treatment, that is, the more potent the agent, the higher tumor response to the same absolute dose. The upper limit of the window is, on the other hand, determined by the drug toxicity profile, that is, the adverse cytotoxic reactions in nontargeted tissues (e.g., the lungs, kidneys or bone marrow). Through direct and indirect mechanisms, exercise training may widen the therapeutic window. Exercise-induced improvement in blood perfusion, and thus improved drug delivery, less intratumoral hypoxia and higher invasion of cytotoxic immune cells, potentially shirts the treatment efficacy curve to the left eliciting a higher tumor response to the same dose or similar response at a lower dose. In parallel, exercise-dependent improvements in treatment toxicity profile by protection against immunosuppression and improved drug compartmentalization (distribution of the toxic agents a to larger mass of metabolic active tissue) may shift the toxicity curve to the right, thus improving treatment tolerability by lower toxicity profile to the same absolute dose or allowing for similar toxicity profile to a higher dose. In concert, this interaction between exercise training and standard therapies can have profound impact on patient management in both adjuvant and palliative settings, but requires full integration of the exercise intervention within standard oncology therapeutic framework regarding prescription, delivery, and evaluation.

dose with similar toxicity profile or experiencing less toxicity with similar dosage (Fig. 11). In concert, this would widen the therapeutic window with important clinical implications throughout the cancer continuum.

Secondary prevention of comorbidities and secondary cancers

Cancer treatments are often associated with long-term adverse reactions which can cause accelerated development, or progression, of various pathologies, which may in turn impact survival and quality of life up to several decades after treatment cessation. Indeed, the risk of dying of treatment-related cardiovascular diseases or secondary cancers increases markedly after cancer therapy, and may in some cases exceed the mortality risk associated with the primary cancer (134). This sequalae is particularly challenging in children and young adults with high cure rates, but has also been extensively described in patients with breast cancer. In this regard, exercise training may be a powerful strategy to mitigate or prevent severe long-term endocrine disturbances, cardiotoxicities, weight gain, and metabolic dysfunction, thus reducing the risk of cardiovascular diseases, and risk of secondary cancers, thereby improving overall survival.

Endocrine disturbances

Long-term endocrine disturbances after cancer treatment have been reported across a wide range of diagnoses. Few, however, are as well described as pediatric oncology regarding the health care challenges of serious treatment-related pathologies following a curable cancer diagnosis. Due to impressive advances over the last three decades, 5-year relative survival rates currently exceed 80% with a steadily growing number of adult survivors from childhood cancer (60). Consistent reports show that pediatric oncology treatment is associated with a myriad of short and long-term complications, constituting major health concerns (48, 121, 128). The combination of prolonged chemotherapy-treatment lasting up to several years with large doses of glucocorticoid steroid treatment

(e.g., dexamethasone or prednisolone), is considered a primary driver of the disrupted metabolic profile found in many childhood cancer survivors (145). Epidemiological evidence has shown an inverse association between self-reported exercise behavior and mortality risk in survivors of childhood cancers, while posttreatment exercise was associated with a 40% reduction in mortality (154). Accordingly, a range of intervention studies during active treatment have been performed, highlighting that exercise training programs during and after the treatment trajectory for children suffering from hematological malignancies or solid tumors are safe and feasible (21,55,149). To date, most exercise intervention studies in pediatric oncology have focused on improvement or maintenance of functional capacity during the prolonged treatment trajectories. However, promising pilot data have also shown long-term (+5 year) childhood cancer survivors can improve fasting insulin levels and body composition by just 16 weeks of home based exercise training (78). Accordingly, large scale RCTs are currently ongoing to further elucidate if longer interventions can improve cardiovascular risk scores (146).

Another critical case where cancer-related endocrine dysfunction comprises a long-term health problem is within testicular germ cell cancer. Due to a remarkable tumor-response to cisplatin-based chemotherapy, testicular cancer was famously labeled a 'model for a curable neoplasm' more than thirty years ago (52). Accordingly, patients today have excellent long-term prognoses, but the survivors are also found to present with markedly increased risk of cardiovascular morbidity and mortality (65), which at least in part is driven by dysregulated endocrine and metabolic homeostasis (23). Few exercise studies have been performed in patients with testicular germ cell cancer. Our group has shown that resistance training performed during chemotherapy mitigated treatment-related loss of muscle mass and strength (25), but did not protect against acute systemic increases in inflammatory cytokines or metabolic markers (27). However, in the only posttreatment exercise trial in testicular cancer patients to date, Adams and colleagues found that 12 weeks aerobic training led to improvement in systemic concentrations of C-Reactive Protein and LDL-cholesterol which translated into significant lowering of CVD risk scores, by, for example, Framingham Risk Score (1).

Cardiotoxicity

Anthracyclines and HER2 directed agents (Trastuzumab) are effective therapeutics, but they are also associated with both early and late cardiotoxicity, leading to heart failure in 2% of the treated patients (163). Observational studies have demonstrated that physical activity is associated with lower risk of any cardiovascular event, coronary disease and death in breast cancer survivors (84), and exercise training has accordingly been suggested to counteract the treatment-induced toxicity through regulation of cardiovascular reserve and endothelial function, proapoptotic signaling, protection from reactive oxygen species (ROS), and decreased autophagy/lysosomal signaling. To test some of these mechanisms in a clinical setting, Campbell and colleagues suggested that one bout of endurance exercise 24 h prior to doxorubicin-based chemotherapy administration could mediate cardiac protective effect, based on the hypothesis that the exercise intervention would attenuate the change in LV longitudinal strain and twist, as well as increase circulating cardiac troponin levels relative to the usual care group (94). Yet, despite their efforts, the exercise training was not capable of affecting these markers of subclinical cardiotoxicity, but the exercise bout was shown to have positive systemic effects on hemodynamics, musculoskeletal symptoms, mood, and body weight in the participating women with breast cancer.

Few exercise trials have studied the effect of exercise training on cardiac related outcomes. One study showed that 12 weeks of aerobic training during anthracycline-based neoadjuvant chemotherapy in 20 breast cancer patients improved endothelial function as determined by flow-mediated dilatation of the brachial artery. Yet, the study observed no changes in hemoglobin levels and resting LV ejection fraction (83). Similarly, 12 weeks of aerobic training in germ cell cancer survivors improved carotid intima-media thickness, carotid distensibility, and arterial stiffness, as well as the Framingham score (1). Thus, the evidence that exercise training may mitigate treatment-induced cardiotoxicity is limited, and the rationale is primary based on preclinical studies in mice and rats, where combined voluntary wheel running or treadmill running has proven efficient in moderating doxorubicin-induced cardiac damage (50,171,181).

Weight gain and metabolic dysfunction

Obesity and adiposity have consistently been shown to increase the risk of cancer (38,100,102), and a meta-analysis found that for every 5 kg of weight gain, the risk of developing an adiposity-related cancer was increased by 9% to 39% depending on diagnosis and use of hormone replacement therapy (91). Moreover, weight gain in response to anti-cancer treatment may be a serious problem for certain cancer diagnoses, in particular patients with breast and prostate cancer. In fact, the majority of women treated for breast cancer experience significant weight gains both during and after treatment (43, 76). For example, Demark-Wahnefried and colleagues found that the women who received chemotherapy, on average, increased their body weight and body fat percentage by 2.1 kg and 2.2%, respectively, during the first year after their diagnosis (43). This weight gain is not just associated with the early stages of breast cancer treatment, but may continue to increase, as reflected by an increasing prevalence longitudinally (178). The clinical importance of this treatment-related weight gain was addressed in a meta-analysis including 12 studies with more than 23.800 breast cancer survivors, showing that a weight gain of more than 5% was associated with all-cause mortality (hazard ratio = 1.12), while a weight gain of more than 10% further augmented risk of all-cause mortality (hazard ratio = 1.23) (140). Excessive weight gain elicits a

vicious cycle of physical inactivity and feeling of tiredness, which further adds to the progressive weight gain. Large consortiums are addressing this problem by placing promotion of physical activity central in the weight management for women with previous breast cancer (44). Although, exercise training is associated with increased energy expenditure, exercise interventions are rarely capable of markedly reducing body weight on their own. Thus, multimodal interventions in particular interventions including diet interventions and recommendations are warranted.

In addition to the burden of excess body weight, obesity is associated with metabolic disturbances, which may further exhilarate cancer development and progress. Accumulation of fat in the adipose tissue is associated with increased infiltration of pro-inflammatory macrophages, which will promote inflammation in the adipose tissue (40). Similarly, ectopic fat accumulation in nonfat-storage organs like liver and muscles are associated with increased intraorgan inflammation (130). This inflammation drives insulin resistance in the affected organs, as part of a protective mechanism, where the organs try to shield themselves from nutrient overload. This peripheral insulin resistance results in a feedback loop, demanding higher central output of insulin to maintain normal blood glucose levels. Together this will lead to systemic hyperinsulinemia and whole-body metabolic disturbances. Here, exercise training can directly regulate the intratissue inflammation, as well as improve muscular glucose uptake, and thus insulin sensitivity.

Prevention of secondary cancers

A prevailing hypothesis within the exercise oncology field has proposed that exercise training may lower the risk of cancer development through reductions in common risk factors, that is, sex hormones, insulin and insulin-related factors and systemic pro-inflammatory cytokines (111). This hypothesis is based on the observations that elevated sex hormone levels, hyperinsulinemia, and chronic low-grade inflammation are associated with increased cancer risk, as well as poor cancer outcomes, including disease progression and reduced survival. Moreover, exercise training may reduce the levels of sex hormones, hyperinsulinemia, and low-grade systemic inflammation, encouraging the hypothesis that these effects are linked.

Sex hormones In premenopausal women, estrogens are primarily produced in the ovaries, while estrogens are produced in the adipose tissue through aromatization of androgen precursors in postmenopausal women. Thus, in postmenopausal women, systemic sex hormone levels and body adiposity are tightly correlated. As estrogen production in premenopausal women is tightly related to the reproductive cycle, the effect of exercise on sex steroid hormone levels is limited. Accordingly, endurance-training interventions in premenopausal women have shown little regulation of sex hormones or SHBG, despite weight loss (164). In postmenopausal women, on the other hand, the effect of exercise on sex hormone levels is tightly linked to the production in the adipose tissue, and training-dependent reductions in sex hormone levels have primarily been observed in overweight women who lose weight during the exercise intervention (112). Compared with exercise alone, diet control in combination with endurance training has been proven superior in reducing the levels of estrogen, estradiol, and free estradiol, and increasing the level of SHBG, which again could be explained by marked weight losses of up to 10 kg in the relevant studies (104). Yet, even if the breast cancer survivor may reduce circulating sex hormones by exercise training, most patients with prior hormone sensitive breast cancer will receive yearlong treatment with antihormone therapy, and any regulation of hormone levels by exercise in these patients is negligible compared with the treatment effect.

Insulin and insulin like growth factor Metabolic disturbances leading to muscular and adipose inflammation result in peripheral resistance in these tissues. Consequently, the central output of insulin will increase, resulting in hyperinsulinemia and elevated plasma levels of Insulin-like Growth Factor (IGF) family members. The main function of insulin is to control blood glucose levels by inducing peripheral glucose uptake, but insulin can also exert direct anabolic and antiapoptotic effects on normal and malignant cells (63). IGF-I resembles insulin in its stimulatory effects on cell proliferation. Exercise improves insulin sensitivity, which through regulatory feedback mechanisms lowers circulating insulin levels. Although improvements in insulin levels and sensitivity can be associated with weight loss, improvements in insulin sensitivity by exercise training is also seen independently of changes in body mass (173). A number of studies have investigated systemic levels of insulin and the IGF-I axis after an exercise intervention in cancer survivors, and these randomized controlled trials yielded inconsistent results (86). To summarize the findings a recent meta-analysis showed a significant, but small, effect of posttreatment physical activity on circulating levels of IGF-I, while no changes were found for insulin and IGF binding protein-3 (86). Although large efforts to promote normalization of hyperinsulinemia has been the aim of large training intervention studies, the translatability of insulin regulation to cancer outcomes remains undetermined, and given the dependence of insulin resistance in muscle, liver and adipose on inflammation, targeting intra-organ inflammation may expedite some of the beneficial effects of exercise.

Proinflammatory markers The main source of proinflammatory cytokines, for example, TNF-alpha, IL-1beta, IL-6, etc., are myeloid immune cells, which sense cellular damage through Toll like receptors (TLR). Most myeloid immune cells reside within tissues, where their contribution to intra-tissue inflammation promotes carcinogenesis and

tumor formation. Exercise has proven to have direct effects on cytokine production from these myeloid immune cells (99). First, during acute exercise the expression of the Toll like receptors are down-regulated, leading to attenuation of the immunological responsiveness to cellular damage (133). Second, exercise training can potentiate the inflammatory response, resulting in a faster resolution of the proinflammatory phase (88). These responses were recently linked to an exercise-dependent protection from diethylnitrosamine (DEN)-induced hepatocarcinoma in mice. In this study, voluntary wheel running reduced the incidence of DEN-induced hepatocarcinoma by 60%, as well as the tumor burden by 75% in affected livers of male mice. The study demonstrated that upon an acute challenge with DEN, the expression of TNF-alpha and IL-1beta peaked earlier in trained mice, and displayed subsequently a faster resolution of the acute inflammatory response (9). In the long run, this will lead to lower accumulation of proinflammatory cytokines and thus low-grade inflammation.

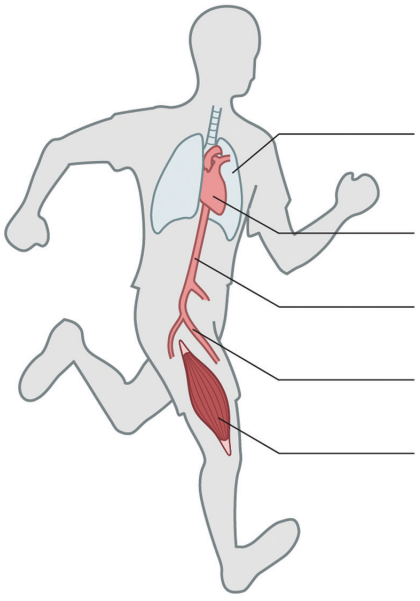
In addition to the protective effects on the acute inflammatory response, exercise training has the potential to disrupt the vicious cycle of chronic inflammation (10). This beneficial effect involves induction of anti-inflammatory cytokines (IL-6, IL-1ra, and IL-10) during each exercise bout, as well as regulation of the more chronic production of inflammatory cytokines from the myeloid immune cells (168). During exercise performance, myokines are produced within skeletal muscles and released into the circulation, and some of these cytokines are categorized as anti-inflammatory cytokines. The best-described myokine is IL-6, and in its role as a myokine, IL-6 elicit anti-inflammatory effects by stimulating the release of other anti-inflammatory cytokines, as well as suppressing TNF-alpha production in response to an inflammatory stimulus (135).

Notwithstanding the underlying mechanisms, several exercise intervention studies have aimed at reducing the levels of inflammatory markers in cancer survivors or in people at risk of cancer. Results from these studies show that long-term exercise training may reduce systemic levels of CRP, TNF-alpha, IL-6, and other proinflammatory factors, but these interventions needed to be of long duration (6, 56). The typical 12 to 16 weeks, which most exercise training interventions last, often fail to regulate systemic low-grade inflammation in cancer survivors. Despite the large efforts to control systemic low-grade inflammation through exercise training, the evidence that such systemic regulation of pro-inflammatory cytokines should result in control of cancer progression has not been experimentally demonstrated. In a simplistic experimental design, serum obtained from breast cancer survivors, who had participated in a 6 months endurance training intervention study, was used for cancer cell incubation studies (46). The exercise intervention resulted in marked improvements in fitness levels, as well as significant reductions in the serum levels of the inflammatory cytokines, TNF-alpha and IL-6. Aside this reduction in systemic inflammation, the training-conditioned serum had no regulatory effect on breast cancer cell growth. In contrast, the study demonstrated that the systemic changes occurring during a session of exercise, which involves large increases of IL-6 and other cytokines known to derive from contracting muscles, could inhibit cancer cell growth *in vitro* (46). These findings question whether systemic adaptations in inflammatory markers in response to training are mediating the beneficial effect of exercise, but instead imply that the accumulative effect of repeated acute exercise responses may lead to control of tumor growth.

Taken together, secondary prevention of cardiovascular morbidity and mortality by protection against endocrine deficiencies, cardiotoxicity, weight gain and metabolic dysfunction, as well as lowering risk of secondary cancers, comprises an important role for exercise training after completion of primary anti-cancer treatment. This long-term sequalae may impact patient survival across many diagnoses, but is of particular relevance in patients with very good cancer prognoses such as children and young adult cancer survivors, and women with early stage breast cancer. Large focus has been on using exercise training in combination with other lifestyle related factors to prevent cardiac disease, weight gain, and systemic increased levels of common risk factors for cancer. These adverse effects can play an important role for long-term survival, when cancer survivors are expected to live without disease relapse for the rest of their life. Yet, exercise training may also be a potential component in preventing disease relapse, and such secondary prevention may play an even greater role in cancer diagnoses with higher rates of relapse. While metabolic disturbances and increases in cancer risk factors might play a role in disease relapse, the evidence of the effect of exercise training on the rate of disease relapse and any molecular pathways included in such protection is still poorly elucidated.

Physiological Outcomes

The physiological response to exercise performance is well characterized in healthy individuals and constitutes a whole subject of exercise physiology. Central responses include engagement of the sympathetic neural circuitry and neuroendocrine signaling to adjust respiration, blood flow, fuel supply and selection, and thermoregulation, in addition to autocrine, paracrine, and endocrine factors operating between tissues providing interorgan cross talk to coordinate fuel supply and selection (66). Classical training adaptations in VO_2max/fitness and muscle strength and mass are routinely evaluated to characterize the response to training. In healthy subjects, these improvements are correlated with health benefits (95, 113), and also in cancer patients have cardiovascular fitness as well as muscle strength and mass been associated with improved prognosis and survival (41, 92, 179). Yet, adaptations in these physiological measurements may also be hampered in cancer patients due to effects of either an active tumor or adverse toxicities of anti-cancer therapy.



Physiological factors determining VO_2max	Time required for exercise adaptation	Pathophysiological regulation in cancer patients
Pulmonary diffusing capacity	Normally no change	Lung tumor or surgery
Cardiac output	Days to weeks	Cardiotoxicity to anthracyclines
Plasma volume	Days	Fluid retention or dehydration
Red blood cell volume	Weeks	Bone marrow suppression
Skeletal muscle vascularization and O_2 extraction	Months	Treatment-induced muscular inflammation and metabolism

Figure 12 Exercise-dependent regulation of cardiopulmonary fitness (VO_2peak) in cancer patients. VO_2peak is determined as the maximum capacity to deliver oxygen to the working muscles, and requires integration of multiple steps known as the oxygen cascade. Here, we outline the various limiting steps in oxygen cascade in cancer patient with regard to the training-time required for exercise-dependent adaptation, as well as cancer-specific pathophysiological impairments in the response potential. The first step involves the oxygen saturation of the blood as a result of pulmonary diffusion capacity from the atmospheric air in the lungs to the blood in the alveoli. This step is extremely rarely a limiting factor for maximum oxygen uptake, but may be significantly hampered in the event of thoracic surgery. The next step involves the capacity to distribute oxygenated blood to the metabolic active tissues. The maximum cardiac output (liters of blood per minute) is determined by the maximum heart rate and the stroke volume of the heart, of which only stroke volume is considered trainable healthy subjects. Cardiac output is a well-established limiting factor of cardiopulmonary fitness in sedentary and recreationally active humans, and constitutes a robust exercise adaptation within days to weeks of commencing an aerobic exercise program. However, various cancer drugs and/or irradiation to closely situated tumors (e.g., thoracic or mammary irradiation) can cause cardiotoxicity in the form of various limiting symptoms including cardiomyopathy, inhibiting the capacity to improve stroke volume. Another key determinant of cardiac output is the total blood volume (in liters), which consists of total plasma volume and red blood cell volume. Integrative physiology research has shown a close correlation between changes in blood volume, especially red blood cell volume, with changes in VO_2peak, and elegant phlebotomy experiments have found that exercise-induced improvements in VO_2peak is abolished when the increase in blood volume is normalized to pretraining levels. Exercise-induced regulation of blood volume in cancer patients has to our knowledge never been examined and may to some extend explain the lack of robust increases in VO_2peak, as normally observed in healthy individuals. Indeed, a number of treatment-related pathophysiological changes may impact, and reduce, particularly red cell blood volume by bone marrow toxicity and/or dehydration due to nephrotoxicity. Finally, extraction of oxygen from the capillaries to the muscle cells and mitochondrial metabolic turnover rate comprise the last steps of the oxygen cascade. The capillary density, that is, "the cross sectional muscle area supply by one capillary" as well as oxidative enzymes are key regulators of intramuscular oxygen utilization, and while these are rarely considered limiting factors for VO_2peak, as they show robust adaptations to exercise in healthy individuals. In patients with cancer, few studies have examined muscular toxicities, but a number of common symptoms, for example, muscular pain from taxanes, which is considered a result of serious muscular inflammation may be so severe, at least in the acute treatment phase, that they significantly limit maximum aerobic exercise performance irrespective of the oxygen delivery capacity.

Cardiopulmonary fitness

Cardiopulmonary fitness is a key determinant of mortality in both the general population and among cancer patients (186). Cardiopulmonary fitness is tightly correlated to maximal oxygen uptake (VO_2peak), and determination of fitness levels by Cardiopulmonary Exercise Test (CPET) or other indirect measures are cornerstones in the assessment of exercise adaptations. Accordingly, 198 exercise intervention studies in cancer patients have included a measure of cardiopulmonary fitness.

VO_2peak is defined as the maximal rate of oxygen consumption measured during incremental exercise, and is an important determinant of endurance capacity during prolonged exercise. Physiologically, VO_2peak depends on the cardiac output and the oxygen carrying capacities of the cardiopulmonary system (106). In health individuals, the greatest adaptations in VO_2peak can be contributed to improvements in cardiac output, due to adaptations in stroke volume and blood volume (Fig. 12). Secondly, capillary density in skeletal muscles plays an important role in the last step of supplying the working muscles sufficient oxygen. While adaptations in cardiac output typically requires moderate to high-intensity endurance training, muscular adaptations in capillary density and thus the muscles ability to extract oxygen from the blood can be obtained at a lower intensities (51).

Generally, untrained individuals will respond to endurance training with improvements in VO_2peak providing that the stimulus exceeds the necessary volume and/or intensity. Such improvements are mainly driven by expansion in the red blood cell volume and the associated enhancement of cardiac output. Exercise trials in cancer patients have generally found increases in VO_2peak following endurance training (165). Thus, little evidence indicates that cancer patients differ significantly in their adaptations to exercise training

compared with healthy individuals. However, some studies fail to find this otherwise robust adaptation in cardiopulmonary fitness, even though the exercise stimulus was substantial both in terms of volume and intensity (34, 177). This discrepancy may be a consequence of toxic effects of anticancer treatment, targeting red blood cell volume, blood volume, and muscular oxygen extraction capacity.

Limitations to exercise adaptations in VO_2peak in cancer patients

Bone marrow suppression is a common side effect of antioncogenic treatment, and while suppression in white blood cell populations is most often seen, reductions in the amount of red blood cells are also a common phenomenon. In relation to fitness levels, the suppression of red blood cell production will directly compromise the oxygen carrying capacity of the blood, thus limiting the exercise-mediated improvement in fitness levels, despite adaptations in cardiac output. In clinical practice, blood transfusion or bone marrow stimulating agents may be administered to treat anemia, and it should be noted that such treatments, which acutely increases the hemoglobin levels, will directly increase VO_2peak without any exercise-mediated regulation.

One of the earliest adaptations to exercise training is an increase in total blood volume (106). After just one bout of exercise training, plasma volume may increase up to 10%, and with long term training the volume of the blood including the plasma volume and the red blood cell compartment may increase with up to 40% (30, 107). This increase in blood volume leads to a higher venous return to the heart, higher cardiac filling, and thus larger cardiac output—a principle component of the VO_2peak measure. Whether this adaptation in blood volume occurs in cancer patients is currently unknown, but cancer patients may experience several challenges to their overall hydration. Some chemotherapy drugs are delivered with large (up to 5 L) amounts of saline to prevent nephrotoxicities. Moreover, supportive care drugs like steroid hormones, lead to fluid retention, and thus hyperhydration of cancer patients. In contrast, some patients may be dehydrated due to diarrhea, infections, and bleedings, which can persistent at moderate levels for longer time. How this hydration state and regulation of blood volume interact with exercise-mediated changes in VO_2max measurements are unknown, but it seems reasonable that this physiological phenomenon could explain some of the large variations seen in exercise-mediated adaptations in VO_2max, where some studies fail to detect adaptations despite high training compliance of the patients.

Lastly, oxygen extraction from the blood to the muscles poses the last step of the oxygen delivery chain. This step is controlled by intramuscular capillary density and mitochondrial content. Very few studies have investigated exercise adaptations at the muscular levels. Mijwel and colleagues analyzed muscle biopsies from the Optitrain study, including women with breast in either an aerobic high-intensity interval training group, a high-intensity resistance training group or usual care. Aerobic training increased the protein levels of complex I, II, and IV, which are functional complexes of the mitochondria, as well as citrate synthase activity. Resistance training did not affect the mitochondrial protein content, but increased muscle fiber cross-sectional area (115). Christensen and colleagues subjected 30 patients with germ cell cancers to 9 weeks of resistance training concurrent with curative intended chemotherapy, and compared their muscular adaptations to healthy age-matched controls (25). While the healthy control subjects demonstrated the expected increases in muscle fiber cross-sectional area and capillary density, resistance training only tended to attenuate the treatment-induced decline in myofiber cross-sectional area in the patients with germ cell cancer, while resistance training had no effect on the number of capillaries per myofiber in these patients. Aside from these two studies, very little is still known of the muscular adaptations in capillary density and mitochondria biogenesis in cancer patients during exercise training.

In summary, VO_2peak may be markedly influenced by bone marrow suppression, blood volume regulation, and muscular impairments in cancer patients, in particular in patients in ongoing anti-cancer therapy. Despite this, VO_2peak has been extensively used as a surrogate marker for cardiotoxicity in cancer patients. A recent review summarized 18 randomized controlled trials evaluating VO_2max or VO_2peak, as evidence for the effect of exercise training on chemotherapy-induced cardiotoxicity (155). Yet changes in VO_2peak may reflect several other cardiopulmonary limitations in cancer patients than cardiotoxicity, making VO_2peak levels an imprecise surrogate marker for cardiotoxicity. More detailed information on limitations to the various steps of the oxygen cascade in patients with cancer remains to be established, but these are likely to differ between cancer populations due to differences in cardiopulmonary and -vascular treatment toxicities. Accordingly, the mechanistic impact of exercise training to counter these detrimental effects may differ and requires detailed integrated physiology experiments to optimize fitness improvement in clinical practice.

Muscle strength and hypertrophy

Skeletal muscle is the largest organ in the human body, constituting up to 40% of the total body mass in healthy nonobese humans. Skeletal muscle function is classically defined by its ability to perform muscular contractions, generating external mechanical force, which enables physical activities of daily living and exercise. In addition, skeletal muscle plays a vital role in primary and secondary disease prevention as an essential regulator of metabolic and inflammatory homeostasis (67, 122). Muscle mass and muscle function, that is, contractile strength, have consistently been demonstrated to be predictors of overall survival, disease progression, and complications to anti-cancer treatment, including postoperative complications and chemotherapy-induced toxicities in cancer patients (24, 41, 161).

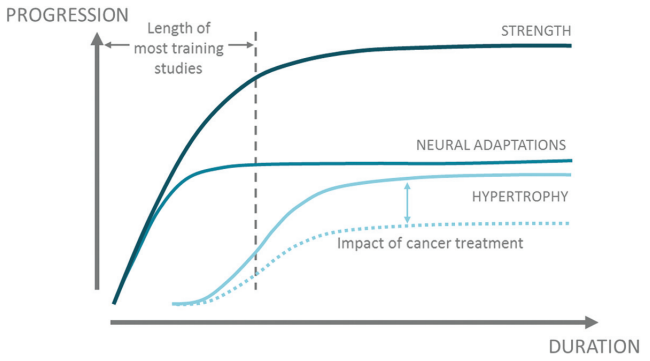


Figure 13 Regulation of muscle function in cancer patients. Overall maximum contractile muscle strength is determined by anatomical features especially the cross-sectional area (mass) and pennation angle, and a neural component, that is, recruitment and synchronization of motor-units. The vast majority of resistance training trials performed in cancer patients have found a significant increase in contractile strength, whereas changes in muscle architecture, which have mostly been evaluated by whole-body and appendicular lean mass, have yielded ambiguous results especially in studies performed during active treatment. One explanation for this apparent lack of muscular adaptation may stem from the relative short duration of most exercise interventions (from 4 to 16 weeks), and the possible counteracting impact of cytotoxic or antiandrogenic treatments, which may impair protein synthesis and/or enhance protein degradation signal in skeletal muscle. Although, this limited or inhibited hypertrophic exercise-response may discourage the clinical application of resistance training in cancer patients, it is important to acknowledge the almost unanimous improvements in muscle strength, irrespective of changes in muscle mass, are reported in almost every exercise intervention studies in cancer patients, including advance stage lung cancer patients and patients treated for head and neck cancer, who are subject to massive muscle wasting due to nutritional deficits.

Skeletal muscle may appear histologically uniform, but at the cellular level, the muscles comprise of myofibers, which differ in respect to size, contractile function, and metabolism. Type 1 slow-twitch myofibers are characterized by slow contraction time and high oxidative capacity, while Type 2 fast-twitch myofibers are reckoned for having a faster contraction time, rapid fatigue profile, and predominant glycolytic metabolism. All muscles contain a mix of these myofibers, ensuring that muscles can adapt to both endurance and strength-based exercises (66). Traditionally, resistance training is recognized as the strongest stimulus for muscular adaptation, as it elicits a range of morphological and neurological adaptations, which contributes to the training-dependent adaptations in muscle size, strength, and power (Fig. 13). Morphologically, the cross-sectional area increases especially in Type 2 fibers, the angle of pennation of each fiber changes, and the proportion of noncontractile tissues, that is, collagen, increases. The hypertrophy response depends on a positive protein synthesis balance, where the rate of newly synthesis protein exceeds protein degeneration, as well as satellite cell fusion with existing myofibers to increase the number of transcriptionally active nuclei per myofiber. Neurologically, improvements in motor unit activation, including firing frequency and synchronization between the motor units, will add to the enhanced muscle strength. Typically, the neurological adaptations precede morphological adaptations, as the later response is dependent on protein synthesis for accretion of contractile proteins. Endurance training, on the other hand, has major impact on muscular metabolism, in particular through enhancement of the oxidative capacity. During each bout of exercise, the breakdown in intramuscular energy stores, that is, glycogen, will elicits a signaling cascade involving induction of AMPK and PGC-1alpha and their downstream targets, resulting in mitochondrial biogenesis, glycogen resynthesis, and thus adaptations in energy substrate utilization.

Assessments of muscle strength and mass, and physical function have been included in the majority of all exercise intervention studies (Fig. 4). Muscle strength is typically measured by a dynamic 1 repetition maximum (RM) test or tests of maximal isometric strength (e.g., hand grip strength), while physical function is assessed using a 30 s sit-to-stand test, tests of gait speed or similar tests. Muscle mass is often assessed by whole-body scans, including DXA scanning or bioelectrical impedance, or extrapolated from CT scans of the thoracic area, e.g. skeletal muscle area at the third lumbar vertebra or psoas muscle volume. Across the vast majority of studies, exercise training, in particular resistance-based training, has been shown to increase muscle strength (42). In contrast, fewer studies have been able to demonstrate effect of exercise training on enhancing muscle mass. Regarding muscular adaptations to training, neurological control is improved before morphological changes, which are dependent on *de novo* protein synthesis and myofibrillar transformation. In this perspective, the length of most cancer exercise-trials is relatively short (<3 months), indicating that while time of neurological adaptations is adequate, the time for morphological changes may be too limited to observe large-enough adaptations to be measured at the macroscopic muscle mass level (51). Moreover, relevant changes in muscle mass require large exercise stimuli and precision of the muscle mass measurement. Brown and colleagues randomized 296 breast cancer survivors at high risk of or with lymphedema to supervised weight-lifting in community-based gyms for 12 months. The weight-lifting group increased markedly in muscle strength (+27% in leg press, $P < 0.001$), but showed no change in appendicular muscles mass, as evaluated by DXA scanning. However, weight-lifting did impede the 220 g loss of appendicular muscle mass ($P = 0.038$), which was observed in the control group (13).

The impact of concurrent treatment may offset the adaptations in muscle strength and mass in cancer patients. This discrepancy between exercise-mediated adaptations in muscle strength and muscle mass is underscored in studies with cancer patients losing substantial amount of weight including muscle mass. One example is a study by Lonkvist and colleagues prescribing resistance training to head and neck cancer patients concurrent with chemoradiotherapy. During the 6 weeks of chemoradiotherapy, patients lost on average 7.7 kg body weight, equivalent to 9% of their body weight. Of this weight loss, the loss of muscle mass was 5.1 kg across the

6 weeks of treatment (105). Despite this marked weight loss and loss of muscle mass, the patients progressed substantially in muscle strength emphasizing that functional adaptations can occur independent of changes in muscle mass.

Limitations in exercise adaptations in muscle strength and mass in cancer patients

Peripheral neuropathies are common adverse effects to many chemotherapeutics. This may be exemplified by agents targeting tubulin, for example, vincristine, which through high-affinity binding to tubulin aborts cell division and cause cell death. This disruption of tubulin assembly and disassembly also directly affect the axonal microtubules, causing axonal swelling and thus nerve damage. As a consequence, the firing capacity of the motor neurons decreases, leading to denervation of muscle fibers and subsequently muscle atrophy (125). It is currently not known if exercise training may interfere with this treatment-induced muscle fiber denervation, but this effect may partly explain the large variation seen in the responses to exercise training in muscle mass during chemotherapy treatment as the extend of peripheral neuropathy also varies considerably between patients.

In the early days of exercise intervention studies in cancer patients receiving concurrent chemotherapy, it was proposed that cytotoxic therapy would target and kill muscle progenitor (satellite) cells if these became proliferative active due to the exercise stimuli (28). Satellite cells are essential for repair of damaged muscle and serve as a source of new myonuclei. When stimulated by heavy resistance exercise, satellite cells are activated to reenter the cell cycle and proliferate, thus a concern was that any treatment-induced loss of satellite cells would lead to problems with maintaining muscle mass in the long run. We only know of three studies, which following have investigated the effect of exercise training and anticancer treatment on satellite cell number in cancer patients. First, a study with patients with germ cell cancer undergoing cisplatin-based standard chemotherapy engaged patients in high-intensity resistance training. In these patients, no acute loss of satellite cells was found across the intervention, suggesting that heavy resistance exercise during chemotherapy was safe in regard to preservation of satellite cells (26). In a second study, Mijwel and colleagues explored satellite cell number in breast cancer patients randomized to aerobic high-intensity interval training, high-intensity resistance training, or usual care. In this study, no decreases in satellite cell number was observed across the intervention, in fact the resistance-training group demonstrated an increased level of satellite cells after the 16 weeks of training (115). Nilsen and colleagues investigated the effect of 16 weeks of resistance training in prostate cancer patients undergoing ADT on muscular outcomes, including satellite cell numbers, and found no adaptations in satellite cell numbers following strength training. Even though this treatment is not directly cytotoxic for proliferating normal cells, prostate cancer patients are plagued with loss of muscle mass, yet this might not be attributed to a treatment-induced loss of satellite cells (126).

Exercise training and muscular adaptations have been extensively explored in the setting of prostate cancer patients on androgen deprivation treatment (ADT). ADT eliminates bioavailable testosterone in men, leading to medical castration levels of this androgen hormone. Accordingly, men on ADT suffer from numerous side effects including loss of muscle mass, as testosterone is one of the strongest hormones in promoting muscle building in men (131). This treatment-induced loss of muscle mass is most pronounced in the first 6 months of therapy, but continues to occur throughout the treatment period. Resistance training in prostate cancer patients in androgen deprivation treatment has been shown to attenuate the treatment-induced muscle loss or even increase muscle mass (32, 57). However, across numerous exercise intervention studies in prostate cancer patients on ADT, large variation in the training responses have been observed, suggesting that interactions between medical castration and exercise adaptations include large inter-individual responses.

In contrast to men on androgen deprivation treatment, who are usually gaining weight but losing muscle mass, there is also a large group of cancer patients, in particular within lung and GI cancer, who loss body weight and muscle mass due to a negative energy balance, resulting from a lack of protein and energy intake and a hypermetabolic state. This catabolic state might in its most extreme form result in cancer cachexia, where patients per definition have an involuntary weight loss of more than 5% of the pre-cancer body weight within 6 months (54). Concerns have been raised as to which extent, cancer patients should be exercise training during anorexia and energy-depleted states. A few exercise intervention studies have addressed the feasibility of training concurrent with treatment-induced weight loss, for example, head and neck cancer patients undergoing concomitant radio-chemotherapy. Here, the conclusions were that it was indeed safe and feasible to train these patients (105, 144). One random observation from these studies was that the exercise intervention might actually promote food and energy intake in these otherwise anorexic patients. None of the exercise intervention studies has addressed the biological mechanisms involved in this enhanced food intake, but a study in mice explored the effect of voluntary wheel running on food intake and maintenance of muscle strength and mass during cisplatin-induced anorexia and weight loss. Here, voluntary wheel running prevented muscle wasting through a normalization of energy intake, which was associated with an exercise-dependent induction of the appetite hormone ghrelin (71). These findings can have relevance for daily clinical practice for the large group of cancer patients struggling with nausea and emesis, as these results point out that exercise may independently improve appetite and energy consumption, and thus ensure sufficient protein and energy for maintaining muscle mass.

Taken together, adaptations to exercise training in cardiopulmonary fitness as well as muscle mass and strength

are well described in healthy individuals, and cancer patients gain, to a larger extent, the same physiological benefits. Yet, in particular during chemotherapy, treatment may lead to bone marrow suppression, fluid regulation, neuropathies, muscular inflammation and anorexia, which can interfere with the normal adaptations to exercise training.

Psychosocial Outcomes

The vast majority of the early exercise intervention studies in cancer patients were designed with the aim of improving health-related quality of life (HRQoL) and cancer-related fatigue. These psychosocial outcomes are of immediate importance for cancer patients, and remains to be universally included as central component outcomes in newer generations of exercise trials. Exercise-associated improvements in these outcomes depend on both psychological and physiological effects. Here, we summarize the collected data of the effect of exercise training on psychosocial outcomes, focusing on HRQoL, depression and cancer-related fatigue, and discuss the few physiological mechanisms, which have been linked to these outcomes. For detailed information and research related to the psychological components, we refer to these excellent reviews/studies for further reading (85, 117, 119).

Health-related quality of life

HRQOL is defined as an individual's perceived physical, mental, social, and functional health and integrates these different domains in a common score, which goes beyond morbidity, mortality and economic status. HRQOL is a valid and strong measure, which has been shown to correlate tightly with longevity, health behavior, mental and physical illness, social connectness, and productivity. HRQOL is evaluated by self-reported questionnaires, of which there is a wide range with the most commonly used in exercise oncology being EORTC Quality of Life Questionnaire Core 30 Items (QLQ-C30), the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement system, the Rotterdam Symptom Checklist (RSCL), and the Symptom Distress Scale (SDS).

In exercise intervention studies in cancer patients, HRQOL is the single most commonly reported outcome (Fig. 4). Accordingly, several systematic reviews and meta-analyses have combined data from all of these trials, and provide compelling evidence on a small but significant effect of exercise training on HRQOL. A recent Cochrane review (98) including 63 studies and 5761 women addressed the effect of exercise interventions in breast cancer patients after completion of primary anti-cancer treatment, and found small-to-moderate beneficial effects on HRQOL, including emotional function, perceived physical function, and anxiety. However, the authors also cautioned their conclusions, given the very low to moderate quality of the evidence, heterogeneity between the interventions and outcome measures, imprecision of estimates and risk of bias in the conducted studies. Another Cochrane review (117) addressed the effect of exercise training during ongoing treatment across all cancer diagnosis in 56 included trials with 4826 patients, and found that exercise interventions had a positive impact on HRQOL, including physical functioning, social functioning, and cancer-related fatigue. In this analysis, the studies with breast cancer patients constitute the majority of studies, but if analyzed separately from breast cancer, exercise interventions in other cancer diagnoses induced greater improvements in HRQOL, including emotional well-being, physical functioning, role functioning, and sleep disturbances. Moreover, this meta-analysis suggested that the beneficial effects were more pronounced in interventions of moderate to vigorous activities compared with milder exercise programs. Also in this review did the authors cautioned regarding the high degree of heterogeneity between the studies and the high risk of bias in many trials.

Buffart and colleagues explored a database of 69 exercise intervention studies to address mediators and moderators of the beneficial effect of exercise on HRQOL. In their analyses, which included factors like demographic (age, sex, marital status, education), clinical (body mass index, cancer type, presence of metastasis), intervention-related (intervention timing, delivery mode and duration, and type of control group), and exercise-related (exercise frequency, intensity, type, time) characteristics, the authors identified an overall beneficial effect of exercise training on quality of life and physical functioning, but of all the evaluated mediators, only supervised training proved to be superior to unsupervised training in improving these outcomes (16). Thus, the beneficial effect on quality of life may not be solely attributable to the physiological effect of exercise training. Although exercise training can induce the release of hormones, giving raise to the happy feeling of runners' high, the more long-term effect of exercise training on quality of life, may have to do with self-empowerment and preclusion of social isolation, which is associated with training in groups, and/or under supervision of training instructors.

The beneficial role of exercise on HRQOL is firmly established although only small in extend and linked to higher training intensity and supervision. Thus, the question is whether exercise interventions should be delivered solely with the aim of improving patients' quality of life, or whether the beneficial effect is merely a bonus in the pursuit for clinical improvements. In traditional oncology, drugs are prescribed with room for high degree of side effects and negative impact of quality of life, given the clinical gain of the drug is high enough. In contrast, if the clinical gain of a drug is limited, the tolerance for impairments in the patients' HRQOL is markedly lower. Thus, measurements of quality of life should always be included in studies, as a mean of determining the patients' acceptability of the intervention. Not all patients enjoy exercise or will willingly engage in exercise programs, but there might be situations in cancer care were the benefits outweigh the opposition, as for instance during the limited period of preoperative optimization, where interventions aim to

condition weak patients for cancer surgery. Here, the threshold for acceptance of exercise training may be lower than if the goal is general health promotion in the survivorship phase.

Depression

One of the more severe psychological adverse effects of cancer and cancer therapy is depression, which is correlated with poor treatment compliance and increased mortality risk in cancer patients (29). The prevalence of depression may be as high as 50% in some cancer diagnoses, but this number can vary greatly according to report, cancer diagnosis, and time in the cancer continuum (108). As for HRQOL, accumulating evidence indicates that exercise training may be beneficial for improving symptoms of depression in the oncological setting, and this is in particular seen in cancer patient population other than breast cancer patients (31, 116, 117, 123).

Evaluation of depression relies on questionnaires, for example, Hospital Anxiety and Depression Scale (HADS) and Beck's Depression Inventory, which score patients' symptoms of depression. These scales typically include a threshold score of what is considered clinically relevant scores of depression. For instance, the threshold is eight on the HADS-D scale. Yet, the vast majority of patients enrolled in exercise intervention studies do not exceed such threshold, and do therefore not present with clinically relevant symptoms of depression. Thus, most of the improvements, which have been reported in exercise intervention studies, are in the range of subclinical improvements. There are some obvious challenges with recruiting patients with symptoms of depression to exercise intervention studies; however, several studies in non-cancer patients with clinical relevant symptoms of depression have demonstrated that it is feasible to train these patients, and that they will benefit from the intervention in regard to their clinical depression (31, 172). Experiences from these studies may be translated to cancer patients with symptoms of depression, ensuring that these patients will be recruited in future targeted exercise interventions.

A molecular link between exercise and depression was recently demonstrated in mice. An exercise-dependent regulation of tryptophan metabolism result in reduced accumulation of neurotoxic products. These toxic tryptophan metabolites were shown to be eliminated in the contracting muscles (2). In cancer patients, the systemic levels of the tryptophan metabolites (kynurenine, 3-hydroxykynurenine (HK) and quinolinic acid) have been shown to be upregulated, and these metabolites are associated with depression and fatigue in both cancer patients and other patient populations (93). The expression of these metabolites is tightly linked to systemic and intratissue inflammation, which drive their production in several tissues (79). In contrast, skeletal muscles were shown to metabolize kynurenine into kynurenic acid, which cannot cross the blood-brain barrier, and therefore leads to protect against depression. The increased conversion of kynurenine to kynurenic acid was shown to be dependent on activation of the transcription factor PGC-1alpha, which is induced with endurance training, providing a link from exercise training to tryptophan metabolism (Fig. 14) (2). In a recent study in healthy individuals, kynurenine was shown to be metabolized in muscles during exercise training, and this involves an upregulation of the catabolic enzymes kynurenine aminotransferases within skeletal muscle (152). Whether these results can be translated into cancer patients for any exercise-mediated alleviation of their depression symptoms remains to be determined.

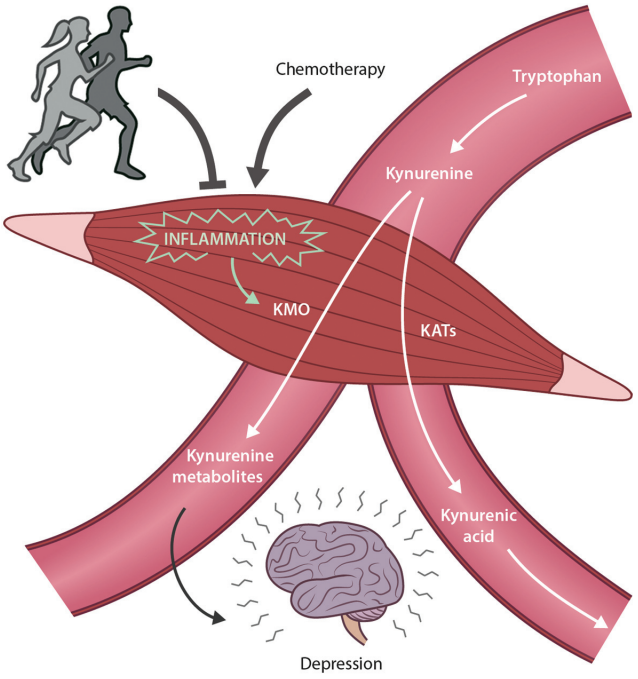


Figure 14 Exercise reduce depression through regulation of kynurenine metabolism. Exercise training has consistently been shown to reduce symptoms of depression in cancer patients. Recently, a mechanism to explain how exercise can regulate symptoms of depression at the molecular level was proposed involving regulation of the Kynurenine degradation products. Degradation of Kynurenine follows one of two possible pathways: Kynurenine is either converted to nicotinamide adenine dinucleotide (NAD) or anthranilic acid through kynurenine 3-monooxygenase (KMO); or converted to kynurenic acid by kynurenine aminotransferases (KATs). The Kyn-NAD pathway is induced by inflammation, which might occur secondary to chemotherapy in muscles of cancer patients. This transformation leads to production of quinolinic acid, a potent NMDA receptor agonist leading to excitotoxicity in the central nervous system. Kynurenic acid, on the other hand, is neuroprotective, acting as an antagonist of the NDMA-receptor and thereby counteracting the neurotoxic effects of quinolinic acid. Moreover, kynurenic acid cannot cross the blood-brain-barrier, so the conversion of kynurenine to kynurenic acid in the periphery can reduce accumulation of kynurenine in central nervous system. The imbalance between these neuroprotective and neurotoxic metabolites has been proposed to be critical for development of symptoms of depression.

Cancer-related fatigue

Cancer-related fatigue is reported by up to 90% of patients during adjuvant treatment with radiation, chemotherapy, and/or biologic therapies, but with large variations according

to report, cancer diagnosis, and timing in the cancer continuum (159). Cancer-related fatigue is evaluated by numerous different questionnaires, for example, The Multidimensional Fatigue Inventory (MFI) and FACT-F, and as for depression, the number of patients suffering from cancer-related fatigue whom have been included in a large number of the conducted exercise intervention trials may not represent the background cancer population.

Cancer-related fatigue has negative impact on the patients' quality of life and is a predictor of long-term sick leave. Cancer-related fatigue can give rise to a vicious cycle, where cancer-related fatigue leads to physical inactivity, which will further promote the feeling of tiredness. To break this vicious cycle of physical inactivity and fatigue, exercise training has been promoted as a promising intervention. Accordingly, cancer-related fatigue has investigated in 145 exercise intervention studies based on our literature search. Recent meta-analyses have exploited the impact of exercise on cancer-related fatigue, and conclude that exercise training mediates beneficial effects, if the patients adhere to more than 80% of the prescribed exercise training. In contrast, if patients adhere to less than 60% of the prescribed training, no beneficial effect was observed, suggesting that it is not enough just be avoid physical inactivity (90). Importantly, it was recently established that exercise training is superior in comparison with any pharmaceutical or psychological interventions for improving symptoms of cancer-related fatigue (119).

The underlying biological mechanisms for cancer-related fatigue are currently not fully understood. Systemic inflammation has been suggested to add to the pathology of cancer-related fatigue, and numerous studies have demonstrated positive correlations between plasma reactive c-protein levels and scores of cancer-related fatigue (129). Based on this association, exercise training has been suggested to mediate its protective effects through its anti-inflammatory effects on systemic inflammation. Yet, this causality has still to be mechanistically proven in exercise intervention studies in cancer patients.

Taken together, psychosocial outcomes have been addressed in most exercise intervention studies in cancer patients, and meta-analyses report a small but significant beneficial effect of exercise training on HRQOL, depression and cancer-related fatigue. These positive effects seem to be larger in other cancers than breast cancer, but since most studies have been performed in breast cancer patients, this group of patients constitute the strongest base of evidence so far. Moreover, early data on the mediators of the beneficial effect of exercise training points to roles for supervision and training intensity. First, supervision by training instructor may ensure higher training intensity, indicating a possible link between these two. Second, the component of supervision, which is also often associated with group-based training, suggest that the psychological part of engaging in exercise training with larger social interaction and connectness play an important role for the psychosocial benefits.

Importance of outcome measures in different cancer settings

In summary, there is solid evidence that exercise training may improve physical functioning and health-related quality of life, in particular in early stage breast cancer patients, and emerging body of evidence suggest that exercise may play an important role ameliorating anti-cancer treatment toxicities and enhancing treatment efficacy, which may translate into improved survival and quality of life (72).

Thus, a strong rationale including promising experimental data, indicate that exercise training directly or indirectly can impact cancer specific outcomes including disease progression, treatment tolerability, and secondary prevention. However, it should be highlighted that cancer patients differ markedly according to their diagnosis, stage of disease, and ongoing therapy, and thus the different outcomes have distinct importance given the individual situation of the patients. To this end, the most important outcomes for early-stage cancer patients may be to complete anti-cancer therapy with a few adverse effects and toxicities as possible, a speedy recovery ensuring regain of physical functioning, return to ones' daily life, and secondary prevention of long term adverse events and disease relapse.

In comparison, cancer patients with advanced stage disease are subjected to a vastly different situation and the potential application of exercise interventions needs to be put into this perspective. When cancer treatment is administered without curative intend, quality of life is of paramount importance, and patients are closely evaluated to determine whether treatment response is satisfactory balanced against the associated toxicities and adverse reactions. In this setting, exercise interventions may improve treatment tolerability, which in some scenarios leads to prolonged time to disease progression. In addition, the considerable symptom burden, that is, pain, loss of appetite, and fatigue are major determinants for the patients' quality of life. Targeted exercise-interventions to control and improve symptom burden in patients with advanced stage disease are largely lacking in the exercise oncology literature, but hold important clinical potential in palliative settings.

Principles of Training and Exercise Training Prescription

The shift in the central paradigm of standard cancer care from "avoid (especially strenuous) activity" to "avoid inactivity" has initiated a quest for identifying the optimal exercise prescription for cancer patients and survivors. Accordingly, large-scale exercise intervention trials have been initiated with the aim of testing various exercise prescriptions against each other (35, 177). These interventions compare exercise training programs, which differ based on characterizations like mode (aerobic vs. resistance training), intensity (moderate vs. high), and/or volume (low vs. high). Findings from these

studies may add directly to the recommendations and national guidelines on physical activity and exercise training, which health authorities and agencies are putting forward. However, it is important to recognize that the intrinsic properties of exercise training are not dichotomized or categorized entities, but comprise of a multi-dimensional continuum. Thus, it is critical to acknowledge that there may be multiple ways of achieving a given exercise adaptation response, while individualizing the exercise training to the capacity and limitations of each cancer patient. This can be achieved by paying attention to the various factors, which can be modulated during exercise training.

Principles of training in exercise oncology

The integrative biology of exercise comprises of highly complex regulation of different organ systems, and this complexity only becomes more elaborate by the physiological challenges induced by anti-cancer treatment. The aim of exercise interventions should be to provide the strongest possible physiological stimuli for obtaining a certain physiological adaptation. This requires careful planning, delivery and evaluation, particularly in the oncological setting. Matching the highly heterogeneous pool of individual cancer patients with a common optimal exercise program is a complex task. However, a considerable body of information derived from the many exercise intervention studies is available and may, with individualized modifications, comprise an effective framework for researchers and clinicians. Several conceptual papers have been published, describing how principles of exercise training can be incorporated into exercise oncology research and practice (82, 120, 150). Here, we outline the importance of four main principles of training, namely, (i) specificity, (ii) individualization, (iii) progressive overload, and (iv) reversibility, and discuss how these factors should be considered when engaging cancer patients in exercise training.

Specificity

First to improve a given physiological function, the exercise program should be designed to target this function optimally. Traditionally, a sharp distinction has been made between aerobic training for improving cardiorespiratory fitness, and resistance training to improve muscle mass and maximal strength. However, all exercise modalities essentially comprise of voluntary activation of skeletal muscles, which in turn must contract against a given external load and with a given repetitive velocity. Depending on the external load and/or intensity and the duration of the given exercise bout, different physiological functions are targeted at discrete efficacies. For instance, exercise performed against a maximal external load at very few repetition maximum mainly targets the central nervous system, that is, motor neuron firing rate and synchronization, improving the rate of force development (RFD) and maximum voluntary force, while exercise performed at a 8 to 12 repetition maximum intensity induces high strain on skeletal muscle, which leads to myofibrillar protein synthesis and subsequently muscle hypertrophy. At the other end of the continuum, traditional endurance training at a relatively low intensity, but which can be continued for up to hours, targets peripheral adaptations in the musculature including oxidative enzymes and fat oxidation capacity. Between these extremes lies the intermediate response to interval-based high-intensity training near maximum VO_2peak intensity, which specifically targets the oxygen delivery system including cardiac output, blood volume, and vascular compliance. Thus, exercise training can be considered as a continuous stimulus, where the degree of external load, intensity, and duration dictates the physiological adaptations, which can be obtained (Fig. 15).

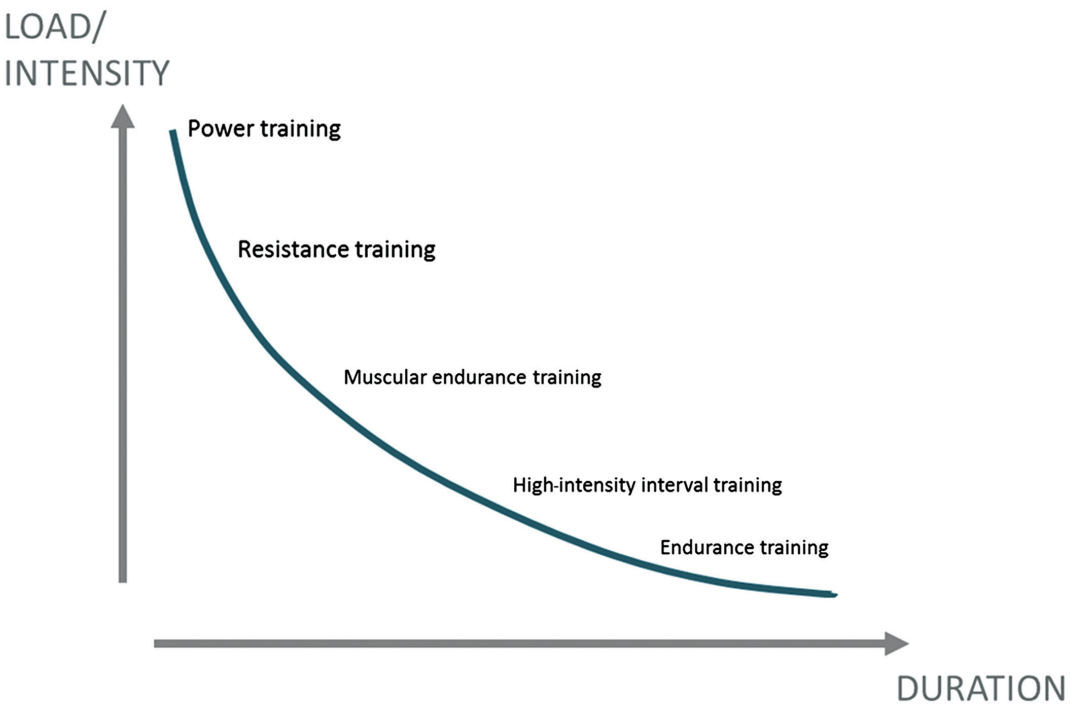
Individualization

It is critical to individualize the prescribed training volume and intensity to the patients' physical capacity. This typically requires baseline assessments using standardized exercise testing to determine the patients' individual maximal cardiopulmonary fitness or muscle strength. Exercise training should always be prescribed relative to the patients' functional level, ensuring that both well-trained and completely untrained and fragile patients are receiving a sufficient physiological stimulus for training adaptations.

Within the individualization of the prescribed exercise program is also a requirement of taking a wide range of structural factors into account. These include for instance physical limitations precluding certain types of exercise, as well as personal preferences for supervised versus unsupervised training, or gym-based versus home-based activities.

Progressive overload

The principle of progressive overload states that a certain physical and metabolic strain is required for physiological adaptions to occur. In clinical populations, strenuous exercise is sometimes discouraged, but this approach comes at the risk of, in the best cases, providing a suboptimal program, and in the worst cases an ineffective program. This links closely up with the individualization principle, since the initial overload of a planned program should be based on the individuals' functional capacity. For example, in frail elderly individuals, low-intensity walking programs will provide components of both cardiovascular and muscle functional strain, whereas sets of heavy resistance training may elicit additive mitochondrial adaptions traditionally associated with long-term endurance training in well-trained subjects due to an increase in motor unit recruitment from glycolytic myofibers. Inclusion of the progressive overload principle in the initial planning of an exercise prescription is important, but often the principle is neglected in the progression of traditional programs. To this end, it is important to appreciate the individuals' capacity changes markedly throughout the exercise-training program. In the initial phase, an untrained individual will often improve dramatically almost regardless of the prescription, but if the



Examples of prescription	Duration of work periods	Relative load/intensity	Work-to-Rest ratio	Main physiological stimuli and response
Power training	<10 s	Maximum external load • 100% of 1-3 RM	1 to >20	Neuromuscular activation, MVC force, RFD
Resistance training	20-30 s	High external load • 50-90% 1RM	1 to 10	Skeletal muscular strain, hypertrophy
Muscular endurance training	30-60 s	Low external load / high ATP turnover • 20-30% 1RM	1 to 1	Ion-balance disturbance, Fatigue tolerance.
High Intensity Interval Training (HIIT)	1-4 min	High ATP turnover rate • 60-100% of max aerobic capacity • Sprint/all out performance	1 to 1	Cardiac output, blood volume. VO2peak
Endurance training	10-120 min	Low ATP turnover rate • <50% max. aerobic capacity	Continuous	Intramuscular energy balance, lipid and glucose metabolism.

Figure 15 The exercise continuum for cancer patients. Exercise training interventions are often divided into distinct categories, typically described as resistance training using weights or fitness machines, and aerobic training using, for example, treadmills and stationary bikes, based on basic exercise physiology outlining that different exercise stimuli elicit different responses to different organ systems. However, all exercise interventions essentially consist of voluntary muscular contractions performed in a manner determined by a continuous relationship between (A) the external load and/or internal energy turnover rate, and (B) the duration of the active work period. Here, we have exemplified five modes of exercise training on the (duration-intensity) continuum with regard to the duration of active work period and the corresponding relative load/intensity, as well as the required work-to-rest time frame-ratio, and the main physiological stimulus and response. This ranges from maximum muscle force-generation performed against high external loads for just a few seconds known as "power training" to very light repetitive contractions performed for up to several hours as endurance training. Naturally, targeted exercise prescriptions stimulate different organ systems with different effectiveness and thus can be applied if specific adaptations are warranted, but it is important to emphasize that all physical exercise interventions involve physiological challenges of the entire continuum. By proper application of the principles of training, this internal feature can be utilized advantageously, when prescribing exercise training for patients with cancer. Most importantly, it provides a unique opportunity for individualization of an exercise program according to patient preferences and/or limitations, and the recognition of the individual's physical capacity, for example, for elderly, frail patients a structured walking intervention can comprise a relatively high-intensity exercise stressing both the oxygen cascade and neuromuscular components. This view of exercise training may also take into consideration training periodization as certain activities may be unfavorable during certain periods in the cancer trajectory. For example, patients who are seriously symptom-burdened during cytotoxic treatment phases may be precluded from performing exercise with highly elevated heart rate and blood pressure associated with high-intensity exercise, but may tolerate lower intensity for a longer duration. Or they may contrarily prefer short-term, high-load activity with high-intensity interval training (HIIT) or heavy resistance training, which can be concluded in short sessions. Abbreviations: RM, repetition maximum; MVC, maximum voluntary contraction; RFD, rate of force development; ATP, adenosine triphosphate.

training volume and intensity is not adapted accordingly to these improvement, no further or minimal additional functional progressions will be observed. To this end, continuous assessments, typically every 3 to 6 weeks, are important to properly match the exercise challenge to the individual's physiological capacity.

The importance of the progressive overload principle is particularly critical in cancer populations, where physiological declines may be expected, including patients undergoing heavy symptom-burdened anti-cancer therapies or patients in a palliative setting. Paradoxically, instructors or physiologists working with these patients are often reluctant to apply physiological testing from the rationale that it is inappropriate or even unethical to test patients who may experience a disease-related physical decline. However, the risk of mismatching the training load is arguably a more serious problem in this scenario. Rather than performing exercise testing as a physical state evaluation, it should be considered as a method to optimize and personalize the exercise prescription.

Reversibility

It is often neglected in exercise interventions in cancer patients that the level of reversibility throughout an exercise program plays a critical role for the overall training adaptations. Particularly, patients undergoing toxic therapies are likely to experience periods with so high symptom burden that exercise training is either discouraged or not possible. The principle of reversibility dictates that any exercise-induced physiological adaptions are lost during inactive periods with a time specific pattern, meaning that adaptations occurring rapidly are the first to be disappear, while long-term adaptations are lost more slowly. In this regard, focus on reducing or minimizing longer periods of inactivity ensure greater training adaptations. In the conducted exercise intervention studies, most studies follow a linear periodization typically involving a gradual increase of intensity over time. However, different approaches to periodization such as undulating periodization with more frequent manipulation of volume and intensity of the training allows for excessive overload in certain periods and less in others with same training effects (17,64,142). Such approach may be advantageous in settings, where the patients' general level of toxic symptoms varies as during chemotherapy treatment. In a periodization design, the exercise training can be planned to compensate for missed training sessions during treatment periods and with a higher training volume in other periods.

Exercise prescription, execution, and evaluation

These key principles of training provide researchers and clinicians with a framework from which to prescribe, execute, and evaluate exercise interventions in patients with cancer. It is important to consider the dynamic process of physiological adaptations to training, which require close attention and possible adjustments of the training programs throughout the cancer continuum. In fact, initial exercise prescriptions should not be considered as more than an overall guideline for improving physiological capacity, and this prescription will need to be customized to account for individuals' preference regarding setting, resources, limitations, and/or training history.

Supervision in individual or group-based programs is often preferred in certain settings of heavy toxic therapies or following major surgery, where a trained instructor can adjust the training volume and intensity according to the symptom burden of the patients. Contrarily, community- or home-based programs are less demanding for time, planning, transportation, and more likely to be adapted as a permanent lifestyle behavior, in particular in patients who have completed primary anti-cancer treatment.

Behavior change interventions have also been suggested to create sustainable lifestyle changes in relation to physical activity, and may be a way of ensuring that cancer patients remain physically active after ending their prescribed exercise interventions (167).

To evaluate if patients are gaining the optimal physiological stimuli from their exercise prescription, it is of course of paramount importance to know whether the patients have followed the prescribed exercise program. Most studies have evaluated adherence to the exercise programs based on the attendance to the planned exercise sessions (120). However, whether the patients have actually performed the given exercise program is more scarcely reported. A recent review found that no exercise intervention studies in women with breast cancer, which were the only ones included in their search, followed all principles of exercise training, reported on all components of the exercise prescription in the methods, and recounted adherence to the prescription in the result section (120), indicating that our knowledge of what the cancer patients have actually been doing, despite solid exercise prescriptions, is quite limited. The authors reported the components and adherence based on the Frequency, Intensity, Time and Type (FITT) principle, showing that for the prescribed/planned training 94% of the studies reported the planned frequency, 70% of the studies the planned intensity, 72% of the studies the planned time, and 82% of the studies the planned type of intervention. In marked contrast, much fewer studies followed up with data, describing the adherence to the planned studies. Of the identified studies, 67% reported on frequency adherence, 16% reported on adherence to the planned intensity, 20% reported on adherence to the planned time, and 20% reported on the adherence to the planned type of intervention. Given that especially intensity and time may be the most important component for optimizing and individualizing the prescribed training, it is disappointing that so few exercise intervention studies are reporting these essential outcomes.

Taken together, exercise training comprises a continuous physiological stimulus, where intensity, time, frequency, and type of intervention intertwine to promote physiological adaptations. In cancer patients, traditional principles of exercise

physiology can be applied to prescribe exercise interventions, but it is important to acknowledge that the challenges that cancer patients are experiencing, which may lead to alterations in the planned training. Here, intensity and time are obvious components to modify to individualize the planned training to the patients' function and capacity. Yet, to fully understand the impact of the performed exercise interventions, these parameters must be more systemically reported as they play a fundamental role in the expected outcomes.

Research Perspectives

With almost 700 unique studies reporting on exercise interventions in cancer patients, it has been firmly established that exercise training is safe and feasible across a broad range of cancer diagnoses with breast cancer patients being the without comparison most studied population. All these studies have certainly advanced the field of exercise oncology, providing valuable scientific insight into the role of exercise in regulation of physiological and psychosocial outcomes. Yet from a critical point of view, the positive effects of exercise in cancer patients should be regarded with caution despite the large volume of studies as the evidence is of low-to-moderate quality, owing to the lack of rigor in the conducted studies, the large heterogeneity between the exercise interventions and outcome measures, imprecision of some estimates and high risk of bias in many trials. Moreover, the use of primary outcomes such as fitness levels (VO_2peak) or body composition (muscle mass) is difficult to interpret in view of its link to cancer disease outcome or survival, which undermine the translation into clinical practice, as these assessments to a large extend are impossible to implement and/or base clinical decision-making on. Furthermore, numerous exercise intervention studies have aimed to improve relevant psychosocial outcomes, that is, depression or cancer-related fatigue, yet failed to recruit patients, whom were heavily burdened by these side effects. Thus, the generalibility of these studies is challenged by the discrepancy between the patients enrolled in exercise trials and the general population of cancer patients. To this end, the patients enrolled in exercise trials have typically been younger and fitter than most cancer patients.

The research field of exercise oncology is presently at a stage while no further middle-sized intervention studies aiming to improve physiological or psychosocial endpoints are needed. In contrast, we propose three areas where further research is warranted: (i) large-scale multiconsortium intervention studies, addressing the effect of exercise training on hard clinical endpoints, like progression-free or overall survival, (ii) symptom-driven targeted interventions, or (iii) smaller proof-of-concept studies, which aim to bridge the mechanistic evidence from preclinical studies with different exercise interventions in cancer patients.

In light of the acquired evidence, clinical research would normally move to large scale phase 3 randomized controlled trials to prove the efficacy of an intervention, in this case exercise training, on hard clinical endpoint. Two large-scale randomized controlled exercise intervention studies in colon and prostate cancer patients are on their way and will once completed have the power to address the impact on disease-free and overall survival. It might seem natural to proceed this way forward, but conducting these large international multiconsortium intervention studies are clearly challenging, time consuming, and expensive. Moreover, in view of all the data consistently pointing to beneficial effects of exercise training, the question arises whether it is ethical acceptable to randomize patients to a control arm. To address this, recent larger studies have not included a usual care group, but compared different levels of training volume or intensity, or compared exercise training to a stretching program. As exercise training can be considered a continuous physiological stimulus, such an approach could undermine to aim of elucidate the actually efficacy of exercise training on relevant clinical outcomes. Yet, we do foresee that in less studied settings and cancer, including patients with poor survival rates and heavy symptom burden, the role of confirmatory randomized controlled trials is still valid.

There is a large drive within the field of exercise oncology to conduct symptom-driven exercise intervention studies. These trials aim to address specific problems, which patients may experience following their cancer disease and treatment. Prominent examples may include weight gain, lymphedema, bone health, etc. Such studies will typically be conducted after primary treatment completion, and are relevant for cancer patients where the cancer disease is under control, and where physical rehabilitation can be directly targeted toward the challenges that each individual has. Obviously, to guarantee full impact of such studies, the studies should ensure that the enrolled patients are selected based on the specific symptom, which the exercise intervention aim to improve.

Thirdly, detailed insight the molecular effect of exercise training on cancer biology is accumulating from preclinical studies, suggesting that exercise training can regulate tumor signaling and metabolism, enhance immune recognition and intratumoral immune cell infiltration, modulate blood perfusion in tumors, and stimulate bone marrow production to prevent the negative impact of chemotherapeutics. These effects might translate into direct control of disease progression and response to treatments, and we foresee that smaller exercise intervention studies with a high level of integrative physiology evaluations will address these specific mechanisms in the right clinical context in the near future. Such studies will provide mechanistic insight into, which physiological stimuli is needed to mediate a direct impact on relevant clinical outcomes, and will thus be vital for which exercise prescriptions and recommendations that are put forward to cancer patients in the future.

Lastly from a research standpoint, future studies should include strong methodological sections, guaranteeing the quality of the studies. This includes comprehensive reporting of adverse events in both the control and intervention groups, detailed description of the prescribed training and

training adherence based both on attendance, as well as any dose reduction according to the prescribed training volume and intensity.

Clinical Perspectives

The collected evidence highlights that therapeutic potential of exercise training in cancer settings, but with the strongest evidence base after primary treatment completion. In the aftermath of all the conducted exercise intervention studies, a move toward implementation of exercise training as an integrated part of cancer care should be the focus of the coming years. Such a move will depend on clinical recognition of the importance of exercise training, and consideration of an exercise prescription should be an integrated part of the clinical evaluation for each patient during and after cancer treatment.

We have reviewed 194 studies during ongoing anti-cancer therapy, including adjuvant or palliative therapy, where exercise training can reduce treatment toxicities and from a theoretical point enhance the efficacy of chemo-, radio-, and immune therapy. Moreover, accumulating data indicate that preoperative optimization through exercise training may ensure patients reach tumor resection in the best possible physical shape, and thus may reduce complications relating to the operation. In these situations, close contact to the treating departments may be needed to ensure tight monitoring of adverse events, individualization, and adjustment of the training volume and intensity, and logistic incorporation into the clinical program. We know of no formal programs, where exercise training has been fully implemented during ongoing cancer therapy under the direction of the treating department. But there are several examples worldwide, where training facilities have been built in connection with oncological departments, or where bicycles or training rooms are available in waiting areas for radiation 'bunkers', providing patients with direct access to training facilities, while waiting for their treatment. Moreover, few programs exist, where patient might engage in exercise training after self-referral.

The largest body of evidence is on the role of exercise training in rehabilitation after primary cancer treatment has been completed. Here, exercise training plays a natural role in regaining physical function, and preventing long-term comorbidities and perhaps potentially disease relapse. The bulk of evidence in this setting calls for implementation into standard cancer care. Scandinavian countries have already implemented government supported physical rehabilitation, which is based in local municipality settings under supervision of health professionals, in particular physiotherapists. Other countries, for example, the United Kingdom and the Netherlands have privately funded community based rehabilitation programs for cancer survivors, under supervision of trained instructors. These examples highlight the efforts being taken to implement exercise training in cancer rehabilitation and stresses that models fitted to the different countries national health systems offers unique platforms to deliver highly esteemed and beneficial programs for the participating patients.

In the future, these early examples of implementation of exercise training for cancer patients may gain more widespread outreach. To this end, it is of outmost importance that the forerunners share their experiences to gain further insight into the translatability of the current bulk of evidence from already conducted exercise intervention studies, and thus unfold the true potential of exercise training in standard cancer care.

Conclusion

In this comprehensive physiology review, we have summarized the evidence from nearly 700 exercise intervention studies performed in cancer patients. The vast majority of studies have been performed in early-stage breast cancer, in particular after completion of primary anti-cancer treatment. The evidence show that exercise training is safe and feasible across the entire cancer continuum, and can improve physical functioning and psychosocial outcomes. Moreover, accumulating data indicate that exercise training may delay disease progression and improve survival, and that these improvements in survival may be linked to the effects exercise training have on reducing chemotherapy-induced toxicities and improving treatment completion rates. Given this large potential of exercise training in improving disease-related, physiological, and psychosocial outcomes, we propose that exercise training should be used as an integrated component of standard cancer care and treatment.

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