Characterizing and Optimizing Physical Function in Lung Cancer Survivors

By

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A Dissertation

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Abstract

Lung cancer is the second most common cancer in men and women in the United States and survival rates are starting to rise. Improving survival rates creates a need for studies of lung cancer survivors that focus on improving the chronic management of lung cancer, including offsetting declines in physical function and mitigating persistent treatment related symptoms, in order to optimize quality of life. The purpose of this dissertation was to understand how physical function changes among lung cancer survivors and how exercise may serve as a possible rehabilitative strategy to restore independence. Four specific aims were set to achieve this purpose: 1) Describe inter-individual differences in the pattern and rate of change of self-reported physical functioning and associated symptoms over one year in lung cancer survivors; 2) Describe the application of exercise as a strategy to improve outcomes in lung cancer patients and specifically summarize the methodology and reporting of exercise interventions in controlled trials; 3) Describe the application of yoga as a strategy to improve outcomes in all cancer types and specifically summarize the methodology and reporting of yoga interventions in controlled trials; 4) Determine the feasibility and preliminary efficacy of a progressive yoga exercise training program to improve physical function during lung cancer treatment. For aim 1, a secondary analysis of self-reported physical function and symptoms over one year in lung cancer survivor was conducted. For aim 2, a systematic review of randomized controlled exercise trials conducted in lung cancer survivors was performed with attention to principles of exercise training. For aim 3, a systematic review of randomized controlled trials employing yoga as the intervention in all cancer types was performed with attention to principles of exercise training. For aim 4, a single group 12-week, supervised yoga intervention in lung cancer survivors was conducted. The results from this dissertation work indicate that significant interindividual variability in trajectories of self-reported physical

functioning exist. Though the number of exercise trials for lung cancer patients is growing, the principles of exercise training are not consistently applied. The components of the exercise prescription were well reported, whereas adherence to each was not. In studies of yoga across all cancer types the principles of exercise training were not well applied, and the reporting of the FITT components and adherence to each were not consistently reported. Yoga is a feasible and safe modality of exercise for lung cancer survivors who are medically well enough to attend supervised classes with potential benefits for improving physical function. This dissertation has made meaningful contributions to the fields of symptom science, application of yoga as a modality of exercise in the cancer population and exercise oncology in lung cancer survivors. This dissertation has immediate implications for the design and selection of exercise interventions to optimize rehabilitation in lung cancer survivors and points to the need for more research to improve the lives of lung cancer survivors.

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Chapter I: Introduction

Background and Significance

Lung Cancer

The American Cancer Society predicts that 234, 030 new cases of lung cancer will be diagnosed in 2018 and that there will be more than 673, 000 lung cancer survivors in the U.S. by 2026 (American Cancer Society, 2018). Evidence in support of low-dose computed tomography screening for lung cancer in high risk individuals (Aberle et al., 2011; Wang et al., 2016) has contributed to an increased number of survivors who were once considered to solely have palliative treatment options. As a result, more people are diagnosed with early stage lung cancer that is potentially more curable. For example, between years 2010 and 2015 there were 8122 fewer deaths from lung cancer (6.4 percentage points) (Cheung, Katki, Chaturvedi, Jemal, & Berg, 2018). Currently, the five year survival rate of those with early stage disease (stages IA-IIB) ranges from 52-93% while 10-36% of survivors with advanced stage disease will survive for at least 5 years past diagnosis (American Cancer Society, 2018). Improving survival rates create a need for studies of lung cancer survivors that focus on improving the chronic management of lung cancer, including persistent treatment related symptoms and physical side effects in order to optimize quality of life.

Lung Cancer Staging and Classification

Almost all lung cancers are carcinomas, that is cancer in the cells lining the airways of the lungs. Lung carcinomas are divided into two groups based on the appearance of the cells: 1) small cell lung cancer and 2) non-small cell lung cancer (NSCLC). NSCLC is much more common and will be the focus of this dissertation work. NSCLC is further divided into the following two main histologic types a) adenocarcinomas, large cell carcinomas, rare cell types and b) squamous cell carcinoma. The type of NSCLC directs the form of recommended treatment and therefore has implications for the types and severity of symptoms and physical side effects that survivors face. Specifically, driver mutations that call for targeted therapies, rather than more toxic platinum-

based chemotherapies, are common in adenocarcinomas and thus survivors who undergo targeted therapies may have less severe symptoms and side effects than those who have other histologic types of lung cancer that requires a more toxic type of treatment. There are 5 stages of lung cancer (including carcinoma-in-situ), with earlier stages requiring less toxic treatments and resulting in better outcomes. The stages categorize the extent of cancer and are based upon the American Joint Committee on Cancer prognostic staging system of tumor, nodes, and metastasis (TNM) and approximately 60% of lung cancer survivors are diagnosed with stage IV disease (National Comprehensive Cancer Network, 2018).

Cancer is a progressive disease that may infiltrate and alter the body's normal physiology. Cancer cells, distinct from normal cells, are unrestrained cells that do not undergo apoptosis (controlled cell death) and can divide and proliferate. In lung cancer, these cells can proliferate into surrounding tissue and without treatment can grow through the airway, invading the bronchus or the pleura, making breathing more difficult. The lethality of cancer cells resides in their ability to metastasize when cells merge with blood or lymph fluid causing metastases and additional major health problems. Though the exact mechanism(s) for metastasis is unknown, aggressive and toxic treatments with curative intent for the primary tumor are utilized in order to limit the spread of cancer cells, and thereby increase survival (Riihimaki et al., 2014). Diagnosing lung cancer at early stages before metastasis occurs, which may depend upon recognizing risk factors related to lung cancer, contributes to longer survival and has been a priority in decreasing deaths from this disease.

There are several risk factors linked to a lung cancer diagnosis (Table 1), of which include behavioral, environmental, and genetic factors.

Table 1

Factors that Increase the Risk of Lung Cancer

Risk Factor	**Indications for Risk**
Smoking	- Strongest risk factor - 50+ compounds in tobacco smoke are known carcinogens
Second-Hand Smoke	- Exposure dependent
Older Age	- Half of diagnoses are in those >70 years
Previous Radiation Therapy	- Exposure to radiation in the chest for cancers including head and neck, Hodgkins lymphoma and breast
Genetic Disposition	- Increased risk if first degree relative has had lung cancer
Cancer Causing Agents	- Asbestos, uranium and radon, metallic metals (arsenic, beryllium, cadmium, chromium, nickel), coal smoke, soot, silica, diesel fumes
Other Lung Diseases	- Chronic obstructive pulmonary disease (COPD), pulmonary fibrosis

(Ettinger et al., 2006)

Treatment for Lung Cancer

The overall physical impact of lung cancer on a patient's quality of life, is highly dependent upon the treatment regimens the person undergoes. The type of treatment depends on tumor stage and histologic classification. Multiple treatment types may be used concurrently or consecutively, which increases the cumulative toxicity of treatments. For example, simultaneous administration of chemotherapy and radiation therapy is common for advanced stages of the disease in cases that have no indication for targeted therapy (Kris et al., 2017; National Comprehensive Cancer Network, 2018) and thus, the patient will incur the symptoms and side effects associated with each type of treatment. Thus, s/he may experience a combination of symptoms and side effects specific to each type of treatment and/or additive effects from multiple types of treatment that produce the same side effect, such as fatigue. Typical treatments for lung cancer and their associated symptoms and side effects are summarized in Table 2

Table 2

Description, Duration, and Side Effects and Symptoms by Type of Treatment for Lung Cancer

Treatment Type	**Stage**	**Description**	**Treatment Duration**	**Side Effects & Symptoms***
Surgery • Thoracotomy • Thorascopy	T1-3N2-M0 (non-fixed, non-bulky, single zone tumors	Thoracotomy: incision between ribs, through muscles of chest wall Thorascopy: 3 or 4 small incisions between ribs on side of chest wall	2-6 hours + several days in hospital	• Pneumothorax • Chance of infection – pneumonia • Swelling • Sore throat • Itching • Nausea & vomiting • Confusion • Muscle aches • Pain • Long-lasting numbness • Scars
Radiation • External Radiation o 3-dimensional conformal radiation (3D-CRT) o Intensity modulated radiation therapy (IMRT) o Stereotactic ablative radiotherapy (SABR)/ stereotactic body radiation therapy (SBRT) o Stereotactic radiosurgery (SRS)	Early stage (stage 0-III) with unacceptable risk of surgical complications OR locally advanced (stage IV) disease when unsuitable for surgery	3D-CRT: Delivers a photon beam the matches shape of tumour IMRT: Further modifies beam intensity SABR: precise, high dose photon beams SRS: Treats cancer in the brain with precise, high-dose photon beam WBRT: Proton beam delivers radiation mostly within the tumor	Daily for 1-6 weeks, type dependent	• Painful swallowing • Skin changes (red, itchy, dark, peeling, cracking) Hair loss at treatment site • Radiation pneumonitis leading to shortness of breath • Fatigue • Heart damage Note: symptoms and side effects are cumulative with the number of radiation treatments

○ Whole brain radiation therapy (WBRT) ○ Photon therapy • Internal (brachytherapy)		Photon therapy: proton beam radiation mostly within the tumor		
Chemotherapy • Carboplatin • Cisplatin • Docetaxel • Etoposide; Etoposide phosphate • Gemcitabine hydrochloride • Paclitaxel • Paclitaxel, albumin bound • Pemetrexed • Vinblastine sulfate • Vinorelbine tartrate	T1-3N1-2M0 (tumors >4cm diameter)	Taken orally or by intravenous infusions; used as neoadjuvant treatment to shrink tumor before surgery, as adjuvant therapy after surgery, concurrent with radiation therapy, or as main treatment option	3-4 cycles of treatment delivered 14-28 days apart	• Low blood cell count • Infections • Loss of appetite • Nausea • Vomiting • Diarrhea • Hair loss • Mouth sores • Heart disease • Hypothyroid levels • Infertility • Lung damage • Cognitive decline • Neuropathy • Sarcopenia, cachexia • Fatigue
Targeted Therapies • Ado-trastuzumab • Afatinib • Alectinib • Bevacizumab • Brigatinib • Ceritinib • Cetuximab • Crizotinib • Dabrafenib • Erlotinib hydrochloride • Efitinib • Osimertinib • Ramucirumab • Trametinib • Vandetanib • Vemuratenib	Advanced disease (stage IV) with identification of tumor specific driver mutation	Target Molecules include: EGFR: surface receptors that trigger growth signals in cancer cells ALK: surface receptor cell is rearranged and overactive VEGF: triggers growth of red blood cells, promoting cell growth ROS1: surface receptor is rearranged and overactive BRAF V600E: Kinase that regulates phosphate signalling,	Multiple times over 2-3 weeks	• Rash • Diarrhea • Loss of appetite • Weakness • Hypersensitivity pneumonitis • Cough • Severe eye, skin, lung, kidney, liver disturbance • Gut tears & bleeding • Blood clots • High blood pressure • Infertility • Joint pain • Fatigue • Cachexia, sarcopenia

		can become overactive when mutated. Others include: HER2, MEK1 and MEK2 (BRAF mutation), BRAF v600F, RET		• Development of other cancers
Immunotherapy PD-1 and PF-L1 Inhibitors	Advanced disease (stage IV)	PD-1 and PF-L1 Inhibitors: turn off immune response, T-cells able to attack cancer cells	Every 2-3 weeks for up to 12 months	- Fatigue - Neurotoxicity - Constipation - Nausea - Loss of appetite - Muscle or bone pain - Organ inflammation - Damage to lung, gut, liver, kidney, hormones, skin

*Symptoms and side effects are organized in order of early (acute) to late (chronic). ALK: Anaplastic lymphoma kinase; BRAF-V600E: gene; EGFR: Epidermal growth factor receptor; IMRT: Intensity modulated radiation therapy; MEK1: protein kinase; PD-1: Programmed cell death protein 1; PF-L1: Pyruvate-formate lyase; RET: gene; ROS1: gene; SABR: stereotactic ablative radiotherapy; SRS: stereotactic radiosurgery; VEGF: Vascular endothelial growth factor; WBRT: whole brain radiation therapy; 3D-CRT: 3-dimensional conformal radiation.

(Ettinger et al., 2006; Kris et al., 2017)

As treatments for lung cancer have advanced to include therapies targeted to tumor specific driver mutations or have included immunotherapy if driver mutations are unknown, additional and potentially more severe treatment related toxicities are likely. It is uncommon for phase III clinical drug trials to include long-term monitoring for chronic symptoms and side effects thus we know less about post-treatment quality of life after these therapies (Ha, Ries, Mazzone, Lippman, & Fuster, 2018). In a study comparing Nivolumab (an immunotherapy PD-L1 blockade) with chemotherapy, chronic symptoms (i.e. neuropathic pain), and side effects (i.e. declines in physical function, cachexia and sarcopenia) were not considered (Carbone et al., 2017). Similarly, in a study of Osimertinib, a targeted therapy of EGFR mutated cases of advanced lung cancer, reports of treatment related side effects included only acute, and readily visible side effects such as vomiting, alopecia, and dry skin, rashes or acne (Soria et al., 2018). A meta-analysis of studies evaluating the efficacy and safety of anti-PD-1/PD-L1 antibodies (nivolumab, pembrolizumab, and atezolizumab) summarized the reported adverse events of which included, decreased appetite, nausea, vomiting and constipation, anemia, neutropenia, febrile neutropenia, fatigue, diarrhea, hypothyroidism and pneumonitis (Zhao, Xie, Lin, You, & Weng, 2018). The endpoints for phase III clinical drug trials is survival and progression free survival rather than assessing symptoms and side effects that may have implications for quality of life during survivorship. Long term outcomes such as sarcopenia and sarcopenic obesity (Baracos, Reiman, Mourtzakis, Gioulbasanis, & Antoun, 2010), reduced functional capacity and quality of life (Duc Ha, Ries, Mazzone, Lippman, & Fuster, 2018) have been reported in survivorship studies of lung cancer patients, but it remains unclear if and how targeted therapies affect these outcomes and thus, they are likely neglected in clinical practice.

Symptoms and Treatment-Related Physical Side Effects

Symptoms are the broad experience and simultaneous perception, evaluation and response to a change an individual's usual feelings (M. Dodd, Janson, et al., 2001). The change in feelings can be in frequency, severity or distress associated with the symptom(s). Symptoms may or may not be related to treatment, rather they could have inputs from elements outside of the cancer survivorship experience. The Theory of Symptom Management includes environmental (physical, social, cultural), person (demographic, psychosocial, physiological, developmental) and health/illness (risk factors, health status and disease/injury) inputs to the symptom experience (M. Dodd, Janson, et al., 2001).

Side effects are physical changes that could be related to biological processes that are part of the pathophysiology of the tumor or to physiological alterations related to cancer treatment. For example, unfavorable changes in body composition (i.e. loss of lean mass) is a direct result of treatment, whereas a symptom, such as fatigue, refers to the patient experience and can have multiple inputs from both cancer and non-cancer related variables. Though symptoms and side effects can be defined separately, they are complex and inter-related. For example, a cancer survivor may have a loss of lean mass as a result of cancer treatment and this can contribute to experienced fatigue during activities requiring work or power. Since side effects and symptoms contribute unique and shared impact on quality of life, both will be addressed within this dissertation work.

Symptoms and side effects are often more severe in lung cancer patients than in patients treated for most other cancer types (Johnsen, Petersen, Pedersen, & Groenvold, 2009), as standard treatments for lung cancer are aggressive and multiple (US Department of Health & Services, 2009). Lung cancer survivors often present with major comorbidities at diagnosis and prior to treatment including chronic obstructive pulmonary disease, diabetes, and congestive heart failure

(Ha et al., 2018). Comorbidities, coupled with treatment toxicities have contributed to reports of persistent and distressing symptoms including fatigue (Nowicki, Piekarska, & Farbicka, 2017), neuropathic pain (D. Jones et al., 2015), and poor mental health (Choi & Ryu, 2016) and physical side effects including deconditioning comprised of weakness (Brown, McMillan, & Milroy, 2005), or reduced functional capacity (Duc Ha et al., 2018) and loss of lean mass and gains in body fat (Baracos, Reiman, Mourtzakis, Gioulbasanis, & Antoun, 2010; Chambard et al., 2018) in lung cancer survivors. While fatigue, pain, depression, deconditioning, and body composition changes can each independently adversely impact patient quality of life, these symptoms and side effects can all contribute to functional declines that have been increasingly observed in lung cancer survivors (Brown et al., 2005; Duc Ha et al., 2018). Later, a Conceptual Framework of Physical Functioning in lung cancer survivors will be presented, but briefly the proposed contributing treatment related side effects and symptoms will be described in detail below.

Side Effects

Body Composition

Changes in body composition *following treatment* are common in lung cancer survivors and may have important associations with survivorship outcomes (Collins, Noble, Chester, Coles, & Byrne, 2014) particularly because treatment-related changes in body composition may lead to declines in physical function (Bennett et al., 2006). Alternatively, individuals diagnosed with lung cancer commonly have unhealthy body composition profiles *prior to treatment*, that are linked to the multi-morbid conditions which are common in lung cancer survivors (Bowden et al., 2017). Unhealthy body composition before or following treatment can shorten overall survival (Bowden et al., 2017), worsen hematologic toxicities (Sjøblom et al., 2017), decrease quality of life

(Sanchez-Lara et al., 2012), decrease tolerance to treatment (Mohan et al., 2008), and lead to declines in physical function (Brown et al., 2005). There are three clinically relevant unhealthy syndromes of body composition, namely cachexia, sarcopenia, and sarcopenic obesity, that can occur in lung cancer survivors and will be introduced in below.

Cachexia

Cachexia, defined as an involuntary loss of body weight combined with a loss of homeostatic control of energy and protein balance (DeWys, 1982), leads to progressive functional impairments, treatment related complications, poor quality of life and cancer-related mortality in the general cancer population (Fearon et al., 2011). Cachexia results from reduced food intake and metabolic changes, that include elevated energy expenditures, excess catabolism, and inflammation (Baracos, Martin, Korc, Guttridge, & Fearon, 2018), as well as anabolic resistance (i.e. the inability to stimulate protein synthesis in response to anabolic stimuli) and disrupted proteostasis and oxidative metabolism (Montalvo, Hardee, VanderVeen, & Carson, 2018). Lung cancer is frequently associated with cachexia due to the common advanced stage of this disease, the direct effects of treatment on appetite, and difficulties with digestion and absorption of nutrients (Baracos et al., 2018). Sarcopenia and sarcopenic obesity are two body composition syndromes that, in lung cancer, may precede cachexia (Recio-Boiles et al., 2018), demonstrating the necessity of evaluating sarcopenia and sarcopenic obesity rather than weight loss alone. Thus, sarcopenia and sarcopenic obesity (described below) will be included as outcomes in this dissertation work rather than cachexia.

Sarcopenia

In contrast to cachexia that is the involuntary loss of general body weight, sarcopenia is the progressive and generalized loss of skeletal muscle mass and strength (Cruz-Jentoft et al., 2010).

The European Working Group on Sarcopenia in Older People have defined the criteria for sarcopenia as having a combination of low skeletal muscle mass with low muscle strength or low physical performance. Sarcopenia is increasingly prevalent with advancing age (Cherin, Voronska, Fraoucene, & de Jaeger, 2014), an important consideration in lung cancer survivors where the mean age of diagnosis is 70 years (American Cancer Society, 2018). In a recent systematic review of 6894 lung cancer survivors prior to treatment it was found that 39% of patients were sarcopenic, and the presence of sarcopenia had significant and independent associations with post-operative complications, chemotherapy-induced toxicity and poor survival (Pamoukdjian et al., 2018). After treatment for lung cancer, 47% of 441 lung cancer survivors were considered sarcopenic (Baracos et al., 2010). Among cancer survivors, sarcopenia is associated with a higher risk of adverse outcomes including disability, poor quality of life and death (Cruz-Jentoft et al., 2010). Though skeletal muscle mass and strength may be compromised in lung cancer survivors, obesity may also be a health concern.

Sarcopenic Obesity

Recent evidence demonstrates that severe depletion of skeletal muscle (sarcopenia) may go undetected in cancer survivors who are obese (Lodewick et al., 2015). The combination of low skeletal muscle and high amounts of adipose tissue is termed sarcopenic obesity (Baumgartner, 2000). In a study of 551 lung cancer patients who were referred to an oncology service (median time to death=265 days), 47.4% were overweight or obese per body mass index (BMI), whereas only 7.5% were considered underweight. In the same sample the overall prevalence of sarcopenia was 46.8% and was present in all BMI categories. Similarly, a study using CT images of NSCLC survivors (n=37) detected that 15% of survivors were sarcopenic, while more (20%) had sarcopenic obesity (Recio-Boiles et al., 2018). The combination of excessive adiposity combined

with the low muscle mass and weakness that make up sarcopenia, creates a potentially even more debilitating health condition that combines the health risks and functional losses of both sarcopenia and obesity. To date, sarcopenic obesity has not been included as a variable to predict physical function in studies of lung cancer survivors.

Symptoms

Fatigue, depressive symptoms and pain, are the most commonly occurring symptom clusters reported by lung cancer survivors (Carnio, Di Stefano, & Novello, 2016). Self-reported fatigue has been correlated with depressive symptoms in multiple studies of lung cancer survivors, where higher fatigue is associated with more depressive symptoms (Brown et al., 2005; Nishiura, Tamura, Nagai, & Matsushima, 2015). With the possible synergistic effects of fatigue, depressive symptoms and pain, each of these symptoms will be introduced below and included as outcomes of interest within this dissertation work.

Fatigue

The symptom of cancer-related fatigue has been described as a severe, unrelenting feeling of fatigue that is not improved by rest or sleep, differentiating it from fatigue in the general population (Kim, Puymon, Qin, Guru, & Mohler, 2013). Fatigue can begin as a symptom of cancer, worsen throughout treatment and persist for months and even years after treatment cessation (Prue, Rankin, Allen, Gracey, & Cramp, 2006). Fatigue is most commonly measured by self-report to assess primarily the perceived aspect of the condition (Minton & Stone, 2008), though studies to assess neuromuscular deficits that may contribute to cancer-related fatigue have been conducted (Kisiel-Sajewicz et al., 2012; Monga et al., 1997; Neil, Klika, Garland, McKenzie, & Campbell, 2013; Yavuzsen et al., 2009), yet a consensus on the contribution of neuromuscular deficits to

cancer-related fatigue has not been made. A review by McNeely and Courneya (2010) has summarized the multitude of proposed contributors of cancer-related fatigue. Physiological mechanisms that may contribute to cancer-related fatigue include reductions in voluntary actvation, muscle strength, endurance, cadiopulmonary fitness, negative changes in body composition, reduced muscle efficiency, inflamatory, endorcrine and metabolic function, muscular damage and anemia. Psychosocial factors may also contribute to cancer-related fatigue and include anxiety, depression, distress, less social interaction. Proposed behavioral factors include reductions in sleep quantity/quality and appetite.

Fatigue is highly common in lung cancer survivors and can impact physical functioning. From diagnosis to end of life, fatigue is present in 57%-100% of lung cancer survivors (Carnio et al., 2016). In a study of stage IIIA-IV lung cancer survivors (n=157) undergoing chemotherapy, 81.5% experienced some degree of fatigue. About one-third of survivors reported that fatigue had interfered with physical activities such as walking (36.3%) or “normal work” (31.8%) (Nishiura, Tamura, Nagai, & Matsushima, 2015). In 38 lung cancer survivors fatigue was significantly correlated with lower Karnofsky performance status scores and longer chair rise time ($p<0.01$).

Depressive Symptoms

Depressive symptoms negatively affect thoughts, actions and cause feelings of sadness and/or a loss of interest in life activities, leading to a variety of emotional and physical problems, and decreased ability to function at work and at home (Center for Behavioral Health Statistics and Quality, 2017). Depressive symptoms are commonly reported in lung cancer survivors. In a meta-analysis of studies assessing depression by clinical interviews (n=3) and self-report instruments (n=4), the prevalence of depression was 3% and 21% respectively (Krebber et al., 2014). Similarly, in a secondary analysis of data from three multi-center RCTs (n=461) 21% of lung cancer survivors

self-reported depressive symptoms (Hopwood & Stephens, 2000). Lung cancer survivors are often stigmatized for having a preventable disease because of the strong association between tobacco use and lung cancer. Consequently, strong feelings of stigmatization may exacerbate symptoms of depression to a greater degree than that typically observed in survivors of other cancers such as prostate or breast cancer (Gonzalez & Jacobsen, 2012). Depressive symptoms are linked to longer hospital stays, poorer adherence to treatment, lower quality of life, disability, and worse survival in lung cancer survivors (Kroenke et al., 2010; Sullivan et al., 2016; Sullivan et al., 2014). More severe depressive symptoms are also significantly associated with greater odds of reporting a functional impairment (Hopwood & Stephens, 2000) thus it is possible that mitigating symptoms of depression early on may limit declines in physical function or it is possible that interrupting the downward trajectory of functional decline could prevent the onset and/or worsening of depressive symptoms.

Pain

Cancer-related pain is an unpleasant sensory and emotional experience that is most commonly a consequence of the malignancy (Mercadante & Vitrano, 2010). Common types of pain in lung cancer survivors include chest and lumbar, nociceptive, somatic, visceral and neuropathic pains (Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996; Mercadante, Armata, & Salvaggio, 1994; Wilkie, Huang, Reilly, & Cain, 2001). The complex and variable types of pain are dependent on the stage of disease and/or treatment (i.e. lung resection may induce chest and lumbar pain, while chemotherapy may induce neuropathic pain) (Mercadante & Vitrano, 2010) . The prevalence of pain among lung cancer survivors is 47%, with higher rates in patients attending treatment centers and in those referred to palliative services (Potter & Higginson, 2004) and up to 90% of survivors with late stage disease reporting pain (Mercadante et al., 1994). Pain is associated

with utilization of emergency department services, and may lead to discontinued cancer therapy, possibly resulting in a greater number of cancer-specific deaths (McNeill, Sherwood, & Starck, 2004), and can result in diminished quality of life (Green, Hart-Johnson, & Loeffler, 2011). Pain and depression may have a synergistic relationship and contribute to low physical function. Increases in pain severity and declines in physical function have been significantly associated with increases in depressive symptoms over one year in lung cancer survivors (Lyons, Bennett, et al., 2014), demonstrating the interrelationships among symptoms that lung cancer survivors experience as a result of treatments.

Summary: As a result of aggressive and multiple treatments, lung cancer survivors are susceptible to chronic and debilitating symptoms and physical side effects that may be associated with low physical function. A conceptual model to distinguish how the symptoms and physical side effects described above may contribute to low physical function that is predictive of disability will be outlined in detail in the following section.

Integrating the Disablement Process and Conceptual Model Physical Function

Disablement refers to the impact that chronic and acute conditions have on the functioning of specific body systems and the ability to complete daily tasks in a usual, expected, and desired way (Verbrugge & Jette, 1994). The disablement process reflects the dynamics of disablement - the trajectory of functional consequences over time and the factors that contribute to the direction, rate and patterns of change. The disability process begins with active pathology (i.e. a disease such as lung cancer), leading to impairments (i.e. symptoms and physical side effects that could be anatomical, physiological or psychosocial), that then cause functional limitations (i.e. declines in

physical function), and ultimately disability, that is the limitation of performance defined within a socio-cultural and physical environment (Nagi, 1965).

The Conceptual Model of Physical Function in Cancer Survivors (Bennett, Winters-Stone, & Nail, 2006) applies concepts from the disablement process to cancer survivors. Predictors (i.e. active pathology, treatments, lifestyle behaviors), symptoms (i.e. fatigue, depressive symptoms, pain) and physical side effects (i.e. negative changes in body compostition,) may all be mediators of physical function. Physical function is a strong predictor of future disability, while also predicting an increased number of acute illnesses, and an increased risk of falls and injuries in older adults, and higher mortality (Guralnik, Fried, & Salive, 1996). Based on the Conceptual Model of Physical Functioning in Cancer Survivors that applies the disablement process in cancer survivors (Figure 1), physical function must be an important consideration for preserving and optimizing quality and quantity of life in lung cancer survivors who have undergone aggressive and multiple treatments.

Once individuals lose their independence, it is challenging to fully reverse functional decrements, thus interventions have been suggested to act as "buffers" to prevent or slow the development of disability by targeting upstream outcomes (Fried, Bandeen-Roche, Chaves, & Johnson, 2000). Interventions include medical care and rehabilitation, medications and therapeutic regimens, external supports (personal assistive devices), modifications of the built/physical/social environment, and lifestyle and behavior changes (Verbrugge & Jette, 1994), such as introducing exercise, an intervention that will be explored within this dissertation work.

This dissertation work will be guided by The Conceptual Model of Physical Function in Cancer Survivors (Bennett, Winters-Stone, & Nail, 2006), of which was selected as it illustrates the pathway of predictors and mediators that can impact physical function within the context of

cancer survivorship. Using this conceptual framework, physical function is identified as the main outcome variable of this dissertation work, while body composition, deconditioning, fatigue, depression, and pain will be explored as possible predictors/mediators of physical function and possibly changes in function over time. Exercise will be explored as an intervention used to mitigate or perhaps reverse functional declines in lung cancer survivors.

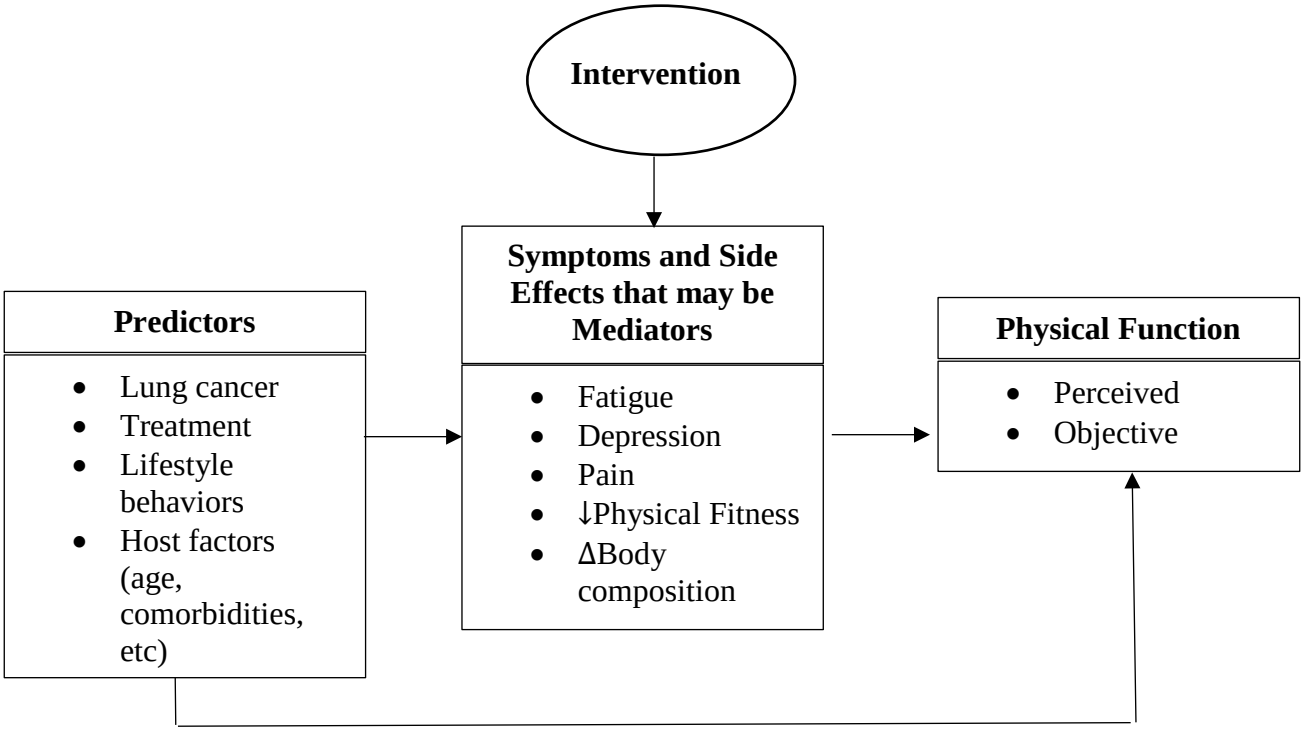

*Figure 1***.** Conceptual model of physical function in cancer survivors.
Adapted from Bennett et al. (2006)

Physical Function in Lung Cancer Survivors

Physical function is the ability to perform fundamental physical tasks requiring mobility (gait and balance) and strength or power, such as activities of daily living (ADLs), (i.e. shopping, cleaning, climbing stairs, caring for dependents) (Bennett et al., 2006). Physical function can be measured either subjectively by patient report or objectively with a battery of physical performance tests. The majority of studies that assess physical function in lung cancer survivors use subjective measures that assess a person's perceived abilities. Common subjective measures of physical

function include the Medical Outcomes Study RAND Short-Form 36 (SF-36) physical component subscale, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) physical function subscale, or the Karnofsky Performance Score (Brocki et al., 2014; Brunelli et al., 2007; Courneya et al., 2009; da Mata Tiezzi et al., 2017; Gaskin et al., 2016).

Objective measures of function may be more sensitive to detecting functional limitations that may differ than those detected by patient report alone. Objective and subjective reports of physical function are not strongly correlated in lung cancer survivors. In a study of 99 lung cancer survivors low correlations were found between the Simmonds Functional Assessment Tool, an objective assessment, and Karnofsky performance status and Edmonton Symptom Assessment Scale scores, both subjective assessments, demonstrating that objective function of patients may not equate with patients' perceptions of their physical function (Montoya et al., 2006). Additionally, subjective measures may not enable physical tasks requiring the upper and lower extremities to be differentiated so that the location of a physical limitation could be determined. Separate objective tasks of the upper and lower extremities allow for a better understanding of where, anatomically, a functional limitation may exist. For this, objective tests to assess physical function have been suggested as complimentary measures to subjective assessments in lung cancer survivors (Dajczman et al., 2008; Duc Ha, Mazzone, Ries, Malhotra, & Fuster, 2016). The most common measure of objective physical function, in a review of 31 studies evaluating measurement properties of outcome measures in lung cancer survivors, was the 6-minute walk test (Granger, McDonald, Parry, Oliveira, & Denehy, 2013), of which 6-minute walk distance (6MWD) is often the outcome that is reported. Other common measures included the Short Physical Performance Battery (SPPB) that consists of timed tests to assess standing balance, gait speed, and lower body

strength and power, and the Senior Physical Fitness Test that includes the back-scratch test (upper-body mobility), 8-foot timed up and go (mobility), and arm curls (upper body strength), in addition to the tests described as a part of the SPPB. It is common for physical function and physical fitness to be used inter-changeably or as a surrogate for one another in the literature, however there is a stark difference between the two terms. Physical function describes the functional ability of an individual to perform standard tasks (i.e. gait speed measured via 4-meter walk test or range of motion measured via back-scratch test), while physical fitness indicates how an individual's body systems perform under taxing conditions that are not necessarily functional activities (i.e. cardiovascular fitness measured via maximal oxygen tests).

Table 3 summarizes studies that have assessed subjective and/or objective physical function both comparing lung cancer survivors with cancer free controls and by comparing physical function before and after treatment.

Table 3

Studies of Lung Cancer Survivors that Describe Physical Function using Subjective or Objective Measurement Tools

Citation	Sample	Treatment Status	Study Design	Subjective Physical Function	Objective Physical Function
			COMPARISONS OF PHYSICAL FUNCTION		
Brown et al. (2005)	Stage IV lung cancer (n=38) vs age-gender matched controls (n=15)	Completed treatment >1 month prior	2-group cross sectional comparison	Lower KPS than controls	Lower grip strength, lower chair rise time in cancer versus controls
Titz et al. (2018)	Stage IIIA-IV lung cancer (n=211) vs normative data	On treatment	Cross-sectional		Lower 6MWD than normative data
Duc Ha et al. (2018)	Stage I-IIIA lung cancer (n=62)	Completed treatment >1 month previous	Cross-sectional		6MWD were 65% of predicted
			TRAJECTOTRIES OF PHYSICAL FUNCTION		
Machado, Saad, Honma, Morcillo, and Zambon (2010)	Stage IIIB-IV lung cancer (n=99)	Completed platinum-based chemotherapy	Prospective (pre-, immediately post-, 6-months post chemotherapy)	Lower ECOG scores at 6-month f/u than pre-chemo	No change in 6MWD between all time-points
Granger et al. (2014)	Stage I-IIIB pre-treatment (n=50) vs similar-aged controls (n=35)	At diagnosis, throughout treatment	Prospective (baseline, 10-weeks, 6-months)	Significant declines in SF-36 PF from baseline to 10 weeks; baseline SF-36 PF 1 SD outside of Australian norm	Significantly lower 6MWD than predicted values at each time point; significant reduction in 6MWD and hand grip strength from baseline to 10 weeks and from baseline to 6-months; lower baseline strength than controls; baseline hand grip strength lower than published norms
Brunelli et al. (2007)	Stage NR, lung cancer (n=156)	Pre-operative to post-operative	Prospective (pre-operative, 1 and 3 months post-operative)	Significantly lower physical function (SF-36) at 1-months, completely recovered at 3-months	
Koczywas et al. (2013)	Stage I-IIIB lung cancer (n=103)	Completed surgery or chemotherapy	Prospective (baseline, 6, 12, 24, 36, 52 weeks)	Significant decrease in KPS at all time points after baseline	TUG increased at 12, 24, 56 weeks compared to baseline and 6 weeks

Kasymjanova et al. (2009)	Stage IIIA-IV lung cancer (n=45)	Pre-post chemotherapy	Prospective (pre-chemotherapy & after 1 or 2 cycles of chemotherapy)	6MWD declined significantly
Kinsey, Ajazi, Wang, Johnston, and Crawford (2018)	Stage III-IV lung cancer (n=232)	Completed chemotherapy	Prospective (baseline & day 84 treatment)	Decline in stair climb power

ECOG: Eastern Cooperative Oncology Group Performance Status Scale; KPS: Karnofsky performance status; NR: not reported; TUG: timed up and go; 6MWD=6-minute walk distance

Physical function is typically lower in lung cancer survivors than in persons without lung cancer. A study comparing 38 stage IV lung cancer survivors with age-gender matched controls found that grip strength was lower and chair rise time was longer in lung cancer survivors, indicating poor upper and lower body muscular strength, respectively (Brown et al., 2005). A recent study that compared the 6MWD of 211 lung cancer to normative data found that lung cancer survivors has significantly lower 6MWD performance ($p<0.01$), with more than 50% of women and 85% of men having lower 6MWD than normative data (Titz et al., 2018). More studies to compare physical function between lung cancer survivors and cancer free controls are necessary to confirm that physical function is indeed lower in lung cancer survivors than those who have not been treated for cancer. However, additional studies have assessed physical function before and after treatment and have described negative changes in physical function that could lead to poor quality of life, disability and/or mortality.

Physical function, measured both subjectively and objectively, is lower following treatment in lung cancer survivors. In a study of stage I-IIIB lung cancer survivors (n=56), 10-weeks post diagnosis and during chemo- and radiation therapy, physical function as assessed by the SF-36 was significantly lower (15% decrease, $p=0.01$) than at diagnosis (Granger et al., 2014). Similarly, in 156 lung cancer survivors physical function assessed by the SF-36 declined significantly (11% decrease, $p<0.05$) 1-month post-lung resection, but improved significantly (16% increase, $p<0.05$) by 3-months (Brunelli et al., 2007). In 50 lung cancer survivors 6MWD was significantly lower at 10-weeks and 6-months post treatment than at baseline (Granger et al., 2014). In 103 lung cancer survivors, timed up and go increased significantly at 12, 24, and 56 weeks compared to baseline and 6 weeks after surgery or the completion of chemotherapy indicating worse physical function than prior to treatment (Koczywas et al., 2013). These studies

demonstrate that physical function appears to decline immediately following treatment, however improvements in physical function may occur as time since treatment is longer. More longitudinal studies are needed to confirm the rate of decline and improvement in trajectories of physical function following treatment and further into survivorship in order to mitigate chronic disability. Additionally, future studies should assess both physical function using both subjective and objective tools to include all aspects of physical function (i.e. mobility, gait, strength and power) of the upper and lower extremities, as well as survivor's perceptions of physical function across time.

As lung cancer survival rates continue to improve (American Cancer Society, 2016), maintaining sufficient physical functioning in lung cancer survivors should become a central concern because of the known pathway from functional decline to disability (Lollar & Crews, 2003). The trajectories of physical function and predictors of change in physical function should be understood to guide potential interventions to improve quality of life, mitigate chronic disablement and reduce mortality. As such, the focus of this dissertation work is to characterize and optimize physical function in lung cancer survivors. The following sections will introduce the four chapters that will make up this dissertation work by 1) describing trajectories and predictors of self-reported physical function, 2) characterizing exercise as a countermeasure to functional decline in lung cancer survivors, 3) assessing the potential for yoga to be considered as another rehabilitative approach to manage symptoms and side effects in cancer survivors, 4) determining the feasibility and preliminary efficacy of yoga as a potential rehabilitative strategy to improve physical function in lung cancer survivors.

Trajectories and Predictors of Self-Reported Physical Function

Despite the importance of understanding changes in physical function, descriptive and comparative studies of physical function are few in lung cancer survivors, while longitudinal studies are relatively rare with mixed results, and associative symptoms contributing to changes in physical function are rarely explored.

Three studies have compared patient-reported physical function at a single timepoint to a control group (Brown et al., 2005), normative data (Titz et al., 2018) or predicted values (Duc Ha et al., 2018). Though these studies indicate that physical function is lower in lung cancer survivors than cancer-free controls, the rate of change (slope) cannot be observed from cross-sectional comparison studies. Without understanding how fast or slow physical function declines from a baseline value, the point of time in survivorship at which physical limitations begin to decline and/or change the quickest remain unclear, and thus rehabilitation strategies may not be well timed to interrupt the downward trajectory in function early on.

Though there are six studies that assessed patient-reported physical function using longitudinal study designs, they do not adequately capture the rate and direction of change in physical function, nor do the results of these studies support each other. Two studies described changes in physical function at only two timepoints thus non-linear trends cannot be identified (Kasymjanova et al., 2009; Kinsey et al., 2018). Three studies assessed physical function at three-time points thus describing changes that may be non-linear, though the differences in the results of these studies does not allow for a firm conclusion of how physical function changes across survivorship. This could be because the studies used a variety of measurement tools, administered at different time-points (i.e. before, during, after treatment), and during different types of treatments of which may have different side effects and symptoms that may differentially impact

physical function. Of the two studies that reported SF-36 physical function scores at the most similar timepoints, Granger et al. (2014) reported that physical function declined significantly from baseline (i.e. pre-treatment) to 10 weeks (i.e. during treatment), whereas Brunelli et al. (2007) reported that physical function scores did not decline significantly from baseline (i.e. pre-operative) to 12 weeks post-operative. One study reported that Karnofsky Performance Status, a subjective physician scored rating of physical function, decreased by 5%, 3%, 4%, 5%, 4%, at 6, 12, 24, 36 and 52 weeks after baseline assessments, respectively (Koczywas et al., 2013). The results of each of these studies differ from one another, particularly as physical function was assessed at variable timepoints, thus there is a gap in clearly understanding how physical function changes in lung cancer survivors.

In addition to an unclear understanding of how physical function changes in lung cancer survivors, studies do not describe the extent to which symptoms co-occur with physical function. As previously described within the symptoms and side effects section of this dissertation and within the Conceptual Model of Physical Function in Cancer Survivors, symptoms of fatigue, depression, and pain may all have an impact on perceived physical function. Thus, it may be more beneficial to consider a broader constellation of symptoms in order to select a rehabilitative intervention that targets more than just physical function to attain optimal therapeutic benefit from a given rehabilitative intervention. Different modalities of exercise may be more or less effective at improving cancer-related outcomes and selection of a modality that targets the underlying contributing factors associated with fatigue in lung cancer survivors may be more effective than an untargeted modality.

With a better understanding of how physical function changes, and if or how other symptoms may contribute to changes in physical function, rehabilitation strategies may be more

appropriately selected and tested with regards to timing, dose and type of rehabilitation. For this, Chapter II will describe a secondary data analysis that examines average and intra-individual trajectories of self-reported physical function and symptom variables that are significantly associated with self-reported physical function.

Exercise as a Countermeasure in Lung Cancer Survivors: Attention to the Principles of Exercise Training

Exercise may be a useful type of rehabilitative approach to improve physical function and symptoms in lung cancer survivors. In exercise physiology a set of established principles are used to guide appropriate exercise prescription, whether or not exercise training is intended to improve human performance or improve human health. The principles of exercise training include specificity, overload, progression, initial values, reversibility and diminishing returns (Table 3) and must be rooted in the exercise prescription to ensure that the intervention is likely to be effective appropriate for the target population (Winters-Stone, Neil, & Campbell, 2014). Similarly, the exercise prescription should be carefully reported to include all components of the FITT principle, that is the frequency (number of sessions/week), intensity of exercise (often based on heart rate, lactate threshold), time (number of minutes/session) and type (modality of exercise). Without reporting the FITT components the exercise prescription is not reproducible, meaning that future studies cannot employ the same prescription to assess if the results hold true in another sample. Additionally, the results of efficacy trials cannot be adequately summarized or compared in systematic reviews or meta-analyses without the FITT components, and thus a consensus of the most appropriate exercise prescription may not be achieved.

Table 4

The Principles of Exercise Training

Principle	
Specificity	Training adaptations are specific to the organ system or muscles that are used during exercise.
Progression	Over time, the body adapts to exercise. For continued improvement, the volume or intensity of training must be increased.
Overload	To improve fitness, the training volume must exceed current habitual physical activity and/or training levels.
Initial Values	Improvements in the outcome of interest will be greatest in those with lower initial values of the outcome.
Reversibility	Once a training stimulus is removed, training-related improvements will eventually disappear.
Diminishing Returns	The expected degree of improvement in fitness decreases as individuals become more fit, thereby increasing the effort required for further improvements. Also referred to as the "ceiling effect."

(Campbell, Neil, & Winters-Stone, 2012; Neil-Sztramko, Winters-Stone, Bland, & Campbell, 2017; Winters-Stone et al., 2014)

Previous systematic reviews focused on the principles of training in studies of breast (Campbell et al., 2012; Neil-Sztramko et al., 2017), all other cancer types (Winters-Stone et al., 2014) and prostate cancer (in preparation for submission) found that of 113 exercise trials, not one included each principle of exercise training, and only two reported each component of exercise prescription (FITT) (Courneya et al., 2008; Courneya et al., 2009). To date, no systematic review specific to exercise trials in lung cancer survivors has assessed the usage and reporting of the principles of exercise training. In lung cancer, the importance of adhering to the principles of training and reporting each component of the prescription is made particularly important by the lack of clarity of the most appropriate exercise prescription for lung cancer survivors (Lim et al., 2010). This dissertation work will aim to summarize the current body of exercise trials in lung cancer survivors, the inclusion of the principles of exercise training and methodological reporting of the FITT principle and adherence of participants to the prescribed exercise program (Chapter III), with an aim to point out the gaps in the design and application of the FITT principle within studies using exercise to improve outcomes for people with lung cancer. Within Conceptual Model of Physical Function in Cancer Survivors (Bennett et al., 2006) that guides this dissertation work,

objective physical function, and treatment related side effects (i.e. physical fitness and body composition) will be the main focus of Chapter III.

Adherence to the Principles of Exercise Training for using Non-Traditional Forms of Exercise in Cancer Survivors

Though systematic reviews have critically appraised the usage of the principles of exercise training and FITT components in studies of aerobic and resistance training programs in breast (Campbell, Neil, & Winters-Stone, 2012; Neil-Sztramko, Winters-Stone, Bland, & Campbell, 2017), prostate (Neil-Sztramko, et al., under review) and all other cancer types (Winters-Stone, Neil, & Campbell, 2014), no critical summary has assessed whether the principles of exercise training and FITT components are upheld in studies of alternative forms of rehabilitative interventions, such as yoga, that are aimed at improving outcomes in cancer survivors.

Yoga has become an increasingly popular modality of exercise in the general population, with The World Health Organization reporting that 70-80% of developing nations practice yoga (WHO, 2008). Yoga originated as an ancient Indian practice that includes variations of physical movement, meditation, and breathing (Fouladbakhsh, Davis, & Yarandi, 2013). This practice aimed at uniting the mind, body, and spirit traditionally contains three basic components: 1) postures (asanas); 2) breathing (pranayama); 3) meditation (dhyana). At least 52 different styles of yoga exist (Cramer, Lauche, Langhorst, & Dobos, 2016). In the general population the most commonly studied styles include Hatha (focused primarily on physiological and psychosocial outcomes) (Feuerstein, 1998), Iyengar (strong emphasis on alignment in yoga postures and additional breathing techniques) (Iyengar & Menuhin, 1995), and Swami Vivekananda Yoga Anusandhana Samasthana (SVYASA) (integrates yoga postures, breathing exercises, meditation,

and relaxation based on ancient Indian texts) (Villacres, Jagannathan, Nagarathna, & Ramakrsihna, 2014).

Within the field of exercise science there is currently a debate on whether or not and how yoga should be considered as a modality of exercise training. Exercise is defined as planned, structured, and repetitive bodily movements that results in energy expenditure through contractions of the skeletal muscles to improve or maintain physical fitness components (Caspersen, Powell, & Christenson, 1985). Based on this definition alone, some yoga practices may be considered exercise. The complexity of defining yoga as a modality of exercise lies in the 52 different styles of yoga that are commonly used in both practice and research (Cramer, Lauche, Langhorst, & Dobos, 2016), that range from meditative practices (i.e. SVYASA style yoga) to practices involving repetitive and sustained muscular contraction of the major muscle groups (i.e. Vinyasa style yoga). Some styles of yoga may not require physical bodily movements, or enough movement to elicit an energy expenditure great enough to produce health benefits. A study of Hatha yoga (i.e. a general practice of physical focused yoga that includes long durations of isometric contractions with the goal of developing strength, balance and flexibility) reported that one 56-minute-long session requires an average energy expenditure of 3.2kcal/min^{-1} or 2.5METS (Hagins, Moore, & Rundle, 2007). These values are below the cut-offs to be considered moderate-vigorous exercise, thus the form of Hatha yoga may not be considered as a modality of exercise to elicit health benefits. Conversely, an hour-long session of vinyasa yoga (i.e. a general practice in which individuals move continuously through poses involving additional concentric and eccentric contractions on top of held isometric postures) requires an average energy expenditure of 4.6kcal/min^{-1} or 3.6 METS, thus meeting the cut-offs for moderate-vigorous exercise. From these two studies alone, the challenges in defining yoga as exercise can be seen.

For the purposes of this dissertation work, yoga in its physical form that requires planned, repetitive bouts of physical bodily movements of both the upper and lower body to improve health outcomes will be considered as exercise. Chapter IV of this dissertation will develop an approach to first categorize yoga programs in cancer survivors as exercise or non-exercise based. Secondly, Chapter IV will determine if the principles of exercise training and FITT components are upheld in studies of yoga that intend to be prescribed as exercise. Finally gaps in the knowledge about yoga for cancer survivors will be identified. Each of these aims will contribute to understanding if yoga should be considered as an exercise recommendation for cancer survivors and guide stronger, reproducible and standardized yoga prescription in future studies. As guided by Conceptual Model of Physical Function in Cancer Survivors (Bennett et al., 2006), Chapter IV will focus on objective physical function and treatment related side effects (i.e. physical fitness and body composition).

Yoga for Lung Cancer Survivors

Yoga may be prescribed as an exercise-based approach in the general, non-cancer population to improve physical function and fitness. A study of untrained volunteers (n=10) who underwent eight weeks of two yoga classes per week (75 minutes per class) reported improvements in isokinetic muscle strength for elbow extension and flexion, and knee extension, and increases in maximal oxygen uptake (i.e. an indicator of cardiorespiratory fitness) (Tran, Holly, Lashbrook, & Amsterdam, 2001). In populations with obstructive airway diseases (other than lung cancer) improvements in pulmonary and musculoskeletal physical function were reported. A study of patients with chronic bronchitis (n=15) demonstrated significant improvements in rate of forced expiratory volume in one second (FEV1) and peak expiratory flow rate (Behera, 1998). In patients with asthma (n=46) significant improvements in physical fitness, as measured by 12-minute walk

distance (8% increase, $p<0.01$) were reported, suggesting possible improvements in physical function, though function was not specifically measured (Jain & Talukdar, 1993).

Studies of yoga to reduce symptoms and side effects, including physical function, following cancer and its treatment have been conducted mostly in breast cancer survivors, with a recent systematic review reporting 26 yoga interventions in this cancer type (Sharma, Lingam, & Nahar, 2016). Such studies have reported feasibility of breast cancer survivors enrolling in and completing a yoga program. In a study of breast cancer survivors, 92% reported that they enjoyed the yoga class "quite a bit or "very much" (Danhauer et al., 2009). Yoga was found to be efficacious in reducing side effects and symptoms, including improvements in self-reported and objectively measured physical function. A study that utilized an oncologist recommended yoga DVD reported a 50% greater improvement in fatigue in the yoga group than the control group independent of age, time since diagnosis, and presence of metastatic disease ($p=0.02$) (Winters-Stone et al., 2018). Culos-Reed, Carlson, Daroux, and Hately-Aldous (2006) reported significant increases in both 6-minute walk distance (39% increase, $p<0.01$) and hand grip strength (11% increase, $p<0.05$) following 7-weeks of yoga in breast cancer survivors (n=20) (Culos-Reed et al., 2006). A study of breast cancer survivors comparing yoga (n=53) with stretching (n=56) and waitlist control (n=54) groups found that the yoga group had greater increases in self report physical function compared to the stretching and waitlist groups at 1 ($p<0.01$) and 3 months ($p<0.01$) post radiation treatment. A recent review of yoga in a variety of cancer types including esophageal, hematopoietic and prostate, concluded with support for yoga as a safe and potentially efficacious intervention to improve physical and mental symptoms and side effects in cancer survivors (Agarwal & Maroko-Afek, 2018). Though the potential for yoga as a strategy to improve perceived functioning in people with cancer grows, studies in lung cancer survivors are rare.

To date, only two studies in lung cancer survivors have explored the efficacy of yoga to improve disease and treatment related symptoms (Table 5). These two studies of yoga in lung cancer survivors used low intensity Tibetan (i.e. joint loosening, physical postures, breath energization and mediation) and Viniyoga (i.e. poses and lateral stretches coordinated with the breath and meditation) consisting of one to three in person sessions per week. Both of these studies demonstrated feasibility with 78% of participants attending more than 50% of sessions, and 89% of participants rating the yoga program as “very useful”, though both studies had small sample sizes (<10 participants) (Milbury, Mallaiah, et al., 2015). The results of these preliminary studies indicate that yoga may be an efficacious method to improve psychosocial aspects of lung cancer survivorship. One study reported improvements in mood (77% increase, $p<0.002$) and sleep efficiency (Fouladbakhsh, Davis, & Yarandi, 2014), while the second study reported improvements in sleep efficiency (percent change not reported, $p<0.02$), quality of life ($t=2.51$, $p=0.04$, $d=0.84$), spiritual well-being ($d=0.31$), benefit finding ($d=0.84$), mental health (66% increase, $p=0.04$) and significant medium effect sizes for sleep disturbances ($d=0.36$) (Milbury, Mallaiah, et al., 2015). Additionally, the 8-week study conducted by Fouladbakhsh et al. (2013) found significant improvements in FEV1 ($F=9.93$, $p=0.001$) in stage I-IIIA survivors ($n=9$) who had completed initial treatment. Though these studies have reported preliminary feasibility and efficacy of yoga to improve mostly psychosocial outcomes, physical function has not yet been assessed following a yoga intervention in lung cancer survivors. Further, the duration of these interventions was brief, lasting five to eight weeks, when improvements in physical function may not occur during this short time.

Table 5

Single group exercise studies of Yoga in Lung Cancer Survivors

Citation	Population	Study Design	Results
Fouladbakhsh et al. (2013); Fouladbakhsh et al. (2014)	NSCLC, stages I-IIIa, completed initial treatment, (n=9 objective measures, n=7 subjective measures)	Design: Quasi-experimental single-arm Frequency: 1 session/week + home practice, 8 weeks Intensity: not reported Time: 45 minutes/session + home practice Type: Viniyoga	-FEV1 values ↑ significantly - Mood, sleep efficiency, QOL significant ↑ - Salivary cortisol ↓ over time
Milbury, Chaoul, et al. (2015); Milbury, Mallaiah, et al. (2015)	NSCLC, stage I-IIIB, receiving at least 5 weeks of radiotherapy, n=10 patients, n=10 caregivers; n=15 patients*, n=15 caregivers*	Single-arm pilot Frequency: 2-3 sessions/week, 5-6 weeks Intensity: low Time: 45-60 min/session Type: Tibetan yoga *dyadic	- Significant ↑ spiritual well-being - Near significant ↑ benefit finding - Significant medium effect sizes for sleep disturbances and depressive symptoms - Small effect sizes for anxiety and mental summary component scores -Significant↑mental health* - Non-significant medium effect sizes in benefit finding, small for distress*

FEV1: Forced expiratory volume in 1-second; NSCLC: Non-small cell lung cancer; QOL: Quality of life.
*Differentiate sample sizes between studies (n=15 patients and n=15 caregivers).

As lung cancer survivors experience functional declines (Ha et al., 2018) that could lead to disability and mortality, it is important to consider a variety of exercise-based strategies, including less traditional forms of training, as possible interventions. Chapter V of this dissertation will include a 12-week, single group, yoga intervention in lung cancer survivors to assess the feasibility, safety and preliminary efficacy of yoga to mitigate functional declines.

Purpose/Specific Aims

The overall purpose of this dissertation work is to understand the consequences of lung cancer and its treatment on physical function and to consider the application and subsequently test exercise as an approach to mitigate functional declines during treatment. To accomplish this purpose, four specific aims have been identified and are summarized in Table 6. These aims will be the focus of four manuscripts including a secondary analysis of self-reported trajectories of physical function, systematic review of the exercise oncology literature in lung cancer, a systematic review of yoga interventions as a non-traditional form of exercise in cancer survivors, and a pilot quasi-randomized controlled yoga trial in lung cancer survivors.

The first aim is to conduct a secondary data analysis to describe levels of self-reported physical function and symptom variables that are significantly associated with self-reported physical function. Covariates that may be associated with low physical function that will be explored in a regression model include age, fatigue, depressive symptoms and pain.

The second aim is to summarize the body of clinical exercise trials in lung cancer survivors while evaluating 1) the principles of exercise training in the design of the exercise prescription; 2) methodological reporting of the FITT components of the exercise prescription; 3) adherence of participants to the prescribed exercise program. This systematic review will summarize current

exercise prescriptions for lung cancer survivors and indicate how alternative modalities of exercise may be of use in this population of individuals with particularly low physical function.

The third aim is to summarize the current controlled trials that assess the efficacy of yoga on physiological and psychosocial outcomes in cancer survivors, while evaluating whether or not the principles of exercise training were applied during the design of the yoga prescription, whether or not the FITT components for the exercise prescription were reported, and whether or not adherence of the participants to the prescribed exercise program was included. This review will provide a timely description of the use of yoga as an intervention to manage cancer and treatment related side effects in cancer survivors.

The fourth aim is to determine the feasibility and preliminary efficacy of a 12-week yoga program to mitigate functional declines in lung cancer survivors. This study will be the first to comprehensively assess physical function of both the upper and lower extremities following a 12-week yoga program in lung cancer survivors. The yoga program will aim to include and report on the principles of training in order to strengthen the yoga and oncology literature with an example of how a yoga prescription can employ and report on the principles of training.

Table 6

Summary of Proposed Manuscripts

Aim	Title of Paper
Aim #1: 1) Describe the direction and rate of change of self-reported physical function over one year both on average and among individual lung cancer survivors and identify symptom variables that are significantly associated with physical function. *Hypothesis: Self-reported levels of physical function will decline significantly over one year in lung cancer survivors, and symptom profiles including fatigue, depressive symptoms and pain may be predictive of low self-reported function.*	*(Chapter II)* Characterizing Trajectories of Change of Self-Reported Physical Function in Lung Cancer Survivors
Aim #2: Summarize the body of randomized controlled exercise trials in individuals diagnosed with lung cancer while evaluating: 1) the principles of exercise training in the design of the exercise prescription; 2) methodological reporting of the FITT components of the exercise prescription; 3) adherence of participants to prescribed exercise program. *Empirical Hypothesis: No study will adequately report each principle exercise training, the FITT components of exercise prescription, nor the adherence of participants to the prescribed exercise program.*	*(Chapter III)* Attention to the Principles of Exercise Training in Exercise Studies of Lung Cancer Survivors
Aim #3: Summarize the randomized controlled trials assessing the efficacy of physical yoga in cancer survivors on physiological outcomes while evaluating: 1) the principles of exercise training in the design of the yoga programs; 2) methodological reporting of the FITT (frequency, intensity, time and type) components of the yoga program; 3) adherence of participants to the prescribed yoga program. *Empirical Hypothesis: No study will adequately report each principle of exercise training, the FITT components of exercise prescription, nor the adherence of participants to the prescribed yoga program.*	*(Chapter IV)* Attention to the Principles of Exercise Training in Physical Yoga Interventions in Cancer Survivors
Aim #4: Determine the feasibility, safety and preliminary efficacy of yoga to mitigate functional declines in lung cancer survivors. *Hypothesis: A 12-week yoga training program will be feasible based on 100% of the accrual target within 6-months; >75% adherence to supervised yoga practice and >80% retention over the study period; and a complete absence of serious adverse events and 2) Yoga will yield at least moderate effect sizes on*	*(Chapter V)* Feasibility and Preliminary Efficacy of Yoga on Physical Function in Lung Cancer Survivors: A Pilot Trial

measures of physical fitness and function over 6 and 12 weeks.

Implications for Practice

This dissertation has several significant implications for nursing practice and oncology care. First, understanding how self-reported physical function and co-occurring symptoms change over the course of a year in lung cancer survivors would be a strong addition to the few studies that have described changes in physical function. Nursing practice could be improved by knowing at what rate physical function changes and if there are symptoms such as fatigue, depression or pain, that could have an impact on physical function that may need to be addressed. With this knowledge nurses could anticipate and manage problematic changes in physical function and increased negative symptoms, educate patients on what to expect following treatment, and seek rehabilitative strategies that may target symptoms and side effects that underlie functional declines. All together this knowledge could strengthen nurses' ability to care for lung cancer survivors.

Secondly, a clear summary of the current evidence to support exercise for lung cancer survivors will be compiled. A strong summary could be a useful resource in nursing practice to guide and educate nurses on the possible benefits of exercise for lung cancer survivors, while also educating nurses on where there are important knowledge gaps in studying exercise for lung cancer survivors.

Thirdly, summarizing and critically evaluating the studies of yoga conducted in cancer survivors may be a strong and timely contribution to nursing practice to possibly introduce yoga as an alternative exercise-based rehabilitation strategy for cancer survivors. From the proposed review, nurses could be more educated about what is currently known about yoga in cancer

survivors and how it could possibly benefit cancer survivors or what knowledge gaps exist in order to incorporate this recommendation into common practice.

Finally, using yoga as an alternative modality of exercise to mitigate declines in physical function in lung cancer survivors could provide nurses with an additional resource to share with survivors as they seek rehabilitation following diagnosis and treatment. If successful, the yoga program could have a strong and positive impact on physical functioning in lung cancer survivors. Further, efficacy trials would set-up future effectiveness and/or implantation studies that could test a nurse-delivered and/or nurse referred yoga program. A collaborative effort between exercise oncology and oncology nursing practice could advance the nursing field and demonstrates a strong multidisciplinary collaborative effort that integrates the disciplines of exercise oncology with nursing science.

Chapter II: Characterizing Self-Reported Physical Function in Lung Cancer Survivors

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This manuscript replaces portions of the methods section and results section of the traditional dissertation. Ms. Medysky was the primary author on this paper; Dr. Karen Lyons was the senior author on this paper. Ms. Medysky conducted the analysis under the supervision of Drs. Lyons and Dieckmann. This manuscript is accepted in the Journal Cancer Nursing that focuses on the whole spectrum of problems arising in the care and support of cancer patients including geriatric cancer patients, patient responses to treatment modalities and specific nursing interventions. The Journal of Cancer Nursing is an indexed and peer-reviewed journal with an impact factor of 2.022. This manuscript is in its final state, pending further revisions from the editor of Cancer Nursing.

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Declaration of Conflict of Interest
None Declared

Key Words: lung neoplasms; physical function; cancer survivors; geriatrics; heterogeneity

Abstract

Background: Lung cancer survivors are at risk for accelerated declines in physical functioning attributed to cancer treatment. However, it is unknown whether patients experience the same rate of functional decline and how symptoms may contribute to different trajectories. **Objective:** To identify inter-individual differences in the pattern and rate of change in self-reported functioning in lung cancer survivors and examine whether and how symptoms are related to physical functioning over time. **Methods:** Secondary data analysis in 72 lung cancer survivors. Multilevel modeling (MLM) was used to estimate trajectories of self-reported physical functioning over one year and assess the relation between functioning, fatigue, depressive symptoms and pain severity across time. **Results:** Within the sample, average physical functioning did not significantly decrease (coefficient=-0.46, 95% CI=-2.85, 0.94) over time. However, among individual lung cancer survivors baseline physical functioning varied significantly (SD=20.76, 95% CI=16.84, 25.59) and changed at significantly different rates over one year (SD=3.50, 95% CI=2.13, 5.68). Fatigue, assessed over one year, was the only significant symptom predictor of physical functioning changes over time (coefficient = 1.03, 95% CI=0.79, 1.27).

Introduction

The American Cancer Society predicts that there will be more than 673, 000 lung cancer survivors in the US by 2026 (American Cancer Society, 2018). Evidence in support of low-dose computed tomography screening for lung cancer in high risk individuals has contributed to an increased number of survivors, who were once considered to solely have palliative treatment options (Wang et al., 2016). As a result, more people are diagnosed with early stage lung cancer that is potentially more curable. For example, between years 2010 and 2015 there were 8122 fewer deaths from lung cancer (6.4 percentage points) (Cheung et al., 2018). The current 5 year survival rate in patients with a non-invasive lung cancer is 55% (American Cancer Society, 2018). Lung cancer patients typically receive aggressive treatments that may be delivered adjunctively or concurrently and include, surgical resection, chemotherapy, radiation, targeted biologic therapy and immunotherapies. Unfortunately, the treatment of this disease may contribute to low physical functioning.

Physical functioning is an important outcome in lung cancer survivorship because functional limitations are strong predictors of clinically meaningful outcomes such as disability, nursing home admission and death (Gill, 2010). Lung cancer is predominantly diagnosed in older adults (average age of diagnosis ~70 years old) (American Cancer Society, 2018), thus maintaining independence in activities of daily living is a major contributor to overall health status (Cress et al., 1995). Therefore, functional status is a particularly important consideration in the clinical care of lung cancer survivors.

Despite the importance of physical functioning in lung cancer survivors, there is limited knowledge regarding this critical outcome. Three studies have compared physical functioning at a single time-point in lung cancer survivors to cancer-free controls (Brown et al., 2005) or to

population means (Duc Ha et al., 2018; Titz et al., 2018), and all reported that physical functioning was significantly lower in lung cancer survivors than comparison groups. However, these cross-sectional studies did not describe the longitudinal pattern of changes in physical functioning or consider whether or not functional declines change similarly across all survivors. Understanding the variability of changes in physical functioning would help identify which patients would be most likely to benefit from rehabilitation strategies.

Though there are six longitudinal studies that report low physical functioning on *average* within samples of lung cancer survivors (Brunelli et al., 2007; Granger et al., 2014; Kasymjanova et al., 2009; Kinsey et al., 2018; Koczywas et al., 2013; Machado et al., 2010), studies reporting mean slopes may not adequately capture the variability in the rate and direction of change in physical functioning among *individual* lung cancer survivors. A recent study of older adult, female cancer survivors undergoing chemotherapy reported that there was significant inter-individual variability in self-reported trajectories of physical functioning when measured 6 times across two cycles of chemotherapy (Wong et al., 2018a). It is unknown whether or not the same variability in functional declines is common in lung cancer survivors, but this would be informative for optimal clinical management where resource allocation may not be universal. Identifying factors, such as treatment symptoms and side effects, that might contribute to changes in physical functioning could also better target clinical management toward underlying causes.

A conceptual model of physical functioning proposed by Bennett, Winters-Stone, and Nail (2006) identifies several health-related factors and symptoms that may be predictive of changes in physical functioning in cancer survivors. Symptoms that are frequently reported in lung cancer survivors include fatigue (Carnio et al., 2016; Nishiura et al., 2015), depressive symptoms (Hopwood & Stephens, 2000; Sullivan et al., 2016), and severe pain (Mercadante et al., 1994;

Potter & Higginson, 2004), and it is estimated that 57-100%, 44-50% and 47% of lung cancer survivors may experience each of these symptoms respectively. Understanding the influence of fatigue, depressive symptoms, and pain on levels of physical functioning would allow the identification of possible underlying reasons why some lung cancer survivors are more prone than others to declines in physical functioning following treatment and assist in selecting more targeted intervention strategies.

We had the opportunity to fill these knowledge gaps using previously collected longitudinal data on a sample of recently diagnosed lung cancer survivors. The aims of this secondary analysis of lung cancer survivors were to: 1) describe inter-individual differences in the pattern and rate of change of self-reported physical functioning over one year and 2) identify symptoms that are significantly associated with baseline and trajectories of physical functioning over one year in lung cancer survivors.

Methods

A secondary analysis (see primary studies: Lyons, Bennett, et al. (2014a); Lyons, Lee, et al. (2014)) of self-reported physical functioning in newly diagnosed lung cancer survivors (n=72) was conducted. A sample of 72 lung cancer survivors was used for this secondary data analysis from the original sample (n=77) as we removed patients who were deceased during the study. With the sample included in this analysis there was 25% attrition over the 12 months. There were no significant differences between those who completed the study at 12 months with respect to age, time since diagnosis, self-reported physical functioning, fatigue, depressive symptoms or pain severity.

The recruitment methods have previously been described (Lyons, Bennett, et al., 2014b; Lyons, Lee, et al., 2014). Inclusion criteria included the following: a primary diagnosis of stages I-IV non-small cell lung cancer (NSCLC) within the past 6-months, 18 years and older, English speaking, and living within 50 miles of Portland, Oregon. Data was collected at baseline (within 6 months of diagnosis), 3, 6, 9 and 12 months. Survivors provided informed consent during a home visit at baseline. The study was approved by the Institutional Review Board at Oregon Health & Science University.

Measures

Participant demographics and health/cancer history (age, gender, marital status, race, education, time since diagnosis and cancer stage) were collected by self-report. Physical functioning and symptoms that may be predictive of low physical functioning, guided by the Conceptual Model of Physical Functioning in Cancer Survivors (Bennett et al., 2006), were assessed five times (baseline, 3, 6, 9 and 12 months) over one year.

Self-reported physical functioning. Self-reported physical functioning was assessed by the 10-item Physical Function subscale of the Medical Outcomes Study Short-Form 36 (SF-36), version 2.0 (Ware Jr et al., 1995). Scores were transformed to 0-100, with 50 indicating the population average and high scores indicating better function. The subscale has high internal consistency is well-established, valid, and sensitive to change over time (Ware Jr et al., 1995). Permission was obtained to utilize the SF-36 in the present study.

Fatigue. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy –

Fatigue (FACT-F) scale. This is a 13 item, uni-dimensional, 5-point Likert scale, measuring physical fatigue over the past week. The scale has high internal consistency (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997) and is widely used in the literature (Andersen et al., 2013).[29]

Depressive symptoms. The Center for Epidemiological Studies-Depression (CES-D) scale was used to assess depressive symptoms over the past week. Each item was rated on a 4-point scale. Scores range from 0 to 60, with high scores reflecting more depressive symptoms. The scale has established reliability and validity estimates in cancer patients receiving surgery or radiation (M. J. Dodd, Miaskowski, & Paul, 2001; Miaskowski et al., 2006). The CES-D has excellent internal consistency in lung cancer survivors (Brown Johnson, Brodsky, & Cataldo, 2014) and strong sensitivity and specificity in a study of cancer survivors (n=33) (Hopko et al., 2007).

Pain Severity. Using the Brief Pain Inventory (BPI), the average of a four-item subscale was used to assess pain severity over the past week on a 0 (no pain) to 10 (worst pain) scale considering pain at its worst, least, on average, and current (Cleeland & Ryan, 1994). This subscale has high internal consistency (Jensen, 2003). Permission was obtained to utilize the BPI in the present study.

Data Analysis

Descriptive statistics and distributions were calculated for participant demographics, physical functioning and symptom variables. Multi-level modeling (MLM) estimated with maximum likelihood was conducted using Stata Version 15 (Stata Corp, College Station, TX). In MLM, repeated measures of the outcome variable are nested within individuals, and change is

represented at two levels: within individuals (level 1) and between individuals (level 2). At level 2, the outcomes are allowed to vary across individuals by adding random variance components. These random effects allow the examination of the variability of individual change across time, which is typically ignored using other methods that focus on average change among a sample (e.g., repeated measures ANOVA). Demographic or clinical characteristics, such as symptom variables, can then be flexibly added as predictors of the outcome at level-1 or level-2 (Raudenbush & Bryk, 2002).

A MLM model was fit to determine changes in physical functioning at baseline, 3, 6, 9 and 12 months. First, an unconditional model revealed significant inter-individual variability in physical functioning, thus two conditional models with fixed and random slopes, respectively, were fit to determine if there was substantial individual variability around the slope. A likelihood ratio test revealed that the unconditional random slope model had a better fit. To determine the pattern of change in physical functioning, a conditional model with a fixed quadratic time effect (i.e. a rate that accelerated or decelerated over time) was compared with a linear time effect (i.e. a constant rate of change) with a likelihood ratio test. To best illustrate the variability in patient trajectories across individuals, we selected a random 50% of the sample to show in Figure 1.

A second model was fit by adding time-varying symptom variables as predictors of physical functioning. Time invariant predictors, time since diagnosis, stage of cancer and demographics were entered into the initial model, however the results were similar to the current model, thus the most parsimonious model including only symptom variables, is reported. Missing outcome data was handled flexibly with all available data included for each person. $P < 0.05$ indicates statistical significance.

Results

Baseline participant characteristics.

Participant characteristics, health history and symptoms (n=72) are presented in Tables 1 and 2. Participants were on average 71 years old (±10 years), with the majority of the sample being male (59.7%), Caucasian (90.3%), married/partnered (75%), and not employed at the time of enrollment (85%). Average time since diagnosis was 3 months (±1.8), and the majority of participants had stage I lung cancer (55%). At baseline participants self-reported an average physical functioning score of 51.5 ±26.8 points. Symptoms of fatigue, depression and pain were on average 31.33±11.9, 11.94±10.9 and 2.38±2.3 points, respectively.

Table 1

Participant Characteristics at Baseline (n=72)

Demographic	**Mean (SD) or n (%)**
Age (years) (mean, *SD*)	70.81 (10.94)
Gender (n, %)	
Male	43 (59.7)
Female	29 (40.3)
Race (n, *%)*	
Caucasian	65 (90.3)
Non-Caucasian	7 (9.7)
Marital Status (n, *%*)	
Married/Partnered	54 (75.0)
Non-married/partnered	18 (25.0)
Education Status (n, %)	
Less than high school	10 (13.9)
High school/GED	23 (31.9)
Some college	16 (22.2)
Completed College	13 (18.1)
Advanced Degree	6 (8.4)
Other	4 (5.6)
Employment (n, *%*)	
Employed	11 (15.3)
Not employed	61 (84.7)

Table 2

Participant Health History and Symptoms at Baseline (n=72)

Characteristic	**Mean (SD) or n (%)**
Cancer Stage[a]	
Stage I	31 (55.4)
Stage II	6 (10.7)
Stage III	15 (26.8)
Stage IV	4 (7.1)
Months Since Diagnosis (mean, *SD*)	3.42 (1.8)
Physical Function (SF-36)	51.49 (26.8)
Fatigue (FACT-F)	31.33 (11.9)
Depressive Symptoms (CES-D)	11.94 (10.9)
Pain Severity (BPI)	2.38 (2.3)

Abbreviations: BPI, brief pain inventory; CES-D, center for epidemiological studies-depression; FACT-F, functional assessment of chronic illness therapy-fatigue; SD, standard deviation; SF-36, short-form 36
[a]Values do not sum to 72 because some survivors did not know their cancer stage.

Longitudinal physical function

The linear conditional model examined how physical functioning changed over one year. Within the full sample physical functioning did not significantly decrease (coefficient=-0.46, -95% CI=2.85, 0.94) over time. A linear trend fit the model best, as depicted by the red line in Figure 1. The model revealed that there was significant variability around the average physical functioning score at baseline (SD=20.76, 95% CI=16.84, 25.59) and around the average slope (SD=3.50, 95% CI=2.13, 5.68) (Table 3), indicating that some survivors experienced improvements in physical functioning and some experienced declines (Figure 1).

Table 3

Model of Physical Function with Random Linear Slopes over One Year

Physical Function	**Coefficient**	**p**	**95% Confidence Interval**
Fixed Effects			
Time	-0.46	.520	-2.85, 0.94
Constant	51.49	<.001	46.09, 56.88
Random Effects			

	Estimate	Standard Error	95% Confidence Interval
Time (SD)	3.48	0.87	2.13, 5.68
SD (constant)	20.76	2.21	16.84, 25.59
Correlation timepoint, constant	-0.11	0.23	-0.52, 0.34

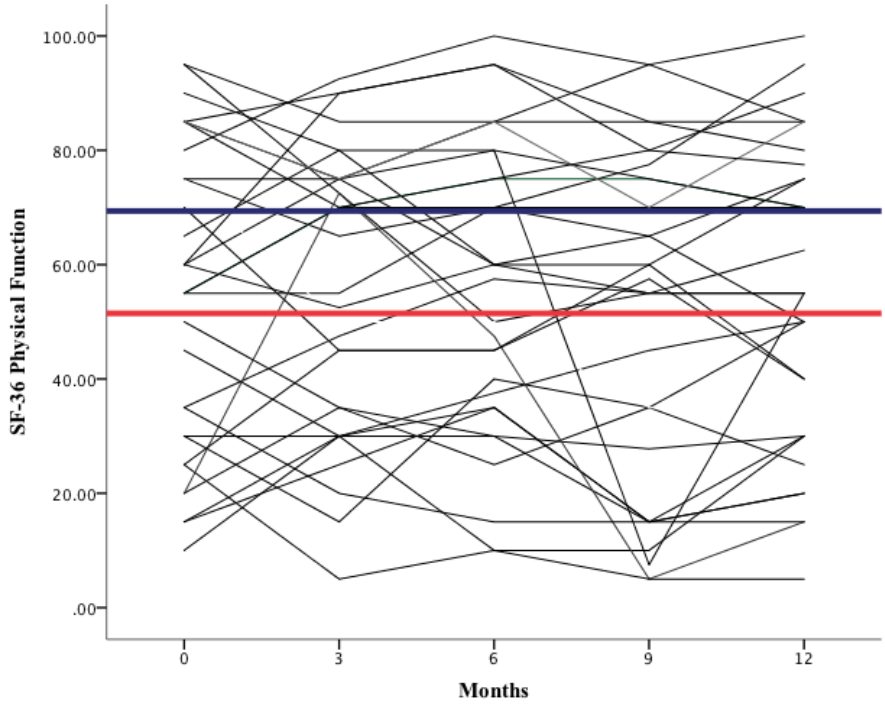

Figure 1. Spaghetti plot of a 50% random sample demonstrating intraindividual variability of SF-36 physical function scores over one year

Red line indicates the average across the sample.
Blue line indicates the United States national norm in the 65-74 age group.

Predictors of self-reported physical functioning over time

The conditional MLM examined how trajectories of physical functioning over one year were associated with symptoms that conceptually may contribute to varying levels of physical functioning in cancer survivors (Bennett et al., 2006). The linear conditional model revealed that changes in fatigue significantly predicted self-reported physical functioning over one year. Lung

cancer survivors with less fatigue reported significantly less declines in physical functioning over time (coefficient = 1.03, 95% CI=0.79, 1.27) (Table 4). Depressive symptoms and pain severity were not significant predictors of self-reported physical functioning over time.

Table 4

Linear Conditional Model with Time-Varying Covariates

Physical Function	**Coefficient**	**p**	**95% Confidence Interval**
Fixed Effects			
Time	-1.69	.05	-2.86, -0.52
Fatigue	1.03	<.001	0.79, 1.27
Depressive Symptoms	-0.04	.799	-0.36, 0.28
Pain Severity	-0.50	.347	-1.54, 0.54
Constant	19.91	.001	9.49, 31.33
Random-Effects			
	Estimate	**Standard Error**	**95% Confidence Interval**
SD Time	2.75	0.75	1.61, 4.71
SD Constant	16.91	1.86	13.62, 20.98
Correlation timepoint, constant	-0.14	0.25	-0.57, 0.35

Discussion

In this secondary analysis of lung cancer survivors, baseline self-reported physical functioning was lower than the US national average in a similar age-group. Similarly, 57% and 26% of lung cancer survivors self-reported clinically significant levels of fatigue and depressive symptoms, respectively. Consistent with previous studies (Brown et al., 2005; Carnio et al., 2016; Duc Ha et al., 2018; Krebber et al., 2014; Potter & Higginson, 2004), the present secondary analysis describes a sample of lung cancer survivors who, on average, self-reported low physical functioning, endure clinically relevant levels of fatigue, and report symptoms of depression. Pain, on average, was reportedly less severe than the US national average in both the 61-70 and 71-80

year old age groups (Nicholas et al., 2019), with some survivors experiencing little to no pain, and others with moderate pain. The majority of the sample (55%) had stage I lung cancer thus their pain may have been low because of limited disease severity. Further, it is possible that the lung cancer survivors in this sample had pain that was controlled by medication, though we did not track this in our study.

The present study was the first to demonstrate that significant inter-individual differences in self-reported physical functioning occur over the initial phase of the lung cancer trajectory. Figure 1 depicts the variability among trajectories of self-reported physical functioning in a random selection of 50% of the sample, and by contrast depicts the average linear trend in physical functioning, which did not change significantly over time on average (illustrated in red). These results are consistent with a recent study of female survivors with mixed cancer types (22% lung cancer) that reported significant inter-individual variability in SF-36 physical functioning over two-cycles of chemotherapy (Wong et al., 2018b). Combined, these results indicate that not all cancer survivors will have the same declines in physical functioning over time, and that this may be independent of cancer type. No study has yet to clearly identify what factors contribute to inter-individual variability in physical functioning in lung cancer survivors. Based on a conceptual framework (Bennett et al., 2006) and previous observational studies, it is possible that many factors alone or in combination could contribute to inter-individual variability in physical functioning including comorbidities, lifestyle behaviors (i.e. smoking, diet, physical activity (Titz et al., 2018)), age, sex, education, income, access to health care, cancer history, (Bezjak et al., 2006) and treatment related symptoms, such as those addressed in the present study.

In the present study, we examined the contribution of symptoms to changes in functioning and found that lower levels of fatigue were significantly associated with more favorable individual

trajectories of physical functioning across time. Fatigue is a severe and debilitating symptom with strong associations to health-related quality of life (Yang et al., 2012) that is reported in 57-100% of lung cancer survivors (Carnio et al., 2016; Nishiura et al., 2015). A significant proportion of our sample reported significant fatigue within the early stages of cancer treatment. Depressive symptoms and pain severity were, however, not significant predictors of trajectories of physical functioning. These findings are consistent with a previous study in patients with advanced lung cancer that reported worsening symptoms of fatigue, but not depression, were associated with poorer Karnofsky Performance Status scores and performance on a test of lower extremity functioning (Brown et al., 2005). Similarly, a recent study in female cancer survivors (22% lung cancer) found that morning fatigue, but not other symptoms such as pain or anxiety, was associated with decreases in physical functioning over two cycles of chemotherapy (Wong et al., 2018b). In another study of stage IIIA-IV lung survivors (n=157), 81.5% experienced some degree of fatigue and about one-third of survivors reported that fatigue had interfered with activities of daily living that require components of physical functioning, such as walking (36.3%) or “normal work” (31.8%) (Nishiura et al., 2015). Together these results indicate that reducing levels of fatigue could buffer declines in physical functioning, thus intervention strategies may focus on mitigating fatigue to seek improvements in physical function.

Strengths of this secondary data analysis include the examination of physical functioning across multiple time points over the first 12-18 months post diagnosis. To the best of our knowledge only one other study (Koczywas et al., 2013) has assessed long term changes (i.e. >1 year) of physical functioning in lung cancer survivors. As 55% of lung cancer survivors are expected to live 5 years past diagnosis (Siegel, Miller, & Jemal, 2019), it is important to assess physical functioning for an extensive duration post diagnosis, rather than assessing physical

functioning only immediately following chemotherapy (Kasymjanova et al., 2009; Kinsey et al., 2018; Machado et al., 2010), surgery (Brunelli et al., 2007), or 6 months post diagnosis (Granger et al., 2014). Finally, this secondary data analysis was the first to use MLM to explore whether there are different individual trajectories of physical functioning that are not explained by looking at average changes within a sample of lung cancer survivors. While average reports of physical functioning may not elucidate significant changes in physical functioning over time, individual lung cancer survivors may experience significant and debilitating changes in physical functioning that require intervention. We also considered how symptoms may influence variability in changes in physical functioning. In the era of patient tailored medicine and survivorship, data to suggest individual trajectories of physical functioning and symptoms is progressive and necessary in order to develop and optimize more personalized survivorship plans within clinical practice.

There are limitations to our study. While our sample size was sufficiently large to examine longitudinal data, we limited the number of predictor variables to ensure robust parameter estimation, and thus could not explore additional associations with other potential predictors. Secondly, other potential predictors such as baseline comorbidities or physical activity level that were not measured in the original study could also contribute to variation in changes in physical functioning. Thirdly, the statistical analysis employed to match the study aims, does not provide enough information to determine if low physical functioning caused increases in fatigue or vice versa. The conceptual model (Bennett et al., 2006) used to guide the analysis suggests that changes in symptoms may influence changes in physical functioning rather than the opposite relationship. Further, physiological alterations to the neuromuscular system from the disease or treatment (e.g. Reduced cardiorespiratory function (Fresard et al., 2016) or reduced force generating capacity in the muscles (Cai et al., 2014)) may exacerbate symptoms of fatigue and in turn be related to

perceptions of reduced physical functioning. Future studies should perform lagged MLMs among physical functioning and conceptually associated variables such as fatigue, depressive symptoms and pain, to better determine causation. Lastly, physical functioning was not assessed using common objective measures (e.g. physical performance battery, gait speed, or timed up and go), that are not subject to bias and are sensitive to early declines in individuals who may not yet perceive functional limitations. However, the SF-36 physical functioning survey is valid, reliable, well used in the cancer survivorship literature (Wong et al., 2018b), and has been associated with survival in lung cancer survivors (Moller & Sartipy, 2012).

Conclusion

This secondary data analysis suggests that although self-reported physical functioning did not appear to decline across a sample of lung cancer-survivors in their first 12-18 months past diagnosis, significant interindividual variability in trajectories of self-reported physical functioning exist. Lung cancer survivors may not all experience the same degree of perceived functional decline, therefore it is important to closely monitor physical functioning in each individual survivor in order to intervene to prevent permanent loss of function. While depressive symptoms were notable among this sample, fatigue appeared to be the driver of functional declines and should be considered as a target for ensuring patients can maintain physical function throughout treatment and into survivorship.

Implications for practice

This secondary data analysis has several notable implications for nursing practice. Nurses working with lung cancer survivors should be aware that survivors may have low physical functioning. Nurses should recognize that not all lung cancer survivors will follow the same

trajectory of decline in physical functioning, thus physical functioning should be closely and regularly monitored. It is more challenging to reverse functional declines once an individual has reached a disabled state, than intervening at a pre-clinical level of disability (Fried et al., 2000), thus it is important to focus on maximizing survivors' level of functioning to prevent irreversible decline. Further, many lung cancer survivors may struggle from cancer-related fatigue that could be indicative of a risk for faster declines in physical functioning. Nurses should monitor levels of fatigue and discuss fatigue management strategies, such as physical activity (Dennett, Peiris, Shields, Prendergast, & Taylor, 2016) with patients who show early risk for functional decline.

Chapter III: Attention to the Principles of Exercise Training in Exercise Studies of Lung Cancer Patients

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This manuscript replaces portions of the methods section and results section of the traditional dissertation. Ms. Medysky will be the primary author on this paper; Dr. Winters-Stone will be the senior author on this paper. Ms. Medysky will conduct the systematic search and extract the data from articles (along with reviewers from the study team, KB, SN), describe the design and results This paper is under review at the Journal of Geriatric Oncology, which is an indexed and peer-reviewed journal with an impact factor of 6.724 that focuses on advancing research in treatment and survivorship issues of older adults with cancer (note: to facilitate ease of submission, manuscript drafted in the past tense).

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Key Words: lung neoplasm; systematic review; aerobic training; resistance training

Abstract

Introduction: Reviews that support the use of exercise to improve physiological outcomes in a variety of cancer types have been conducted. However, whether and how well the principles of exercise training have been attended to within trials in lung cancer patients has not been considered. **Purpose:** To summarize exercise trials in lung cancer patients on the following: 1) attention to the principles of exercise training (e.g., specificity, overload, initial values, reversibility, diminishing returns) in the design of the exercise prescription; 2) methodological reporting of the FITT (frequency, intensity, time and type) components of the exercise prescription; 3) reporting on adherence of participants to the prescribed FITT. **Methods:** A systematic search of OVID Medline, Embase, CINAHL, and SPORTDiscus databases was conducted. Randomized controlled trials of exercise that reported on at least one physical fitness, physical function or body composition outcome in lung cancer patients were included. **Results:** Of 16 trial arms included, none incorporated all of the principles of exercise training. Across all trials arms, *specificity* was included by 94%, *progression* by 44%, *overload* by 69%, and *initial values* by 75%, while none considered the principles of *reversibility* or *diminishing returns*. Eleven trial arms clearly reported all of the FITT components in the methods, however no interventions reported adherence to each component in the results. **Conclusions:** Though the number of exercise trials for lung cancer patients is growing, the principles of exercise training are not consistently applied. Though the FITT components of the exercise prescription were well reported, adherence to each was not, thus the doses of exercise attained in these trials remains unclear. Including the principles of exercise training and reporting on the FITT components will contribute to a better understanding of the efficacy of exercise for lung cancer patients and ultimately inform effective exercise prescriptions for this patient population.

Introduction

Lung cancer is highly prevalent in older adults, (mean diagnosis age: 70 years (American Cancer Society, 2018)) and is the leading cause of cancer mortality. Treatment for lung cancer commonly includes surgery, chemotherapy, radiation, targeted therapy and/or immunotherapies. Lung cancer patients are at risk of disease and/or treatment related symptoms and side effects, most notably pain and fatigue (Tanaka, Akechi, Okuyama, Nishiwaki, & Uchitomi, 2002), cachexia and/or sarcopenia (Baracos et al., 2010), reduced pulmonary and lower-body physical function (Brown et al., 2005; Sarna et al., 2004) and poor quality of life (Kenny et al., 2008).

As lung cancer survival rates have increased (Henschke et al., 1999; National Lung Screening Trial Research Team, 2011a, 2011b), a number of randomized controlled trials (RCTs) have recently been conducted to evaluate the potential for exercise to be used as countermeasure to disease and treatment related side effects (Peddle-McIntyre et al., 2019). The focus of exercise studies in lung cancer patients has been primarily on pre- and post-operative pulmonary rehabilitation, because in lung cancer surgical resection is the most effective treatment option (Sherwood & Brock, 2007). A 2010 systematic review summarized randomized controlled exercise trials for lung cancer patients that had undergone all treatment types (Granger, McDonald, Berney, Chao, & Denehy, 2011). The authors concluded that further research is required to establish the efficacy of exercise during and after lung cancer treatment, and the optimum type of training and delivery setting (Granger et al., 2011). In advanced staged lung cancer patients, a recent meta-analysis including six exercise RCTs, involving 221 participants found that fitness and quality of life were improved in participants randomized to exercise than control participants (Peddle-McIntyre et al., 2019) However, authors note that the risk of bias was high for included studies, and the overall quality of evidence for all outcomes was low (Peddle-McIntyre et al.,

2019). Together these systematic reviews indicate that across lung cancer patients of all stages and who have undergone various treatments, no consensus exists for the most efficacious exercise prescription. One potential reason for the lack of clarity around the efficacy of exercise for lung cancer patients is that the principles of exercise training are not appropriately incorporated into the trial design and exercise prescription.

To ensure that exercise trials are designed to yield optimum outcomes for any population, a set of well-established principles should be followed (Table 1). Attention to the principles of training will increase the likelihood of exercise to maximally benefit those with the greatest need of improvement, while failing to apply the principles of exercise training could lead to erroneous conclusions regarding the potential benefit of exercise for persons with lung cancer. Previous reviews of exercise intervention studies in breast (Campbell, Neil, & Winters-Stone, 2012; Neil-Sztramko, Winters-Stone, Bland, & Campbell, 2017), prostate (Neil-Sztramko, Medysky, Campbell, Bland, & Winters-Stone, 2019) and mixed cancer types not exclusive of lung cancer (K.M. Winters-Stone, Neil, & Campbell, 2014) found that training principles were inconsistently reported and/or misapplied in the design and implementation of the training programs. It is currently unknown whether previous exercise RCTs in lung cancer patients appropriately utilized the principles of exercise training. In addition to the principles of training, unclear reporting of the trial design and adherence to the FITT components of the exercise prescription could also potentially contribute to the lack of clarity for the efficacy of exercise for lung cancer patients.

Table 1

Principles of Exercise Training

Principle	**Criteria for this review**	**Example**
Specificity: Training adaptations are specific to the organ system or muscles trained with exercise	Appropriate population targeted and modality selected based on primary outcome	Aerobic exercise such as brisk walking is more appropriate for an intervention aimed at increasing cardiovascular fitness than strength training

Progression: Over time, the body adapts to exercise. For continued improvement, the volume or intensity of training must be increased	Stated exercise program was progressive and outlined training progression	Increase duration of walking program by 5% every two weeks depending on exercise tolerance
Overload: For an intervention to improve fitness, the training volume must exceed current habitual physical activity and/or training levels	Rationale provided that program was of sufficient intensity/exercise prescribed relative to baseline capacity	Prescribing intensity in a resistance training program based on % of measured and/or estimated 1-repetition maximum
Initial values: Improvements in the outcome of interest will be greatest in those with lower initial values	Selected population with low level of primary outcome measure and/or baseline physical activity levels	Selecting a sample with high baseline fatigue levels to participate in an aerobic training program to increase cardiovascular fitness and reduce fatigue
Reversibility: Once a training stimulus is removed, fitness levels will eventually return to baseline	Performed follow-up assessment on participants who decreased or stopped exercise training after conclusion of intervention	Participants who maintained training after a supervised exercise program preserved strength whereas those who stopped exercising returned to baseline
Diminishing returns: The expected degree of improvement in fitness decreases as individuals become more fit, thereby increasing the effort required for further improvements. Also known as the 'ceiling effect'	Performed follow-up assessment of primary outcomes on participants who continued to exercise after conclusion of intervention	Gains in muscle strength are greatest in the first half of a training program unless the training stimulus continually increases

(Campbell et al., 2012; Neil-Sztramko et al., 2017; Winters-Stone et al., 2014)

It is necessary for exercise RCTs to clearly report the trial design and adherence to the exercise prescription in order for the cumulative dose of exercise attained to be established in subsequent systematic reviews that are aimed at determining the efficacy of exercise for cancer patients. The FITT (frequency, intensity, time and time) components, and the adherence to each component need to be clearly reported. Without full and accurate details of trial design and exercise prescriptions in relation to the principles of training and the intended cancer population, the dose-response of exercise and ability of the exercise programs to be effectively reproduced, analyzed and translated into practice will remain unclear. Thus, the purpose of this systematic review is to summarize randomized controlled exercise trials in individuals diagnosed with lung cancer while evaluating: 1) the principles of exercise training in the design of the exercise prescription; 2)

methodological reporting of the FITT (frequency, intensity, time and type) components of the exercise prescription; 3) adherence of participants to the FITT prescription.

Methods

This systematic review followed the same protocol as previously published reviews (Campbell et al., 2012; Neil-Sztramko et al., 2019; Neil-Sztramko et al., 2017; K.M. Winters-Stone et al., 2014). A search of Medline, CINAHL, SPORTDiscus and EMBASE databases was conducted with dates ranging from January 1 2012 to November 7 2018. The search terms, as previously used, included cancer (neoplasm, carcinoma) and exercise (physical activity, aerobic, resistance, walking) specified for each database, in combination with the AND term. Studies of lung cancer patients from our previous review of cancer types other than breast (K.M. Winters-Stone et al., 2014) were extracted and included in this review. Only English-language publications were included. Other systematic reviews of lung cancer patients were manually searched for relevant publications for inclusion (Cavalheri & Granger, 2017; Cavalheri, Tahirah, Nonoyama, Jenkins, & Hill, 2014; Sommer et al., 2018).

Eligibility criteria included: 1) RCTs with one or more arms involving at least four weeks of aerobic and/or resistance exercise; 2) reported one physiological outcome related to exercise (e.g. aerobic capacity, muscular strength, physical function, body composition); 3) included lung cancer patients of any stage diagnosis or treatment status. Exclusion criteria included: 1) alternative forms of exercise (i.e. yoga, Pilates or tai chi) or complimentary alternative methods (i.e. physical therapy, stretching); 2) studies not exclusive to lung cancer patients; 3) studies that focused on physical activity and/or nutrition behaviour change. Unlike our previous reviews, this review did not exclude prehabilitation interventions, as prehabilitation is particularly common in the lung cancer population.

Two reviewers (MM, SNS) independently determined eligibility using an online software system (Covidence Systematic Review software, Veritas Health Innovation, Melbourne, Australia). Independently, reviewers assessed titles and abstracts for study eligibility, and full-text versions of relevant papers were then reviewed for inclusion. Discrepancies were discussed and resolved by the input of a third team member (KC/KWS) as required.

Two reviewers (MM and KB) independently extracted the data using the online software system, followed by a discussion and resolution of discrepancies between reviewers. Data extraction included: sample size, timing of intervention delivery (before, during, or after treatment), treatment type, duration and mode of intervention delivery (supervised or home-based), timing of follow-up measures, primary and secondary outcomes, and study findings. "FITT" (*frequency* of sessions per week, relative or absolute *intensity* of exercise, *time*/duration of exercise, and *type* of exercise) was used to summarize the exercise prescription. Adherence of the sample to each of the FITT principles was obtained to determine the dose of exercise achieved.

For each exercise principle, reviewers used a pre-determined rating system where a '+' was assigned if the principle was comprehensibly reported, a 'NR' was assigned if it was evident that the principle was not used in the exercise prescription and a '?' was assigned if the principle was mentioned but the description would not have allowed for replication of the prescription or was otherwise unclear. These ratings were also applied to the reporting of participant the FITT components of the exercise prescription, and adherence to the prescription. Within multi-arm trials, the application of principles of exercise training and the FITT components were evaluated separately for each intervention arm meeting our eligibility criteria. For the single study included in our previous reviews across all cancer types (Arbane, Tropman, Jackson, & Garrod, 2011), no new publications from the same trial/data set were identified, thus the same ratings were included

in the present review. Following the same methods as our previous review, counts of studies meeting the criterion for each exercise principle were reported.

Results

The screening and selection process of articles in this paper is detailed in Figure 1. Since our previous search in 2011 (Winters-Stone et al., 2014), 15 publications reporting on 14 studies were identified and included here. One multi-arm trial included two distinct interventions, thus a total of 16 interventions are reported and evaluated here and herein referred to as trial arms (Table 2). Thirteen trial arms (81.3%) prescribed combined aerobic plus resistance exercises (Arbane et al., 2014; Arbane et al., 2011; Brocki et al., 2014; Cavalheri et al., 2017; Edvardsen et al., 2015; Granger, Chao, McDonald, Berney, & Denehy, 2013; Henke et al., 2014; Licker et al., 2017; Salhi et al., 2015; Sebio Garcia et al., 2017; Sommer et al., 2016; Stigt et al., 2013), while three (18.8%) trial arms prescribed aerobic exercise only (Hoffman et al., 2017; Hwang, Yu, Shih, Yang, & Wu, 2012; Morano et al., 2013). No trial arms prescribed resistance training only. Twelve (75%) trial arms compared aerobic and/or combined aerobic plus resistance exercise versus usual care (Arbane et al., 2014; Arbane et al., 2011; Brocki et al., 2014; Cavalheri et al., 2017; Edvardsen et al., 2015; Granger et al., 2013; Henke et al., 2014; Hoffman et al., 2017; Hwang et al., 2012; Licker et al., 2017; Sebio Garcia et al., 2017; Stigt et al., 2013), one (7%) trial arm compared aerobic exercise versus standard post-operative chest physiotherapy treatment (Morano et al., 2013), one (7%) trial arm compared exercise versus whole body vibration training versus usual care (Salhi et al., 2015) and one trial arm was a comparative effectiveness trial comparing timing of exercise (Sommer et al., 2016). Three trial arms (19%) were pre-habilitative (i.e. intervention before surgery) (Licker et al., 2017; Morano et al., 2013; Sebio Garcia et al., 2017), ten (63%) trial arms intervened following surgery (Arbane et al., 2014; Arbane et al., 2011; Brocki et al., 2014;

Cavalheri et al., 2017; Edvardsen et al., 2015; Granger et al., 2013; Hoffman et al., 2017; Salhi et al., 2015; Stigt et al., 2013), one (6%) trial arm was conducted during the perioperative period (i.e. before and after surgery) (Sommer et al., 2016), one trial arm was conducted exclusively during chemotherapy (Henke et al., 2014) and one during targeted therapy after completing various combinations of treatments (Hwang et al., 2012). The length of studies varied from 25 days to 20 weeks, some with post-intervention follow up periods lasting up to 52 weeks.

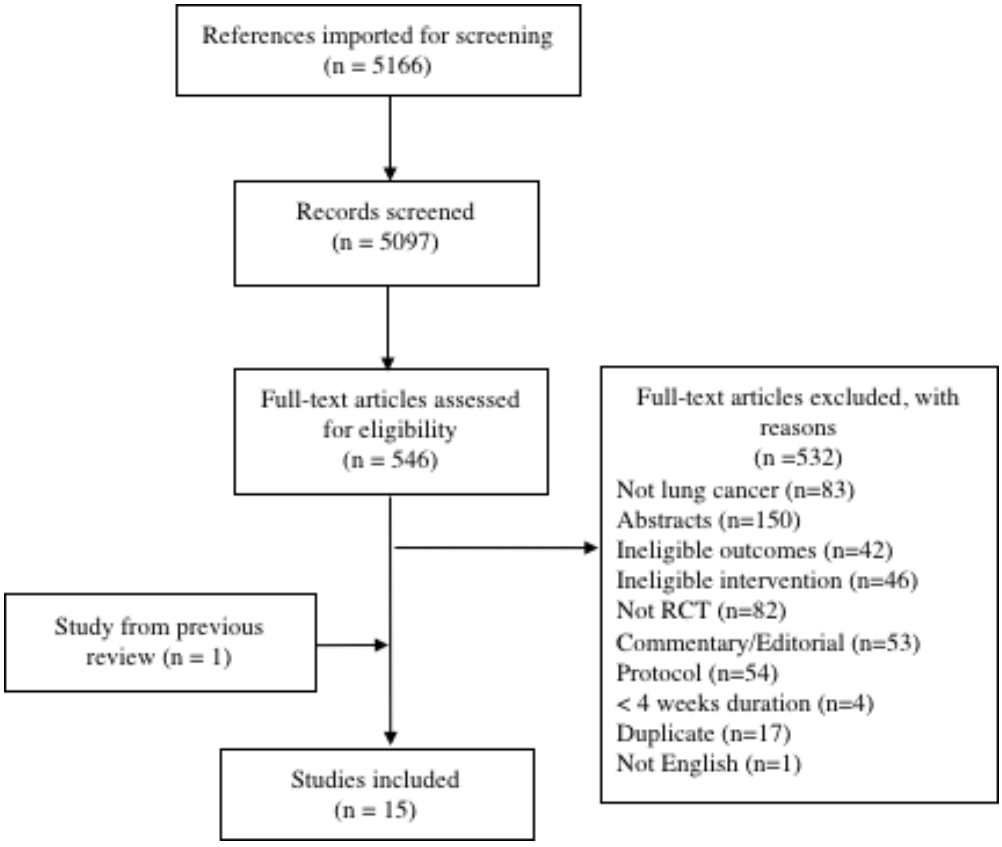

Figure 1. Flow chart of study selection process.

Table 2

Description of Studies

Reference	Timing	Tx Type	N	Intervention Setting	Length (weeks)	Primary Outcome (Tool)	Other Outcomes (Tool)
				Combined Aerobic + Resistance Exercise			
Arbane et al. (2011)	1 day post-op	C/S	53	Sup + home	12	Aer capacity (6MWT), strength (magnetic stimulation)	BMI, length of stay, post-op complications
Arbane et al. (2014)	1 day post-op	S	131	Sup + home	4	Physical activity (actigraphy)	Aer capacity (shuttle walk), lower body strength, length of stay, post-op complications
Brocki et al. (2014)	3 weeks post-op	S	78	Sup + home	10	QOL	Aer capacity (6MWT), Pulmonary function (FEV1, FVC, FEV1/FVC)
Cavalheri et al. (2017)	6-10 weeks post-op	S ±C	17	Sup	8	Aer capacity (CPET)	Aer capacity (6MWT), fatigue, handgrip strength
Edvardsen et al. (2015)	4-6 weeks post-op	S ±C/R	61	Sup	20	Aer capacity (CPET)	Spirometry, MVV, Tlco, hip + knee strength (1RM), muscle mass, chair stands, steps, balance, dyspnea
Granger et al. (2013)	1 day post-op	S ±C	15	Sup + home	12	Safety + feasibility	Aer capacity (6MWT), TUG
Henke et al. (2014)	During	C	29	Sup	3 cycles of C	ADLs	Aer capacity (6MWT), stair climbing, strength, dyspnea (MBS)
Licker et al. (2017)	Pre-op	S ±C	151	Sup	Median 25 days	Post-op morbidity	Aer capacity (6MWT + VO_2peak, AT, HRmax), post-op complications, length of stay, ICU admission
Salhi et al. (2015)	8 days post- op	S ±C/R	70	Sup	12	Aer capacity (6MWT)	Spirometry, diffusion capacity, Aer capacity (Wmax, VO_2max), handgrip + leg strength, fatigue, pain, dyspnea
Sebio Garcia et al. (2017)	Pre-op	S	22	Sup	Mean 54 days	Aer capacity (constant load test)	Aer capacity (6MWT), 30s chair stands, arm curl test, length of stay, post-op complications
Sommer et al. (2016)	Pre-op + post-op Post-op only	S ±C	40	Sup + home Aer + Res	Varied 12	Safety and feasibility	Aer capacity ($V0_2$peak, 6MWT, O_2 delivery), pulmonary function, muscle strength, disease related outcomes
Stigt et al. (2013)	4 weeks post-op	S ±C	49	Sup	12	QOL	Pulmonary function (FEV1, FVC), aer capacity (6MWT)
				Aerobic Exercise Only			

Hoffman et al. (2017)	4 days post-hospital discharge	S ±C	73	Home	6	Feasibility	Fatigue, aer capacity (6MWT)
Hwang et al. (2012)	Receiving targeted therapy	T	24	Sup	8	Aer capacity ($V0_2$peak)	Muscle oxygenation (NIRS), insulin resistance, c-reactive protein, BMI, muscle strength, endurance (knee flexor/extensor)
Morano et al. (2013)	Pre-op	S	24	NR	4	NR	Spirometry, MIP, MEP, Aer capacity (6MWT), blood gas parameters, length of stay, post-op complications

1RM, one-repetition maximum; 6MWT, six-minute walk test; ADLs, activities of daily living; Aer. Aerobic; BMI, body mass index; C, chemotherapy; CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRQOL, health-related quality of life; ICU, intensive care unit; IMT, inspiratory muscle training; MBS, modified Borg scale; MVV, maximum voluntary ventilation; NIRS, near-infrared spectroscopy; NR, not reported; QOL, quality of life; S, surgery; Sup, Supervised; T, targeted therapy; Tlco, carbon monoxide transfer factor; TUG, timed-up-and-go; Tx, treatment; WBVT, whole-body vibration training; Wmax, maximum watts.

Application of the Principles of Exercise Training in Intervention Design

The principles of exercise training were inconsistently applied in the design of exercise intervention programs (Figure 2). *Specificity* was included in all but one trial arm (94%) (Stigt et al., 2013). *Progression* was clearly included in seven trial arms (44%) (Brocki et al., 2014; Granger et al., 2013; Henke et al., 2014; Hoffman et al., 2017; Morano et al., 2013; Sebio Garcia et al., 2017; Sommer et al., 2016) but was unclear in six (37%) (Arbane et al., 2014; Cavalheri et al., 2017; Edvardsen et al., 2015; Hwang et al., 2012; Licker et al., 2017; Sommer et al., 2016) and not included in three (19%) (Arbane et al., 2011; Salhi et al., 2015; Stigt et al., 2013) others. *Overload* was included in 11 (69%) trial arms (Arbane et al., 2014; Brocki et al., 2014; Cavalheri et al., 2017; Granger et al., 2013; Henke et al., 2014; Licker et al., 2017; Morano et al., 2013; Salhi et al., 2015; Sebio Garcia et al., 2017; Sommer et al., 2016) but was unclear in three (19%) (Edvardsen et al., 2015; Hwang et al., 2012; Stigt et al., 2013) and not reported in two (12%) trial arms (Arbane et al., 2011; Hoffman et al., 2017). Three trial arms (19%) did not apply the principle of *initial values* (Arbane et al., 2011; Licker et al., 2017; Morano et al., 2013), and one trial arm (Sommer et al., 2016) (6%) was unclear in its attention to initial values. The remaining 12 (75%) trial arms clearly attended to the principle of initial values. *Reversibility* and *diminishing returns* were not applied appropriately or described fully in any of the trial arms; however, five (31%) trial arms applied *reversibility* (Brocki et al., 2014; Sebio Garcia et al., 2017; Sommer et al., 2016; Stigt et al., 2013) and *diminishing returns* (Brocki et al., 2014; Sebio Garcia et al., 2017; Sommer et al., 2016; Stigt et al., 2013), respectively in an unclear manner.

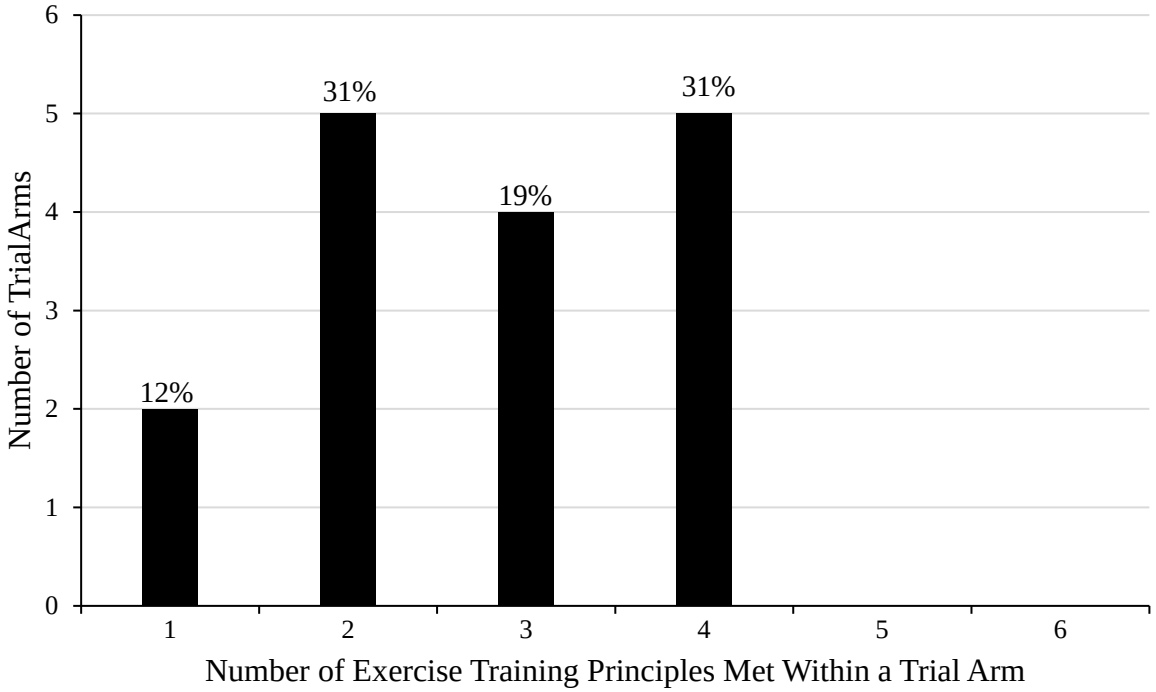

Figure 2. Count of exercise training principles met within a trial arm.

Six exercise training principles was the maximum

Table 3

Utilization of the Principles of Exercising Training and Significant Outcomes in Exercise Interventions in Lung Cancer Patients

Reference	Specificity	Progression	Overload	Initial Values	Reversibility	Diminishing Returns	Significant Results**
				Combined Aerobic + Resistance Training			
Arbane et al. (2011)	+	NR	NR	NR	NR	NR	↑strength (inpatient only)
Arbane et al. (2014)	+	?	+	+	NR	NR	Null
Brocki et al. (2014)	+	+	+	+	?	?	Null
Cavalheri et al. (2017)	+	?	+	+	NR	NR	↑VO_{2peak}*, ↑6MWT
Edvardsen et al. (2015)	+	?	?	+	NR	NR	↑VO_{2peak}*, ↑Tlco, ↑1RM leg, ↑stair climb, ↑chair stands, ↑BMI, ↑LM
Granger et al. (2013)	+	+	+	+	NR	NR	↑TUG, ↑6MWT
Henke et al. (2014)	+	+	+	+	NR	NR	↑ADL*, ↑6MWT, ↑stair climb, ↑strength
Licker et al. (2017)	+	?	+	NR	NR	NR	↑VO_{2peak}, Peak WR ↑6MWT, ↓PC, ↓atelectasis, ↓LoS
Salhi et al. (2015)	+	NR	+	+	NR	NR	↑6MWT*
Sebio Garcia et al. (2017)	+	+	+	+	?	?	3-month FU: ↑aer capacity*, ↑arm curls, ↑chair stand
Stigt et al. (2013)	NR	NR	?	+	?	?	↑6MWT (3 mo)
				Aerobic Training			
Hoffman et al. (2017)	+	+	NR	+	NR	NR	↑6MWT
Hwang et al. (2012)	+	?	?	+	NR	NR	↑VO_{2peak}*, ↑work load, ↑TV
Morano et al. (2013)	+	+	+	NR	NR	NR	↓Post-operative morbidity, ↓LoS, ↓chest tube use
				Multi-Armed Trial			
Sommer et al. (2016) (Pre+Post-op)	+	?	+	?	?	?	Not analyzed***
Sommer et al. (2016) (Post-op)	+	+	+	+	?	?	Not analyzed***

*Primary outcome, **Significant results for physiological outcomes between groups only. ***Analysis not yet conducted on efficacy outcomes.
+, the principle was clearly reported; ?, the principle was unclear; NR, the principle was not reported; 6MWT, 6 minute walk test; BMI, body mass index; HR, heart rate; LM, lean mass; LoS, hospital length of stay; PC, pulmonary complications; PF, physical function; PN, peripheral neuropathy; QoL, quality of life; Tlco, carbon monoxide transfer factor; VO_{2peak}, peak volume of oxygen consumed.

Reporting the FITT Components of the Exercise Prescription

Eleven trial arms adequately reported on all of the components of the exercise prescription (Figure 3). Fifteen (94%) trial arms reported a prescribed *frequency*, while one (6%) trial arm was unclear about how often patients were expected to exercise (Arbane et al., 2011). Two trial arms (12%) were unclear in reporting a prescribed *intensity* (Arbane et al., 2011; Stigt et al., 2013), while the remaining 14 trial arms (88%) clearly reported the prescribed intensity (Arbane et al., 2014; Brocki et al., 2014; Cavalheri et al., 2017; Edvardsen et al., 2015; Granger et al., 2013; Henke et al., 2014; Hoffman et al., 2017; Hwang et al., 2012; Licker et al., 2017; Morano et al., 2013; Salhi et al., 2015; Sebio Garcia et al., 2017; Sommer et al., 2016). The prescribed amount of *time* of exercise was reported by 12 trial arms (75%) (Brocki et al., 2014; Cavalheri et al., 2017; Granger et al., 2013; Henke et al., 2014; Hoffman et al., 2017; Hwang et al., 2012; Licker et al., 2017; Morano et al., 2013; Salhi et al., 2015; Sebio Garcia et al., 2017; Sommer et al., 2016), but was unclear in three trial arms (18%) (Arbane et al., 2014; Arbane et al., 2011; Edvardsen et al., 2015) and not reported in one trial arm (6%) (Stigt et al., 2013). Three trial arms (19%) were unclear in reporting the prescribed *type* of exercise (Arbane et al., 2011; Sommer et al., 2016; Stigt et al., 2013), while the remaining 13 trial arms (81%) clearly reported the prescribed type of exercise (Arbane et al., 2014; Brocki et al., 2014; Cavalheri et al., 2017; Edvardsen et al., 2015; Granger et al., 2013; Henke et al., 2014; Hoffman et al., 2017; Hwang et al., 2012; Licker et al., 2017; Morano et al., 2013; Salhi et al., 2015; Sebio Garcia et al., 2017; Sommer et al., 2016).

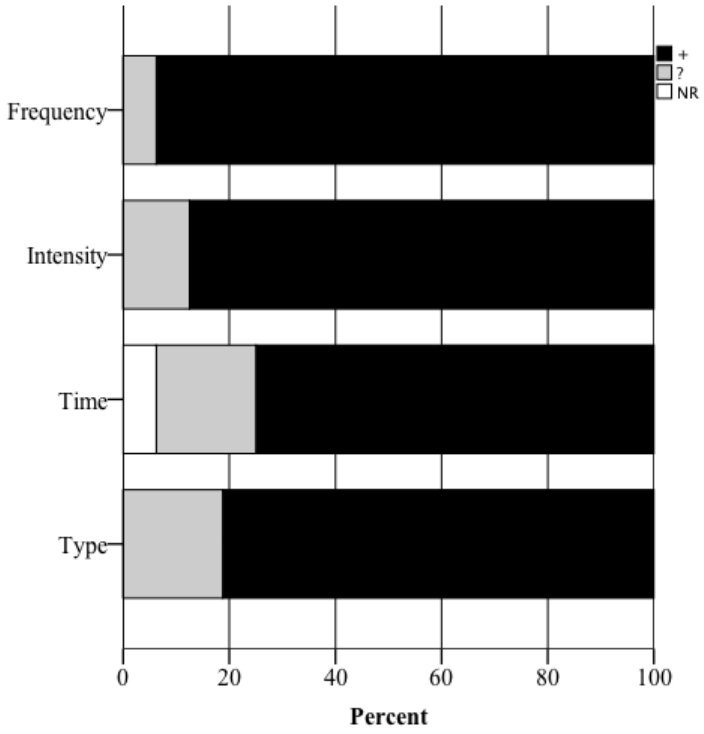

Figure 3. Reporting of components of exercise prescription.

Black=component was clearly reported; grey=component was not clearly reported; white=component was not reported

Reporting Adherence to the FITT Components of Exercise Prescription

Reporting on adherence to the component of the exercise prescription was inconsistent (Figure 4). Adherence to the prescribed frequency was clearly reported in 12 (75%) trial arms (Brocki et al., 2014; Cavalheri et al., 2017; Edvardsen et al., 2015; Granger et al., 2013; Hoffman et al., 2017; Hwang et al., 2012; Licker et al., 2017; Morano et al., 2013; Sebio Garcia et al., 2017; Sommer et al., 2016; Stigt et al., 2013), unclear in one trial arm (6%) (Salhi et al., 2015) and not reported in three trial arms (19%) (Arbane et al., 2014; Arbane et al., 2011; Henke et al., 2014). Only one trial arm (6%) adequately reported adherence to the prescribed exercise intensity (Edvardsen et al., 2015). Three interventions were unclear in their reporting of adherence to intensity (Brocki et al., 2014; Sommer et al., 2016) and the remaining 12 trial arms (75%) did not report adherence to intensity at all. No study adequately reported adherence to the duration or type of exercise prescribed. One trial arm was unclear in reporting of adherence to time (6%) (Arbane et al., 2011) and two trial arms within the same study were unclear in their reporting of adherence to type of exercise (13%) (Sommer et al., 2016).

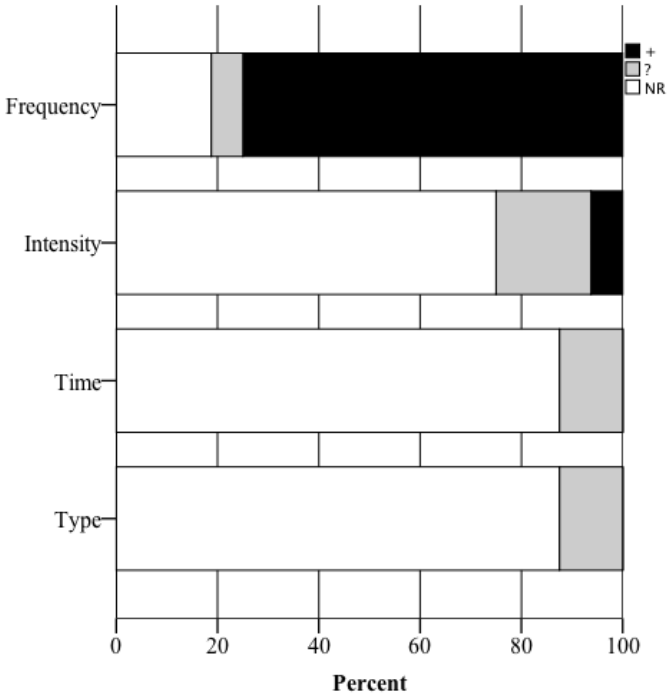

Figure 4. Reporting of adherence to components of exercise prescription.

Black=component was clearly reported; grey=component was not clearly reported; white=component was not reported.

Discussion

Since our previous systematic review of attention to exercise training principles that included only one exercise study in lung cancer patients (Winters-Stone et al., 2014), 14 additional studies in lung cancer patients were published. The increase in the number of studies examining the efficacy of exercise to improve physical outcomes in lung cancer patients demonstrates the increasing recognition of exercise as a potential therapeutic strategy to mitigate negative consequences of the disease and its treatments in this population (Johnsen, Petersen, Pedersen, & Groenvold, 2009). Just over half of trial arms prescribed a combination of aerobic plus resistance training after surgery, and two prescribed aerobic plus resistance training preoperatively only, or

in the perioperative phase. Three trial arms prescribed aerobic exercise alone preoperatively, postoperatively and during targeted therapy (Hwang et al., 2012). Only one trial arm specifically tested the benefits of exercise during chemotherapy. Despite the increased number of trial arms conducted, the inclusion of pre-operative intervention designs, and the broader range of treatment types included beyond surgery, the trial arms summarized in this review have not consistently incorporated the principles of exercise training into the design of interventions (Figure 2). Though the FITT components of exercise protocols were generally well reported in the study methods, adherence to each component was rarely reported (Figures 3-4).

Reporting of the Principles of Exercise Training

Specificity was the most frequently reported principle of exercise training, with all but one trial arm clearly reporting how the training mode was specific to the primary outcome. In this review, the exercise interventions were primarily combined aerobic and resistance training with the goal of improving post-operative outcomes such as pulmonary function and aerobic exercise capacity, thus the principle of specificity was well applied.

The principle of *progression* was sufficiently reported in 44% of the trial arms, but was unclear in 37% of studies and was not reported in 19% of studies. One trial arm clearly prescribed a progressive in-hospital exercise program (length ~5 days), however upon discharge the 4-week prescription given to participants did not describe any program progression (Arbane et al., 2014). Without more progression, the benefits of exercise may begin to plateau and limit the degree of change that can be expected from more training. Progression was also differentially reported by type of intervention. Two trial arms of combined training modalities clearly reported progression for the aerobic component of the prescription, but not for the resistance training component (Cavalheri et al., 2017; Licker et al., 2017), while other trial arms did not report any progression

(Arbane et al., 2011; Salhi et al., 2015; Stigt et al., 2013). It remains unclear whether training programs that did not employ progression were adequate enough to produce desired improvements.

The principle of *overload* was clearly reported in a good proportion (69%) of trial arms, but was unclear or not reported in just under one-third of trials. Overload was ensured in the majority of studies by prescribing exercise per each individual's levels of baseline fitness. Trial arms that did not adequately report whether or not sufficient overload might be occurring across a program risk failing to see a response from exercise as a result of an insufficient exercise stimulus. Again, there was differential reporting by type of intervention, with some trial arms that clearly included the principle of overload in the aerobic component of the prescription but did not prescribe in the resistance training component off of a baseline test (Edvardsen et al., 2015; Stigt et al., 2013). Employing overload in the resistance training component of the prescription may be of particular importance, given the high prevalence of sarcopenia and cachexia in patients with lung cancer, and potentially greater need for an adequate resistance training stimulus to maintain or improve muscle function and mass during and post-treatment.

The principle of *initial values* was only well reported in a quarter of the trial arms. By screening out participants who are already physically fit or who have high (i.e. positive) baseline values of the primary outcome measure (i.e. fatigue, depressive symptoms), a ceiling effect in adaptations to training may be avoided. To test the efficacy of an exercise prescription, eligibility criteria to target individuals that are most in need (i.e. inactive, less physically fit, severe symptoms that are study outcomes) are necessary.

None of the trial arms clearly included the principles of *reversibility* and *diminishing returns*. In order to include both of these principles, at least one follow-up period beyond the immediate completion of the exercise intervention must have been included. Without the principles

of *reversibility* and *diminishing returns*, it is not possible to demonstrate that participants will be absent of exercise-related improvements once they stop exercising and that improvements decrease as participants become more physically fit. One trial arm included multiple follow-up periods but only for self-reported QoL rather than including physical assessments (Stigt et al., 2013), and a second trial arm did not report or control for exercise levels during the 3-month follow up period, thus the principles of *reversibility* and *diminishing returns* were not adequately applied. Particularly in the lung cancer population where surgical resection is the most effective treatment option (Sherwood & Brock, 2007), making pre to post-operative exercise interventions prevalent, it is important to know the time course of which exercise may be particularly beneficial, and what dose of exercise must be sustained for the benefits of exercise to persist over time.

Reporting and Adherence to the FITT Components of Exercise Prescription

The FITT components were better reported in studies of lung cancer than in previous studies in breast (Neil-Sztramko et al., 2017) and prostate (Neil-Sztramko et al., 2019) cancers. Eleven trial arms adequately reported on all of the FITT components in the prescribed exercise program, with the *frequency* and *intensity* being the two most commonly reported with nearly all (94% and 88%) of trial arms reporting on each component, respectively. Two trial arms that were unclear of the *intensity* reported the intensity for the aerobic but not the resistance training component of the intervention (Arbane et al., 2011; Stigt et al., 2013). It is important to be consistent with reporting each component of the exercise prescription so that the dose of prescriptions that combine aerobic and resistance training can be established. The amount of *time* prescribed exercising in a session was generally well reported, with only 18% of trial arms unclearly reporting time. Similarly, the *type* of exercise prescribed was well reported, with only

18% of trial arms unclearly reporting the type of exercise prescribed. Vague terms (i.e. muscle training (Stigt et al., 2013) and adapted home strengthening program "relevant to patient hobbies" (Arbane et al., 2011)) were used to describe the type of exercise and thus would not allow for the exercise programs to be replicated. Overall, the FITT components were generally well described, particularly in trial arms of aerobic training. Future trial arms of both aerobic and combined aerobic plus resistance training should report more precise FITT prescriptions for resistance training so that the dose of exercise prescribed could be clearly determined and implemented into practice.

Though sometimes challenging to quantify, reporting on adherence to the prescribed FITT components is important in order to know the actual dose of exercise that participants achieved. Otherwise, the efficacy of exercise for lung cancer patients may not truly be reflected because the received dose may be different from the prescribed dose and thus participants could "undertrain". On the other hand, a lower received dose of exercise could be as effective as the prescribed dose but more feasible and realistic for a given patient population. Consistent with previous findings in breast (Neil-Sztramko et al., 2017) and prostate (Neil-Sztramko et al., 2019) cancer patients, none of the trial arms included in this review adequately reported on adherence to all components of the exercise prescription (Figure 3). Adherence to the prescribed *frequency* was the most commonly reported component, with 75% of trial arms adequately describing participant attendance, though frequency does not provide enough information to quantify the dose of exercise attained. Most trial arms (88%) did not report adherence to the prescribed exercise *intensity,* though one trial arm described the average percent of one-repetition maximum attained, however the percent of time spent at that intensity was not reported (Sommer et al., 2016). None of the studies reported adherence to the prescribed *time* nor *type* of prescribed exercise. Details of the number of minutes participants were able to complete and what types of modifications were provided could be

reported in order to improve what is known about the ability of lung cancer survivors, a vulnerable and less studied population, to adhere to an exercise prescription. Future studies should be designed so that the adherence of each component could be reported (i.e. track attendance, monitor intensity objectively or by self-report, record minutes of exercise completed, track modifications to type of exercise prescribed). Reporting the adherence to a prescribed exercise intervention is necessary in order for studies to be replicated, a necessary step to determine the true efficacy of exercise for lung cancer patients. Additionally, reporting the adherence to a prescribed program is important for implementation as efficacy trials begin to be translated and implemented into cancer care.

Limitations

There are limitations to this systematic review. Authors were not contacted to gather missing information, and it is possible that word and page limits were a barrier to reporting full details and results of the trials. As a result, some of the trials included in this review may have adhered to the principles of exercise training, but could not clearly report them. For this it is recommended that full details of the exercise prescription are published in tables or supplemental documents. We recognize that it can be logistically challenging to track the compliance to each of the FITT components due to the financial feasibility that may limit study design (i.e. studies with multiple long term follow ups) or resources (i.e. actigraphs) to quantify compliance to each component. As lung cancer survivorship continues to improve and the number of exercise trials specific to lung cancer patients increases, it is vital that the principles of exercise training and FITT components are rigorously adhered to and reported so that exercise guidelines specific to lung cancer survivors can be developed and implemented into practice.

The number of studies to determine the efficacy of exercise for physical outcomes in lung cancer patients has increased with 14 new studies published in the past seven years and are conducted most commonly during the pre-operative and post-operative time period. Cumulatively the current exercise studies in lung cancer have not demonstrated strong efficacy for exercise in this population (Cavalheri & Granger, 2017; Cavalheri et al., 2014; Sommer et al., 2018). Our review of the literature demonstrates that the principles of exercise training and FITT components are inconsistently utilized and reported in exercise RCTs and thus may contribute to the variability in findings about the efficacy of exercise for lung cancer patients. The results of the present systematic review illustrate the opportunity for investigators to strengthen the field by designing and reporting exercise prescriptions based on the principles of training and FITT components. To determine the dose of exercise that lung cancer patients receive in exercise interventions, the adherence to the FITT components need to be reported. In order to aid in the development of exercise guidelines that could be translated safely and effectively into clinical practice and community settings for lung cancer survivors, rigorously designed and reported exercise RCTs are necessary.

Chapter IV: Attention to the Principles of Exercise Training in Physical Yoga Interventions in Cancer Survivors

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This manuscript replaces portions of the methods section and results section of the traditional dissertation. Ms. Medysky will be the primary author on this paper; Dr. Winters-Stone will be the senior author on this paper. Ms. Medysky will conduct the literature search and describe the methods and results. Ms. Medysky and Dr. Chowdhury will determine articles for inclusion and extract the data. This paper will be submitted to British Journal of Sports Medicine, which is an indexed and peer-reviewed journal with an impact factor of 7.867. This journal focuses on a model of comprehensive cancer treatment that includes conventional therapies coupled with integrative therapies such as lifestyle and exercise. This manuscript will be submitted prior to the defense of the dissertation (note: for ease of submission, manuscript drafted in the past tense).

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Declaration of Conflict of Interest
None Declared

Key Words: neoplasm; systematic-review; complementary therapies; muscle stretching exercises

Abstract

Introduction: Previous systematic reviews of yoga interventions in cancer survivors have summarized and described the yoga programs and preliminary efficacy, but no study to date has systematically categorized the various types of yoga programs with attention to the principles of exercise straining and reporting components. **Purpose:** To summarize physical yoga trials in cancer survivors on the following: 1) attention to the principles of exercise training (e.g., specificity, overload, initial values, reversibility, diminishing returns) in the design of the exercise prescription; 2) methodological reporting of the FITT (frequency, intensity, time and type) components of the exercise prescription; 3) reporting on adherence of participants to the prescribed FITT. **Methods:** A systematic search of Pubmed, CINAHL, and Sport Discus databases was conducted databases was conducted. Randomized controlled trials of physical yoga in were included. **Results:** Of 25 studies included, none incorporated all of principles of exercise training. Across all studies, *specificity* was included by 100%, *progression* by 12%, *overload* by 0%, and *initial values* by 72%, while 8% considered the principles of each *reversibility* or *diminishing returns*. No studies clearly reported all of the FITT components in the methods nor the adherence to each component in the results. **Conclusions:** Studies of yoga did not uniformly apply the principles of exercise training nor the FITT components and adherence to each component. Including the principles of exercise training and reporting on the FITT components will contribute to a better understanding of the efficacy of exercise for lung cancer patients and ultimately inform effective exercise prescriptions for this patient population.

Introduction

Yoga is an emerging strategy for improving both physical and psychosocial side-effects of cancer and its treatment. A recent systematic review of randomized controlled yoga trials in cancer survivors reported on 29 studies during and after cancer treatment, most commonly in breast cancer survivors (Danhauer et al., 2019). Studies have prescribed the multiple components of yoga that range from breathing exercises (Pranayama), progressively deeper states of concentration (Dharana), meditation (Dhyana) and physical postures (Asanas). At least 52 different styles of yoga exist (Holger Cramer, Lauche, Langhorst, & Dobos, 2016), making it difficult to classify, compare and reproduce studies of yoga. Some styles of yoga do not include physical body movements and instead focus on breathing exercises, meditation, and relaxation based on ancient Indian text, such as Swami Vivekananda Yoga Anusandhana Samasthana (SVYASA) (Villacres, Jagannathan, Nagarathna, & Ramakrsihna, 2014). Other styles of physical yoga require planned repetitive bouts of movement that include muscular contractions and passive lengthening of the body's muscle groups to stretch and strength the muscles such as Hatha and vinyasa yoga.

The different components of yoga have been applied to address symptoms of cancer and its treatment and related side effects. Breathing exercises have been used to strengthen the respiratory muscles, particularly in cancer types where lung function is compromised (Barassi et al., 2018) and for improvements in fatigue, sleep disturbance, anxiety, and stress (Chakrabarty et al., 2015; Dhruva et al., 2012). Components of yoga that focus on concentration and meditation have been applied to address psychosocial aspects of cancer survivorship, such as reducing anxiety, depressive symptoms, and stress (Vadiraja et al., 2009) and improving self-esteem (Kovacic & Kovacic, 2011). Physical yoga that employs postures to stretch and strengthen the muscles has been used to improve physical function (Annette Loudon, Barnett, Piller, Immink, &

Williams, 2014b; Yağlı et al., 2015), fatigue (Ben-Josef et al., 2017; Winters-Stone et al., 2018b), quality of life (Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Culos-Reed, Carlson, Daroux, & Hately-Aldous, 2006) and sleep (Mustian et al., 2013). Styles of yoga that apply physical postures requiring elements of fitness (i.e. strength, flexibility, aerobic capacity) are similar to traditional aerobic and resistance training programs where improvements in physical function and psycho-social aspects of cancer survivorship are also investigated.

A strong body of evidence supports conventional aerobic and resistance training exercise programs to mitigate many side effects of cancer and its treatment (Buffart et al., 2017; Scott et al., 2018) and as such several exercise recommendations for these modes of training have been published (Cormie et al., 2018; Schmitz et al., 2010). Physical yoga that involves fitness elements similar to aerobic and resistance training, was not included in those recommendations and continues to be excluded from the most recent ACSM Roundtable exercise guidelines for cancer survivors (Campbell, et al., 2019, in press), despite an accumulation of evidence demonstrating positive improvements on fatigue, quality of life, sleep, anxiety, depressive symptoms and biomarkers of cortisol regulation and inflammatory markers (Danhauer et al., 2019). Yet, it is unknown if the inattention to the same training principles as aerobic and resistance exercise makes it unmanageable to systematically review and evaluate yoga alongside other forms for training, thus limiting the translation of yoga into standardized exercise recommendations.

To build a case for yoga's inclusion among evidence-based exercise recommendations, it should be prescribed similarly as other modes of training and should confirm to well established training principles. A first step in this process is a critical review of yoga interventions used in randomized controlled trials (RCTs) for following principles of specificity, overload, progression,

initial values, reversibility and diminishing returns (Table 1). Without using these basic principles, interventions may be unsuccessful and non-significant or erroneous findings about the efficacy of exercise may be reported (Campbell et al., 2012). Additionally, in order for trials to be reproduced and translated to practice, sufficient details of the exercise prescription (i.e. FITT components: frequency, intensity, time and type; Table 2) and adherence of participants the prescribed program should be reported. Several systematic reviews of aerobic and resistance training RCTs to improve physiological outcomes in cancer survivorship (i.e. physical function, body composition, physical fitness) have been conducted and have summarized the application of the training principles and reporting of FITT components and adherence (Campbell et al., 2012; Neil-Sztramko et al., 2019; Neil-Sztramko et al., 2017; Winters-Stone et al., 2014). Recommendations were made to strengthen the field of aerobic and resistance training studies yet it is unknown if the same principles and reporting components have been included in studies of yoga.

Table 1

Principles of Exercise Training and FITT Components Applied to Studies of Yoga

Principle	**Criteria for this review**	**Example Specific to Yoga**
Specificity: Training adaptations are specific to the organ system or muscles trained with exercise	Rationale provided that yoga may directly improve physical outcomes or mechanisms of psychosocial outcomes	Standing poses requiring muscular strength are more appropriate for a yoga intervention aimed at increasing lower body physical functioning
Progression: Over time, the body adapts to exercise. For continued improvement, the volume or intensity of training must be increased	Stated exercise program was progressive and outlined training progression	Poses progressed from seated in the first 6 weeks to standing poses for the following 6 weeks
Overload: For an intervention to improve fitness, the training volume must exceed current habitual	Rationale provided that program was of sufficient	Prescribing poses at an intensity relative to measured and/or estimated baseline testing

physical activity and/or training levels	intensity/exercise prescribed relative to baseline capacity	(i.e. chair stand test) or initial levels of yoga experience
Initial values: Improvements in the outcome of interest will be greatest in those with lower initial values	Selected population with low level of primary outcome measure and/or baseline physical activity levels	Selecting a sample with high baseline fatigue levels to participate in a yoga program to reduce fatigue
Reversibility: Once a training stimulus is removed, fitness levels will eventually return to baseline	Performed follow-up assessment on participants who decreased or stopped exercise training after conclusion of intervention	Participants who maintained training after a supervised yoga program preserved strength whereas those who stopped doing yoga lost strength
Diminishing returns: The expected degree of improvement in fitness decreases as individuals become more fit, thereby increasing the effort required for further improvements. Also known as the 'ceiling effect'	Performed follow-up assessment of primary outcomes on participants who continued to exercise after conclusion of intervention	Gains in muscle strength are greatest in the first half of a yoga program unless the training stimulus continually increases

Adapted from: Campbell et al., 2012; Neil-Sztramko et al., 2017; Winters-Stone et al., 2014

Table 2

FITT Components and Criteria Required Specific to Yoga Interventions

FITT Component	**Criteria for this Review**
Frequency	The number of yoga sessions per week was clearly stated
Intensity	The estimated intensity of the yoga program was described (i.e. rate of perceived exertion or heart rate)
Time	The length (i.e. minutes) of each yoga sessions was clearly stated
Type	Specific poses that could be replicated were reported

Previous systematic reviews of yoga interventions in cancer survivors have summarized and described the yoga programs and preliminary efficacy (Buffart et al., 2012; Danhauer et al., 2019), but ignored any attempt to systematically categorize the various types of yoga programs that could inform an overall exercise prescription based on the FITT formula. Thus, the purpose of this systematic review is to summarize the RCTs that assessed the efficacy of physical yoga in

cancer survivors on physiological and psychosocial outcomes while evaluating: 1) the principles of exercise training in the design of the yoga programs; 2) methodological reporting of the FITT (frequency, intensity, time and type) components of the yoga program; and 3) adherence of participants to the prescribed FITT components.

Methods

This systematic review followed the same protocol as similar published reviews (Campbell et al., 2012; Neil-Sztramko et al., 2019; Neil-Sztramko et al., 2017; Winters-Stone et al., 2014). On September 21st 2018 a search of Pubmed, CINAHL, and Sport Discus databases was conducted. The search terms included cancer (OR neoplasm, carcinoma) and yoga (OR yogic or asana) specified for each database, in combination with the AND term, with only studies written in English included. Systematic reviews of yoga for cancer survivors were manually searched for relevant publications for inclusion (Buffart et al., 2012; Danhauer et al., 2019; Sharma, Lingam, & Nahar, 2016).

Eligibility criteria included: 1) RCTs with one or more arms involving at least four weeks of yoga requiring purposeful active and passive muscular contractions to perform physical postures (i.e. poses/asanas) using the upper and lower body; 2) included cancer survivors of any type, stage, diagnosis or treatment status. Exclusion criteria were: 1) yoga studies including only meditation, breathing and/or deep relaxation/concentration. Different from previous reviews (Campbell et al., 2012; Neil-Sztramko et al., 2019; Neil-Sztramko et al., 2017; Winters-Stone et al., 2014) studies assessing both physiological and psychosocial outcome were included in the present review as the number of yoga studies to assess physiological outcomes were limited. The criteria for each of the principles of training were expanded to also include psychosocial outcomes as described in Table 1. Eligibility of each manuscript was determined by two independent reviewers (MM and TC)

using an online software system (Covidence Systematic Review software, Veritas Health Innovation, Melbourne, Australia). Titles and abstracts were assessed first for eligibility, and full-text versions of relevant manuscripts were then reviewed for inclusion in this review. Discrepancies between independent reviewers were discussed and resolved by a third team member (KWS) as required. Articles that included a secondary or supplemental analysis of an already published study were not counted as an additional study.

Data was extracted using the online software system by each independent reviewer, followed by a comparison and resolution of discrepancies between reviewers. Data extraction included: sample size, timing of yoga intervention delivery (before, during, or after treatment), cancer type, treatment type, duration and mode of yoga intervention delivery (supervised or home-based), timing of follow-up measures, primary and secondary outcomes, and study findings. To summarize the yoga prescription the "FITT" components (Table 2; *frequency* of sessions per week, relative or absolute *intensity* of exercise, *time*/duration of exercise, and *type* of exercise) were obtained. Adherence of the sample to each of the FITT components was extracted to establish the approximate dose of yoga that participants attained. Most studies suggested supplemental "at home yoga" which was not considered when applying ratings to the primary yoga prescription because of a lack of sufficient detail describing home training.

For each principle of exercising training (Table 1), a rating was assigned per the use of each principle by independent reviewers. If the principles clearly reported, a '+' was assigned, whereas 'NR' was assigned if it was clear that the principle was not applied in the yoga prescription. A '?' was assigned if the principle was mentioned but replicating the prescription would not be possible because the description was unclear or incomplete. These ratings were also

applied to the reporting of participant adherence to the prescription. Counts of studies meeting the criterion for each exercise principle were reported.

Results

The literature search identified 1649 potential articles, of which 25 were considered eligible for this review (Figure 1, summarized in Table 3). The majority of studies were group-based yoga programs (92%) and two studies used a home video based delivery approach (Stan, Croghan, Croghan, Jenkins, , et al., 2016; Winters-Stone et al., 2018b). Just over half of the studies (56%) "encouraged" supplemental home-based yoga practice, though the focus of the manuscripts that prescribed supplemental home-based practice was on describing the group-based yoga program. The yoga interventions ranged from 4-24 weeks long. Sample sizes ranged from smaller pilot samples (n=18) to fully powered multi-armed RCTs (n=356). Nineteen (76%) of the studies were conducted in breast cancer survivors (Anestin, Dupuis, Lanctot, & Bali, 2017), four studies included mixed types of cancer and a singular study was conducted in each colorectal and prostate cancers. The majority of studies (68%) included cancer survivors who had completed treatment, while six studies included individuals on treatment (24%) and two studies included survivors at any treatment phase (8%), with treatment types ranging from surgery only to include combinations of radiation, hormone and chemotherapies.

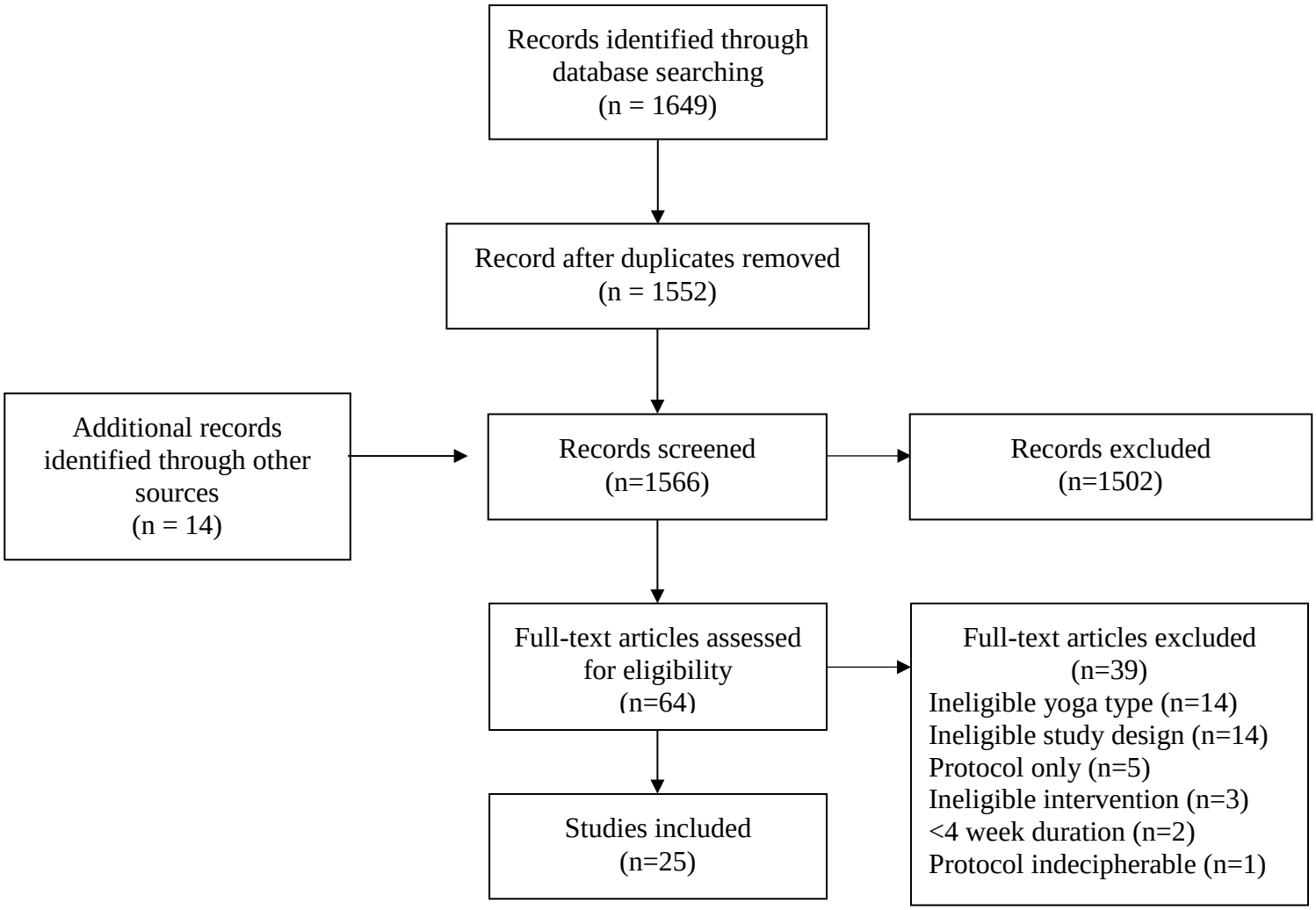

Figure 1. PRISMA diagram to illustrate flow of participants through study protocol.

Table 3. *Description of Studies*

Reference	**Cancer Type**	**Timing**	**Tx Type**	**N**	**Intervention**	**Intervention Length (weeks)**	**Primary Outcome**	**Other Outcomes**
Anestin, Dupuis, Lanctôt, & Bali (2017)	Breast	During	CT	82	Yoga vs WLC	8	Nausea, vomiting	Anxiety
Banasik, Williams, Haberman, Blank, & Bendel (2009)	Breast	After	NR	18	Yoga vs WLC	8	N/A	QOL, salivary cortisol, fatigue
Banerjee et al. (2007)	Breast	During RT	RT, S, CT	68	Yoga vs supportive counseling	6	Anxiety, depressive symptoms, stress	Radiation-induced DNA damage
Ben-Josef et al. (2017)	Prostate	During	RT	68	Yoga vs UC	6-9	Fatigue	Erectile dysfunction, urinary incontinence, QOL
Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al. (2012)	Breast	After	RT, CT, HT	31	Yoga vs education	12	Fatigue	Vigor, sleep quality, depressive symptoms, stress, physical function (chair stands, sit and reach), inflammation (TNF receptor type II, IL-1 receptor antagonist, IL-6, CRP, salivary cortisol), transcription factor analysis
Carson, Carson,	Breast	After	S, CT,	37	Yoga vs WLC	8	Hot flash frequency	Joint pain, fatigue, negative mood, sleep

Porter, Keefe, & Seewaldt (2009)			RT, HT					disturbance, night sweats, symptom-related both, relaxation, vigor, acceptance
Chandwani, et al. (2014)	Breast	During	RT	163	Yoga vs stretching vs WLC	6	QOL	Fatigue, depressive symptoms, sleep disturbances, cortisol
Chao-Jung et al. (2014)	Breast	During	CT	30	Yoga vs UC	8	N/A	Anxiety, depressive symptoms, fatigue
Clark, Cortese-Jimenez, & Cohen (2012)	Mixed	After	CT	36	Reiki vs yoga vs meditation	6	N/A	CIPN, QOL, mindful attention, fatigue
Cramer, Pokhrel, et al. (2016)	Colorectal	After	S	54	Yoga vs WLC	10	HRQOL	Fatigue, sleep, psychological distress, body awareness & dissociation, body efficacy
Cramer, Rabsilber, Lauche, Kummel, & Dobos (2015)	Breast	After	S, RT, CT	40	Yoga vs UC	12	Menopausal symptoms	QOL, anxiety, depressive symptoms
Culos-Reed et al. (2006)	Mixed	After	NR	38	Yoga vs UC	7	N/A	Mood, stress, QOL, PA, grip strength, flexibility, perceived exertion, functional capacity (6MWD)
Danhauer et al. (2009b)	Breast	After	S	44	Yoga vs UC	10	N/A	QOL, fatigue, spirituality, sleep, positive & negative affect
Hughes et al. (2015)	Breast	After	S, CT, RT	94	Yoga vs AER+RES+FLEX vs self-selected exercise	24	N/A	Co-morbidities, hemodynamics, fitness (VO_2max), chair stands, shoulder & arm

								strength, flexibility, range of motion, BMI, BMD, BF%, inflammatory markers
Kiecolt-Glaser et al. (2014b)	Breast	After	S, CT, RT	200	Yoga vs WLC	12	Fatigue, vitality, depressive symptoms, inflammatory markers	PA, dietary intake, sleep quality
Littman, et al. (2012)	Breast	After	S, CT, RT	63	Yoga vs WLC	24	N/A	QOL, fatigue, PA, anthropometrics (height, weight, BMI, hip & waist circumference), knowledge of yoga
Lötzke et al. (2016a)	Breast	During	CT, RT, HT	92	Yoga vs UC	12	QOL, life satisfaction, fatigue, mindfulness, spiritual attitude & coping with illness	
Loudon et al. (2014b)	Breast	After	S, CT, RT	28	Yoga vs UC	8	Lymphedema (arm volume, tissue induration, sensations, pain) fatigue, QOL	ROM, grip & upper body strength
McCall, McDonald, Thorne, Ward, and Heneghan (2015b)	Mixed	During	CT, RT, HT	15	Low vs medium vs high dose yoga*	4	HRQOL	N/A
Moadel et al. (2007a)	Breast	During/After	S, CT,	164	Yoga vs WLC	12	N/A	QOL, fatigue, spirituality, mood

			RT, HT					
Mustian et al. (2013)	Mixed	After	S, CT, RT	356	Yoga vs UC	4	Sleep quality	Fatigue, symptom burden
Siedentopf et al. (2013)	Breast	After	S	93	Yoga vs WLC	5	QOL	PA
Stan, Croghan, Croghan, Jenkins, et al. (2016)	Breast	After	S	34	Yoga vs RES	12	Safety, fatigue	QOL
Vardar Yagli et al. (2015)	Breast	After	CT	52	Yoga+AER vs AER	6	Functional capacity (6MWT)	Hand grip, upper & lower body strength, fatigue, QOL
Winters-Stone et al. (2018b)	Breast	After	CT	95	Yoga vs exercise recommendations**	8	Fatigue	Mood states, exercise readiness, self-efficacy for exercise, PA

*The range of yoga exposure ranged from one 50-minute session to 24-sessions in four weeks.
**Exercise recommendations from the American Cancer Society (Rock et al., 2012) and The American College of Sports Medicine.
AER, aerobic exercise; BF%, body fat percent; BMD, bone mineral density; BMI, body mass index; CIPN, chemotherapy-induced peripheral neuropathy; CT, chemotherapy; FLEX, flexibility exercise; HRQOL, health-related quality of life; HT, hormone therapy; N/A, not applicable; PA, physical activity; RES, resistance exercise; RT, radiation therapy; S, surgery; Tx, treatment; UC, usual care; WLC, wait-list control; 6MWD, 6-minute walk distance.

Application of the Principles of Exercise Training

All of the studies included the principle of specificity. Progression was not included in 64% of studies (Ben-Josef et al., 2017; Carson et al., 2009; Chandwani, et al., 2014; Clark et al., 2012; Danhauer et al., 2009b; Hughes et al., 2015; Littman, et al., 2012; Lötzke et al., 2016a; Loudon et al., 2014b; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, Sutherland, et al., 2016; Taso et al., 2014; Winters-Stone et al., 2018b; Yağlı et al., 2015), with three (12%) studies that clearly included progression (Anestin, Dupuis, Lanctot, et al., 2017; H. Cramer, Pokhrel, et al., 2016; Kiecolt-Glaser et al., 2014b) while six (24%) were unclear (Banasik et al., 2009; Banerjee et al., 2007; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Cramer et al., 2015; Culos-Reed et al., 2006; McCall, McDonald, Thorne, Ward, & Heneghan, 2015a). Overload was unclearly applied in 1 (4%) study (Hughes et al., 2015), while the remaining 24 (96%) studies did not apply the principle. The principle of initial values was considered in 72% of studies (Anestin, Dupuis, Lanctot, et al., 2017; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et al., 2014; Clark et al., 2012; Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Kiecolt-Glaser et al., 2014b; Littman, Bertram, Ceballos, Ulrich, Ramaprasad, McGregor, & McTiernan, 2012; Lötzke et al., 2016a; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, et al., 2016; Vardar Yagli et al., 2015) and was not included in 7 (28%) of studies (Banasik et al., 2009; Banerjee et al., 2007; Culos-Reed et al., 2006; Danhauer et al., 2009b; Hughes et al., 2015; Loudon et al., 2014b; Winters-Stone et al., 2018b). The principles of diminishing returns and reversibility were clearly included in two (8%) studies (Carson et al., 2009; Kiecolt-Glaser et al., 2014b) while

7 (28%) studies were unclear about whether or not this principle was considered (Chandwani, et al., 2014; Chao-Jung et al., 2014; Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Lötzke et al., 2016a; Loudon et al., 2014b; Stan, Croghan, Croghan, Jenkins, et al., 2016). The remaining 16 (64%) studies not including either diminishing returns or reversibility (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Banerjee et al., 2007; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, & Greendale, 2012; Clark et al., 2012; Culos-Reed et al., 2006; Danhauer et al., 2009b; Hughes et al., 2015; Littman, et al.,, 2012; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Vardar Yagli et al., 2015; Winters-Stone et al., 2018b).

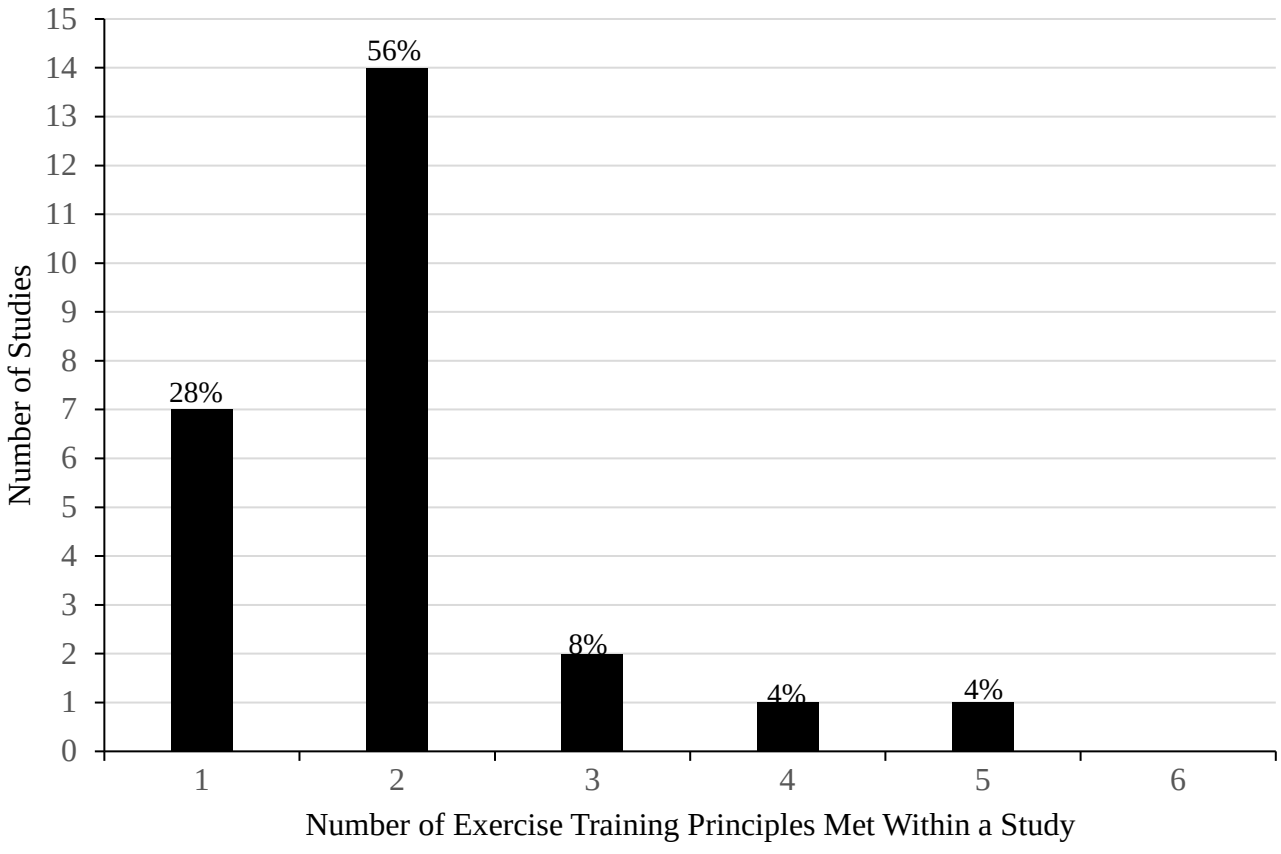

Figure 2. Count of the number of exercise training principles met within the 25 included studies. Studies could have met up to six exercise training principles.

Table 4

Usage of the Principles of Exercising Training and Significant Outcomes in Yoga Interventions in Cancer Survivors

Reference	**Specificity**	**Progression**	**Overload**	**Initial Values**	**Reversibility**	**Diminishing Returns**	**Significant Results***
Anestin, Dupuis, Lanctôt, et al. (2017)	+	+	-	+	-	-	Null
Banasik et al. (2009)	+	?	-	-	-	-	↓fatigue, ↓morning & 5pm cortisol
Banerjee et al. (2007)	+	?	-	-	-	-	↓anxiety, ↓depressive symptoms, ↓DNA damage
Ben-Josef et al. (2017)	+	-	-	+	-	-	↓fatigue, ↑sexual health, ↑emotional, physical & social QOL
Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al. (2012)	+	?	-	+	-	-	↓fatigue severity, ↑vigor, ↑self-efficacy for managing fatigue
Chandwani, et al. (2014)	+	-	-	+	?	?	↑physical QOL, ↑physical function, ↓(steepness) cortisol slop
Carson et al. (2009)	+	-	-	+	+	+	↓hot flash frequency & severity, ↓joint pain, ↓fatigue, ↓sleep disturbance, ↓symptom-related both, ↑vigor, ↑mood,

							relaxation, ↑acceptance
Chao-Jung et al. (2014)	+	-	-	+	?	?	↓fatigue
Clark et al. (2012)	+	-	-	+	-	-	Null
Cramer, Pokhrel, et al. (2016)	+	+	-	+	?	?	↑emotional well-being, ↓sleep disturbances, ↓anxiety, ↓depressive symptoms
Cramer et al. (2015)	+	?	-	+	?	?	↓total menopausal symptoms, ↓fatigue, ↑QOL
Culos-Reed et al. (2006)	+	?	-	-	-	-	↑global QOL, ↑emotional function, ↓diarrhea
Danhauer et al. (2009a)	+	-	-	-	-	-	↑mental health, ↑positive affect, ↑spirituality/meaning, ↓depressive symptoms
Hughes et al. (2015)	+	-	?	-	-	-	↑forward reach
Janelsins et al. (2016)	+	-		+	-	-	↑sleep quality, ↑sleep efficiency, ↓daytime dysfunction, ↓wake after sleep onset, ↓medication use
Kiecolt-Glaser et al. (2014a)	+	+	-	+	+	+	↑vitality, ↓fatigue, ↓inflammation
Lötzke et al. (2016b)	+	-	-	+	?	?	Null

Littman, et al. (2012)	+	-	-	+	-	-	↑QOL, ↓WC
Loudon, Barnett, Piller, Immink, and Williams (2014a)	+	-	-	-	?	?	↓tissue induration, ↑lymphoedema-related QOL
McCall et al. (2015b)	+	?	-	+	-	-	Null
Moadel et al. (2007b)	+	-	-	+	-	-	↑QOL, mood, spiritual, emotional & social well-being
Siedentopf et al. (2013)	+	-	-	+	-	-	Null
Stan, Croghan, Croghan, Jenkins, , et al. (2016)	+	-	-	+	?	?	Null
Vardar Yagli et al. (2015)	+	-	-	+	-	-	↑6MWD, ↑hand grip strength, ↑ should abduction, ↑global QOL, ↑emotional, social & role functioning, ↓constipation, ↓fatigue severity, ↓insomnia
Winters-Stone et al. (2018a)	+	-	-	-	-	-	↓fatigue, ↑exercise readiness, ↑physical activity

*Between groups. ↓, decrease or negative decline; ↑, increase or maintenance.

Reporting of the FITT prescription components

Prescribed frequency was reported by 88% of the studies (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, et al., 2014; Chao-Jung et al., 2014; Clark et al., 2012; Cramer, Pokhrel, et al., 2016; Danhauer et al., 2009b; Hughes et al., 2015; Kiecolt-Glaser et al., 2014b; Littman, et al., 2012; Lötzke et al., 2016a; Loudon et al., 2014b; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, , et al., 2016; Vardar Yagli et al., 2015; Winters-Stone et al., 2018b), was not reported in two (8%) (Banerjee et al., 2007; Culos-Reed et al., 2006) and was unclear in one (4%) study (Cramer et al., 2015). Intensity of training was not reported in 92% of studies (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Banerjee et al., 2007; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et al., 2014; Clark et al., 2012; Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Culos-Reed et al., 2006; Danhauer et al., 2009b; Hughes et al., 2015; Kiecolt-Glaser et al., 2014b; Littman, et al., 2012; Lötzke et al., 2016a; Loudon et al., 2014b; McCall et al., 2015a; Alyson B Moadel et al., 2007a; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, , et al., 2016; Vardar Yagli et al., 2015), and was unclear in two (8%) studies (Mustian et al., 2013; Winters-Stone et al., 2018b). A prescribed duration was reported in 92% of studies (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Banerjee et al., 2007; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et al., 2014; Clark et al., 2012; Cramer, Pokhrel, et al., 2016; Culos-Reed et al., 2006;

Danhauer et al., 2009b; Hughes et al., 2015; Kiecolt-Glaser et al., 2014b; Lötzke et al., 2016a; Loudon et al., 2014b; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, , et al., 2016; Vardar Yagli et al., 2015; Winters-Stone et al., 2018b), and was unclear in two studies (8%) (Cramer et al., 2015; Littman, et al., 2012). The type of yoga poses prescribed was clearly reported in 84% of studies (Anestin, Dupuis, Lanctot, et al., 2017; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, & Greendale, 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et al., 2014; Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Culos-Reed et al., 2006; Danhauer et al., 2009b; Hughes et al., 2015; Kiecolt-Glaser et al., 2014b; Littman, et al., 2012; Lötzke et al., 2016a; Loudon et al., 2014b; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, , et al., 2016; Vardar Yagli et al., 2015; Winters-Stone et al., 2018b), not reported in two studies (8%) (Clark et al., 2012; McCall et al., 2015a) and unclear in two others (8%) (Banasik et al., 2009; Banerjee et al., 2007).

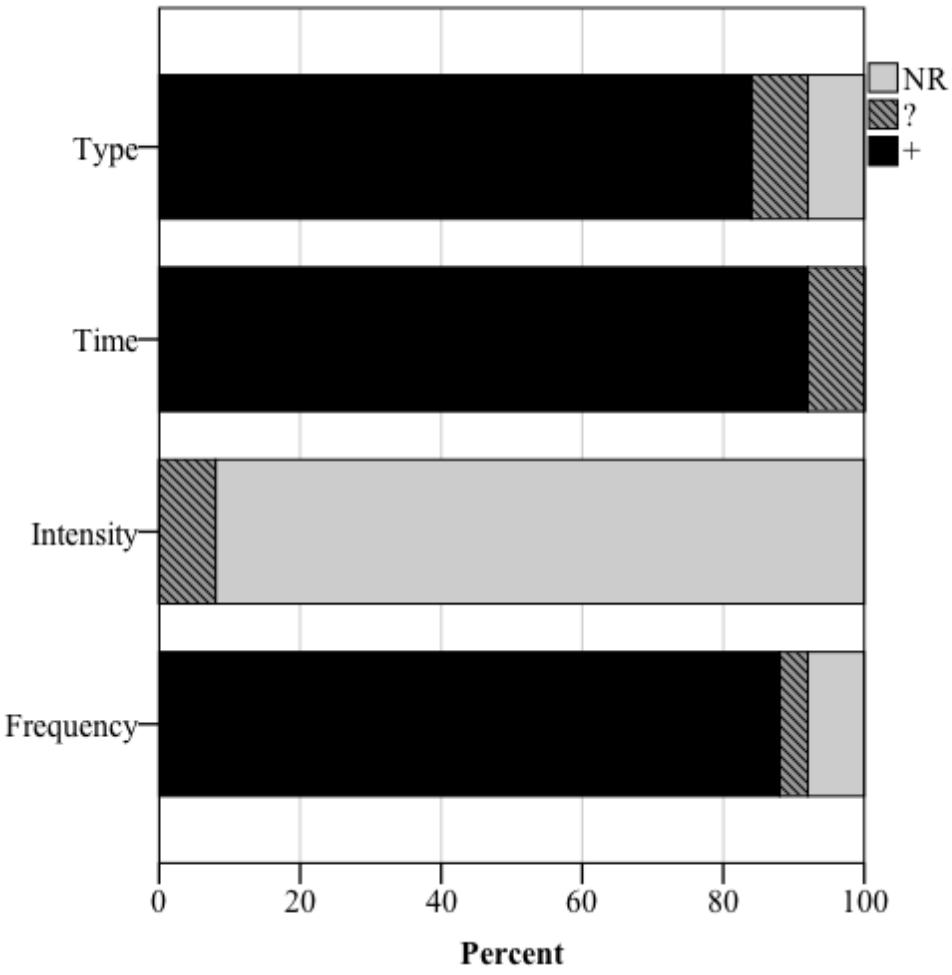

Figure 3. Reporting of the FITT components.

The percentage of studies that correctly reported the component of the exercise prescription (+) was unclear with their reporting of the exercise prescription (?) or did not report the component of the exercise prescription (NR).

Adherence to the FITT Prescription Components

Adherence to the frequency was reported in 72% of the studies (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, & Greendale, 2012; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Clark et al., 2012; Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Danhauer et al., 2009b; Kiecolt-Glaser et al., 2014b; Littman, et al., 2012; Loudon et al.,

2014b; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, et al., 2016; Winters-Stone et al., 2018b), was not reported in six (24%) studies (Banerjee et al., 2007; Chao-Jung et al., 2014; Culos-Reed et al., 2006; Hughes et al., 2015; Lötzke et al., 2016a; Vardar Yagli et al., 2015), and was unclear in one (4%) (Carson et al., 2009). Adherence to the prescribed intensity failed to be reported in 96% of the studies (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Banerjee et al., 2007; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, Wei, et al., 2014; Chao-Jung et al., 2014; Clark et al., 2012; Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Culos-Reed et al., 2006; Danhauer et al., 2009a; Hughes et al., 2015; Kiecolt-Glaser et al., 2014a; Littman, et al., 2012; Lötzke et al., 2016b; Loudon et al., 2014a; McCall et al., 2015a; Moadel et al., 2007b; Stan, Croghan, Croghan, Jenkins, et al., 2016; Vardar Yagli et al., 2015; Winters-Stone et al., 2018a), with only one (4%) study reporting the average intensity using the average rate of percieved exertion (Mustian et al., 2013). Adherence to time failed to be reported in 88% of the studies (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Banerjee et al., 2007; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, Wei, et al., 2014; Chao-Jung et al., 2014; H. Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Culos-Reed et al., 2006; Danhauer et al., 2009a; Hughes et al., 2015; Littman, et al., 2012; Lötzke et al., 2016b; Loudon et al., 2014a; McCall et al., 2015a; Moadel et al., 2007b; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, et al., 2016; Vardar Yagli et al., 2015; Winters-Stone et al., 2018a), with only three studies (12%) that clearly reported the average number of minutes trained (Cramer, Pokhrel, et al., 2016; Kiecolt-Glaser et al., 2014b; Mustian et

al., 2013). Adherence to the type of yoga poses prescribed was only reported in one study in which classes were audited and the adherence prescribed yoga poses was reported (Kiecolt-Glaser et al., 2014b).

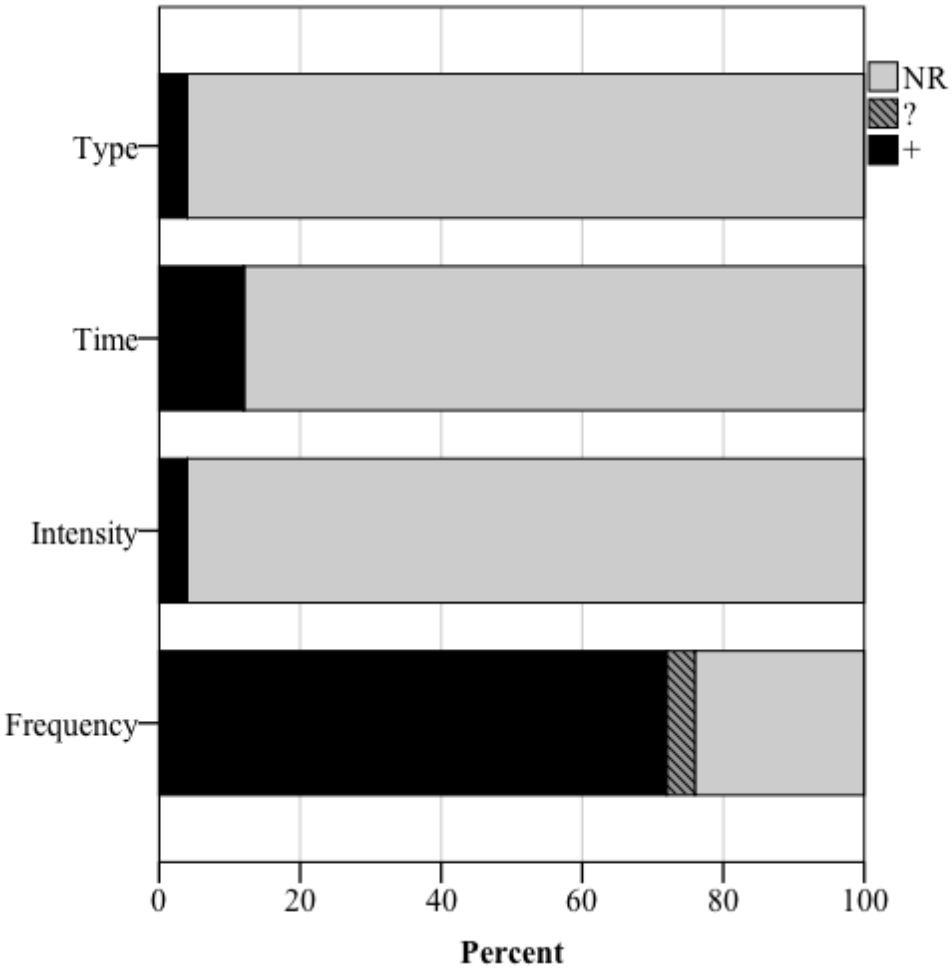

Figure 4. Reporting of the adherence to the FITT components.

The percentage of studies that correctly reported the component of the exercise prescription (+) was unclear with their reporting of the exercise prescription (?) or did not report the component of the exercise prescription (NR).

Discussion

Previous systematic reviews of yoga interventions in cancer survivors have summarized and described yoga programs and preliminary efficacy (Buffart et al., 2012; Danhauer et al., 2019), yet yoga is not included in recent exercise guidelines for cancer survivors (Campbell, et al., 2019,

in press), despite being an increasingly popular and potentially efficacious mode of exercise to combat many of the symptoms and side effects that cancer survivors face (Danhauer et al., 2019). The present systematic review found that 56% of studies applied only two of the six principles of exercise training in the yoga intervention design (Figure 2) and that the FITT components were not well-reported specifically with regards to the adherence of participants to each FITT component (Figures 3-4). Not including the principles of exercise training in the design of yoga interventions and poor reporting on FITT components could contribute to yoga's exclusion from exercise recommendations for cancer survivors because programs cannot be systematically evaluated nor replicated.

Application of the Principles of Exercise Training

The principle of specificity, that states the exercise must challenge a specific system or muscle in order to elicit training benefits, was applied in all of the included studies. Different from our previous reviews (Campbell et al., 2012; Neil-Sztramko et al., 2019; Neil-Sztramko et al., 2017; Winters-Stone et al., 2014) of conventional aerobic and resistance training programs where only physiological outcomes were included, this review also includes psychosocial outcomes due to the small number of yoga studies that assessed only physiological outcomes. Thus, the principle of specificty was expanded beyond a specific body system or muscle to include any psycho-social outcome with adequate evidence to support the use of yoga to yield improvements in the primary outcome. To apply specificity to psychosocial outcomes rationale to support how yoga could influence changes in underlying mechanisms of psychosocial outcomes was required. The application of specificty was well demonstrated in a trial aimed at reducing depressive symptoms (Banasik, Williams, Haberman, Blank, & Bendel, 2011). Rationale was provided for the selection

of yoga beaccuseit is known that stress and cortisol dysregulation could influence inflammation and immune function in ways that promote depression (Sephton & Spiegel, 2003) and there is evidence that the relaxation component of yoga may reduce cortisol levels (Carlson, Speca, Patel, & Goodey, 2004).

The principle of progression, that states the exercise must provide adequate overload in order to elicit improvements over time, was applied in only three (12%) of the studies (Anestin, Dupuis, Lanctot, et al., 2017; Cramer, Pokhrel, et al., 2016; Kiecolt-Glaser et al., 2014b). Though different from conventional aerobic and resistance training where the sets, repetitions and weight/intensity can be easily manipulated to stimulate overload, the poses held in yoga could too, be thoughtfully altered in a progressive manner. In yoga the manipulation of how body weight is positioned can be used as a proxy for dumbell or machine weight increases as used in conventional resistance training prescriptions (Tsuzuku, Kajioka, Sakakibara, & Shimaoka, 2018). A yoga program aimed to improve physical function could apply progression by prescribing less difficult seated poses (i.e. seated warrior one) that require less balance, strength and power during the initial phase of the prescription and then progressing to standing poses that require more muscles to be recruited and activated during the later weeks of the intervention. Cramer, Pokhrel, et al. (2016) provides an example of a yoga program aimed to improve colorectal cancer survivor specific quality of life that progressed the difficulty and intensity of poses weekly and clearly reported the progression in a week-by-week description of the yoga program. Some studies listed the specific yoga poses that were prescribed, though it was unclear if the order of the poses was the same throughout the intervention or if they progressed from less strenuous poses to poses that required more balance, strength and power (Carson et al., 2009; Hughes et al., 2015; Mustian et al., 2013; Siedentopf et al., 2013). Other studies mentioned that the poses progressed from less to more

strenuous, though not enough detail was provided for the progression to be replicated (Banasik et al., 2009; Banerjee et al., 2007). Future studies should clearly state the progression through the series of poses or the intensity (via heart rate or rate of percieved exertion) in relation to the primary aim of the yoga intervention (i.e. progression from seated to standing poses in studies aimed to improve strength or progression in the rate of percieved depth of stretch in studies aimed at improving flexibility).

The principle of overload states that exercise must be performed above usual levels in order to cause training adaptations. Overload was included in an unclear manner in one study that compared traditional aerobic and resistance training exercise with yoga and was unclear if the submaximal aerobic fitness test was used to formulate the yoga prescription (Hughes et al., 2015). In conventional aerobic and resistance training programs, baseline fitness testing is one approach to determine each individual's exercise starting intensity. Functional exercise tests (i.e. chair stand, chair sit and reach and back scratch tests or balance tests) could help triage participants to a particular yoga class (i.e. a less difficult style of yoga for those with more functional limitations or a strenuous style yoga for those who have higher levels of initial functioning) that may best match levels of functioning or yoga experience. This information could also help an instructor to modify poses in a class for individuals to ensure overload is sufficient.

The principle of initial values states that those with lower baseline fitness levels or poor psychosocial outcomes will have the greatest improvements. Initial values was included in 72% (Anestin, Dupuis, Lanctot, et al., 2017; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et al., 2014; Clark et al., 2012Cramer, Pokhrel, et al., 2016; H. Cramer et al., 2015; Kiecolt-Glaser et al., 2014b;

Littmanet al, 2012; Lötzke et al., 2016a; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, et al., 2016; Vardar Yagli et al., 2015) of studies by including participants who test for low levels of the primary outcome at baseline, thus they could stand to improve from the intervention (i.e. a yoga intervention to improve fatigue should exclude those who do not report or exhibit fatigue). The 28% of studies that did not apply the principle of initial values run the risk of a ceiling effect as a result of participants with acceptable initial levels of the outcome of interest (Banasik et al., 2009; Banerjee et al., 2007; Culos-Reed et al., 2006; Danhauer et al., 2009b; Hughes et al., 2015; Loudon et al., 2014b; Winters-Stone et al., 2018b). The studies included in this review rarely specified a primary outcome and instead assesseed a large battery of varying outcomes, thus screening participants on a single primary outcome would not be possible thereby posing a major methodological limitation contributing to the exclusion of yoga from current exercise guidelines for cancer survivors (Campbell, et al., in press).

The principle of diminishing returns, stating that training-related improvements decrease as participants become more fit, and reversibility stating that training-related improvements are lost when regular exercise is stopped, were excluded from 64% of studies (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Banerjee et al., 2007; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, & Greendale, 2012; Clark et al., 2012; Culos-Reed et al., 2006; Danhauer et al., 2009b; Hughes et al., 2015; Littman, et al., 2012; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Vardar Yagli et al., 2015; Winters-Stone et al., 2018b). These principles were unclearly applied in 28% of studies where a follow-up assessment was conducted because it was not clear whether or not exercise following the cessation of the intervention was tracked (Chandwani, Perkins, Nagendra, Raghuram,

Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et al., 2014; Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Lötzke et al., 2016a; Loudon et al., 2014b; Stan, Croghan, Croghan, Jenkins, et al., 2016). Though, as many of the included studies were pilot studies, financial and time contraints may have limited the ability to conduct a follow-up assessment after the cessation of the intervention. Regardless, it is necessary that studies are designed appropriately to apply the principles of training thereby signaling the need for larger trials of yoga rather than additional feasibility studies.

Reporting of the FITT prescription components

In order for trials to be reproduced and translated to practice, sufficient details of each FITT component must be reported. In general, with the exception of intensity, the FITT components were well-reported in the included studies (Figure 3). The majority (88%) of studies reported frequncy of yoga sessions (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et al., 2014; Clark et al., 2012; H. Cramer, Pokhrel, et al., 2016; Danhauer et al., 2009b; Hughes et al., 2015; Kiecolt-Glaser et al., 2014b; Littmanet al., 2012; Lötzke et al., 2016a; Loudon et al., 2014b; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, , et al., 2016; Vardar Yagli et al., 2015; K.M. Winters-Stone et al., 2018b) which is comparable to levels reported in studies of conventional aerobic and resistance training (Neil-Sztramko et al., 2019; Neil-Sztramko et al., 2017).

A target intensity was not reported in 92% of studies (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Banerjee et al., 2007; Ben-Josef et al., 2017; Bower, Garet, Sternlieb,

Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et al., 2014; Clark et al., 2012; Cramer, Pokhrel, et al., 2016; Cramer et al., 2015; Culos-Reed et al., 2006; Danhauer et al., 2009b; Hughes et al., 2015; Kiecolt-Glaser et al., 2014b; Littman, et al., 2012; Lötzke et al., 2016a; Loudon et al., 2014b; McCall et al., 2015a; Moadel et al., 2007a; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, et al., 2016; Vardar Yagli et al., 2015) and was unclear in two (8%) studies that provided some indication of intensity that would not be replicable (Mustian et al., 2013; Winters-Stone et al., 2018b). Defining and report a prescribed target intensity in yoga can be challenging. In conventional aerobic and resistance training, watts on an ergometer or weight lifted can define a target intensity. In yoga, the intensity stems largely from the type of yoga or poses that are prescribed and should match the aims of the study. More intense poses require the participant to support more of their own body weight, similar to how an increase in dumbell weight will stimulate a higher intensity of effort (Tsuzuku et al., 2018). How intensity was adjusted and in turn achieved needs to be reported in detail so that the prescription could be replicated and summarized in order to be included in exercise guidelines. It is suggested that intensity be rated based off of if a rate of perceived exertion, estimated energy expenditure, average heart rate or metabolic equivalents that could be predicted or captured during supervised yoga classes.

A prescribed duration (minutes per yoga session) was the most frequently reported FITT component, with 92% of studies reporting a prescribed duration (Anestin, Dupuis, Lanctot, et al., 2017; Banasik et al., 2009; Banerjee et al., 2007; Ben-Josef et al., 2017; Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012; Carson et al., 2009; Chandwani, Perkins, Nagendra, Raghuram, Spelman, Nagarathna, Johnson, Fortier, Arun, & Wei, 2014; Chao-Jung et

al., 2014; Clark et al., 2012; Cramer, Pokhrel, et al., 2016; Culos-Reed et al., 2006; Danhauer et al., 2009b; Hughes et al., 2015; Kiecolt-Glaser et al., 2014b; Lötzke et al., 2016a; Loudon et al., 2014b; McCall et al., 2015a; Moadel et al., 2007a; Mustian et al., 2013; Siedentopf et al., 2013; Stan, Croghan, Croghan, Jenkins, , et al., 2016; Vardar Yagli et al., 2015; Winters-Stone et al., 2018b). The duration prescribed is typically less well reported in conventional aerobic and resistance training studies, particularly because the time for separate aerobic versus resistance components is not always specified (Neil-Sztramko et al., 2019; Neil-Sztramko et al., 2017). In the current review, studies that provided the amount of time prescribed were considered as including the time component, however the amount of time in each pose, or each component of yoga (i.e. physical postures, breathing exercise, meditation) was not considered when rating studies. Reporting the duration spent in each pose can become complex specifically when the style of yoga transitions (i.e. flows) continuously between poses, as done in types of yoga such as vinyasa. It is necessary for studies to clearly report the amount of time spent in each of the core elements (i.e. standing versus supine poses) rather than duration spent in each pose such that an exercise prescription could be easily summarized for inclusion in exercise guidelines.

Similar to reporting on conventional aerobic and resistance training programs, the *type* of exercise (i.e. yoga poses that could be replicated) was well reported in the majority of studies. Studies that were unclear provided the general type of yoga, but did not provide the names of poses prescribed. Simply stating the type of yoga does not provivde adequate detail for the prescription to be replicated, particularly as there is overlap among the core components applied in the various schools of yoga. For example, Hatha yoga uses a “series of body postures, movements (asanas), and breathing techniques (pranayama)” (Woodyard, 2011), which cannot be easily differentiated from the Satyananda style of yoga that includes “breathing, and pranayama, physical postures,

mediatation and relatxion techniques" (Loudon et al., 2014b). Hatha yoga can also encompasses Iygenar yoga that places an emphasis on inversions and backbends (Bower, Garet, Sternlieb, Ganz, Irwin, Olmstead, Greendale, et al., 2012). For this, stating the "type" of yoga does not provide details sufficient to replicate the study or generate yoga recommendations for cancer survivors. Invesetigators should state the distinct poses that make up the type of yoga that is prescribed in order to first understand what yoga elements (i.e. meditation, breathing, physica postures) each type of yoga consists. A clear understanding of the types of yoga could then translate into exercise recommendations.

Adherence to the FITT Prescription Components

As with conventional aerobic and resistance training studies, reporting adherence to each of the FITT components is necessary for the determining dose of exercise attained in relation to measured changes in study outcomes. Traditional aerobic and resistance training prescriptions do not adequately report the adherence to each FITT component with the exception of frequency (Neil-Sztramko et al., 2019; Neil-Sztramko et al., 2017). In the resent review adherence to frequency was reported in the majority (72%) of studies but adherence to the intensity, time and type was even more poorly described in studies of yoga.

Adherence to the intensity was reported in only one study of which reported intensity as a rate of percieved exertion achieved in the yoga program (Mustian et al., 2013). Intensity could be assessed with heart rate monitors or rate of percieved exertion at different time increments tied to the different components of the yoga prescription (i.e. standing versus supine poses) throughout each yoga class. Capturing the intensity could add an additional time and cost burden, however this data is important in order to understand the dose of yoga that is tolerable in cancer survivors in order to inform exercise guidelines.

Adherence to time and type was reported in only 12% and 4% of studies, respectively. It is necessary to report the average amount of time that participants are able to complete during each yoga session because some participants may not be able to complete a full class due to physical limitations, thus the true dose of yoga attained would be unknown. Similarly, it is necessary to report the type of yoga that was completed, particuarly as yoga offers numerous modifications which may contribute to varying intensities and dose of exercise attained (Sherman, 2012). For instance, in participants who are unable to stand up from their chair during prescribed standing postures, modifications should be clearly reported. Investigators should report details of planned modifications (i.e. seated modifications for each standing pose) and the percentage of participants who adhered to the planned modifications versus the intended prescription in order to generate data on what type of yoga is tolerable in cancer survivors.

Limitations

There are limitations to the current review. We did not contact authors of studies where an unclear or not reported rating were assigned, thus is is possble that some of the principles of training may have been applied but were not reported. Similarily page limits could prevent the full reporting of the prescription including the FITT components. Including supplemental documents that give details of the full yoga prescription (i.e. a weekly account all of the yoga poses prescribed) could be valuable when interpreting study findings, replicating protocols and implementing programs.

Conclusion

Yoga is an increasingly studied intervention in cancer survivorship (Danhauer et al., 2019) though it is not included in the most recent exercise guidelines for cancer survivors (Campbell, et al., 2019) despite the potential benefits of yoga (Danhauer et al., 2019). The present review found

that studies of yoga did not uniformly apply the principles of exercise training. Investigators are urged to apply the principles of exercise training in yoga interventions in order to determine the efficacy of yoga for cancer survivors, particularly in studies where physiological outcomes are sought. Paying attention to the principles of training may avoid erroneous conclusions about negative trial outcomes that may be attributed to a poorly designed intervention rather than a lack of exercise efficacy (Winters-Stone et al., 2014). Though the majority of yoga studies reported the basic details of the FITT components, the intensity prescribed was rarely reported. The adherence to each FITT component was poorly reported, thus the tolerability of yoga in cancer survivors is largely unknown. Yoga may be a useful additional modality of exercise as it limits some of the known barriers to exercise in cancer suvivors in that it can be done at home, with little equipment and at a low intensity (Wasley et al., 2018). We urge investigators to include the principles of exercise training in the design of yoga interventions, report FITT prescriptions and adherence to each of the FITT components to assist in the development of specific exercise guidelines for cancer survivors that can be translated safely and effectively into clinical practice and community settings.

Chapter V: Feasibility and Preliminary Efficacy of Yoga on Physical Function in Lung Cancer Survivors

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This manuscript replaces portions of the methods section and results section of the traditional dissertation. Ms. Medysky will be the primary author on this paper; Dr. Winters-Stone will be the senior author on this paper. Ms. Medysky will conduct the study and describe the design and results under the supervision of Dr. Winters-Stone. This paper will be submitted to Journal Integrative Cancer Therapies, which is an indexed and peer-reviewed journal with an impact factor of 1.923. This journal focuses on a model of comprehensive cancer treatment that includes conventional therapies coupled with integrative therapies such as lifestyle and exercise. (Note: for ease of submission, manuscript drafted in the past tense).

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Declaration of Conflict of Interest
None Declared

Key Words: lung neoplasm; physical function; yoga; exercise

Abstract

Introduction: Lung cancer survivors self-report and demonstrate declines in physical function during and following treatment. Yoga may be a feasible and efficacious method to improve physical function in lung cancer survivors. Only two studies of yoga in lung cancer have been conducted and neither assessed physical function nor if yoga is a feasible exercise intervention in lung cancer survivors on active treatment. **Purpose:** 1) Determine the feasibility of a yoga program for lung cancer survivors; 2) Determine the preliminary efficacy of yoga to improve physical function in lung cancer survivors who were on or completed treatment. **Methods:** This study was a single group 12-week pilot trial of low-moderate intensity vinyasa yoga in stage I-IV lung cancer survivors (n=16) on or following treatment. Assessments conducted at baseline, 6- and 12-weeks included 6-minute walk test, hand grip strength, back scratch and sit and reach tests and the physical performance battery. **Results:** Retention at 6-weeks was 56% with seven individuals withdrawing from the study due to poor health with no further withdrawals that occurred at 12-weeks. Adherence to the intervention was 80% and 92% at 6 and 12-weeks, respectively, among participants (n=9) who completed the entire study. Large effect sizes in flexibility outcomes (back scratch and sit and reach), and medium effects were seen in submaximal aerobic capacity (6-minute walk distance) outcomes across the 12-week program. **Discussion:** In a sample of lung cancer survivors a 12-week vinyasa style yoga program was a modestly feasible, but safe and potentially beneficial modality of exercise. Future randomized controlled trials to determine the efficacy of yoga to mitigate declines in physical function in lung cancer survivors, both during and following treatment, are warranted.

Introduction

In 2018, approximately 234, 030 new cases of lung cancer will be diagnosed in the United States, making lung cancer the second most common cancer in men and women (American Cancer Society, 2018). Standard treatment for lung cancer is aggressive and typically includes surgery, (e.g. lobe resection, full pneumonectomy), singlet or doublet chemotherapy, radiation, targeted and/or immunotherapies. Lung cancer survivors often present with major comorbidities, including chronic obstructive pulmonary disorder, diabetes, and congestive heart failure (Islam, Jiang, Anggondowati, Lin, & Ganti, 2015), and when combined with treatment can lead to adverse health outcomes, such as low physical function.

Physical function is a particularly important health outcome to consider across the entire cancer spectrum. Most studies assess physical function objectively using submaximal aerobic capacity, strength or range of motion that are typically a fitness tests but are early indicators of impending functional declines (Bennett et al., 2006). Ha et al. (2018) reported that 60% of lung cancer survivors had low physical function as measured by 6-minute walk distance. In metastatic lung cancer survivors who had previously undergone surgery, radiation or chemotherapy chair rise time was slower and grip strength was lower than in age and gender matched cancer-free controls (Brown et al., 2005). Additionally, in stage I-IIIB lung cancer survivors significant reductions were seen in 6-minute walk distance and shoulder strength from diagnosis to 10-months post diagnosis (i.e. during chemotherapy or radiation therapy) and quadriceps strength was significantly lower than in cancer-free controls across 10-months (Granger et al., 2014). In order to improve the low physical function that lung cancer survivors experience a rehabilitative strategy is needed.

There is evidence to support exercise to improve physical function in lung cancer survivors (Bade, Thomas, Scott, & Silvestri, 2015). While controlled trials in lung cancer survivors have shown that aerobic and/or resistance exercise can preserve physical function (Sommer et al., 2018),

lung cancer survivors often report low self-efficacy for engaging in aerobic and resistance training due to concerns that exercise could worsen symptoms and cause harm (Wasley et al., 2018). Lung cancer survivors report that they prefer low intensity activities done on their own, in a home setting over moderate to high intensity exercises done in a fitness center, hospital or community setting (Wasley et al., 2018). Yoga is a modality of exercise that may be more feasible for lung cancer survivors because it can be easily modified for each individual's ability (Bower, Woolery, Sternlieb, & Garet, 2005) and can be done at a lower intensity (i.e. seated poses) (Speed-Andrews & Courneya, 2009) and can be done safely in supervised or home settings (Fouladbakhsh, Davis, & Yarandi, 2014; Milbury et al., 2015). Yoga can also improve flexibility better than traditional aerobic and resistance training exercises (Tekur, Nagarathna, Chametcha, Hankey, & Nagendra, 2012). Since flexibility is an important contributor to physical functioning in older adults (Speer, 2005), and most lung cancer survivors are older, yoga may be a particularly effective exercise modality.

To date, two single-arm pilot studies of yoga training in lung cancer survivors have been conducted and these studies reported significant improvements in anxiety, mental health, sleep, and spiritual wellbeing (Milbury, Chaoul, et al., 2015) and improved lung function (Fouladbakhsh et al., 2013). Neither study assessed physical function, thus the efficacy of yoga to improve physical function in lung cancer survivors at any point in the treatment trajectory remains unknown. Both trials were in survivors who had already completed treatment, thus there is no evidence to suggest whether or not yoga is also feasible for survivors undergoing treatment. To address these gaps, we conducted a pilot study to determine the feasibility and preliminary efficacy of yoga on physical function in lung cancer survivors who were undergoing or who had completed cancer treatment. We also included measures of physical fitness (i.e. submaximal aerobic capacity,

muscle strength and flexibility) because they are known to be upstream indicators of future functional decline, can be used as fidelity markers of the exercise response, and can be used to compare yoga to studies that use other modes of exercise. We hypothesized that: 1) A 12-week yoga training program will be feasible based on 100% of the accrual target within 6-months; >75% adherence to supervised yoga practice and >80% retention over the study period; and a complete absence of serious adverse events and 2) Yoga will yield at least moderate effect sizes on measures of physical fitness and function over 6 and 12 weeks.

Methods

Study Design. This study was a pre-post single group trial to determine the feasibility and preliminary efficacy of yoga to improve physical and psychosocial outcomes in lung cancer survivors during or following treatment. This paper reports on objective physical function as part of a larger study that enrolled survivors and their support partner with a primary endpoint of patient depression, which will be reported elsewhere. Beginning in October 2018 lung cancer survivors were recruited from oncology clinics at Oregon Health and Science University (OHSU) and the Portland Veterans Affairs Medical Center (PVAMC) and by mailings to individuals in the OHSU cancer registry. Eligibility criteria included the following: 1) confirmed diagnosis of stage I-IV lung cancer; 2) age $\geq$18 years; 3) completed surgery at least two weeks prior, or currently undergoing or completed radiation, targeted, immune or chemotherapies; 4) patient health questionnaire (PHQ-2) score $\geq$2; 5) cleared by treating physician to participate in mild to moderate intensity exercise and 6) have a partner available to participate in the yoga program. Participants provided informed consent during the screening visit. All study procedures were approved by the

OHSU and PVAMC institutional review board. The trial is registered in ClinicalTrials.gov (NCT 03649737).

Yoga Intervention. A 12-week, progressive Vinyasa style yoga program was instructed by trained research staff (MM). The program was designed with a combination of supervised and home-based delivery where the reduction of in-person instruction frequency was meant to transition participants toward independent exercise as it is likely that a combination of both self-managed and supervised exercise programs will be optimal (Newton, 2018) and cost effective (D. Ha et al., 2019). The first 6-weeks of the program consisted of two supervised sessions per week at OHSU and encouraged participants to follow an instructional yoga DVD (Winters-Stone et al., 2018) at home at least once per week. During the following 6-weeks, participants were to attend one, supervised group class at OHSU and at least two home-based, unsupervised sessions using the instructional DVD were encouraged per week (Figure 2).

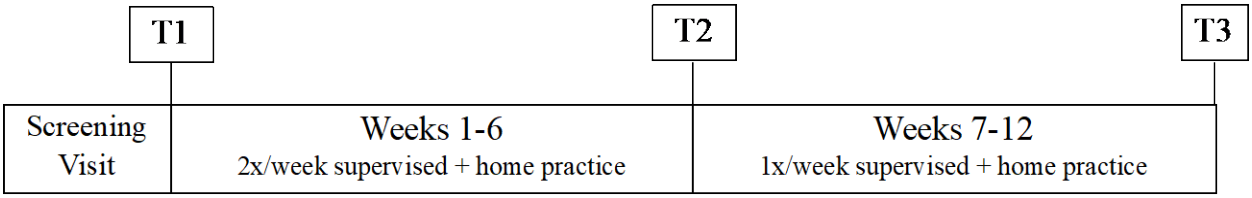


Figure 1. Schematic of intervention delivery and data collection timing.
Data collection occurred at time points T1-T3.

The supervised yoga program consisted of a low-moderate intensity, 60-minute yoga class focused on exercises that emphasized isometric muscle actions and increasing joint range of motion. The program followed a Vinyasa style of yoga that incorporates a sequential flow of poses that emphasize stretching and strengthening multiple large muscle groups of the body (i.e. hip flexors/extensors, abdominals, shoulder rotators). The poses were selected specific to improving measures or upstream predictors of physical function (i.e. balance, flexibility, strength). Each of

the poses could be modified as necessary to accommodate physical limitations, individual tolerance and ability, and allow for progression in intensity and complexity over the intervention period (see supplementary material for a detailed yoga prescription). In addition, props such as foam blocks, blankets and mats were used to increase participant comfort and to assist with poses when participants were physically limited.

The yoga DVD was meant to compliment the in-person yoga program, and consisted of low intensity, restorative poses meant to improve whole body flexibility and be safe for participants during active treatment or for those with advanced disease in a home setting. The DVD offered modifications to the standing poses by sitting on an exercise ball (modification to increase difficulty) or sitting in a chair (modification to decrease difficulty) to meet varying levels of functional ability.

Measures

Participant Demographics and Health History

Demographics (age, sex, race) and healthy history (cancer stage, time since diagnosis, treatment history, presence of bone metastases) were extracted from the electronic medical record.

Feasibility Measures

Recruitment and Retention. Recruitment (start date and methods of recruitment), screening (breakdown of participants excluded with reasons) and enrollment efforts (total number of participants enrolled) are reported in accordance to the CONSORT guidelines for pilot and feasibility trials (Eldridge et al., 2016). Retention was assessed as the proportion of participants who did not withdraw from the program out of those enrolled.

Adherence and Safety. Participant adherence for supervised yoga sessions were recorded and calculated at six and 12-weeks as: adherence = total # sessions completed / total possible # of

sessions. The number and severity of all adverse events were reported. Adverse events were self-reported by participants, recorded by research staff (MM) and then ranked by the primary investigator (DS) from mild to severe.

Outcome Measures

Research staff (MM) not blinded to the intervention collected the following outcomes at three time points: 1) Baseline (T1); 2) 6-weeks and prior to the transition of reduced supervised practice (T2); 3) Post intervention (T3) (Figure 1).

Submaximal Aerobic Capacity. The 6-minute walk test is the most commonly used non-lab test to measure submaximal aerobic capacity in lung cancer survivors (Granger et al., 2013). Participants were asked to walk laps of a 20-meter corridor at the fastest pace they could maintain for 6-minutes and the total meters walked was recorded. The 6-minute walk test was validated, has good test retest reliability (r=0.88-0.94) (Rikli & Jones, 1998), is strongly correlated with respiratory function tests (forced expiratory volume) (r=0.53) (Mao et al., 2007) and is predictive of post-operative outcomes, post-operative length of hospital-stay and survival in lung cancer survivors. 6-minute walk test has a minimal important difference of 22-42 meter (9.5% change) in lung cancer survivors (Granger, Holland, Gordon, & Denehy, 2015).

Upper Extremity Strength. Upper extremity strength was assessed by hand grip strength (via dynamometer) measuring maximal voluntary isometric muscle force in kilograms. The handgrip strength test has excellent test retest reliability (r=0.954) (Bohannon & Schaubert, 2005). Handgrip strength is predictive of complications in lung cancer patients both, hospitalized (Guo, Zhang, Ma, Zhang, & Huang, 1996), and undergoing surgery (Kalfarentzos, Spiliotis, Velimezis, Dougenis, &

Androulakis, 1989) and has previously been used as a measure of upper body physical function in lung cancer survivors (Tanaka et al., 2017; Wiskemann et al., 2016).

Range of Motion. To assess improvements in lower and upper body flexibility chair sit and reach and back scratch range of motion assessments of The Senior Fitness Test were utilized (Rikli & Jones, 2013). For the chair sit and reach test participants were asked to sit in a chair with one leg extended and reach their stacked hands toward their toes. The centimeters between the tip of the middle fingers and the big toe was recorded. For the back scratch test participants were asked to extend the dominant arm over head with the elbow flexed so the fingers pointed downward. The non-dominant hand was placed behind the back, palm up, with the fingers pointing upward. The distance in centimeters between the two middle fingers was recorded. In cases where participant could reach past their toes (chair sit and reach) or slide their middle fingers past each other (back scratch test) a negative value, indicating a positive range of motion, was recorded. These tests quantify the degree of range of motion and have previously been used in studies of lung cancer survivors (Burnham & Wilcox, 2002; Dhillon et al., 2012).

Short Physical Performance Battery (SPPB). The sPPB quantifies physical functioning as a composite of gait, balance and lower-extremity strength by measuring time to walk 8 feet, standing balance, and time to rise from chair and return to the seated position 5 times, respectively. Each of the measures is scored from 0 to 4 and then summed, with higher scores indicating greater physical function. The sPPB has good to excellent test retest reliability (r=0.69 to 0.99) for each of the components measured (Simmonds, 2002). This measure was validated in 7000 older adults, has acceptable internal consistency (α=.76) (Guralnik et al., 1994), is widely accepted and responsive to clinically meaningful change (Gill, 2010), and has been used in cancer survivors (J. Brown,

Harhay, & Harhay, 2015; Bylow et al., 2008). Chair stand time (seconds), a functional measure of lower body strength predictive of disability (Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995) was also reported as a continuous variable.

Power and Sample Size. The present study was not fully powered to detect statistical significance. The focus of this study was to generate effect sizes with confidence intervals for future larger trials.

Statistical Analyses. Descriptive statistics were reported on the sample (Table 1). Feasibility data (adherence, retention and adverse events) were reported as percentages (Aim 1) from baseline to 6-weeks and baseline to 12-weeks to account for the decrease in frequency of supervised yoga sessions during the second half of the trial. To determine the preliminary efficacy of the yoga program to mitigate functional declines throughout the 12-week yoga program, effect sizes and 95% confidence intervals (95% CIs) were calculated from baseline to 6-weeks and baseline to 12-weeks (Aim 2). Effect sizes were calculated for each physical function outcome in two ways: 1) Cohen's d_z calculated as d_z = standardized test statistic/square root of the total number of observations (Rosenthal, 1984) and 2) Glass's delta calculated as d=mean1-mean2/standard deviation at baseline (Glass, Smith, & McGaw, 1981). Effect sizes were interpreted as "small" effect, $d \leq 0.1$, "medium" effect, $d \leq 0.3$, and "large" effect, $d \leq 0.5$ for Cohen's d_z and as "small" effect, $d \leq 0.2$, "medium" effect, $d \leq 0.5$, and "large" effect, $d \leq 0.8$ for Glass's delta (Cohen, 1988). Exploratory comparisons of means were assessed with Wilcoxon Signed Ranked tests for each physical function outcome.

Results

Participant Demographics and Health History

Participant characteristics are presented in Table 1. Sixteen male (n=5) and female (n=11) lung cancer survivors were enrolled into the trial. The majority of participants were Caucasian (94%). Participants had a median age of 66 years, ranging from range 47-85 years old. Participants had a median body mass index of 23.2 kg/m^2, ranging from 14.6 kg/m^2 (underweight) to 32.1 kg/m^2 (overweight). Nine (56%) of survivors had stage IV disease, with 25% of the total sample having bone metastases at the spine and/or pelvis. Survivors were on average 16 $\pm$ 14 months from diagnosis, with 62% of survivors on treatment during the trial. Primary treatment type was chemotherapy in 43% of participants, surgery in 38% of participants, and radiation in 19% of participants. Treatments that participants were undergoing during the trial were adjuvant and included targeted therapy in 40% of participants, and immune or chemotherapy in each 30% of participants.

Table 1

Participant Characteristics (n=16)

Variable	**Mean (SD) or % of sample**	**Range**
Age (years)	66 (11)	47-85
Sex		
Female	7 (44)	
Male	9 (56)	
Race		
Caucasian	15 (94)	
Non-Caucasian	1 (6)	
BMI (kg/m^2)	23.2 (5.5)	24.6-32.1
Stage		
I	6 (38)	
III	1 (6)	
IV	9 (56)	
Presence of Bone Metastases	4 (25)	
Time Since Diagnosis (months)	16 (14)	1-48

Primary Treatment Type	
Chemotherapy	7 (43)
Surgery	6 (38)
Radiation	3 (19)
Treatment Status	
On Treatment	10 (62)
Following Treatment	6 (38)
Treatment During Intervention Period	
Targeted Therapy	4 (40)
Immunotherapy	3 (30)
Chemotherapy	3 (30)

Recruitment and Retention

Of the 677 participants who received a letter with details about the study or who were approached by research staff in clinic, 86 lung cancer survivors were screened for eligibility and invited to participate in the study, however 45% were ineligible and 35% declined to participate citing transportation barriers (n=18), lack of time (n=6), already exercising (n=2) and other unknown reasons (n=14) (Figure 2). Sixteen individuals were eligible and consented to participate in the study. Average retention at 6-weeks was 56%. Four individuals withdrew from the study due to entry into hospice or homecare, two of whom were deceased within 12-weeks of withdrawing while three participants withdrew from the study due to hospitalization for chronic obstructive pulmonary disorder (n=2) or rotator cuff surgery (n=1). Of participants who withdrew from the study four (57%) had stage IV cancer, three of which were on an adjuvant targeted therapy and one was on adjuvant chemotherapy, while three (43%) had stage I cancer and had recently completed surgery, with one participant who had completed surgery and was undergoing chemotherapy during the study. The participants who withdrew had a median time since diagnosis of 14.0 months (range 1-36 months) compared to 17.0 months (range 1-48 months) among those who completed the trial. At 12-weeks, the retention rate remained at 56% as no additional participant withdrawals occurred by week-12 of the study.

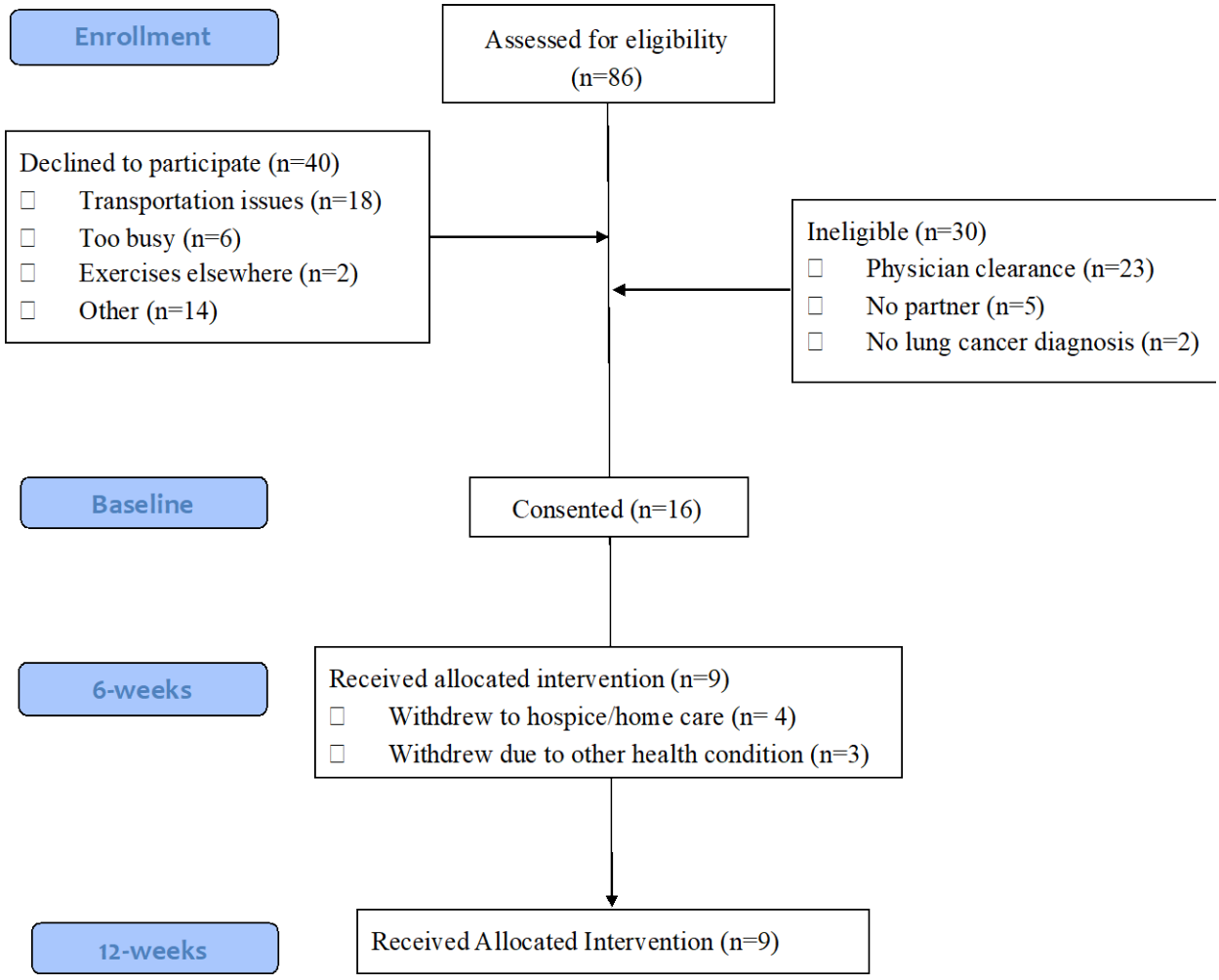


Figure 2. Flow of participants throughout the study

Adherence and Safety

Adherence to the intervention was 80% over weeks 1-6 and 92% over weeks 7-12, among participants (n=9) who completed testing at 6 and 12-weeks. There were no deviations from the yoga protocol among participants who completed the intervention. Among participants who withdrew from the intervention prior to 6-week testing, planned adaptations (i.e. participants maintained a seated or lying position) were made in order to adjust the intensity and complexity of poses within the yoga protocol. Adherence in participants who withdrew from the intervention

was 17% prior to withdrawing before 6-weeks. Two mild adverse events occurred out of a total of 84 yoga classes (2.4%) and included chronic low back pain (n=1) and light headedness and nausea (n=1). The chronic low back pain was pre-existing to the yoga intervention and caused the participant to withdraw from the study in order to seek physical therapy before returning to an exercise program. The light headedness and nausea quickly resolved following the administration of oral glucose and rest as recommended by the American College of Sports Medicine Guidelines for Exercise Prescription and Testing (Pescatello, 2013). There were no serious adverse events.

Outcome Measures

Non-parametric and Glass's effect sizes are provided in Table 2, while below we describe Glass's effect sizes and 95% CIs. Each outcome measure improved over baseline to 6-weeks when supervised practice was twice weekly and then generally plateaued over the second half of the program when supervised practice was reduced (Figures 3A-F). A 12% improvement (45 meters) in 6-minute walk distance occurred from baseline (mean=379.14 $\pm$94.49) to 6-weeks (mean=424.00 $\pm$76.22) yielding a medium effect size (d=0.57, 95%CI: -0.49, 0.70). Chair stand time improved by 18% (2.30 seconds) from baseline (mean=12.84 $\pm$7.88) to 6-weeks (mean=10.54 $\pm$5.33) yielding a small effect size (d=0.29, 95% CI: -0.13, 1.13). Hand grip strength improved by 2.5% (0.71 kilograms) from baseline (mean=28.11 $\pm$10.60) to 6-weeks (mean=28.82 $\pm$10.14) yielding a small effect size (d=0.07, 95%CI: -0.10, 1.18). Back scratch and sit and reach tests improved by 59% and 53% (11.64 and 8.99 centimeters), respectively, from baseline (back scratch mean=19.69 $\pm$13.54; sit and reach mean=16.99 $\pm$7.59) to 6-weeks (back scratch mean=8.05 $\pm$10.67; sit and reach mean 8.00 +9.24) yielding large effect sizes (back scratch d=0.76, 95% CI: 0.26, 1.73 and sit and reach d=1.11, 95% CI: -0.16, 1.09). Physical performance battery summary

score improved by 5% (0.56 points, with the maximum possible score of 12 points) from baseline (mean=10.44 +1.74) to 6-weeks (mean=11.00 ±1.32) to yield a medium effect size (d=0.32, 95% CI: -0.28, 0.93).

Improvements in each physical function and fitness outcomes were also seen across the entire 12-week period of the study. Six-minute walk distance improved by 8% (33 meters) from baseline to 12-weeks (mean=411.62 ±80.93) yielding a medium effect size (d=0.34, 95% CI: -0.30, 0.31). Chair stand time improved by 15% from baseline to 12-weeks yielding a small effect size (d=0.24, 95% CI: -0.11, 1.33) and exploratory comparisons of means between baseline and 12-weeks revealed a statistically significant improvement (p=0.038). Hand grip strength improved by 5% from baseline to 12-weeks (mean=29.64) yielding a small effect size (d=0.14, 95% CI: 0.16, 1.77) and exploratory comparisons of means between baseline and 12-weeks revealed a statistically significant improvement (p=0.021). Back scratch distance improved by 39% from baseline to 12-weeks (mean=9.52 ±8.64) yielding a medium effect size (d=0.30, 95% CI: -0.09, 1.36) and an exploratory statistically significant change in means (p=0.005). Sit and reach distance improved by 59% from baseline to 12-weeks (mean=6.55 ±13.76) yielding a large effect size (d=1.25, 95 CI: 0.14, 1.29). Physical performance battery total score improved by 5% yielding a small effect size (d=0.05, 95 CI: -0.29, 1.07).

Table 2

Non-Parametric Effect Sizes and Within Group Comparisons of Objective Physical Function and Fitness from Baseline to 6-weeks and Baseline to 12-weeks

Variable	**Baseline (n=16)**		**6-Weeks (n=9)**		**Within Group Difference**			**12-Weeks (n=9)**		**Within Group Difference**		
	Mean	SD	Mean	SD	p	d_z	Glass's Δ (95% CI)	Mean	SD	p	d_z	Glass's Δ (95% CI)
6-minute walk distance (m) ↑	379.14	96.49	424.00	76.22	0.110	.31	0.57 (-0.49, 0.70)	411.63	80.90	**0.021**	0.44	0.34 (-0.30, 0.31)
Chair Stand (sec) ↓	12.84	7.88	10.54	5.33	0.139	0.29	0.29 (-0.13, 1.13)	10.93	7.78	**.038**	0.39	0.24 (-0.11, 1.33
Hand Grip Strength (kg) ↑	28.11	10.60	28.82	10.14	0.173	0.27	0.07 (-0.10, 1.18)	29.64	10.56	**0.021**	0.44	0.14 (0.16, 1.77)
Back Scratch (cm) ↓	18.40	13.54	8.05	10.67	0.008	0.52	0.76 (0.26, 1.73)	9.52	8.64	**0.005**	0.35	0.30 (-0.09, 1.36)
Sit and Reach (cm) ↓	16.08	7.59	8.00	9.24	0.115	0.31	1.11 (-0.16, 1.09)	6.55	13.76	0.154	0.27	1.25 (-0.14, 1.29)
PPB Sum	10.44	1.74	11.00	1.32	0.317	0.19	0.32 (-0.28, 0.93)	11.11	1.17	0.276	0.20	0.05 (-0.29, 1.07)

Significant differences ($p<0.05$) in bold. ↓ indicates a decrease is a positive change. ↑ indicates an increase is a positive change.
d_z, Cohen's effect size; ES, non-parametric effect size; in, inches; kg, kilograms; m, meters; SD, standard deviation sec, seconds.

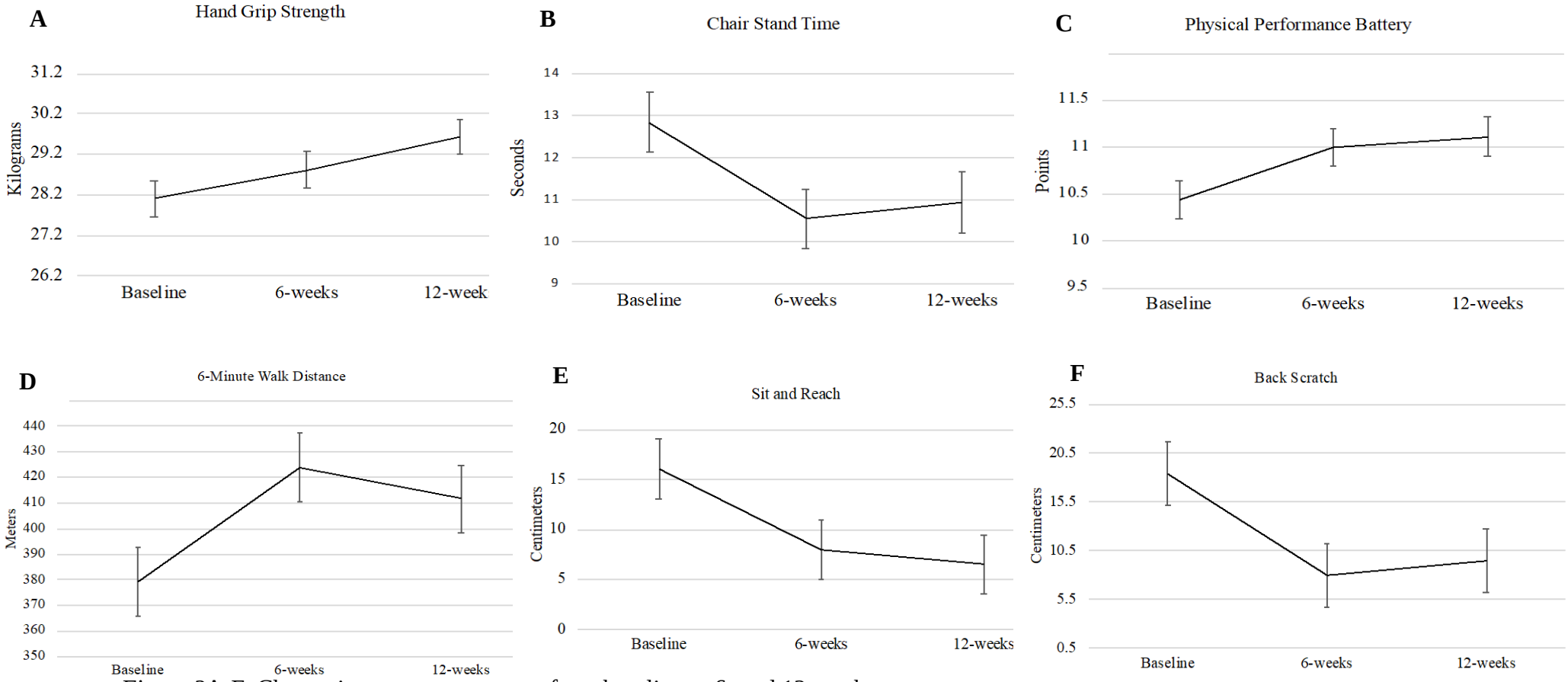


*Figure 3*A-F. Change in outcome measures from baseline to 6- and 12-weeks
A. Hand grip Strength **B.** chair stand time **C.** physical performance battery **D.** 6-minute walk test **E.** sit and reach **F.** back scratch. Line plots indicating average change across 12-weeks. Error bars indicate standard error.

Discussion

In our sample of lung cancer survivors across range of disease severity and treatment status, a 12-week vinyasa style yoga program was a modestly feasible, safe, and potentially beneficial modality of exercise to improve physical function. Preliminary trends toward improvements in physical function were demonstrated in a population that without intervention experiences a decline in physical function (Brown et al., 2005; Granger et al., 2014; Ha et al., 2018). Though retention was below our target of 80% due to early participant withdrawal for poor health, adherence to supervised practice among those participants who were able to complete the intervention exceeded the target goal. Our study suggests that a facility-based supervised yoga program may not be initially feasible for individuals who are more medically fragile. Other approaches, such as tele-rehabilitation are being studied in advanced-staged cancer patients and could be a more appropriate option for survivors who are on medically frail (Cheville, Moynihan, Herrin, Loprinzi, & Kroenke, 2019). In lung cancer survivors whose health status is allows them to travel to and participate in a supervised yoga program, yoga seems feasible and beneficial.

Despite the prescription of a physical yoga program involving postures that require activation of multiple large muscle groups (i.e. warrior I, II and chair poses) and balance (i.e. tree pose), no serious adverse events occurred demonstrating that physical yoga, in contrast with other yoga programs that focus on breathing and meditation (Fouladbakhsh et al., 2014; Milbury et al., 2015), may be safe for those with lung cancer. Our study was the first yoga trial to include metastatic lung cancer survivors. Among our sample 56% had metastatic cancer and 25% of participants had bone metastases. Two participants with bone metastases withdrew from the study but notably, concerns of safety were not cited as reasons for withdrawal. Current exercise guidelines often do not apply to survivors with metastatic cancer due to the limited number of trials

that have included survivors with metastatic cancer (Nadler, Desnoyers, Langelier, & Amir, 2019). Additionally, physicians have expressed concerns around the safety of exercise in the metastatic setting given the lack of evidence to demonstrate safety (Nadler et al., 2017; Tsiouris et al., 2018).

To our knowledge our pilot trial is the first study to evaluate the benefits of yoga on physical function outcomes in patients that span the treatment trajectory since more than half of our sample was in active treatment. While other studies of yoga in lung cancer are few, the two small pilot trials in lung cancer survivors showed that yoga was feasible post cancer treatment and improved anxiety, mental health, sleep disturbances, and spiritual wellbeing (Milbury, Chaoul, et al., 2015) and improved lung function (Fouladbakhsh et al., 2013). In our study effect sizes were large in flexibility outcomes (back scratch and sit and reach), and medium effects were seen in submaximal aerobic capacity (6-minute walk distance) outcomes across the 12-week program. The average improvement in 6-minute walk distance was greater than the minimally important clinical distance of 42 meters reported in lung cancer survivors (Granger, Holland, Gordon, & Denehy, 2015), though was lower than the mean difference (69.33 meters) reported in a systematic review of six aerobic and resistance training interventions conducted in advanced lung cancer survivors (Peddle-McIntyre et al., 2019). Chair stand time improved more than the minimally important clinical difference of 1.7 seconds reported in patients with chronic obstructive pulmonary disease (Jones et al., 2013). The largest improvements in outcomes were seen within the first 6-weeks of the trial when participants attended two supervised yoga sessions per week, whereas improvements seemed to plateau over weeks 7-12 when in person yoga sessions were reduced. The larger initial improvements demonstrate the exercise training principle of diminishing returns when non-exercisers who begin an exercise program are likely to experience initial gains, but the magnitude will decrease over time unless the training load is increased (Neil-Sztramko et al., 2019). Despite

our intentions of transitioning survivors to independent exercise, our results indicate that if further functional improvements are desired, supervised classes may yield superior benefits to home-based exercise, a finding that is supported by a previous systematic review of exercise trials, including yoga, in cancer survivors (Stout, Baima, Swisher, Winters-Stone, & Welsh, 2017). Yet, the plateau in improvements after supervised sessions were reduced demonstrates that the benefits of yoga could be maintained with home-based exercise which is desirable in lung cancer survivors (Wasley et al., 2018) and is cost effective (Ha et al., 2019).

Our yoga intervention resulted in benefits that are similar to those achieved with aerobic or resistance training programs to improve components of physical function in lung cancer survivors (Granger et al., 2011; Peddle-McIntyre et al., 2019). A study that prescribed high intensity aerobic and resistance training for 60-minutes, thrice per week, for 20-weeks, 5-7 weeks after surgery found an improvement in hand grip strength of 2.4 kilogram (Edvardsen et al., 2015) whereas we saw a 1.5 kilogram improvement. A study of 23 post-surgical lung cancer survivors reported a 35 meter improvement in 6-minute walk distance after twice weekly cycling (intensity: 60-80% of peak cycling load) and “muscle training” sessions for 12-weeks, whereas we saw a 45 meter improvement in our sample of lung cancer survivors. Our preliminary results indicate that yoga could have benefits similar to traditional forms of exercise training. No studies of aerobic and resistance training have measured changes in range of motion (Medysky et al., under review) In our yoga study we found improvements in upper and lower body flexibility, an outcome not measured in aerobic or strength training trials in lung cancer, but one that is associated with a functional outcomes in older adults (Bergstrom et al., 1985), which may suggest a unique benefit of yoga over other modalities. The preliminary evidence from our 12-week yoga program suggests that yoga could be a useful type of exercise in addition to aerobic and resistance training,

particularly as yoga requires minimal equipment, can be modified according to individual levels of functioning and performed at a low intensity in survivors during or following treatment.

There were limitations to this study. We did not track participant adherence for at home yoga sessions but rather focused on delivery and receipt of supervised training, thus the full dose of yoga attained by participants is unknown. It is unclear if the plateaus in improvements were a result of a decline in the frequency of training or if the participants had reached a ceiling in improvements. Since our study focused on feasibility and we were concerned about participant burden, we did not add methods to track intensity during the program such as the use of heart rate monitors, thus we don't have a quantifiable way to report intensity or progression of intensity of yoga practice to compare to conventional aerobic and resistance training protocols. However, among participants who completed the study no modifications were required thus the yoga program as delivered and based on prior work was felt to be low to moderate intensity. Future studies should use heart rate monitors or obtain a rating of perceived exertion periodically throughout each yoga session in order to better track and report the intensity at which participants are exercising at. Rolling recruitment limited our ability to follow a standardized progression of poses in supervised classes that could be made up of participants who were at various time points within the study, however an attempt to follow a progression of poses was made, as detailed in the supplementary materials. The small sample size limited our ability to employ more robust statistics to better determine the effects of yoga on physical function and contributes to the increased margin of error in our estimates. The single group study design selected to match our aim of feasibility threatens internal validity such that we cannot draw firm conclusions regarding the efficacy of yoga to improve physical function without considering alternative causes of the positive improvements in function, such as changes in treatment status, symptoms, and other predictors of

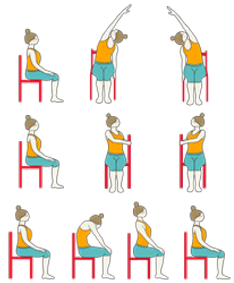
physical function (Bennett et al., 2006) or the possibility of a learning effect in the outcome measures. However, the observed effect sizes suggest that a larger fully-powered randomized controlled trial to determine the efficacy of yoga on physical function in lung cancer survivors is warranted. Research staff who collected the data was not blinded to the intervention thus the results could be influenced by experimenter bias. To limit bias research staff followed standard operating procedures for all outcome measures.

Conclusion

Physical function is a particularly important consideration in the treatment, management, and survivorship of lung cancer. A 12-week vinyasa yoga trial was found to be safe and feasible in survivors who were not medically frail, which could support recommendations that survivors can benefit from low intensity exercise programs such as yoga. The 12-week yoga trial demonstrated preliminary evidence to support improvements in physical function in a cancer population that without intervention, experiences declines in physical function. Future randomized controlled trials to determine the efficacy of yoga on physical function in lung cancer survivors, both on and immediately following treatment, are warranted.

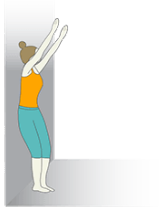
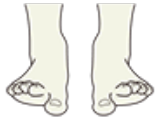
Supplementary Material

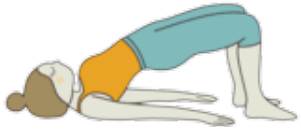
Table A. Detailed Description of Prescribed Yoga Program Including Modifications, Illustrations, Duration Held, and Inclusion in the Progression for each Yoga Pose.

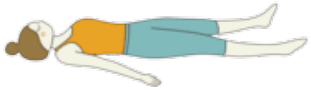
				~Progression (weeks)					
English Pose Name *Sanskrit Post Name*	**Modifications**	**Illustration**	**~Duration of Pose**	**1/2**	**3/4**	**5/6**	**7/8**	**9/10**	**11/12**
Seated Relaxation	n/a		1 minute	x	x	x	x	x	x
Seated Breathing Sequence Single arm extension, double arm extension, overhead with back bend, seated twist	n/a		30 seconds each	x	x	x	x	x	x
Modified Downward Dog *Adho Mukha Svanasana*	↓Arms extended against a surface that is higher than the head (pictured)		1 minute	x	x	x	x	x	x

Modified Cat/Cow *Bitilasana/Marjaryasana*	↓Seated in chair with palms on thighs, gentle chest extension and flexion (pictured)		1 minute	x	x	x	x	x	x
Mountain to Forward Fold *Tadasana to Uttanasana*	↓Seated with arms over head to a seated forward fold or if standing half fold onto a chair rather than full forward fold		~8x	x	x	x	x	x	x
Warrior I (left and right) *Virabhadrasana I*	↓Seated on the side of a chair with legs in a pseudo-lung position with arms over head (pictured)		1 minute, 2x/side	x	x	x	x	x	x
Warrior II (left and right) *Virabhadrasana II*	↓Seated on the side of a chair with legs in a pseudo-lung position with arms extended off shoulders (pictured)		1 minute, 2x/side		x	x	x	x	x

Star *Utthita Tadasana*	↓Seated with legs wide and arms extended over head		1 minute, 2x/side	x	x	x	x	x
Extended Side Angle *Utthita Parsvakonasana*	↓Side stretch seated in chair (pictured)		1 minute, 2x/side		x	x	x	x
Extended Triangle *Utthita Trikonasana*	↓Side stretch seated in chair with 1 leg extended long		1 minute, 2x/side			x	x	x
Goddess *Utkata Konasana*	↓Seated with legs out wide and knees bent, arms extended		30 secondsx2			x	x	x

Chair *Utkatasana*	↓Wall sit (pictured)		30 seconds x2			x	x	x	x
Calf Raises	↓Seated in chair with balls of the feet pressed into the floor (pictured)		Hold 5 seconds, rest 5 second, x5	x	x	x	x	x	x
Toe Raises	↓Seated in chair with heels pressed into the floor		Hold 5 seconds, rest 5seconds, x5	x	x	x	x	x	x
Hip Abduction	↓Assist balance by holding wall, chair, ballet bar		Abduct 5 seconds, adduct 5 second, x5	x	x	x	x	x	x
Tree *Vrksasana*	↓Seated with arms extended; ↑Standing with arms extended overhead.		30 seconds/side			x	x	x	x

Seated Hamstring Stretch	n/a		30 seconds/side	x	x	x	x	x	x
Assisted Back Scratch	n/a		30 seconds/side	x	x	x	x	x	x
Childs *Balasana*	↓Bolster for head or bottom (pictured)		1-2minutes	x	x	x	x	x	x
Thread the Needle	↓Seated tricep stretch		30 seconds/side	x	x	x	x	x	x
Bridge *Setu Bandhasana*	↓Seated pelvic tilt and tuck		Increasing from 8-14reps	x	x	x	x	x	x

Knees to Chest *Apanasana*	↓Seated with one knee to chest at a time		30 seconds	x	x	x	x	x	x	
Corpse *Savasana*	↓Props used to elevate legs if supine or participant seated in a chair		5 minutes	x	x	x	x	x	x	

↓, less difficult modification; ↑, more difficult modification.
Illustrations from www.tummee.com

Chapter VI

Discussion, Summary and Implications

Mary E. Medysky, MSc

Discussion

Lung cancer survival rates are increasing. Evidence in support of low-dose computed tomography screening for lung cancer in high risk individuals (Aberle et al., 2011; Wang et al., 2016) has contributed an increased number of people that are diagnosed with early stage lung cancer that is potentially more curable. The American Cancer Society predicts that there will be more than 673, 000 lung cancer survivors in the U.S. by 2026 (American Cancer Society, 2018). Improving survival rates creates a need for studies of lung cancer survivors that focus on improving the chronic management of lung cancer, including persistent treatment related symptoms and physical side effects in order to optimize quality of life.

Accordingly, the purpose of this program of research was to fill the gaps in what was unknown about symptoms and side-effects that may contribute to low physical function and how exercise could play a role as a rehabilitative strategy. This discussion will present a summary of the findings from four manuscripts (Chapters II-V, not presented in numerical order), along with an integration with previous research centered on three areas: 1) symptom science in lung cancer survivorship, 2) application of yoga as an exercise modality for cancer survivors, and 3) exercise trials in lung cancer survivors. Following this, the dissertation will be summarized and theoretical, practical and methodological implications will be discussed, and strengths, weakness and directions for future research will be described.

Symptom Science in Lung Cancer Survivorship

The first key area where this program of research has contributed is symptom science in lung cancer survivorship. Symptom science is the study of the self-reported perceptions of an individual's experience of disease or physical disturbance. Symptom science informs targets for therapeutic and clinical interventions (Cashion, Gill, Hawes, Henderson, & Saligan, 2016).

Maintaining sufficient physical functioning in lung cancer survivors is a important to survivors, their families, health care providers and health insurance providers because of the known pathway from functional decline to disability (Lollar & Crews, 2003) where more severe disability states are associated with a significantly high medical cost (Dai, Roberto, Tom, Gentry, & Stuart, 2017).

Chapter II of this dissertation examined physical function across multiple time points over the first 12-18 months after a lung cancer diagnosis. Since over half of lung cancer survivors are expected to live 5 or more years past diagnosis (Siegel et al., 2019), understanding how physical function continues to change in the longer term can provide information that can be used for long term management of lung cancer and to guide potential interventions to improve quality of life, mitigate chronic disablement and reduce mortality. To the best of our knowledge only one other study (Koczywas et al., 2013) assessed long term changes (i.e. >1 year) in physical functioning in lung cancer survivors and found that though physical function fluctuated when measured four times over 24 weeks, physical function decreased over time. It was unknown if the "fluctuations" in physical function were a result of high amounts of variability of physical function among individual lung cancer survivors and/or if other symptoms were contributing to the fluctuations in physical function. Chapter II utilized a robust statistical model to explore whether or not there were different individual trajectories of physical function that could not be detected by looking at average changes within survivors. The results indicated that individual trajectories of physical function exist in lung cancer survivors suggesting that some patients decline more so than others and that figuring out what may drive these differences is important. Worsening fatigue was associated with lower physical function suggesting that this symptom could be a potential mechanism for declining function and also a target for intervention.

The results Chapter II are informative for optimal clinical management where resource allocation may not be universal. Identifying fatigue as a key symptom contributing to low physical function could allow for better targeted and personalized clinical management as it is known that targeting specific subgroups of individuals with high fatigue and low physical function during or immediately following treatment will lead to the best improvements (Buffart et al., 2018). Survivors identified with high fatigue could be triaged first to rehabilitative programs to improve function before further functional declines occur.

After describing yearlong trajectories of physical function and symptoms in Chapter II, a pilot trial of yoga was employed as a potential therapeutic strategy to improve physical function. The feasibility of a vinyasa yoga program in survivors on and completed treatment was unknown, thus a pilot feasibility design was employed. Retention rates were below target rates of 80% over 12 weeks with 7 participants withdrawing early on due to poor health, however among those who stayed in the trial adherence was high (80% and 92% at 6 and 12-weeks respectively) across the 12-week intervention demonstrating feasibility in participants who were able to complete the intervention. Yoga may not be the appropriate rehabilitative approach for medically fragile lung cancer survivors and other approaches, such as tele-rehabilitation are being studied in advanced-staged cancer patients and could be a more appropriate option for survivors who are on hospice/home-care (Cheville et al., 2019). No serious adverse events occurred during the trial in a sample of lung cancer survivors that included those with metastatic disease including bone metastases. Thus, yoga was found to be a safe modality of exercise in a sample of cancer survivors who are often excluded from exercise trials because there is limited evidence regarding the safety of exercise in advanced stage cancer survivors (Nadler et al., 2019). Yoga may be a useful

therapeutic alternative to traditional aerobic and resistance training where musculoskeletal injuries have been reported (Heywood, McCarthy, & Skinner, 2017) in lung cancer survivors.

While previous studies have assessed psychosocial changes following a yoga intervention in lung cancer survivors (Fouladbakhsh, Davis, & Yarandi, 2013; Milbury et al., 2015), our yoga intervention (Chapter V) was the first to assess changes in physical function. The yoga intervention yielded medium to large effect sizes in objective measures of physical function, thus demonstrating preliminary evidence to suggest that yoga could be a potential therapeutic strategy to improve physical function in lung cancer survivors. The yoga trial was limited by a small, single-group sample thus threats to internal validity are present, yet the trial demonstrated feasibility and benefits for a subgroup of participants. Thus a fully powered randomized controlled trial (RCT) is warranted to determine the efficacy of yoga on physical function in lung cancer survivors.

Application of Yoga as an Exercise Modality for Cancer Survivors

The second key area to which this program of research has contributed is the application of yoga as an exercise modality in cancer survivors. Yoga is a set of principles and practices to promote health and well-being through the integration of the body, breath and mind (Hayes & Chase, 2010). This dissertation studied yoga in its physical form as a type of exercise. Though yoga is an increasingly popular intervention applied in cancer survivors and preliminary evidence has accumulated in support of yoga for improving psychosocial outcomes such as anxiety, depressive symptoms, pain, and biomarkers of stress, inflammation and immune function (Danhauer et al., 2019), yoga is excluded as a recommended modality in exercise guidelines for cancer survivors (Campbell, et al., in press). In order for exercise guidelines to be developed that include yoga interventions appropriate and quality exercise interventions need to carefully match

the FITT formula to the study goals through the attention to the basic principles of exercise training (K.M. Winters-Stone et al., 2014).

It was unknown if studies of yoga employed the principles of exercise training, FITT components or adherence of participants to the FITT components. In Chapter IV we summarized and critically evaluated studies of yoga in cancer survivors. We found that the majority (56%) of studies applied only two of the six principles of exercise training in the yoga intervention design and the components of the exercise prescription (FITT) were not well-reported nor was the adherence of participants to each FITT component. Chapter IV contributes to the field of yoga research by making concrete suggestions to improve the application of yoga as a modality of exercise for cancer survivors so that yoga could eventually be icluded in exercise recommendations for cancer survivors.

Integrated with the recommendations provided in Chapter IV, Chapter V employed a pilot yoga intervention that was designed intentionally to consider the principles of exercise training and FITT components. The application of both the principles of exercise training and FITT components within the yoga intervention are rated following our criteria in Chapter IV, and are summarized in Table 1.

Table 1

Summary and Ratings of the Application of the Principles of Exercise Training and FITT Components in the Yoga Intervention (Chapter V)

Principles of Exercise Training		
Principle	**Rating**	**Application in the Yoga Trial**
Specificity	+	The type of yoga and poses were selected specific to the aims of the study. The poses were chosen to stretch and strengthen the muscles and improve balance, which are the pillars of physical function.
Progression	?	The poses were planned to be progressed from less difficult to more difficult as participants advanced through the program. Due to the rolling recruitment it was not possible to retain a standardized progression at all times.

Overload	?	Participants had recently completed treatment or were on treatment thus participants initially had low physical function. The poses prescribed were of sufficient intensity per their baseline capacity, however no formal baseline test was conducted to confirm baseline capacity.
Initial Values	+	None of the participants actively participated in yoga upon initiation into the trial.
Reversibility	-	Not applied
Diminishing Returns	-	Not applied
		FITT Components
Component	**Rating**	**Application in the Yoga Trial**
Frequency	+	Weeks 1-6: 2x/week supervised, 1x/week home-based. Weeks 7-12: 1x/week supervised, 2x/week home-based.
Intensity	-	A specific intensity was not prescribed.
Time	+	60 minutes per session.
Type	+	Vinyasa. Specific poses and modifications detailed within the manuscript.

Due to practical constraints with a pilot study we were also limited, not all of the principles of exercise training and FITT components could be applied or reported. Reversibility and diminishing returns require a follow-up assessment after the exercise intervention ends which requires more financial and research staff resources not afforded by the pilot study. Similarly, the intensity was not recorded via heart rate monitors or rate of perceived exertion due to limited funds to purchase heart rate monitors and availability of staff time to record rate of perceived exertion. Both of these limitations are common in pilot studies though should be key considerations in rigorously designed and properly powered controlled trials (Leon, Davis, & Kraemer, 2011).

Exercise Oncology in Lung Cancer Survivors

The third key area to which this program of research has contributed is exercise oncology within the lung cancer population. Exercise oncology is the study of exercise with the intention of attenuating negative symptoms and side effects throughout the cancer trajectory that can range

from diagnosis to long-term survivorship. We have contributed to the field of exercise oncology by studying lung cancer survivors, critically reviewing current exercise RCTs and expanding what is known about yoga as a potential therapeutic strategy to be included in exercise oncology recommendations.

First, this dissertation work contributes to the exercise oncology field by studying the lung cancer population. Lung cancer is understudied despite lung cancer being the second most common type of cancer in both men and women (Siegel et al., 2019). In Chapter III a review of exercise RCTs in lung cancer survivors that assessed physiological outcomes revealed that only 15 studies have been published to date, which is 1-1.5 times fewer trials than those in breast or prostate cancer, respectively. Reasons for why lung cancer survivors are understudied could include that lung cancer survivors are a population that face more unfavorable outcomes than individuals with other cancer types such as breast or prostate cancer and require complicated treatment plans making interventions particularly difficult in studies that require weekly in-person attendance (Johnsen et al., 2009). Additionally, lung cancer survivors experience stigma, shame and blame for having caused their cancer from smoking such adds a barrier to seeking care and participation in research trials (Chapple, Ziebland, & McPherson, 2004). Interestingly, up to 20% of people who die from lung cancer in the United States have never smoked or used any form of tobacco (American Cancer Society, 2018).

We added to the number of exercise studies in the lung cancer population with the first yoga intervention to assess the impact of a non-traditional and low intensity exercise program on physical function (Chapter V). The yoga intervention was especially notable as it included metastatic survivors who are often excluded from exercise studies for safety reasons. The most recent systematic review of exercise trials that included metastatic patients found only 15 studies

across all cancer types (Nadler et al., 2019), of which severely limits the ability for exercise to be safely prescribed in these patients. Our trial adds important data that could be summarized in future systematic reviews in order to create guidelines and recommendations for metastatic lung cancer survivors.

To continue filling gaps in what is known about exercise oncology in lung cancer survivors a summary, critical evaluation and recommendations were made to strengthen the design and reporting of exercise RCTs in lung cancer survivors. A review of the exercise RCTs in lung cancer survivors across stages of treatment and disease that critically evaluates studies to determine if the principles of exercise training are upheld and if the FITT (frequency, intensity, time and type) components and adherence of participants to prescribed programs are clearly reported had not yet been conducted. The principles of exercise training and FITT components are inconsistently utilized and reported in exercise RCTs and thus may contribute to the variability in findings reported on the efficacy of exercise for lung cancer survivors (Granger et al., 2011; Peddle-McIntyre et al., 2019). The results of this systematic review illustrate the opportunity and provide recommendations for investigators to strengthen the field by designing and reporting on exercise prescriptions based on the principles of training and FITT components. One approach could be that adherence to the intensity and time of yoga practice could be tracked by collecting heart rate and activity data with actigraphs.

The major limitation of the chapters within this program of research that contribute to exercise oncology in lung cancer survivors is the small sample size of participants enrolled in the yoga trial and the small number of RCTs included in the review. The small sample size does not enable claims to be made about the efficacy of exercise for lung cancer survivors, though the preliminary evidence and descriptive results provide a framework for future larger studies.

Summary and Implications

Some lung cancer survivors may experience greater declines in physical function than others that may be driving by fatigue and without intervention may eventually result in disability. Fortunately, studies of exercise have been suggested as a rehabilitative strategy. Our systematic review of exercise RCTs found that the principles of exercise training were not consistently applied and the exercise prescriptions were not adequately reported on. Studies of yoga do not yet fully utilize the principles of exercise training within the study design and inadequate reporting of both the yoga prescription and adherence of participants may contribute to the current exclusion of yoga as a rehabilitative strategy in cancer survivors. However, our pilot study of a 12-week yoga intervention suggests it could be another type of exercise besides traditional aerobic and resistance training that could be safe and feasible in lung cancer survivors who are able to participate in supervised practice (Chapter V). Altogether this program of research has made progress toward characterizing and optimizing physical function in lung cancer survivors.

Theoretical Implications

The Conceptual Model of Physical Function in Cancer Survivors (Bennett et al., 2006) was used to guide this dissertation work. The model provides a framework for how predictors, symptoms and side effects can contribute to declines in physical function, in order to guide the application of intervention strategies to reduce the onset of disability. The cumulative results from Chapters II-V were mapped onto The Conceptual Model of Physical Function in Cancer Survivors further corroborating the utility of this model as a guide for cancer survivorship studies aimed at physical function.

Future programs of research that use the Conceptual Model of Physical Function in Cancer Survivors as a framework might consider the variability in trajectories of physical function as described in Chapter II and how variability in physical function, predictors, symptoms and/or side effects could have implications for identifying patients in need of intervention and guiding the selection of different types of interventions. The important concept of variability in physical function, predictors, symptoms and/or side effects was shown in the yoga trial (Chapter V) where seven participants withdrew from the yoga intervention who were medically fragile. Four dropouts had stage IV disease and were unable to attended classes because they required at home care and three dropouts had stage I disease but other health conditions requiring hospitalization. Yoga may not have been the appropriate intervention for the participants who were in poorer health. Instead interventions such as tele-rehabilitation might be more appropriate for survivors who are on hospice/home-care (Cheville et al., 2019) in order to reduce barriers to participating in supervised exercise such as fatigue (Mikkelsen, Nielsen, Vinther, Lund, & Jarden, 2019) or travel (Sheill, Guinan, Brady, Hevey, & Hussey, 2019). In the remaining 11 participants who completed the trial adherence was high and yoga appeared to improve physical function. Future iterations or use of the Conceptual Model of Physical Function in Cancer Survivors should consider the importance of recognizing that variability in physical function, predictors, symptoms and/or side effects could exist and have implications for selecting the optimal intervention strategy for each individual survivor.

Methodological Implications

This program of research employed advanced statistical methods and strong methodological approaches to guide critical reviews of the state of the literature in yoga and exercise in lung cancer survivors. Multi-level modeling (MLM) was used as a robust statistical

method to take a deeper look into how physical function changes within individual lung cancer survivors. Our study was the first to use MLM to assess physical function over one year in lung cancer survivors. The use of MLM was a timely contribution to the exercise oncology field which is beginning to shift toward understanding individual responses to cancer and its treatment, as well as exercise training (Hecksteden et al., 2015).

We used a systematic review to critically evaluate exercise studies in lung cancer survivors and studies of yoga in all cancer types. Though previous systematic reviews of exercise studies have summarized the current knowledge base of exercise for lung cancer survivors (Peddle-McIntyre et al., 2019; Sommer et al., 2018), no study had critically evaluated the design and reporting of the integral components of the exercise prescription, thus the quality of exercise prescriptions and reporting was unknown. Our systematic review of exercise RCTs in lung cancer survivors has filled this gap by identifying problems in the design and reporting of exercise studies that currently limit our understanding of the types and doses of exercise that can improve a variety of cancer-related health outcomes in lung cancer survivors. Our systematic review that critically evaluates the design and reporting of the integral components of the exercise prescription in yoga interventions also should advance the science of exercise oncology. This review provides a novel appraisal of the design and reporting of yoga interventions with implications for if and how yoga may be included in future exercise recommendations for cancer survivors.

Finally, we piloted a yoga intervention intentionally rooted in the principles of exercise training that reported the FITT components. Though the yoga intervention has limitations inherent to a pilot study design as explained above and in Chapter V, the yoga intervention provides an example of how the many of the principles of training and FITT components can be employed in a yoga intervention. Additionally, the pilot yoga study provided effect sizes, rather than only

comparisons of means, that could be used in the future larger trials in order to determine the number of participants likely required to avoid type II error (Sullivan & Feinn, 2012).

Clinical Implications

This program of research provides new information to support clinical practice that could enhance clinical care for lung cancer survivors. Primarily, characterizing patterns in self-reported physical function and co-occurring symptoms in lung cancer survivors (Chapter II) could assist clinicians in understanding that lung cancer survivors experience changes in physical function at different rates and that fatigue could signal impending functional declines. With this knowledge health care providers could anticipate and manage threats to physical function by monitoring symptoms, like fatigue. Further, health care providers could educate patients on what to expect following treatment, and seek rehabilitative strategies that may target symptoms and side effects that underlie functional declines. By mitigating declines in physical function, the risk of disability and loss of independence could be delayed or avoided (Jack M Guralnik, Fried, & Salive, 1996), thus the implications of understanding changes in physical function and suggesting intervention strategies in clinical care are significant.

Beyond characterizing reductions in physical function, we have suggested yoga as a safe (i.e. no adverse events or withdrawals due to safety concerns) and potentially feasible modality of exercise for lung cancer survivors whose health was well enough for them to attend supervised yoga classes. Our study was the first to assess how yoga might improve physical function in lung cancer survivors. As yoga is an extremely popular type of exercise in Western culture (Danhauer et al., 2019), our study provides information that may be helpful to clinicians caring for lung cancer survivors in providing advice to patients about healthy behaviors, and to understand safety of yoga practice (Nadler et al., 2017). The Oncology Nursing Society (ONS) has a national quality

campaign, “Get Up Get Moving” to encourage oncology nurses to implement evidence-based change in practice and recommend physical activity to cancer survivors during cancer treatment. Our study of yoga may be considered by ONS when developing physical activity recommendations for cancer survivors during treatment. Currently there is no specific yoga prescription that is recommended in guidelines for cancer survivors (Campbell, et al., in press), however both our pilot trial and the review in Chapter IV will contribute to shaping how studies inform guidelines and how clinicians are able to refer patients to yoga programs.

Strengths and Weaknesses

This program of research has many strengths. First, two of the studies (Chapters II and V) used a longitudinal study design. Longitudinal study designs are advantageous because change over time can be assessed rather than describing an outcome at a single timepoint which is important in a clinical population where the rate and direction of change in physical function has associations with future disability and mortality (Guralnik, Fried, & Salive, 1996). Secondly, we have employed a robust set of both subjective (Chapter II) and objective measures (Chapter V) to assess physical function in lung cancer survivors. In much of the literature only a single method (i.e. self-reported physical function using the Medical Outcome Study short-form survey or fitness using a submaximal aerobic capacity test) to assess physical function is used (Brocki et al., 2014; Brunelli et al., 2007; Nomori, Watanabe, Ohtsuka, Naruke, & Suemasu, 2004), thus measuring a more composite view of physical function rather provides more rich data on the various components or upstream predictors of physical function (i.e. functional strength, flexibility, submaximal aerobic capacity) than a single measure.

Though this program of research has many strengths, there are also limitations. First, the participants that in both the secondary analysis and the yoga intervention were recruited from the

Portland metro area and accordingly was a mostly Caucasian and well-educated sample. The participants in the yoga study were all treated from a single academic medical center, of which the treatments commonly included costly clinical trials of immunotherapies and targeted therapies for advanced disease. Thus, our results can only be generalized to this subgroup of lung cancer patients. Future studies should target lung cancer survivors of diverse racial backgrounds and sociodemographic statuses to determine if declines in physical function and symptoms are more or less severe and if a employing a yoga intervention is feasible. Secondly, this dissertation work does not provide a clear mechanistic explanation for the changes in physical function reported without (Chapter II) intervention and after the yoga intervention (Chapter V) thus firm conclusions for the changes in physical function cannot be made. Moderation analyses of upstream predictors of physical function (i.e. symptoms, medications, treatments, body composition, fitness and sociodemographic factors) could be conducted in order to draw conclusions about the mechanisms contributing to changes in physical function. Future studies should conduct moderationor mediation analyses in a larger sample thus providing statistical power in order to better understand the mechanisms underlying changes in physical function. Finally, the two systematic reviews (Chapter III and IV) do not include meta-analytic data to suggest the efficacy of conventional exercise and yoga programs to improve physiological and psychosocial outcomes in cancer survivors. However, the novel aspect of these reviews is that the studies were critically evaluated around methodology in order to make recommendations that could strengthen the field by improving the design and reporting of exercise prescriptions, including yoga, in studies of lung cancer survivors

Future Research

Though this dissertation work has provided incremental, yet scientifically and practically useful new information, additional research is necessary to continue advancing lung cancer survivorship. Table 2 summarizes suggestions for future research within the three main topic areas of research within this dissertation. The immediate next step in this program of research would be to conduct a fully powered RCT of yoga in lung cancer survivors that employs the principles of training in order to determine the efficacy of yoga.

Table 2

Future Research in Lung Cancer Survivorship

Area of Research	Future Research Suggestions
Symptoms Science in Lung Cancer Survivors	- Assess physical function using objective measurement tools in longitudinal (>1 year) studies. - Use cross-lagged models to determine causality among physical function and symptoms. - Employ latent class models to determine sub-groups of survivors who exhibit the most severe symptoms. - Explore symptoms among survivors who have undergone newer targeted and immunotherapies.
Exercise Oncology in Lung Cancer Survivors	- Design exercise RCTs rooted in the principles of exercise training to better determine the efficacy of exercise for lung cancer survivors. - Determine the efficacy of yoga to improve performance outcomes in RCTs. - Determine the feasibility and safety of implementing a tele-video based yoga program in lung cancer survivors.
Application of Yoga as an Exercise Modality for Cancer Survivors	- Design and implement a RCT to determine the efficacy of yoga in lung cancer survivors. - Summarize future yoga studies to determine a prescription that could be included in exercise guidelines and recommended by clinicians to cancer survivors. - Determine preferences and barriers for participation in yoga for lung cancer survivors.

Conclusions

This dissertation has made meaningful contributions to the fields of symptom science and exercise oncology in lung cancer survivors as well as the application of yoga as a modality of

exercise in the cancer population. Important theoretical, methodological and clinical implications are imparted by this collection of research studies. This dissertation has immediate implications for the design and selection of exercise interventions to optimize rehabilitation in lung cancer survivors and points to the need for more research to improve the lives of lung cancer survivors.

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OREGON HEALTH & SCIENCE UNIVERSITY

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Appendix A: Human Research Subjects Informed Consent Form

OHSU Knight Cancer Institute Consent and Authorization Form: Participants with Lung Cancer

Title Pilot Study of A Progressive Exercise Program among Lung Cancer Patient-Partner Dyads

OFFICIAL STUDY TITLE FOR INTERNET SEARCH ON HTTP://WWW.CLINICALTRIALS.GOV: PILOT STUDY OF PROGRESSIVE EXERCISE PROGRAM AMONG LUNG CANCER PATIENT-PARTNER DYADS

Investigator: Donald Sullivan, MD

WHO IS PAYING FOR THE STUDY?: Borchard Foundation,Knight Cancer Institute Support Grant and Hartford Center for Gerontological Nursing Excellence

DO ANY OF THE RESEARCHERS HAVE A CONFLICT OF INTEREST WITH THIS STUDY?: The investigator and the research staff have no conflicts of interest with this study.

Table of Contents

OVERVIEW AND KEY INFORMATION

What Am I Being Asked To Do?

We are asking you to take part in a pilot trial, a type of research study, done to determine if a larger, future study is possible. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer. In this study, we are trying to test if an exercise program is helpful for people with lung cancer and their loved ones.

Medical personnel who carry out research studies are called "investigators." The investigator will explain the pilot trial to you. Pilot trials include only people who choose to take part. Please take your time to make your decision about taking part. You can discuss your decision with your friends and family. You can also discuss it with your health care team or another doctor. If you have any questions, ask the investigator.

Do I have to take part in this study?

Taking part in this study is your choice. You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "**WHERE CAN I GET MORE INFORMATION?**" section for resources for more clinical trials and general cancer information.

Why Is This Study Being Done?

This study is being done to answer the following question:

Can patients with lung cancer complete an exercise program?

This is a research study and not in place of any treatment. The purpose(s) of this study is to test the feasibility of an exercise program for people with lung cancer and an exercise partner who is identified as having a supportive relationship with the participant with lung cancer. We want to test how this program may affect the mood, quality of life, and the relationship of participants with lung cancer and their chosen exercise partner. To determine this, participants with lung cancer and their exercise partners will complete an exercise program, series of surveys and physical tests. Additionally, participants with lung cancer will be asked to have

two **optional** blood draws so that we may analyze biomarkers. A biomarker can indicate certain processes or conditions in the human body, such mood and inflammation.

This study involves a 12 week progressive exercise program, called *PEP-LC*, that includes supervised group exercise classes in a studio at the OHSU School of Nursing and home-based, unsupervised exercise sessions via an instructional DVD. The program we are studying is experimental. We do not know if it will lead to better quality of life for study participants or people with lung cancer in general.

You have been invited to be in this research study because you have been told you have lung cancer and have been determined to have the capacity to engage in light to moderate exercise.

We are asking you to provide *information* for a *data* bank, also called a repository. These samples will be stored indefinitely and may be used and disclosed in the future for research.

We are also asking you to participate in two blood draws for use in the future. These samples will be collected by trained personnel from the Oregon Clinical Translational Research Institute (OCTRI), and stored in an OCTRI lab until our analysis of the blood is complete.

The repository and the request to provide and store blood are optional components of the study. If you choose not to agree to have your information and blood stored in a repository, you may still participate in the other parts of the study. For more details, read the "Optional" section at the end of this consent form.

What Are My Choices If I Decide Not To Take Part In This Study?

Participation in this study will not affect your care in any way. If you do not participate, you and your healthcare provider will still work to determine the preferred treatment for your lung cancer diagnosis.

What will happen if I decide to take part in this study?

All study procedures will be done for research purposes and will not be completed if you decide not to take part in the study. Study staff will be responsible for explaining the risks of participation in each part of the study.

You will participate in the exercise program for 12 weeks. This includes in-person sessions located in the OHSU School of Nursing, Room 248, and unsupervised home sessions guided by an instructional DVD. There will also be a follow up interview 1-2 months after completion of the program. Study staff will continue to review your

electronic medical record up to 6 months following completion of the exercise program, mainly to determine completion of your lung cancer treatments.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will participate in the following study *procedures*:
3 surveys, each taking approximately 45 minutes to complete (at week 1, week 6, and week 12 of the study)
Physical tests conducted by a certified exercise professional at week 1, week 6, and week 12 of the study
Monitoring of activity using a wrist Fitbit to be worn outside of in-studio exercise sessions
A 1-2 month brief post-program interview to evaluate the exercise program
There are also optional study components that you may choose to take part of (See Optional Section at the end of this form). Choosing not to will not prevent you from participating in the main study:
Optional: A whole body dual energy x-ray absorptiometry (DXA; (Hologic-QDR Discovery A) scan to measure body composition at week 1 and week 12
Optional: Two research-related blood tests at week 1 and week 12

See the "PROCEDURES
and "Optional" sections for more detailed information about what will happen if you take part in this study.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "**WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?**" section.

If you choose to take part in this study, there is a risk that the exercise program may not contribute to your health or well-being.

There is always a slight risk of injury during physical testing and exercise. You may experience fatigue or muscles soreness as a result of the exercise.

Some other common risks that the investigators know about are:
You may lose time at work or home and spend more time in the hospital or doctor's office than usual.
You may be asked sensitive or private questions which you normally do not discuss.

Some questions may seem very personal or embarrassing. They may upset you. You may refuse to answer any of the questions that you do not wish to answer. If the questions make you very upset, we will help you to find a counselor.
As with most research studies, there are privacy and confidentiality risks. The risk of a breach of confidentiality is low due to the strong data security culture at both the Portland VA and OHSU.
For the **optional blood draws**, you may experience temporary discomfort.
For the **optional DEXA x-ray,** you will be exposed to a small dose of radiation.

There may be some risks that the investigators do not yet know about.

Benefits

You may or may not personally benefit from being in this study. However, by serving as a participant, you may help us learn how to benefit people with lung cancer in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let the investigator know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the investigator know how you are doing.

You may also choose to stop participating in optional portions of the study (blood draws, DEXA x-ray, repository) without leaving the full study.

The investigator will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The investigator may take you off the study if:

Your health changes and the study is no longer in your best interest.
New information becomes available and the study is no longer in your best interest.
You do not follow the study rules.
The study is stopped by the National Cancer Institute (NCI), Borchard Foundation, Knight Cancer Institute (KCI), Institutional Review Board (IRB), Food and Drug Administration (FDA).

It is important that you understand the information in the informed consent before making your decision.

Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask the investigator or nurse.

STUDY CONTACT INFORMATION

Purpose	Role	Contact Name	Contact Phone Number	Email
For medical questions about the study	Principal Investigator	Donald Sullivan, MD, MA	503-220-8262 x58087	sullivad@ohsu.edu
For questions about the study	Research Coordinator	Anna Tyzik	503-220-8262 x53037	Tyzik@ohsu.edu
For questions about research in general	Ethics Committee	ORIO	503-494-7887	irb@ohsu.edu
For non-medical questions about the study	Study Coordinator	Philip Tostado, MA	503-220-8262 x53030	Tostado@ohsu.edu
For 24-hour medical emergencies	911	Emergency Dispatch	911	
	Oncologist On-Call	OHSU Operator	503-494-8311	

INTRODUCTION

WHAT IS THE USUAL APPROACH TO MY *LUNG CANCER DIAGNOSIS*?

This is most dependent on your disease stage, but may include a combination of surgery, chemotherapy and/or radiation. A treatment plan is determined between you and your doctor. This study does not take the place of any treatment you may receive for your lung cancer diagnosis.

Treatments for cancer cause side effects such as fatigue. People who do not take part in this study will receive recommendations, such as encouragement to exercise, and/or ways to adjust their daily activities so they are less tired. People who participate in this study may still receive such recommendations, which may also be partially met by the exercise program.

WHAT ARE MY OTHER CHOICES IF I DO NOT TAKE PART IN THIS STUDY?

This study is research, and does not choosing to participate--or not participate--will not affect your care in any way:

you may choose to take part in a different study, if one is available

PURPOSE

WHY IS THIS STUDY BEING DONE?

This is a research study and not in place of any treatment. The purpose(s) of this study is to test the ability of patients with lung cancer and an exercise partner to complete an exercise program. Exercise partners can be any person identified as having a supportive relationship with the participant with lung cancer. We want to test how this program may affect the mood, quality of life, and relationship satisfaction of particiants with lung cancer and their chosen exercise partner. To determine this, both participants with lung cancer and their exercise partners will complete an exercise program and a series of surveys and physical tests.

The program we are studying is experimental. We do not know if it will lead to benefits for patients with lung cancer and/or partners.

You have been invited to be in this research study because you have been told you have lung cancer and have been determined to have the capacity to engage in light to moderate exercise.

The exercise program we are studying is investigational. We do not know if it is helpful for you, otherswith lung cancer, or your exercise partner.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

As many as 33 patient-partner pairs (66 participants) at OHSU and VAPORHCS people will take part in this study, which will be conducted at Oregon Health & Science University and VAPORHCS. Of these participants, 22 patient-partner pairs (44 participants) will participate in the study at OHSU.

PROCEDURES

WHAT ARE THE STUDY GROUPS?

All participants will be enrolled in the exercise program. Lung cancer participants and their chosen exercise partners will undergo some different study procedures. Participants with lung cancer will be asked additional questions pertaining to their cancer diagnosis.

Participants with lung cancer will be asked to participate in electronic physical activity monitoring, an optional x-ray, and optional blood tests, all of which are explained in this document.

HOW LONG WILL I BE IN THIS STUDY?

You will participate in the exercise program for 12 weeks. There will also be a follow up interview 1-2 months after completion of the program. Study staff will continue to review your electronic medical record 3-6 months after the completion of exercise program.

WHAT TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?

This study will be conducted at both the VAPORHCS and OHSU.

During the study:

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will participate in the following study *procedures*:

3 surveys

Physical tests conducted by a certified exercise professional

A 12-14 week stretching exercise program for you and your partner containing both in-person and at-home DvD sessions.

Monitoring of activity using a wrist Fitbit to be worn outside of in-studio exercise sessions

A 1-2-month post-program interview to evaluate the exercise program

There are also optional study components that you may choose to take part of (See Optional Section at the end of this form). Choosing not to will not prevent you from participating in the main study:

A whole body dual energy x-ray absorptiometry (DXA; (Hologic-QDR Discovery A) scan to measure body composition at week 1 and week 12

Two research-related blood draws at week 1 and week 12

See the study schedule at the end of the consent form for more information on when these procedures will take place.

The three survey assessments will each take about 40 minutes. You will complete survey assessments during week 1, week 6, and week 12 of the exercise program. These assessments will measure mood, physical functioning, relationships and quality of life. They can be administered over the phone or in person, depending on your preference. The study team will explain the potential risks and benefits of the study and conduct the surveys.

Physical tests will be conducted by a certified exercise professional during week 1, week 6, and week 12 of the exercise program. The Short Physical Performance Battery (PPB) tests balance, walking, and standing motions. Handgrip strength will be measured by simply gripping a testing device as hard as you can. The 6 minute walk test is a self-paced exercise test in which you will be asked to move as fast as you can along a course for 6 minutes. We will record the total distance walked and the time it takes to reach 400 meters. In the range of motion (ROM) test, we record observed loss of motion in your joints.

You will also be given a wrist Fitbit Flex™, an electronic device that uses an accelerometer to record physical activity. It calculates distance traveled based on the number of steps taken and the height and gender of the user. such as the average number of steps and miles a person takes in a week. A user guide on how to set up and use the device will be provided upon receipt of the Fitbit. Study staff will also assist in the set up at the first session of the exercise program. We will record physical activity information periodically during your participation. No other information from the Fitbit will be recorded.

This is a 12-week progressive exercise program. For the first 6-weeks, the exercise program consists of three sessions: two are a supervised group exercise class in a studio at OHSU in the School of Nursing and one is a home-based, unsupervised exercise session via an instructional DVD. The next 6-weeks of the program consist of three exercise sessions: one is a supervised group exercise class and two are home-based, unsupervised exercise sessions via the DVD. After the program is complete, we encourage you to exercise times a week using the instructional DVD.

Both the in-studio and DVD portions feature a stretching program focused on increasing flexibility and muscle endurance. A certified exercise trainer with experience working with participants with functional limitations and cancer will guide the program. Both portions will

provide variations of exercises in order to accommodate any physical or ability limitations you may have. The exercise trainer may also modify the challenge of the program over time to adapt to any increases in your joint range of motion and muscle endurance. The DVD is a 30-minute program designed for unsupervised, home-based exercise. It will be provided to you at the beginning of the study, and may also be made available via a website link.

An exercise partner of your choice will participate in all sessions. In this study, the patient-partner pair will consist of you and a person you identify as a primary caregiver and/or source of social support. The partner can be a spouse, sibling, adult child, friend, or any other person you share a significant relationship with.

1-2 months after completion of the program, we will contact you by telephone to complete a brief follow-up interview. In this interview, we will ask about your satisfaction with the program, ways to improve the program, your treatment status, and current physical activity. The interviews will be audio recorded.

We also ask for your permission to periodically review your medical chart. We will track information such as demographics, smoking history, current medications, lung cancer staging and treatment, and hospitalizations. We will check your record up to 6 months after you have completed the exercise program.

Optional study procedures include a type of x-ray to measure body composition and blood draws to collect inflammatory and depression biomarkers, indicators used to identify certain processes or conditions in the human body. Both will be obtained during week 1 and week 12 of the program. We are also asking you for permission to store research data from this study in a "repository" so that it may be used in future research studies. These optional study components are all explained in the "Optional" section at the end of this Consent form.

Data from study procedures will be recorded on paper, then added to the Portland VA's RedCap, a secure, electronic program used to document such information. Your information will be coded. Only approved study staff will be able to link recorded information to you.

RISKS

WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

PHYSICAL RISKS

The physical tests and exercise intervention face similar risks. Both can cause muscle soreness, but this typically resolves after two days. There is always a slight risk of injury during physical testing and exercise. However, this risk is low. These procedures will be conducted by a

certified exercise professional who is trained to ensure proper body mechanics during testing and exercise to avoid risk of injury. All exercises will be presented with varying levels of physical ability. Participants who may be fall risks or are otherwise uncomfortable with certain exercises have the option of skipping the exercise or performing it while sitting.
If you experience significant discomfort or have a pre-existing condition that could be exacerbated by a particular test, you will be given the option to refuse to participate in that test(s). If you experience tiredness, you will be told you can stop any procedure--including answering questions--and begin again at a later time. You may rest as often as needed.
Let your investigator know of any questions you have about possible risks or side effects. You can ask the investigator questions about side effects at any time.

Other Types of Risks
If you choose to take part in this study, there is a risk that:
You may lose time at work or home and spend more time in the hospital or doctor's office than usual.
You may be asked sensitive or private questions which you normally do not discuss.
Some questions may seem very personal or embarrassing. They may upset you. You may refuse to answer any of the questions that you do not wish to answer. If the questions make you very upset, we will help you to find a counselor.
As with most research studies, there are privacy and confidentiality risks. The risk of a breach of confidentiality is low due to the strong data security culture at both the Portland VA and OHSU. All data collected for this study is stored in secure facilities and computers at OHSU and the Portland VA.

BENEFITS
WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?
You may or may not personally benefit from being in this study. However, by serving as a participant, you may help us learn how to benefit people with lung cancer in the future.

PRIVACY
Access to your test results
We do not plan to share your research test results with you or your primary care provider. However, if we discover information that is important for your health care, either in this study or in the future, Dr. Sullivan or your treating provider will contact you and ask if you want to know the results. If you choose to receive the results, you may need to have the test repeated in a non-research laboratory. You may learn information that is upsetting to you.

Who will see my medical information?

As with most research studies, there is a risk of a breach of confidentiality. We will take steps to keep your personal information confidential, but we cannot guarantee total privacy. We take the protection of human subjects very seriously; a breach is low due to the strong data security culture at both the Portland VA and OHSU. All hard copies of participant data will ultimately be stored at the Portland VA, Building 6 in a locked file cabinet behind a locked office. Only the study PI and approved study staff will have access to this locked file cabinet. Any digital study documents including participant data will ultimately be stored in secure computer files and/or and online database behind VA firewall and requiring password access. This includes audio recordings and transcriptions of participant interviews. All identifiers will be excluded in transcription to the best of our ability to ensure confidentiality. OHSU study staff will also store any information they collect in secure, locked file cabinets and/or digital folders.

We will create and collect health information about you as described in the WHY IS THIS STUDY BEING DONE and the WHAT TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY sections of this form. Health information is private and is protected under federal law and Oregon law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form.

The investigators, study staff and others at OHSU and the Portland VA may use the information we collect and create about you in order to conduct and oversee this research study. If you agree, it will also be stored in a data repository for use in future research.
We will not release this information to others outside of OHSU, the Portland VA, or The National Cancer Institute.
Those listed above may also be permitted to review and copy your records, including your medical records.
We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your special permission.

Under Oregon law, suspected child or elder abuse must be reported to appropriate authorities.

When we send specimens or information outside of OHSU, they may no longer be protected under federal or Oregon law. In this case, your specimens or information could be used and re-released without your permission.
A code number will be assigned to your study information and optional blood samples. Only the investigators and people involved in the conduct of this study will be authorized to link the code number back to you. The researchers use of the optional blood samples may also be given a

code that could be used to identify you. For further information on the storage and use of optional blood samples, see the "optional" section at the end of this form.
If you choose to participate in the optional repository, study information may be given to researchers for other research studies. The information will be labeled using the code number assigned to you.
We may continue to use and disclose your information as described above indefinitely. Some of the information collected and created in this study may be placed in your OHSU medical record. While the research is in progress, you may or may not have access to this information. After the study is complete, you will be able to access any study information that was added to your OHSU medical record. Ask the investigator if you have questions about what study information you will be able to access, and when it will be available.

Additional protections for special types of information
We will collect mental health information about you from your electronic medical record and from questionnaires in this study. We may disclose this information to a provider and/or direct you toward a mental health professional.

PARTICIPATION
CAN I STOP TAKING PART IN THIS STUDY?
Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the investigator know as soon as possible so you can stop safely. Another reason to tell the investigator that you are thinking about stopping is to discuss what testing, follow-up, or additional treatment could be most helpful for you. If you stop, you can decide whether or not to let the investigator continue to provide your medical information to the organization running the study.

If your exercise partner chooses not to stop taking part in this study, you, the participant with lung cancer, can continue to participate in the exercise program. Your exercise partner, however, will not be able to continue participating if you choose to leave the study.

If you choose to withdraw, you will not need to complete any additional procedures. However, we will ask you if we can still review your electronic medical record.

You may also choose to stop taking part in optional study components, but continue participation in the main study.

If in the future you decide you no longer want to participate in this research, we may be able to remove your name and any other identifiers from your blood and information, but the material will not be destroyed and we will continue to use it for research.

The investigator will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.
The investigator may take you out of the study:
If your health changes and the study is no longer in your best interest
If new information becomes available
If you do not follow the study rules
If the study is stopped by the sponsor, IRB or FDA.

WHAT ARE MY RIGHTS IN THIS STUDY?
Your participation in this study is voluntary. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights. If you have any questions, concerns, or complaints regarding this study now or in the future, contact the principal investigator listed at the beginning of the form.

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to the IRB at (503) 494-7887 or irb@ohsu.edu if:
Your questions, concerns, or complaints are not being answered by the research team
You want to talk to someone besides the research team
You have questions about your rights as a research subject
You want to get more information or provide input about this research.

You may also submit a report to the OHSU Integrity Hotline online at https://secure.ethicspoint.com/domain/media/en/gui/18915/index.html or by calling toll-free (877) 733-8313 (anonymous and available 24 hours a day, seven days a week).

You do not have to join this or any research study. You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study. Some parts of the study are optional. You can choose not to participate in some or all of the optional parts but still participate in the rest of the study.

If you do join the study and later change your mind, you have the right to quit at any time. This includes the right to withdraw your authorization to use and disclose your health information. You can choose to withdraw from some or all of the optional parts of this study without withdrawing from the whole study. If you choose not to join any or all parts of this study, or if

you withdraw early from any or all parts of the study, there will be no penalty or loss of benefits to which you are otherwise entitled, including being able to receive health care services or insurance coverage for services. Talk to the investigator if you want to withdraw from the study or change which parts of the study you are participating in.

If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to:

Knight Cancer Institute Clinical Trials
Email: trials@ohsu.edu
Please call 503-494-1080 for current mailing address
Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already taken action based on your authorization.

You will be told of any new information that might make you want to change your mind about continuing to be in the study.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
There are no costs for taking part in this study.

WHAT HAPPENS IF I AM INJURED OR HURT BECAUSE I TOOK PART IN THIS STUDY?
If you believe you have been injured or harmed as a result of participating in this research and require treatment, contact ***Donald Sullivan, PI, at 503-220-8262 ext. 58087.***

If you are injured or harmed by the procedures, you will be treated. OHSU, VAPORHCS, KCI, and the Borchard Foundation not offer any financial compensation or payment for the cost of treatment if you are injured or harmed as a result of participating in this research. Therefore, any medical treatment you need may be billed to you or your insurance. However, you are not prevented from seeking to collect compensation for injury related to negligence on the part of those involved in the research. Oregon law (Oregon Tort Claims Act (ORS 30.260 through 30.300)) may limit the dollar amount that you may recover from OHSU or its caregivers and researchers for a claim relating to care or research at OHSU, and the time you have to bring a claim.
If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

WHAT IS COMMERCIAL DEVELOPMENT AND HOW DOES IT AFFECT ME?
Samples and information about you or obtained from you in this research may be used for commercial purposes, such as making a discovery that could, in the future, be patented or licensed to a company, which could result in a possible financial benefit to that company, OHSU, and its researchers. There are no plans to pay you if this happens. You will not have any property rights or ownership or financial interest in or arising from products or data that may result from your participation in this study. Further, you will have no responsibility or liability for any use that may be made of your samples or information.

The research team does not expect or plan to use this research for commercial purposes, but cannot fully deny the possibility.

ADDITIONAL INFORMATION

WHERE CAN I GET MORE INFORMATION?
You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.clinicaltrials.gov/ as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

When visiting either of these websites, use the search term(s) "lung cancer, physical activity, and quality of life" to locate information on this trial.
If you want more information about this study, ask the investigator.
Who can answer my questions about this study?
You can talk to the investigator about any questions or concerns you have about this study or to report side effects or injuries. Outside of regular clinic hours, you can speak with an oncologist on-call. Refer to the beginning of this consent form for contact names and phone numbers.

OPTIONAL
This part of the consent form is about optional study procedures that you can choose to take part in. As with the main study, you may or may not personally benefit from agreeing to participate in these procedures. However, by serving as a participant, you may help us learn how to benefit people with lung cancer in the future.

The results will not be added to your medical records and you will not know the results.

You will not be billed for these optional procedures. You can still take part in the main study even if you say "no" to any or all of these procedures. If you sign up for but cannot complete any of these procedures for any reason, you can still take part in the main study.

1. Optional Sample Collections for Laboratory Studies and/or Storage for Possible Future Studies
Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems, as well as to increase the quality of life of people with such problems.

A. Optional Blood sample collection: If you participate in this optional procedure, trained personnel from the Oregon Clinical Translational Research Institute (OCTRI) will draw no more than 2 tablespoons from a vein in your arm in adherence with OHSU Patient Care Services policy on venipuncture techniques for blood sampling. Blood draws will occur at week 1 and week 12 of the intervention. The sample and some related health information will be stored in an OCTRI lab in accordance to OCTRI protocol.
The results will not be added to your medical records and you will not know the results. However, as with the main study, if we discover information that is important for your healthcare, we may contact your provider or treating oncologist to determine the best course of action.

Blood samples will be given a code that only study staff can use to link back and identify you. Blood samples will be disposed of in accordance with OCTRI standards of procedure after they are analyzed for the purposes described in this section. Outside of the future, related study described above, qualified researchers will not be able to use the materials stored in the lab.

If you choose to take part in this procedure, the investigator for the main study would like to collect blood samples for research on changes in biomarkers. A biomarker can indicate certain processes or conditions in the human body, including mood and inflammation. We want to see if these biomarkers change from the beginning to the end of the exercise program.

The investigators wish to conduct analysis of this blood in the future. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for the research described above. Your sample and some related health information will be stored in the OCTRI lab, along with samples and information from other people who take part. The samples will be kept until they are analyzed by the Primary Investigator, Dr. Donald Sullivan, and other researchers and study staff.

Risks
The most common risks related to drawling blood from your arm are brief pain and possibly a bruise.
There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New Health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

B. Optional Research Repository: We are also asking you for permission to store your research data from this study in Dr. Slatore's Health Services Research Repository at the VA Portland Health Care System. A repository stores approved data from studies that have ended so that it may be used for future research studies. Future research studies that may use your research data may involve topics such as: lung cancer, pulmonary conditions and diseases and patient-centered outcome research. All data will be kept secure and confidential and will not be released to other investigators without approval from Dr. Slatore and an appropriate IRB board. If you agree to have your data included in a repository, when this study is closed your data will be stored indefinitely in a repository at the VA Portland Health Care System for future research studies. You will not be able to request information about these studies or the findings of these studies.

Risks:
As with most research studies, there is a risk of a breach of confidentiality. This risk is low due to a strong data security culture at both the Portland VA and OHSU, but the possibility of such a breach still exists
There is a possibility that information about you stored in the repository may be linked back to you.

2. Optional procedure study – extra procedure
Whole body dual energy x-ray absorptiometry (DEXA): If you choose to take part in this optional study component, you will have a whole body dual x-ray absorptiometry (DEXA). The DEXA an established procedure used to measure body composition. This scan is not part of your cancer treatment plan. Researchers would use this DEXA to measure total body mass, fat-free masses (kg), % body fat and fat distribution. We are collecting these measurements to see if the light exercise program results in any changes to fat and bone density.
Trained research personnel will perform the DEXA as part of the baseline and final visits if you choose to participate in this optional study component.
If you choose to participate in the optional DEXA scan, you will be exposed to radiation during the whole body dual energy x-ray absorptiometry (DEXA; Hologic-QDR Discovery A) scan. While

we cannot be sure any dose of radiation is entirely safe, the amount you will be exposed to in this study is not known to cause health problems.
If you are a female participant less than 45 years old and choose to participate in the DEXA scan, we will first ask you to perform a self-administered urine test to rule out pregnancy. A study staff member will read the pregnancy test and inform you of the result. If the pregnancy test is positive, you will be unable to have a DEXA scan, but you will still be able to participate in other study procedures.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Samples and/or information obtained from this optional study will be managed in the same way as sample and information in the main study. For more information, refer to the WHO WILL SEE MY MEDICAL INFORMATION section.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If in the future you decide you no longer want to participate in this research, we will stop collecting your samples and data. However, once provided to the sponsor, we may not be able to destroy your samples or data and it will continue to be used for research. Samples or related information that have already been given to or used by researchers will not be returned.

If you wish to no longer participate, you can call the investigator listed on page one of this consent form.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the investigator listed at the beginning of this consent form.

PARTICIPANT OPTIONS:

Please initial to show whether or not you would like to take part in each option. You can still participate in the main part of the study even if you choose not to participate in the optional parts.

	Yes, I agree	*No, I decline*
I give my consent to collect extra blood samples and for these samples to be used for the research described in this form. See Optional Study #1.A.	_____ *Participant initials*	_____ *Participant initials*

	Yes, I agree	*No, I decline*
Information about me collected during my study participation may be kept in a repository for use in future health research. See Optional Study #1.B.	_____ *Participant initials*	_____ *Participant initials*

	Yes, I agree	*No, I decline*
I choose to take part in the optional DEXA scan for body composition measurement. See Optional Study #2.	_____ *Participant initials*	_____ *Participant initials*

This is the end of the section about optional studies.

SIGNATURE

My Signature Agreeing to Take Part in the Main Study

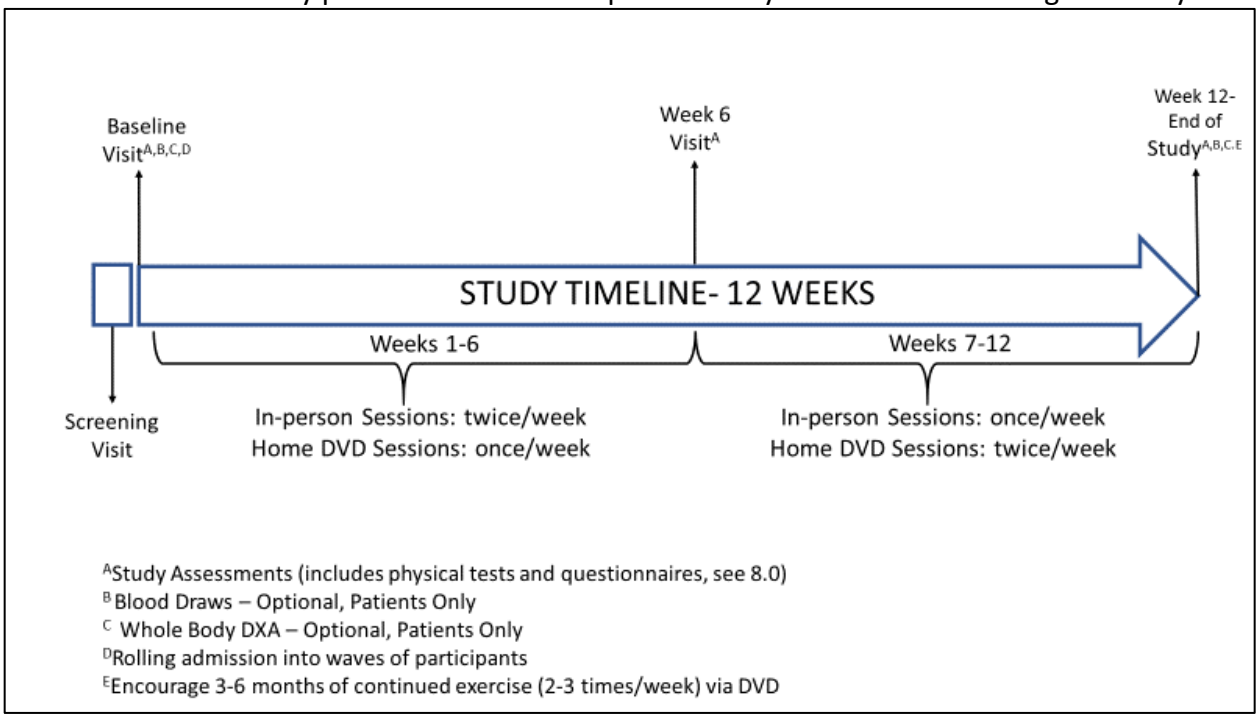
Your signature below indicates that you have read this entire form and that you agree to be in this study *and any additional studies where I initialed next to 'Yes, I agree'.*
We will give you a copy of this signed form.

Participant Printed Name	**Participant Signature**	**Date**

Person(s) Obtaining Consent Printed Name	**Person(s) Obtaining Consent Signature**	**Date**

STUDY SCHEDULE

This schedule lists study procedures as well as procedures you would have during the study.



[A]Study Assessments (includes physical tests and questionnaires, see 8.0)
[B] Blood Draws – Optional, Patients Only
[C] Whole Body DXA – Optional, Patients Only
[D]Rolling admission into waves of participants
[E]Encourage 3-6 months of continued exercise (2-3 times/week) via DVD