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Sarcopenic Obesity in Older Female Cancer Survivors and the Association with Physical Fitness and Function

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Abstract

This dissertation described sarcopenic obesity in underactive older female cancer survivors treated with chemotherapy. Using different definitions of sarcopenic obesity identified from the literature, the frequency of sarcopenic obesity; demographic, health, and clinical variables significantly associated with sarcopenic obesity; association of sarcopenic obesity with objective measures of physical fitness and function; and comparison of sarcopenic obesity definitions that explain the most variance in objective physical fitness and function were described. Results show that the frequency of sarcopenic obesity ranged from 0 to 33% across definitions; some demographic, health, and clinical variables were significantly associated with sarcopenic obesity but had inconsistent significant associations across definitions; sarcopenic obesity was significantly associated with maximal leg strength but not measures of physical function; and sarcopenic obesity explained 3-12% of variance in maximal leg strength. Depending on the definition used, sarcopenic obesity may be a prevalent condition in older female cancer survivors and is strongly associated with poor strength compared to women without sarcopenic obesity which is a poor outcome needing prevention and intervention. The results of this study may contribute to clinical nursing practice by helping nurses be able to more efficiently and effectively implement early prevention and intervention efforts in education and therapy in cancer survivors at high risk of sarcopenic obesity. These data may also contribute to nursing science by helping guide investigation into sarcopenic obesity definitions most strongly associated with declines in objective measures of physical fitness and prompt research into longitudinal studies that could reveal the development of sarcopenic obesity changes over time through the course of cancer treatment and throughout cancer survivorship.

Sarcopenic Obesity in Older Female Cancer Survivors and the Association with Physical Fitness and Function

Chapter 1

Introduction

Cancer and its treatment are associated with localized and systemic adverse side effects. By causing adverse physiologic changes, cancer and its treatment can affect the body with systemic side effects such as inflammation, cellular dysregulation, and signaling disruption (Fried et al., 2010; National Cancer Institute, 2015) that may be associated with declines in physical fitness and function. Impaired physical fitness and function predisposes survivors to early onset disability and other health threats (Laird, et al., 2013; Silver, Dietrich, & Murphy, 2007). Adverse changes in body composition are one frequent treatment related side effect for cancer survivors (Speck, Courneya, Masse, Duval, & Schmitz, 2010) that are theorized to precede (Bennett, Winters-Stone, & Nail, 2006) declines in physical fitness and function in cancer survivors (Prado et al., 2013). The most common changes in body composition are reduced muscle mass that can lead to *sarcopenia* (Ryan et al. 2016) and increased fat mass that can lead to *obesity*, (Sheean, Hoskins, & Stoley, 2012). Both sarcopenia and obesity are associated with additional short and long-term poor health outcomes in cancer survivors (Chan et al., 2014; Going, Williams, & Lohman, 1995; Iannuzzi-Sucich, Prestwood, & Kenny, 2002; Malietzis et al., 2015; Playdon et al., 2015). Sarcopenia and obesity are directly associated with poor physical fitness and function (Hewitt, Rowland, & Yancik, 2003; Rolland et al., 2009; Tao Visvanathan, & Wolff, 2015), and poor physical fitness and function is associated with long-

term poor health outcomes including disability and death. In particular, cancer survivors may be at heightened risk sarcopenic obesity (Biolo, Cederholm, & Muscaritoli, 2014), a body composition phenotype that is defined as a concurrent combination of sarcopenia and obesity (Heber et al., 1996). Sarcopenic obesity is thought to contribute to increased risk of poor health outcomes more than either sarcopenia or obesity alone, but little is known about sarcopenic obesity in cancer survivors. In addition, disagreement remains about what thresholds should be used to define sarcopenic obesity, which further delays the movement towards understanding the long-term consequences of sarcopenic obesity.

Almost 14 million cancer survivors living in the US today (American Cancer Society, 2014), but little research has been conducted describing the frequency of sarcopenic obesity in cancer survivors regardless of the definition of sarcopenic obesity used (Thibault, Cano, & Pichard, 2011), little is known about what factors may be associated with increased risk of sarcopenic obesity in cancer survivors, and no research has been conducted in cancer survivors describing the association of sarcopenic obesity with objective measures of physical fitness and function. Studies in non-cancer populations with sarcopenic obesity, and conceptual models and evidence of the adverse physiologic affects of cancer treatment indicate that cancer survivors with sarcopenic obesity may be a subgroup at higher risk of multiple long-term poor outcomes than cancer survivors without sarcopenic obesity (Fried et al., 2010; Prado et al., 2012). The requisite first steps in understanding if cancer survivors with sarcopenic obesity are at higher risk of poor health outcomes such as disease, disability and death, than cancer survivors without sarcopenic obesity are to describe the frequency of sarcopenic obesity in

cancer survivors, identify variables which are associated with increased risk of sarcopenic obesity, and describe the association of sarcopenic obesity with physical fitness and function.

Currently, multiple competing definitions of sarcopenic obesity make it difficult to even describe the frequency of sarcopenic obesity in cancer survivors (Figure 1-2), and no sarcopenic obesity definition has been explored for the association with physical fitness and function or identifying subsets of survivors at risk for functional decline. In addition to describing the frequency of sarcopenic obesity in cancer survivors, identifying a definition of sarcopenic obesity that is best associated with objective measures of physical fitness and function is also needed to advance the science. Such a definition would allow for more effective and efficient implementation of sarcopenic obesity prevention and physical fitness and function interventions, possibly years before a cancer survivor recognizes that their functioning has become limited. This dissertation will fill these gaps in our knowledge of sarcopenic obesity in cancer survivors and will provide critical knowledge for addressing the long-term association of sarcopenic obesity and poor physical fitness and function in cancer survivors who may be at increased risk of poor outcomes including disability and death.

Purpose of the Study

The purpose of this dissertation is to identify the frequency of sarcopenic obesity in underactive older female cancer survivors treated with chemotherapy and to describe the association of sarcopenic obesity with measures of physical fitness and function, as well as identify demographic, health, and clinical variables significantly associated with sarcopenic obesity in cancer survivors. In order to accomplish this, a secondary data analysis was

performed of a subsample of 142 participants from an ongoing three-group parallel design randomized controlled exercise trial (R01CA163474) in underactive older female cancer survivors treated with chemotherapy who had measures of body composition and objective measures of physical function collected. The purpose of the parent study was to compare fall rates among participants randomly assigned to one of three exercise intervention groups: 1) strength training to 2) tai chi to 3) stretching as a control condition. Secondary data analysis was performed of a cross-sectional descriptive design of baseline data collected prior to exercise interventions. In order to achieve the purpose of this study, the following specific aims were examined:

Specific Aim 1) Describe and compare the frequency of sarcopenic obesity in a sample of cancer survivors among published definitions of sarcopenic obesity.

> **Hypothesis 1.1)** The frequency of sarcopenic obesity in cancer survivors will differ significantly across published definitions.

Specific Aim 2) Identify demographic, health, and clinical variables significantly associated with sarcopenic obesity in cancer survivors among published definitions of sarcopenic obesity.

> **Hypothesis 2.1)** Older age, cancers other than breast cancer, increased comorbidities, and low physical activity will be significantly positively associated with sarcopenic obesity.

Specific Aim 3) Compare results on objective measures of physical fitness and function between cancer survivors with and without sarcopenic obesity among published definitions of sarcopenic obesity.

Hypothesis 3.1) Cancer survivors with sarcopenic obesity will perform significantly worse on objective measures of physical fitness and function than cancer survivors without sarcopenic obesity across sarcopenic obesity definitions.

Specific Aim 4) Identify the sarcopenic obesity definitions that explain the most variance in objective physical fitness and function.

Hypothesis 4.1) The sarcopenic obesity definitions that explain the most variance in objective measures of physical fitness and function will be those that utilize percent body fat rather than BMI for obesity and which have thresholds for non-bone appendicular lean mass (nbALM) ≤ 5.67 kg/m^2.

Significance of the Problem

Existing definitions of sarcopenic obesity vary in the variables included in the definition and the cutoffs used for determining if someone has sarcopenia or not and obesity or not. For example, sarcopenia thresholds of adjusted appendicular skeletal mass range from 4.59 kg/m^2 to 6.29 kg/m^2, and obesity definitions differ in assessment method including percent body fat, BMI, waist circumference, and visceral fat area (Yip et al., 2015). Universal agreement on a definition of sarcopenic obesity has therefore yet to be determined. This has not prevented continuing research in sarcopenic obesity, nor prevented introduction of further variations in definition. However, a lack of adopted definition creates an underlying problem since individuals can be classified differently depending on which sarcopenic obesity definition is applied or method of measurement used (Batsis et al., 2015; Romero-Corral et al., 2008). A lack of a standardized definition of sarcopenic obesity is problematic to continuing research for

several reasons. First, sarcopenic obesity frequency rates may be under or overestimated depending on definition used. Second, results across studies are not directly comparable because of differing definitions. And third, the association of sarcopenic obesity with outcomes of interest can change in significance and strength depending on definition used. A lack of established definition is a major barrier to further understanding of sarcopenic obesity, particularly for cancer survivors who may be at high risk of sarcopenic obesity as well as increased risk of poor physical fitness and function associated with sarcopenic obesity.

Preventing and reducing declines in physical fitness and function in cancer survivors is an active area of research (Sheean et al., 2012), but it is not known what associations sarcopenic obesity has with physical fitness and function in cancer survivors. Evidence from studies in non-cancer populations with sarcopenic obesity support the theory that cancer survivors with sarcopenic obesity may have worse physical fitness and function than cancer survivors without sarcopenic obesity (Goisser et al., 2015; Poggiogalle, Migliaccio, Lenzi, & Donini, 2014). Many studies on physical function in cancer survivors focus on assessment of physical function by self-report rather than on objective measures physical function (Ibrahim & Al-Homaidh, 2011). Mounting evidence supports conceptual models (Bennett, Winters-Stone, & Nail, 2006; Fried et al., 2010) that objective measures of physical fitness and function precede self-reported changes in physical function (Smith et al., 2014). Self-report may not accurately capture declines in physical function since progressive decline in physical fitness and function may go unrecognized despite being clinically detectable (Fried, Herdman, Kuhn, Rubin, & Turano, 1991). Self-report also may not accurately capture poor physical function because of mis-reporting due to social desirability, poor attentiveness to symptoms, and selection bias of

what to report, all of which may mask accurate reports (Stone, Turkkan, Bachrach, Jobe, Kurtzman, & Cain, 2009). Furthermore, self-reported poor physical function often does not accurately reflect the magnitude of physiologic changes able to be measured through objective measures (Smith et al., 2014), which would indicate worse physical function than was self-reported (Brach, VanSwearingen, Newman, & Kriska, 2002). According to Fried, Bandeen-Roche, Chaves, & Johnson (2000), older women with unrecognized and unreported declines in clinically detectable physical function when using objective measures are at high risk for progressing to more severe disability. Understanding the association of sarcopenic obesity with objective measures of physical fitness and function in cancer survivors is an important step toward preventing or limiting further long-term adverse side effects sooner than when cancer survivors may self-report poor physical function.

Implications for Nursing

Nurses play numerous roles in the prevention, treatment, and recovery stages for cancer survivors, and knowledge produced from this dissertation will inform nursing practice in these roles. If and to what extent cancer survivors with sarcopenic obesity are at increased risk of poor physical fitness and function is currently unknown since accurate frequency and variables associated with sarcopenic obesity in cancer survivors have not been described. Therefore, key knowledge for nurses resulting from this dissertation will be better understanding of the frequency of adverse changes in body composition in cancer survivors, and that sarcopenic obesity is a specific body composition phenotype that cancer survivors may be at increased risk of developing. Further knowledge for nurses will also be that cancer survivors with sarcopenic

obesity may be at increased risk of poor physical fitness and function. In addition, knowledge of variables that may be associated with sarcopenic obesity in cancer survivors will be produced from this study. With knowledge gained from this dissertation, nurses may be able to accurately screen cancer survivors who may be at higher risk of sarcopenic obesity and poor physical f fitness and unction, and nurses may be able to more efficiently and effectively target early prevention and intervention efforts in education and therapy in cancer survivors at high risk of sarcopenic obesity.

In addition to contributions to clinical practice, the knowledge gained from this dissertation will inform nursing research. Future a priori studies will be better able to select a most useful definition from the multiple definitions of sarcopenic obesity from knowledge of the differences in frequency rates of sarcopenic obesity across definitions. Epidemiologic studies of sarcopenic obesity could better establish reference points for frequency of sarcopenic obesity in cancer subgroups and severity of possible associations with physical fitness and function. Longitudinal studies in cancer survivors will reveal how the development of sarcopenic obesity changes over time; which interventions are most effective at preventing, reducing, or reversing adverse changes in body composition and physical function; and whether interventions are most effective targeting sarcopenic obesity and/or physical fitness and function. Expanded studies with larger populations will allow for better identification of the significance of variables possibly associated with sarcopenic obesity such as cancer type, cancer treatment, demographics, comorbidities, and other possible risk factors.

Conclusion

Understanding the extent and magnitude of sarcopenic obesity in cancer survivors and its association with poor physical fitness and function may improve cancer care. Early screening, identification, and intervention for cancer survivors at high risk of sarcopenic obesity will improve long-term clinical outcomes such as physical function and reduce or delay distant patient outcomes such as disability and premature death.

CHAPTER 2

Review of the Literature and Theoretical Framework

Significance

Cancer Incidence & Survival

Cancer is one of the most common diseases with almost 40% of all Americans diagnosed with cancer at some point during their lifetime (SEER Cancer Statistics Review, 2015). Incidence rates of cancer in the United States have remained relatively stable for the past 20 years, but as the U.S. population increases and ages, the absolute number of Americans newly diagnosed with cancer continues to grow by millions each year (Colby & Ortman, 2015; U.S. Census Bureau Population Division, 2014). For 2016 alone, it is estimated that almost 1.7 million new cancer cases will be diagnosed in the US (American Cancer Society, 2016). In addition, overall mortality rates have slowly decreased in recent years (American Cancer Society, 2016). Between 1991 and 2012, overall deaths from all cancers dropped 23%, and deaths from the most common cancer types such as breast cancer dropped by almost half (Siegel, Miller, & Jemal, 2016). The drop in overall deaths during this period is equivalent to a projected decrease in cancer deaths of greater than 1.7 million people (Howlader et al., 2016). Though cancer mortality has decreased, but the burden of long-term side effects for cancer survivors is increasing in conjunction with increased longevity.

Incidence and survival rates across cancer types vary widely despite overall an increase in cancer survival. Projected 2030 data predict that all-cancer survival rates will continue to rise significantly (Clegg et al., 2009; Rahib et al., 2014; Siegel, Miller, & Jemal, 2016). Common cancers with low mortality represent the largest sub-group of cancer survivors, therefore the

majority of cancer survivors may be at higher risk of long-term side effects such as poor physical fitness and function associated with adverse changes in body composition. It is important to recognize that degree of risk of long-term side effects experienced by cancer survivors may differ across cancer types. A strength of this dissertation is inclusion of multiple cancer types as well as subgroup analysis of cancer type as a possible factor associated with sarcopenic obesity and physical fitness and function.

Finally, it is important to note that survival rates must be interpreted within the context of lifespan since cancer is primarily diagnosed in older adults. Survival rates are typically reported as survival within 5 years of diagnosis (Siegel, Miller, & Jemal, 2016). Of all cancer cases diagnosed in the United States, 78% are diagnosed in adults aged 50 and older, and the average age at time of diagnosis is currently 66 years old (American Cancer Society, 2016). The average age of diagnosis is more than a decade less than the average American lifespan. Therefore, the total length of survival is a significant consideration since cancer survivors may live for decades after diagnosis. For example, almost a million cancer survivors are alive today who were diagnosed 20+ years ago (American Cancer Society, 2016). Millions of cancer survivors can expect to live many productive years after diagnosis, but they also live with increased risk of long-term poor health outcomes that threaten their functional status and quality of life.

Cancer Survivorship

A cancer survivor is defined as any person alive at the time of cancer diagnosis regardless of treatment or length of survival (National Cancer Institute, 2016). Treatment, the first stage of survivorship, can be the most intensely stressful and tumultuous stage of

survivorship for cancer survivors (Foglino et al., 2016; National Cancer Institute, 2015; Piet, Wurtzen, & Zachariae, 2012). The goal of treatment is, first, to eradicate the cancer; and second, to extend survival while also maintaining the highest possible quality of life. However, after treatment, many survivors cope with some number of long-term side effects associated with their cancer diagnosis and/or treatment (Bodai & Tuso, 2015; Glare et al., 2014; Harrison & Scwartz, 2015).

In previous decades, cancer research was focused primarily on disease treatment. A watershed report by the Institute of Medicine in 2006, *From Cancer Patient to Cancer Survivor: Lost in Transition* (Hewitt & Ganz, 2006), called for a unified focus on managing the health needs and concerns of cancer survivors. The designation of survivorship as a distinct and integrated phase of cancer care was the first recommendation of the IOM report. As treatment efficacy and survivorship rates have increased in the last three decades, recognition of survivorship burden has increased and survivorship research has tripled (Harrop, Dean, & Paskett, 2011). Professional research and clinical attention are now better addressing the side effect burdens of cancer survivorship. This dissertation contributes to that body of knowledge by focusing on the common side effects of adverse body composition and poor physical fitness and function experienced by cancer survivors.

Cancer Side Effects and Outcomes Model

Poor physical function in cancer survivors does not result directly from cellular level damage from cancer treatment, but rather is preceded by cell damage that leads to impaired physiological systems. These physiologic changes—increased systemic inflammation,

neuroendocrine dysregulation, coagulation dysfunction, and signaling pathway disruption—contribute in various ways to side effects (Fried et al., 2010) and are strongly associated with poor physical function (Laird et al., 2013; Silver et al., 2007). How impaired physiological systems, specifically sarcopenic obesity, are associated with poor physical fitness and function in cancer survivors is not yet known. This dissertation will contribute understanding to the progression from cancer and its treatment to long-term adverse health outcomes.

The theoretical model guiding this dissertation is the Conceptual Model of Physical Function in Cancer Survivors proposed by Bennett, Winters-Stone, & Nail (2006), which was developed to suggest physical fitness and function measures appropriate for studies in cancer survivors. The Conceptual Model of Physical Function in Cancer Survivors model is an ideal model to guide the research question and aims of this dissertation since it describes specific measures for interpreting outcomes of physical fitness and function within the context of cancer survivors, and details risk factors associated with physical function in cancer survivors. The Bennett, Winters-Stone, & Nail model founded on the pioneering Model of Disablement first developed by Nagi (1976) which traces a generalized progression from disease to disability. Further research by Verbrugge & Jette (1994) expanded on Nagi's model with the Disablement Process by including personal and environmental factors that either speed or slow disablement resulting in a biopsychosocial model. Such a biopsychosocial model presents disability as an outcome of the interactions among biological, social, and personal factors that result in disability, rather than disability as an attribute or social construct of the individual (Jette, 2006). In cancer survivors, a biopsychosocial disability model means that disability results from the combination and interaction of cancer, cancer treatment, and other risk factors. Soon after the

development of the Disablement Process, Lawrence & Jette (1996) published further research in samples of older women, which clarified the position of musculoskeletal problems as directly influencing poor physical function that in turn lead to the eventual onset of disability. Musculoskeletal problems such as adverse body composition are thus an intermediary force preceding disability, and describing what factors influence physical fitness and function in cancer survivors and how to best measure physical function is the focus of the Conceptual Model of Physical Function in Cancer Survivors.

Though the Conceptual Model of Physical Function in Cancer Survivors describes the full progression from cancer to disability, a gap exists in cancer survivor literature of describing the specific link of how the adverse body composition phenotype of sarcopenic obesity might be associated with poor physical fitness and function in cancer survivors. A simplified figure of the Conceptual Model of Physical Function in Cancer Survivors (Bennett, Winters-Stone, & Nail, 2006) is presented in Figure 1-1. The figure summarizes the progression from cancer to disability with sequential steps through impairment, objective limitations, and self-report limitations along the way. The scope of this dissertation contributes to further understanding of the Conceptual Model of Physical Function in Cancer Survivors by focusing on describing the links between risk factors and sarcopenic obesity, as well as sarcopenic obesity and objective limitations.

Figure 1-1

Proposed relationships between cancer, side effects, and physical Function

Risk Factors →	**Impairments** →	**Objective Limitations** →	**Self-report Limitations**
Cancer type	Muscle loss, fat gain	Objective physical function	Self-report physical function
Etiologic factors	(sarcopenic obesity)	(gait speed, balance, strength)	(difficulty with actions)
Sociodemographics	Pain, fatigue, neuropathy		
Treatment	Deconditioning		

The aims of this dissertation focus on specific links along this progression. First, Aim 1 establishes the magnitude of sarcopenic obesity in cancer survivors by describing and comparing frequency rates across multiple definitions identified from the literature. This is important for research since the presence or severity of sarcopenic obesity in cancer survivors may be over or under estimated depending on the definition of sarcopenic obesity used. Aim 2 identifies socio-demographic, clinical, and treatment variables significantly associated with sarcopenic obesity in cancer survivors. This is important for research since it is unknown what variables may increase risk of sarcopenic obesity, important knowledge for future research investigating prevention or intervention associated with sarcopenic obesity. Aim 3 addresses the gap in the literature of the association of objective measures of physical fitness and function between cancer survivors with and without sarcopenic obesity across definitions of sarcopenic obesity. This is important for understanding the first step in the progression from impairment to disability. Finally, Aim 4 identifies the sarcopenic obesity definitions that explain the most variance in objective measures of physical fitness and function. This provides support for meaningful interpretation of the significance of sarcopenic obesity as a risk factor associated with poor physical fitness and function which will improve the application of the knowledge of Aim 3 for future studies choosing which definition of sarcopenic obesity to utilize in research.

Cancer Treatment

Advances in modern cancer treatments have revised the historical perspective that a cancer diagnosis meant certain death. Research continues to refine understanding of the efficacy and impact of treatment on cancer survivors (Masters, et. al., 2015). Vastly more cancer survivors

live for years longer after their cancer diagnosis and initial treatment than those in previous generations who died quickly from cancer when curative medical treatments were unavailable or ineffective (National Cancer Institute, 2011). Greater than three times as many people today are diagnosed with cancer each year than those who die from it (SEER Cancer Statistics Review, 2015), but cancer treatments cause physiologic damage that is associated with long term side effects.

Cancer is abnormal unregulated cell growth caused by genetic mutations (National Cancer Institute, 2015). Treatments of all cancer types share common modalities that attack rapidly dividing cells (chemotherapy and radition), removal of tumors (surgery), boosting the immune systems defenses (biotherapy), blocking hormones necessary for cancer growth (hormone therapy). Unfortunately, in the process of killing cancer cells, current treatment methods also affect healthy cells throughout the body. Chemotherapy is particularly egregious in indiscriminately affecting both cancer cells and healthy cells. Cancer treatments cause notable short- and long-term side effects because of their adverse affect on healthy cells. Adverse physiological, biological, and behavioral changes such as energy imbalances, fatigue, and inactivity are changes that can result from cancer treatment (Tonorezos & Jones, 2013). Clustered changes such as energy imbalances, fatigue, and inactivity can then contribute to or exacerbate adverse changes in body composition such as increased fat mass and decreased lean mass, with common modes of cancer treatment being associated with changes in body composition, which is the focus of this dissertation.

Chemotherapy

Chemotherapy is one of the most commonly used cancer treatments because of its broad efficacy against numerous types of cancer. Chemotherapy is cytotoxic through systemic chemical administration and attacks cells by interfering with cell division at a mechanical or genetic level and limiting cancer cells' ability to replicate (Sausville & Longo, 2015; Khlief, Rixe, & Skeel, 2016). Because of the broad mechanisms of action of chemotherapy, chemotherapy also indiscriminately targets other cells in the body besides cancer cells. The adverse effect of chemotherapy on healthy tissues is most readily apparent as side effects in other quickly dividing cells, such as hair loss, gastrointestinal distress, and myelosupression (American Society of Clinical Oncology, 2015). However, there are numerous side effects that chemotherapy causes that aren't understood in detail because of their chronicity or late onset months or years after treatment, such as fatigue, memory and concentration problems, muscle weakness, declines in physical function, and neuropathy (American Cancer Society, 2016). The physiological basis for long-term side effects results from the cellular-level damage chemotherapy causes through oxidative stress, DNA damage, cell senescence, and triggered inflammation (Collins & Supko, 2010). These processes cause cascading damage throughout the body and degrade numerous necessary and normal cellular functions. Though effective treatment for cancer because of the damage they cause to cancer cells, these avenues of cellular damage may also contribute to impairment of healthy physiological systems and lead to fatigue and inactivity which is associated with changes in body composition including increased fat and decreased muscle (Speck et al., 2010) and muscle weakness (Schmitz et al., 2010).

Fatigue and inactivity associated with changes in body composition can eventually lead to poor physical fitness and function (Walston, Hadley, & Ferucci, 2008).

Chemotherapy has long been associated with adverse body composition changes in cancer survivors. The most common adverse changes in body composition include increased weight and fat mass as well as decreased lean mass, and these changes in body composition are exacerbated by inactivity and fatigue which are other common side effects of chemotherapy treatment (Jones, Eves, Haykowsky, Freedland, & Mackey, 2009; Jones et al., 2010; Visovsky, 2006). An early longitudinal study describing the body composition changes underlying weight change in cancer survivors treated with chemotherapy found that 7 of 8 women experienced significant gains in fat mass (mean 4.4kg) and loss of lean mass (mean 1.3kg), regardless of direction of weight change (Cheney, Mahloch, & Freeny, 1997). Similarly, another early study around the same time (Aslani, Smith, Aleen, & Levi, 1998) found that breast cancer survivors treated with chemotherapy (n=15) all experienced significant gains in weight (mean 1.2kg, $p<0.0001$) and fat mass (mean 1.1kg, $p<0.01$) and non-significant loss of lean mass (0.1kg, $p=0.42$). Another study comparing 26 breast cancer survivors to 51 healthy age-matched controls found that, compared to controls, breast cancer survivors treated with chemotherapy showed no significant changes in weight but significant increase in percent body fat (+2.3±4%, $p=0.02$) and significant decrease in lean mass (−2.2±4%, $p=0.02$) (Freedman et al., 2009). Many different chemotherapeutic agents have been associated with adverse body composition. Of note, anthracyclines were some of the first chemotherapeutic agents to gain widespread use in the emergent field of chemotherapy, and remain one of the most commonly used chemotherapeutic classes today (Hanada, 2012). However, one of the common and severe side

effects of anthracyclines is striated muscle dysfunction (Gilliam & St Clair, 2011; Sorensen et al., 2016), which contributes to muscle atrophy and weakness (Miyamoto et al., 2015).

Increases in fat mass and decreases in lean mass are not universal for cancer survivors treated with chemotherapy, particularly for cancer types other than breast cancer. A study of 47 oesophagogastric cancer survivors treated with chemotherapy found that over the course of treatment, participants lost a mean of 2.3kg in weight but had greater losses of lean mass (-2.9±4.7 kg, $p<0.0001$) than losses of fat mass (-1.3±3.2 kg, $p<0.007$). Another study of ovarian cancer survivors who received chemotherapy treatment (n=33) found significant loss of weight (-3.1kg), fat mass (-2.6kg), and lean mass (-0.2kg) at 3 months after diagnosis, and then rebound gain in weight (+1.8kg above baseline) and fat mass (+3kg above baseline) but a maintained loss of lean mass (-0.2kg) (Gil, Frasure, Hopkins, Jenison, & Gruenigen, 2005). These two studies demonstrate that adverse changes in body composition are common after chemotherapy treatment, but that not all changes are increased weight and fat mass and decreased lean mass. Unfortunately, neither of these two studies described reported tissue percentages so it is impossible to deduce the relative changes in body composition. However, the fact that both groups lost more lean mass than fat mass indicates that participants experienced sarcopenic obesity-like changes in body composition, which may represent the overall trend in body composition changes associated with chemotherapy regardless of cancer type or chemotherapeutic agent received.

Radiation Therapy

Radiation therapy attacks cancer through unique pathways different from chemotherapy. Targeted ionizing radiation causes irreversible damage to rapidly dividing cancer

cell DNA necessary for replication. Radiation therapy is administered through targeted beams of radiation focused on cancerous masses, or by implanted radioactive seeds that emit radiation within a tiny radius. Radiation therapy also causes indiscriminate damage to normal tissues of all kinds, which limits it application to localized use rather than systemic use.

Regardless of localized treatment, radiation therapy causes systemic damage in addition to localized damage. Damage to localized healthy tissues from radiation therapy is incurred when, in order to ensure complete exposure of microscopic cancer cells to treatment, margins of healthy tissue are included around tumors (American Cancer Society, 2016; Pazdur, Wagman, Camphausen, & Hoskins, 2008). Localized side effects from radiation are limited to the region of treatment exposure, which differs by cancer type and location. Yet all side effects from radiation are not limited to a localized response. Underlying physiologic responses to radiation therapy cause systemic changes that are associated with chronic side effects (Hauer-Jensen, Fink, & Wang, 2004). Damage to irradiated neuromuscular, vascular, and mesenchymal tissues trigger cellular signaling that can lead to systemic inflammation and tissue remodeling. Changes of systemic inflammation and tissue remodeling can then lead to decreased neurovascular innervation and muscle atrophy which are associated with adverse changes in body composition and physical fitness and function (Stubblefield, 2011). A model explaining this process proposes that the predominant mechanism by which radiation damages tissues is induction of apoptosis via DNA damage caused by free radicals (Hauer-Jensen et al., 2004). Localized damage triggers ever-expanding feedback loops beyond the affected tissue through activation of inflammation, coagulation, fibrogenic, and remodeling pathways that can cause

fatigue and inactivity, which can lead to late delayed side effects months or years after treatment (Cross & Glantz, 2003).

Studies show that radiation therapy is associated with adverse changes in body composition. A study of body composition in head and neck cancer survivors treated only with radiation found significant large changes in body composition of weight loss of 6-12% of nearly two-thirds of which consisted of lean mass loss, which was furthermore significantly associated with physical performance decline ($r=0.71$, $p=0.004$) and increased functional dependence ($r=0.58$, $p=.02$) (Silver et al., 2007). Another study in head and neck cancer survivors that described changes in total body composition in survivors treated with radiation therapy as well as chemotherapy found significant changes to body composition throughout treatment larger than those described by Silver et al. (2007) in survivors who received only radiation therapy. Cancer survivors lost a mean weight of 10.2% ($p=0.0002$), lean mass 10.2% ($p=0.001$), and fat mass 11.1% ($p=0.001$) (Jackson et al., 2014). Head and neck cancers may have complicating factors of intake and nutrition related to body composition change. However, radiation therapy in other cancers is also associated with changes in body composition. A study of breast cancer survivors who received curative radiation therapy found significant gains in body fat ($r=0.50$, $p=0.002$, $+0.6\pm1.3$ kg) and lean mass ($r=0.42$, $p=0.01$, $+0.5\pm1.2$ kg) over just 6 weeks post-treatment (Genton, Kyle, Majno, & Pichard, 2006), the first study of body composition during curative radiation therapy in breast cancer survivors. Though the results of some studies are not representative of the sarcopenic obesity phenotype (concurrent gain of fat mass and loss of lean mass), they show that radiation treatment is associated with adverse changes in body composition, which may evolve further into a sarcopenic obesity phenotype. In addition,

radiation therapy is often used in conjunction with chemotherapy and/or hormonal therapy. This suggests that cancer survivors may be at risk of higher risk of sarcopenic obesity because of chemotherapy, but that other treatments such as radiation may further compound adverse changes in body composition.

Hormone Therapy

Hormone therapy is another common modality of cancer treatment, but its use is limited to a subset of cancers whose growth is dependent on sex hormones. The subset of cancers responsive to hormone therapy is prostate, breast, uterine, ovarian, and kidney cancers, and these are some of the most prevalent cancer types. Although hormone therapy modulates naturally occurring pathways to fight cancer rather than utilizing cytotoxic therapies, it can also cause acute and long-term systemic side effects since non-cancer tissues responsive to hormones are also disrupted (American Cancer Society, 2016; Cecchini, Yu, Ptovin, D'souza, & Lock, 2015; Ellis, Hendrick, Williams, & Komm, 2015). Hormone treatment can therefore result in common side effects such as fatigue and inactivity, which can lead to musculoskeletal changes in cancer survivors (Madeddu, Mantovani, Gramignano, & Maccio, 2015), which are associated with declines in physical fitness and function (Walston, Hadley, & Ferucci, 2008).

Early hormonal therapy drugs, particularly selective estrogen receptor modulators such as tamoxifen, have long been associated with weight gain (Hoskin et al., 1992; Malinovszky et al, 2004; Rose, Connolly, Chlebowski, Buzzard, & Wynder, 1993) as well as adverse changes in body composition. A seminal study exploring body composition in breast cancer survivors treated with tamoxifen found no significant difference between breast cancer survivors (n=26) and cancer-free controls (n=31) in lean mass, but did find significantly higher percent body fat

in those receiving tamoxifen as measured by dual energy x-ray absorptiometry (DXA) (+3.3%, $p<0.05$) as well as across 4 additional body composition measurement methods (Ali, al-Ghorabie, Evans, el-Sharkawi, & Hancock, 1998). Soon after, Nguyen, Stewart, Banerji, Gordon, & Kral (2001) described significantly higher visceral fat area (135±1.0cm^2 v 81±0.7 cm^2, $p<0.0001$) in breast cancer survivors receiving tamoxifen (n=32) than controls (n=39). More recent research comparing tamoxifen with newer aromatase inhibitor hormonal therapy shows that women who switched from tamoxifen to aromatase inhibitor exemestane had lost a significant amount of weight and fat mass after 12 months ($p<0.01$), while women who remained on tamoxifen had no significant difference in weight or fat mass (Francini et al., 2006). In contrast, a randomized control trial of breast cancer survivors receiving aromatase inhibitors compared to those who received none showed that both groups gained an equally significant amount of weight (1.79±0.74kg v 1.76±0.66kg) after 24 months, however, the women receiving aromatase inhibitors had a significant increase of 1.16±0.28kg ($p<0.05$) in lean mass compared to the control women who gained in percent body fat instead (1.2±0.4%, $p<0.05$) (van Londen et al., 2011). Hormone therapy and its association with adverse changes in body composition is mixed. Older selective estrogen receptor modulators such as tamoxifen are strongly associated with adverse changes in body composition, however, newer aromatase inhibitor hormone therapies do not appear to have the same adverse affects. This difference in treatment modality side effects is a factor to be taken into consideration that may or may not contribute to risk of sarcopenic obesity and poor physical fitness and function.

In summary, cancer treatments act at the cellular level by interrupting regular cellular processes, thereby destroying cancer through an inability to replicate. Accordingly, these

indiscriminate mechanisms of action also interrupt the cellular processes of healthy tissues and cause adverse physiological changes. The physiological changes from treatment are associated with acute and long-term side effects in cancer survivors. Consequently, cancer survivors, though often cured of detectable cancer, are left to endure prevalent and sometimes severe side effects, possibly for the remainder of their lives. Increased fat mass and decreased lean mass are common side effects of cancer and cancer treatment and each may be associated with poor physical fitness and function, which may increase risk of disability and death. The logical conclusion is that concurrent increased fat mass and decreased lean mass would be associated with high risk of poor physical fitness and function, but since research describing sarcopenic obesity and physical fitness and function in cancer survivors has not yet been conducted, it remains unknown whether cancer survivors with sarcopenic obesity are at higher risk of poor physical fitness and function. Accurate categorization of the sarcopenic obesity phenotype in cancer survivors will provide more understanding about the adverse changes in body composition that cancer treatment can cause.

Long-term Physical Side Effects in Cancer Survivors: Linking Sarcopenic Obesity to Declines in Physical Fitness and Function

Long-term physical health effects suffered by cancer survivors, such as poor physical fitness and function, may stem from cancer treatment related physiologic impairments and side effects such as adverse changes in body composition. Understanding what limitations in physical fitness and function cancer survivors experience and how physiologic impairments such as changes in body composition may lead to poor physical fitness and function will contribute to

improved care for those at highest risk of developing limitations. The following sections review the literature of adverse body composition from cancer treatment as an underlying cause of poor physical fitness and function in cancer survivors. Prominent gaps in the literature are identified that informed the purpose and aims of this dissertation.

Physical fitness and function in cancer survivors

Declines in physical fitness and function are an expected aspect of aging, but poor physical fitness and function is reported significantly more often in cancer survivors than those who have never had cancer. In addition, declines in physical fitness and function may be accelerated in cancer survivors compared to those who have never had cancer (Ganz et al., 2002; Ganz et al., 2003). Physical fitness is defined as health- or skill-related attributes that enable an individual to perform physically activities including but not limited to, strength, speed, power, stamina, flexibility, and endurance (Bennett, Winters-stone, & Nail, 2006; Caspersen, Powell, & Christenson, 1985; Painter, Stewart, & Carey, 1999).Bennett, Winters-stone, & Nail (2006) include three dimensions: objective mobility (i.e. gait and balance), perceived mobility (i.e. self-report functions e.g. can you walk up stairs unaided), and life activities (self-report participation in activities of daily living and instrumental activities of daily living). Physical function is defined as “a person’s ability to do discrete actions or activities” (Jette & Haley, 2002). Common physical function activities assessed in research include walking up steps, lifting or carrying a moderately heavy object, and standing from an armless chair. Different types of physical function are necessary for participating in common life activities at home and in society. Declines in physical fitness and function are a particular focus of research

since poor physical fitness precedes functional declines, which in turn precede the development of disability (Mohile et al., 2009) and death (Brown, Harhay, & Harhay, 2014).

Utilizing self-report methods, many studies on physical function in cancer survivors (Fossa, Vassilopoulou-Sellin, & Dahl, 2008) show that compared to controls with no cancer history, cancer survivors are more likely to report an inability to do activities requiring mobility and strength (Sweeney et al., 2006) and that long-term cancer survivors are more likely to report reduced mobility and problems performing activities of daily living (Keating, Norredam, Landrum, Huskamp, & Meara, 2005). Data from National Health and Nutrition Examination Survey (NHANES) quantifies that half of cancer survivors self-report physical limitations at a rate 1.5 to 1.8 times greater than those persons with no cancer history (Ness, Wall, Oakes, Robinson, & Gurney, 2006). More specifically, a particularly large study by Hewitt et al., (2003) found that in a U.S. sample of cancer survivors (n=4,878) compared to those without a history of cancer (n=90,737), cancer survivors were significantly more likely to report being in fair or poor health (odds ratio, OR=2.97) and to report increased likelihood of limitations of activities of daily living (ADL) or instrumental activities of daily living (IADL) (OR=2.22). Similarly, another large study in a similar cohort (cancer survivors n=2,143; cancer-free controls n=72,618) found significantly increased prevalence of lower-body functional limitations in long-term (≥5 years) cancer survivors compared to controls (57.0% v 26.6%, $p<0.05$). The study also found differences in prevalence of lower-body functional limitations across cancer type ranging from 44.9% (lymphoma survivors) to 88.8% (lung cancer survivors), and differences across cancer type in odds of reporting lower-body functional limitations compared to controls, ranging from 1.35 (breast cancer survivors) to 7.91 (lung cancer survivors) (Schootman, Aft, & Jeffe, 2009).

Furthermore, cancer survivors who received multiple and/or more aggressive cancer treatment modalities report worse function, and survivors diagnosed at older ages are particularly prone to declines in physical function (Hewitt et al., 2003; Jensen et al., 2013; Mols, Vingerhoets, Coebergh, & van de Poll-Franse, 2005; Sweeney et al., 2006). Large studies consistently confirm that cancer survivors self-report more and worse physical limitations than people who have never had cancer, even after controlling for sociodemographic variables and the downstream consequences can be life-threatening.

Functional declines in cancer survivors are a significant health threat since poor physical fitness and function is significantly predictive of mortality. For example, a large seminal study including 7417 eligible participants compiled from 30 randomized controlled trials from the European Organization for Research and Treatment of Cancer found that self-reported poor physical function is significantly associated with shorter survival (HR=0.94, 95%CI=0.92–0.96, $p<0.0001$) (Quinten et al., 2009). In the U.S., a recent study utilizing NHANES data of 428 cancer survivors of both genders and including multiple cancer types also found that self-reported physical function limitations (difficulty performing five common tasks) were significantly associated with objectively measured poor physical function (gait speed over 2.4 meters) and was significantly associated with earlier death (Brown, Harhay, & Harhay, 2016). Each additional reported functional limitation was associated with a 19% increase in risk of death (95%CI=9%-29%, $p<0.001$) with the reported difficulty of walking up 10 steps being the most predictive factor for mortality in the adjusted model (HR=1.49, $p=0.035$) (Brown et al., 2016). The association of self-reported poor physical function with early death in cancer survivors is an important finding, but it is not completely known if there are identifiable factors prior to self-

report that may be more sensitive to change in self-reported physical function such as objective measures of physical fitness and function.

Self-report measures of physical function may underestimate the prevalence of functional limitations and time of onset after cancer treatment since changes in perceived limitations usually manifest after objective measures can detect some level of impairment (Fried et al., 1991). Evidence suggests that self-report may not accurately capture poor physical fitness and function because of mis-reporting due to social desirability, poor attentiveness to symptoms, and selection bias of what to report, all of which may mask accurate reports (Stone et al., 2009). It is concerning that self-report may not accurately capture declines in physical function since progressive decline in physical fitness and function may go unrecognized despite being clinically detectable (Fried et al., 1991) by objective measures of physical fitness and function at an earlier juncture in survivorship than self-report methods alone (Bennett, Winters-Stone, & Nail, 2006; Fried et al., 2010). Studies on the validity of self-report represent cancer survivor populations (Breetvelt & Van Dam, 1991; Brinksma et al., 2014; Groenvold, 2010) and topics related to physical function such as quality of life (McPhail, Beller, & Haines, 2010), disability (Razmojou, Schwartz, & Holtby, 2010) and reveal that self-report may significantly over or underestimate the severity of a perceived variable (McClimans et al., 2013), particularly changes in self-reported function in response to recent health problems (Daltroy, Larson, Eaton, Phillips, Liang, 1999).

Though not performed in cancer populations, a body of research comparing self-reported and objective measures of physical function exists that consistently shows that objective measures of physical function identify more limitations that do self-report measures. One study

to identify early decline of physical function in older community-dwelling women (n=170) found that the majority of participants self-reported no functional limitations (activities of daily living (ADL)=77%, instrumental activities of daily living (IADL)=61%) but only 7% scored at the ceiling of the 7-item Physical Performance Test (PPT) and 30% scored at the ceiling for gait speed (defined as >1.2 m/s) (Brach et al., 2002). A recent large study (n=7,609) utilizing National Health and Aging Trends Study (NHATS) to compare self-reported and objective measures of physical function found that self-report was only accurate in distinguishing between older adults at the lowest end of the spectrum (unable versus others) but not those with mid or high function, while in contrast, objective measures of physical function (balance, walking speed, chair stands, grip strength, and peak air flow) were able to accurately discriminate among levels of physical function across the spectrum of function (Kasper, Chan, & Freedman, 2016). Also, a study of the predictive validity of poor health outcomes of self-report compared to objective measures revealed that objective measures (Short Physical Performance Battery OR=0.74, 95%CI=0.60-0.90, p=0.0024; stair climb OR=0.76, 95%CI=0.61-0.94, p=0.0105; 400-m walk OR=1.54, 95%CI=1.26-1.88, p<0.0001; gate speed OR=0.75, 95%CI=0.62-0.92, p=0.0054) were slightly better at predicting hospitalizations than self-report (Late-Life Function and Disability Instrument (LLFDI) function OR=0.72, 95%CI=0.58-0.88, p=0.0017; LLFDI basic lower extremity OR=0.77, 95%CI=0.63-0.95, p=0.0129; LLFDI advanced lower extremity OR=0.72, 95%CI=0.59-0.89, p=0.0017), but the study was only two years in length and did not include longer term outcomes such as disability and death (Beauchamp et al., 2015). Such comparative studies support the theory that self-reported poor physical function often does not accurately reflect the magnitude of physiologic changes identified through objective measures (Smith et al., 2014)

which indicates that people tend to have worse physical fitness and function than they self-report.

According to Fried et al. (2000), people with unrecognized and unreported declines in clinically detectable objective measures of physical fitness and function are at high risk for progressing to more severe disability. It is therefore critical to incorporate objective measures of physical fitness and function in cancer survivor studies. Adverse changes in body composition as a result of cancer and its treatment are theorized to precede objective declines in physical fitness and function, but the frequency of sarcopenic obesity and its association with physical fitness and function in cancer survivors has not yet been described. This dissertation addresses the gap in understanding about how adverse body composition, particularly sarcopenic obesity, is associated with poor physical function in cancer survivors and focuses on objective measures of physical function rather than self-reported physical function since evidence support the theory that objective declines in physical function precede self-reported declines in physical function.

Body composition in cancer survivors

Adverse changes in body composition are a common physiological side effect among cancer survivors. Adverse changes in body composition include increases in body weight and fat mass, and decreases in lean mass (Speck et al., 2010). The three classic body composition phenotypes were once considered to be obese, sarcopenic, and normal, but sarcopenic obesity is now recognized as a fourth phenotype (Waters & Baumgartner, 2011). Defined simply, sarcopenia is low muscle mass, obesity is high fat mass, and sarcopenic obesity is a concurrent combination of both low muscle mass and high fat mass. Little research has been performed in cancer

survivors describing sarcopenic obesity phenotype, which is a gap in understanding about what magnitude of a problem sarcopenic obesity presents to cancer survivors and the possible association of sarcopenic obesity with poor health outcomes.

A critical observation is that different adverse changes in body composition are more common in some cancer types than others. For example, increased weight and fat mass without increased lean mass (or loss of lean mass) is commonly reported in breast cancer survivors (Sheean et al., 2012). In contrast, weight loss is almost universal in head and neck cancer survivors (mean -26lbs, range +1 to -61lbs) (Hunter & Jolly, 2013) with 71.7±21% of weight loss during treatment from loss of lean body mass (Silver et al., 2007). Differences in changes of body composition across cancer types, combined with differences in prevalence and survival rates across cancer types makes summarizing the impact of cancer treatment on body composition across cancer types difficult, but indicates that some cancer types may be at greater risk of sarcopenic obesity and than others. Identifying factors such as cancer type, cancer treatment type, age, and other variables is an important gap in understanding what risk factors are associated with sarcopenic obesity because some may modifiable and some may influence clinical decisions. This dissertation addresses this gap in Aim 1 by describing differences in prevalence of sarcopenic obesity between cancer types, and in Aim 2 by describing variables that may be significantly associated with sarcopenic obesity.

Body Composition

Weight vs. Body Composition

Weight is one of the most commonly reported variables in studies of cancer survivors. Weight gain in cancer survivors, particularly in those treated with chemotherapy, is

an adverse outcome reported on since the 1970s. At first an unexpected finding (Dixon, Moritz, & Baker, 1978), weight gain soon became an expected side effect of some cancer treatments, consistently confirmed by multiple investigations (Boyd et al., 1981; DeConti, 1982; Heasman, Sutherland, Campbell, Elhakim, & Boyd, 1985; Levine, Raczynski, & Carpenter, 1991). The prevalence of weight gain (4-10kg, depending on chemotherapy regimen received) was quickly established to occur in the majority of breast cancer survivors treated with chemotherapy (Foltz, 1985), and other studies confirmed that weight gain was less (1.5-2.0kg) but also common in breast cancer survivors not treated with chemotherapy (Goodwin, Panzarella, & Boyd, 1988; Hoskin, Ashley, & Yarnold, 1992). Further studies confirmed that weight gain in breast cancer survivors exceeded weight gain predicted in the general population from other factors (Del Rio et al., 2002). Recent work continues to affirm weight gain as a side effect in cancer survivors. An updated review in 2011 of 23 studies not included in Demark-Wahnefried, Winter, & Rimer's seminal 1993 review of weight gain in breast cancer survivors found a similar rate of weight gain in 50-95% of cancer survivors short-term after completion of treatment (Vance et al., 2011). Long-term studies of weight have shown that most cancer survivors are likely never to return to their pre-cancer diagnosis weight, with one study quantifying that 6 years after diagnosis only 10% of women ever returned to their weight prior to diagnosis (Saquib et al., 2007). Weight gain is often incorrectly assumed to be an accurate surrogate for body composition, particularly for gains in fat. Unfortunately, weight is not able to accurately describe underlying body composition nor accurately explain changes in fat and lean mass tissues since significant body composition changes can occur without any change in weight (Garrow & Webster, 1985).

Early studies began to identify and quantify the body composition changes associated with weight gain in cancer survivors. A study by Winningham, MacVicar, Bondoc, Anderson, & Minton (1989) represents a pioneering effort of body composition intervention in a randomized control trial in cancer survivors with an aerobic exercise intervention group (bicycle ergometry) versus a sedentary control group. The control group, who did not exercise, experienced a significant gain in percent body fat (+2.19%). Another early study examined the relationship between changes in weight and changes in body composition and found significant differences between weight and lean mass (de Graaf, Meeuwsen-van der Roest, Schraffordt Koops, & Zijlstra, 1987). Lymphocytic leukemia survivors who gained weight (0.5±0.3kg, $p=0.191$) and osteosarcoma survivors who lost weight (-2.4±0.9kg, $p=0.018$) both had significant loss of lean mass (respectively -0.8±0.4kg, $p=0.097$, and -3.5±0.7kg, $p<0.001$), though small round cell sarcoma survivors did not have significant changes in weight or lean mass. These studies are examples of early efforts that identified changes in body composition that were significantly independent of weight in cancer survivors and suggested that lean and fat tissues should be investigated separately regardless of whether a cancer survivor had a change in weight or not.

Body composition measurement

Multiple techniques for assessing body composition are in common use but techniques differ in their accuracy and ability to describe tissue distribution by compartment. Three techniques, dual energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and computed tomography (CT), are the most accurate methods for body composition

measurement because of direct imaging. DXA is generally accepted as the gold standard for determining body composition since it measures whole body fat and lean mass and allows for regional analysis of individual limbs, trunk, and head (Thibault, Genton, & Pichard, 2012), whereas CT and MRI are localized imaging techniques that project whole body tissues percentages algorithmically. Other body composition measurement techniques include bioelectrical impedance analysis (BIA) and air plethysmography (Bod Pod), which are able to quantify total body tissue amounts but not regional compartments. Less accurate methods are indirect algorithmic proxies utilizing anthropometric data such as waist circumference and Body Mass Index (BMI). BIA and BMI are the cheapest and easiest measures to use and can be performed anywhere, hence they are often utilized in studies despite being less accurate than other methods. DXA, MRI, CT, and Bod Pod are often prohibitive because of cost of equipment and operating personnel. In addition, DXA and CT involve radiation exposure, which limits the exposure patients can receive. These considerations account for decisions of which body composition measure to use in a research study. Many studies may already have access to existing clinical data for analysis, such as CT scans and anthropometric data and not seek additional measures, though such data quality must be evaluated for research.

Whole body DXA imaging is the only body composition measure that directly measures all tissues. However, whole body DXA scans are usually only done for research purposes, therefore DXA scans must be ordered in addition to any clinical images cancer survivors may have received. Of benefit in cancer populations is the fact that CT imaging is often used in clinical oncology to detect tumors in the abdomen or thorax, therefore cancer survivors often have CT scans available for algorithmic body composition analysis. CT utilizes an abdominal

cross-section with algorithmic estimates of total body lean mass and fat mass which have been correlated with DXA scans (Mitsiopoulos et al., 1998; Shen et al., 2003; Mourtzakis et al., 2008), but CT images do not directly measure nor completely account for appendicular tissue. This is a practical and theoretical weakness for accurate reflection of all body compartments as well as accurate reproducibility. A strength of this dissertation is the inclusion of whole body DXA measures.

Waist circumference, BMI, and waist/hip ratio have been shown to be poorly correlated with total body fat mass and percent body fat for decades (Garrow & Webster, 1985, Xiao et al., 2006), and recent research has specifically shown that the BMI cutoff for obesity of ≥30kg/m^2 does not adequately detect sarcopenic obesity because it significantly underestimates fat (Romero-Corral et al., 2008) and is the least inclusive diagnostic criteria of sarcopenic obesity when compared to fat mass measures (Siervo, Stephan, Nasti, & Colantuoni 2012). It is a prominent gap in the literature that BMI measures are utilized for defining obesity rather than accurate measures of body composition. Studies of sarcopenic obesity should utilize the most accurate measures of body composition available. This dissertation will be comparing multiple definitions of sarcopenic obesity including those which utilize BMI for defining obesity, with the expectation that that definitions including BMI will have significantly low prevalence rates, and thus may underestimate the magnitude of SO, and poorly account for explained variance in association with objective measures of physical function.

Sarcopenia in cancer survivors

Sarcopenia, or low muscle mass, has been shown in numerous populations to contribute to fatigue, poor physical function, reduced treatment tolerance, lower quality of life, and decreased survival (Going et al., 1995; Iannuzzi-Sucich et al., 2002). Estimates are that sarcopenia affects 20-70% of cancer survivors, though specific rates are largely dependent on cancer type (Ryan et al. 2016). Associations between sarcopenia and overall survival have been made in multiple cancer population samples. These include survivors of adrenocortical carcinoma (Miller et al. 2012), biliary tract (Mir et al., 2012), bladder (Psutka et al., 2014), breast (Prado et al., 2008), colorectal (Martin et al, 2013), lung (Jebb, Osborne, Dixon, Bleehen, & Elia, 1994; Martin et al., 2013), ovarian (Rutten et al., 2016), and pancreatic (Tan, Birdsell, Martin, Baracos, & Fearon, 2009) cancers. For example, in a sample of obese Canadians with lung or gastrointestinal cancer, 15% had sarcopenia, and sarcopenia was found to be significantly associated with poor functional status ($p= 0.009$) and a significant decrease in median survival (10 months vs 21 months, $p<0.0001$) (Prado et al., 2008). The aformentioned study and all the others cited in other cancer types above found that low skeletal muscle mass was significantly related to mortality even after controlling for confounders such as sex, age, cancer stage, and cancer site.

Besides sarcopenia being associated with poor survival, other studies have found strong associations between sarcopenia and adverse outcomes during cancer treatment. Multiple studies have associated sarcopenia with increased dose-limiting or treatment discontinuation chemotherapeutic toxicity (≥ grade 3 toxicity) (National Cancer Institute, 2006) in cancer survivors undergoing chemotherapy treatment (Antoun, Baracos, Birdsell, Escudier, & Sawyer, 2010; Del Fabbro et al., 2012; Huillard et al., 2013), which suggests that lean mass is a better

measure for normalizing chemotherapeutic dosing (Prado et al., 2009; Prado et al., 2011) than the routinely used body surface area reference (Gurney, 1996). Chemotherapeutic toxicity is problematic because of increased drug exposure over a shorter period time because of low volume of distribution and poor drug metabolism/clearance (Collins & Supko, 2010) which can lead to dose reduction, treatment discontinuation, hospitalization, and even death (Tomiak et al., 2000). Sarcopenia has also been associated with other adverse outcomes in patients undergoing cancer treatment. A study in colorectal cancer survivors found that sarcopenia was associated with increased risk of postoperative infection (OR=4.6, 95%CI=1.5-13.9, $p<0.01$) and delayed recovery from colorectal resection surgery (OR=3.1, 95%CI=1.04-9.5, $p<0.04$) (Lieffers, Bathe, Fassbender, Winget, & Baracos, 2012). Another study of the risk of chemotherapeutic toxicity in breast cancer survivors found a prevalence of toxicity of 50% in sarcopenic patients compared to 20% in non-sarcopenic patients ($p=0.03$), as well as shorter time to tumor progression in those with sarcopenia compared to patients without sarcopenia (101.4 vs 173.3 days, $p=0.005$) (Prado et al., 2007). The sarcopenic phenotype may be associated with development into a sarcopenic obesity phenotype and association with long-term poor physical fitness and function.

Obesity in cancer survivors

Studies have shown that increases in fat mass and percent body fat are common in cancer survivors and that cancer survivors often have higher percent body fat than the average population, though obesity is often cancer type dependent. Breast cancer survivors in particular average 3-10 points percent body fat significantly higher than the general population

(McTiernan et al., 2003; Sheean et al., 2012). Studies in other cancer types have described obesity and adiposity as well including colorectal cancer (Malietzis et al., 2015), pancreatic cancer (Preziosi, Oben, & Fusai, 2014), and non-Hodgkins lymphoma (Terret, Albrand, Rainfray, & Soubeyran, 2015). Obesity in cancer survivors is significantly associated with cancer recurrence (Demark-Wahnefried, at al., 2012; Travis et al., 2012), and increased adiposity in cancer survivors is significantly associated with shortened survival and overall mortality across many cancer types (Chan et al., 2014; Malietzis et al., 2015; Playdon et al., 2015).

Besides just cancer type, increased adiposity and obesity have been described across cancer treatment types. In breast cancer survivors, numerous studies have shown an increase in adiposity in women who have received chemotherapy (Cheney et al., 1997; Campbell, Lane, Martin, Gelmon, & McKenzie, 2007) despite variation in the timing of measurements of body composition changes. Demark-Wahnefried et al. (2001) described significant increase in percent body fat from baseline to 12 months in women who had received chemotherapy (n=36, +2.2±0.6%, adjusted p=0.04) compared to women treated with surgery alone or surgery plus radiation therapy (n=17, -0.1±0.4%, adjusted p=0.04). In addition, studies have long described significant increases in adiposity in women treated with tamoxifen (Ali, al-Ghorabie, Evans, el-Sharkawi, & Hancock, 1998; Nguyen et al., 2001), though in contrast, other studies have shown that the new generation of hormonal treatment with aromatase inhibitors may decrease percent body fat because of increases in lean mass (Montagnani et al., 2008). Few direct comparisons have been made of increased adiposity and obesity across multiple treatment types within the same populations (van Londen et al., 2011), which is problematic since cancer

treatment is not homogeneous and certain treatments present different levels of risk of changes in fat mass.

Both obesity and sarcopenia are associated with long-term negative health outcomes in cancer survivors. It is unknown whether the presence of both concurrently, the sarcopenic obesity phenotype, puts cancer survivors at increased risk of poor physical fitness and function. Studies in populations other than cancer survivors have described the association of sarcopenic obesity and physical fitness and function, and other studies in cancer survivors have described the association of sarcopenic obesity with other poor health outcomes. This evidence is outlined in the following section. However, no study in cancer survivors has yet described the association of sarcopenic obesity with physical fitness and function.

Sarcopenic Obesity

Heber et al. published the first description of sarcopenic obesity as a condition in 1996, and Baumgartner operationalized its phenotype classification in 2000 from a regional convenience sample. Sarcopenic obesity is theorized as a synergistically adverse condition, a simultaneous combination of the health risks and adverse outcomes of both sarcopenia and obesity. In populations other than cancer survivors, sarcopenic obesity has been associated with lower self-reported quality of life (Pedrero-Chamizo et al., 2015), increased length of hospital stay (Peng et al., 2011; Tsaousi et al., 2016), reduced ability for instrumental activities of daily living (Balachandran, Krawczyk, Potiaumpai, & Signorile, 2014; Baumgartner et al., 2004), increased frailty and loss of independence (Batsis et al., 2015; Woo, Leung, Sham, & Kwok, 2009), and increased mortality (Batsis, Mackenzie, Barre, Lopez-Jimenez, & Bartels, 2014). Though it could

be speculated that cancer survivors have a higher frequency of sarcopenic obesity based on the increased prevalence of each sarcopenia and obesity independently in cancer survivors, it remains unknown what associations sarcopenic obesity has with adverse health outcomes in cancer survivors.

Determining the frequency of sarcopenic obesity in any population is a challenging task because a variety of definitions of sarcopenic obesity have been proposed and utilized. Heber et al. (1996) described sarcopenic obesity simply as, "reduced lean mass with excess fat as a percentage of body weight" (p. 474S), but did not describe threshold low or high levels for lean mass and fat mass, respectively. Baumgartner's (2000) operationalized definition for sarcopenic obesity outlined sarcopenia as lean mass with, "values less than –2 [standard deviations] below the sex-specific mean for [relative skeletal muscle index] in a healthy, younger person (mean age = 29 years), or less than 7.26 kg/m^2 in men, and less than 5.45 kg/m^2 in women", and outlines obesity as, "values greater than the median [percent body fat] for each sex, or greater than 27% in men and 38% in women". These cutoffs of lean mass for sarcopenia and body fat percentage for obesity, obtained by accurate measures of body composition (e.g. DXA), continue to be the most commonly adopted throughout current literature on sarcopenic obesity, though variances in sarcopenic and obese cut-offs confuse comparisons between studies and generalizability because of differing definitions (Prado et al., 2012).

Other attempts have been made at defining sarcopenic obesity because of competing conceptual definitions of sarcopenia and obesity and/or utilizing available datasets for secondary analysis where the body composition variables were not critical to the original aims and thus the measures used are not optimal. Anthropometrics, bioelectrical impedance, and

measures of muscle strength have been proposed as alternative components of sarcopenic obesity, but these methods depart from the original proposed basis of sarcopenic obesity as defined by accurate body composition measurement only. Alternative definitions such as those utilizing BMI or waist circumference have wide margins of error identifying obesity when comparing across methods (Batsis et al., 2016a; Siervo et al., 2012; Stenholm et al., 2008) and/or debatable flaws (Thibault et al., 2012) and are not currently as widely represented in the literature compared to accurate body composition measurement methods but are often used in secondary analysis of epidemiologic data because of measure availability (Kim et al., 2012; Levine & Crimmins, 2012; Schrager et al., 2007). As described above, DXA is the gold standard for whole body measurement of composition, but other measures are often substituted because of convenience.

The first alternate definition of sarcopenic obesity utilizing measures other than accurate measures of body composition was by Newman et al. in 2003. Their study explored two alternate definitions of sarcopenia and mentions how the frequency rates of sarcopenic obesity changed when adjusting for height. The authors sagely suggest that, “selection of a single standard definition should be based in large part on its relevance to health and physical functioning” (p. 1603), and that variations in definition possibly identify different groups as having sarcopenic obesity and that different populations (gender, ethnicity, nationality, etc.) may have differing risk of poor physical fitness and function. The authors recognized that the practical utility of different definitions of sarcopenic obesity may be dependent on the outcome variable of interest.

Regardless of measurement method used to assess body composition, the frequency rates of sarcopenic obesity vary widely across definitions in every population that has compared frequency by multiple definitions. In a recent study, Batsis et al. (2013) applied eight different sarcopenic obesity definitions gathered from the literature to an NHANES sample and described a range of frequency of 4% to 84% in men and from 4% to 94% in women, depending on the sarcopenic obesity definition employed. The usefulness of such large ranges is problematic since it is unknown how each definition associates with outcomes of interest. No study has yet been performed in any population that includes multiple definitions of sarcopenic obesity and their association with an outcome variable that lies in the pathway between pathology and disability. This dissertation will be the first to compare the association of sarcopenic obesity with a dependent variable (objective measures of physical fitness and function) across multiple sarcopenic obesity definitions.

Sarcopenic obesity and physical fitness and function

A number of studies in recent years have begun to explore the association of sarcopenic obesity and physical fitness and function in populations other than cancer survivors but none described these associations across multiple sarcopenic obesity definitions. Though heterogeneous in design, aims, sample size, gender, measurement methods, sarcopenic obesity definition/criteria, and physical function measures, most studies found a significant association between sarcopenic obesity and poor physical function. The earliest study describing the association between sarcopenic obesity and physical function precedes the majority of other studies (Baumgartner et al., 2004). This longitudinal study followed 451 elderly men and

women for eight years and found that participants with sarcopenic obesity at baseline were two and half times more likely to report Instrumental Activities of Daily Living (IADL) disability than sarcopenic or obese participants even after adjusting for age, sex, physical activity, and comorbidities (RR=2.63, 95%CI=1.19-5.85). The study was limited by a relatively low frequency rate of sarcopenic obesity (5.8%, n=26) which restricted analysis; however, enrollment criteria was designed to specifically exclude participants with significant illness history, including cancer requiring surgery, radiation therapy, or chemotherapy. Furthermore, the definition of sarcopenic obesity selected utilized a unique threshold for obesity (>60th percentile body fat percentage of study sample; men=28%+, women=40%+) that the authors acknowledge was arbitrary since consensus definitions for sarcopenia, obesity, and sarcopenic obesity were not available. Criteria also limited participants to those with an IADL score of eight or higher, and decline in function was defined as a drop of two or more points in IADL score from baseline score. All together, the criteria decisions of the study likely biased the sample as less likely to have baseline sarcopenic obesity and to be higher functioning, and may not have captured small but significant declines in function. Nonetheless, the study represents the first description of the association of sarcopenic obesity with physical function, but by excluding cancer survivors did not address a population possibly at high risk of sarcopenic obesity.

Since Baumgartner et al.'s 2004 study, 14 additional studies identified through systematic review have explored the association of sarcopenic obesity and physical function, as well as two reviews of interventions and treatment of sarcopenic obesity (Goisser et al., 2015; Poggiogalle et al., 2014), and one randomized control study protocol publication whose results have yet to be published (de Souza Vasconcelos et al., 2013). Multiple studies had large sample sizes which

increases confidence in accuracy of frequency estimates for the definition used because of normalized distribution, and contributes confidence to the generalization of findings. Eight of the studies had notably large sample sizes of 2000 or more participants: n=2287 (Levine & Crimmins, 2012), n=2548 (Joppa et al., 2016), n=2747 (Pedrero-Chamizo et al., 2015), n=4000 (Woo, Leung, & Kwok, 2007), and n=4984 (Batsis et al., 2015), though two of these eight studies shared the same sample (n=3153) within an overlapping research team to publish on different topics related to sarcopenic obesity and physical function (Auyeung, Lee, Leung, Kwok, & Woo, 2013; Woo, et al., 2007). The remainder of the studies varied in sample size from n=21 (Balachandran et al., 2014) to n=491 (Moreira et al., 2016). As a whole, these studies are well-designed and represent large, normally distributed populations. However, without categorization of subgroups such as cancer survivors it is unknown whether such groups represent a higher frequency rate of sarcopenic obesity as theorized compared to those in the general population without cancer.

Methodology & Classification

Methods of body composition, diagnostic criteria and thresholds, and thus definitions for sarcopenic obesity varied widely across studies of sarcopenic obesity and physical fitness and function in non-cancer populations. Measurement of body composition was primarily taken by DXA (10 studies) and those studies which did not utilize DXA used BIA for body composition measurement instead (6 studies). This is an encouraging advance towards consensus methodology and predictive correlation between measurement methods since many older studies in sarcopenic obesity have relied on body composition predictive algorithms from BMI.

All studies also collected BMI, and some collected waist circumference, both of which were unfortunately often used for obesity designation in studies that had DXA body composition data (Batsis et al., 2015; Gadelha, Paiva, Gauche, de Oliveira, & Lima, 2016; Levine & Crimmins, 2012; Meng et al., 2014). The continued utilization of BMI or waist circumference despite the presence of percent body fat, fat mass, or fat mass index data from more accurate DXA measurements is a methodological shortcoming. DXA was chosen as the primary body composition measurement method for this dissertation because of its accuracy and reproducibility. Other definitions of sarcopenic obesity are included for descriptive comparison in Aims 1 & 4, but are theorized to reveal low frequency rates and poor association with measures of physical function.

Association of Sarcopenic Obesity with Physical Function Measures

Every identified study that described the association of sarcopenic obesity with measures of physical fitness and function (n=13) found a significant or positive association between sarcopenic obesity and worse objective and/or self-reported physical fitness and function compared to study participants who did not have sarcopenic obesity. Specifically, eleven of thirteen studies with sarcopenic obesity as an independent variable described significant associations with poor physical function. Two other studies described insignificant but trending associations between sarcopenic obesity and poor physical function. Four of the studies included self-reported measures of physical function and all found significant associations between sarcopenic obesity and poor self-reported physical function. As described above, the earliest study of sarcopenic obesity and physical function found that participants

with sarcopenic obesity at baseline were significantly more likely to report IADL disability than either sarcopenic or obese participants even after adjusting for age, sex, physical activity, and comorbidities (RR=2.63, 95%CI=1.19-5.85) (Baumgartner et al., 2004). Two subsequent studies also included only self-report measures: Levine & Crimmins (2012) found that participants with sarcopenic obesity were 91% more likely than healthy controls to have problems with physical function (prevalence ratio, PR=1.91; 95%CI=1.54–2.38, p<0.001) as measured by self-reported difficulty with 6 ADLs; Batsis et al. (2015) found that in a multivariable logistic regression adjusting for age, race, smoking status, and comorbidities, that sarcopenic obesity by two different definitions was almost universally significantly associated (p<0.05) with self-reported physical limitations (ALM+%BF: OR=1.98, 95%CI=1.06-194) (ALM/BMI+%BF: OR=2.93, 95%CI=1.86-4.64), ADLs (ALM/BMI+%BF: OR=1.90, 95%CI=1.24-2.90), and IADLs (ALM+%BF: OR=1.75, 95%CI=1.02-3.02)(ALM/BMI+%BF: OR=1.69, 95%CI=1.00-2.85). Auyeung et al. (2013) found significant association between three newly described definitions of sarcopenic obesity as fat to muscle ratios (1. body fat/lower limb muscle mass, 2. body fat/fat-free mass, and 3. body weight/fat-free mass) and self-reported physical limitation doing moderate activities or climbing several flights of stairs (body fat/lower limb muscle mass: adjOR=1.136, 95%CI=1.018-1.266, R^2=0.017, p<0.022)(body fat/fat-free mass: adjOR=1.125, 95%CI=1.009-1.254, R^2=0.017, p<0.033) (body weight/fat-free mass: adjOR=1.125, 95%CI=1.009-1.254, R^2=0.017, p<0.033). The odds ratio (OR) of the Auyeung et al. study represents OR increase per one standard deviation (SD) increase in fat to muscle ratio e.g. an additional 1.7% increase in OR accounts for each SD increase in OR of fat/muscle ratio. Though these studies all show significant associations between sarcopenic obesity and poor self-reported physical function, the

heterogeneity of sarcopenic obesity definition (including 5 newly proposed definitions) and heterogeneity of functional limitation and ADL measures make it challenging to compare the studies to each other in any other meaningful interpretation. This gap in the literature could be solved with a standardized self-report measure of physical function such as the well-validated Late Life Function and Disability Instrument (LLFDI) which was developed specifically for community-dwelling older adults, or even better, with objective measures of physical fitness and function.

All but three of the thirteen studies that associated sarcopenic obesity and measures of physical function included one or more objective measures of physical function. Of the objective measures included in studies of sarcopenic obesity, eight studies included grip strength (Barbat-Artigas, Filion, Plouffe, & Aubertin-Leheudre, 2012; Meng et al., 2014; Moreira et al., 2016; Neto et al., 2012; Stoever, Heber, Eichberg, Zijlstra, & Brixius, 2015; Woo et al., 2007; Woo et al., 2009), all of which except one (Neto et al., 2012) described significantly worse grip strength in women with sarcopenic obesity; six studies included 6 meter walk (Aueyang et al., 2013; Joppa et al., 2016; Meng et al., 2014; Moreira et al., 2016; Stoever et al., 2015; Woo et al., 2007), all of which except one (Meng et al., 2014) described significantly worse gait speed in women with sarcopenic obesity; and five studies included chair stands (Barbat-Artigas et al., 2012; Moreira et al., 2016; Pedrero-Chamizo et al., 2015; Stoever et al., 2015; Waters et al., 2010), all of which described significantly worse chair stand times in participants with sarcopenic obesity. Other objective measures were included but in fewer studies, including balance (Barbat-Artigas et al., 2012; Pedrero-Chamizo et al., 2015; Waters, Hale, Grant, Herbison, & Goulding, 2010), one-rep maximum bench press and leg strength (Stoever et al.,

2015), timed get-up-and-go (Waters et al., 2010), step test (Barbat-Artigas et al., 2012), knee extension torque (Moreira et al., 2016), and arm curl, sit & reach, 30 meter walk, 6 min walk, and back scratch (Pedrero-Chamizo et al., 2015). The vast majority of these studies described significant associations of sarcopenic obesity with poor physical fitness and function. This suggests that sarcopenic obesity may be a useful indicator of poor physical fitness and function, though the strength of the association may differ depending on the objective measure and definition of sarcopenic obesity utilized. However, further research could identify a sarcopenic obesity definition that explains the most variance in objective measures of physical fitness and function, which is Aim 4 of this dissertation study, and is useful in contributing to prediction of poor physical function.

In summary, current studies describing the association between sarcopenic obesity and physical fitness and function support the Bennett, Winters-Stone, & Nail theoretical model above that suggests that sarcopenic obesity is associated with objective measures of poor physical fitness and function. An association between sarcopenic obesity and poor physical fitness and function has clearly been established in the existing body of literature outside of cancer. None of the existing studies of sarcopenic obesity and physical fitness and function was conducted solely in cancer survivors, but the evidence strongly suggests that this dissertation will also find a significant association between sarcopenic obesity and poor physical fitness and function in this clinical population. This dissertation hypothesizes that cancer that cancer survivors with sarcopenic obesity will have significantly worse physical function than cancer survivors without sarcopenic obesity.

Sarcopenic Obesity in Cancer Survivors

As a relatively newly recognized body composition phenotype, few studies in cancer survivors have yet included sarcopenic obesity as a variable of interest despite its growing use in other populations. The epidemiologic frequency of sarcopenic obesity in non-cancer populations has only been measured by a handful of studies, most by convenience sampling design. These studies provide early insight into possible frequency rates in the general population with the average frequency being approximately 8% in women older than 50. However, these epidemiologic studies utilize a variety of sarcopenic obesity definitions, which reduces the generalizability of results, and none designate frequencies within cancer survivors as a subgroup of interest, if cancer survivors were included at all.

More than a dozen studies of body composition in cancer survivors mention the term "sarcopenic obesity" in background or discussion sections and some even report "sarcopenic obesity-like" changes, but these terms refer to the most general of sarcopenic obesity definitions, an increase in fat mass without gains in lean mass (Heber et al., 1996). None of the studies that mention sarcopenic obesity in discussion quantify the frequency of sarcopenic obesity in the studies. Unique in this group of studies describing general sarcopenic obesity phenotypes, and almost a decade earlier than other studies in cancer survivors, was a seminal study by Demark-Wahnefried, Kenyon, Eberle, Skye, & Kraus (2002) that looked to prevent sarcopenic obesity in breast cancer survivors through exercise and diet interventions. Compared to historic controls, breast cancer survivors who participated in 6 months of strength and aerobic exercise and a diet consisting of ≤20% fat and rich in fruit, vegetables and calcium, avoided adverse changes in body composition: body weight +2.2±0.4kg v −2.0±1.3kg ($p=0.02$);

percent body fat +1.8±1.6% v −1.3±1.2% (p=0.002); lean mass −0.3±0.01kg v +0.1±1.5kg (p=0.80); and fat mass +2.0±0.3kg v −1.2±1.5kg (p=0.04). Regardless of the inclusion of mentions of sarcopenic obesity or results that describe avoidance of adverse changes in body composition, without identification of definitive sarcopenia and obesity thresholds in a sarcopenic obesity definition, the interpretation of these studies is limited to body composition trends. In contrast to this obvious gap in interpretability, other studies of sarcopenic obesity in cancer survivors do utilize specific sarcopenic obesity definitions. Figure 1-2 includes all known studies in cancer survivors that include a specified definition of sarcopenic obesity and describes the measurement methodology and sarcopenia and obesity thresholds utilized in the definition, as well as other defining characteristics such as cancer type, design, and frequency of sarcopenic obesity if provided in the study.