Strength, Water Compartments and Phase Angle in Breast Cancer Survivors

Dissertação elaborada com vista à obtenção do Grau de Mestre em

Exercício e Saúde

Orientador: Professora Doutora Analiza Mónica Lopes de Almeida Silva

Co-orientadora: Professora Doutora Catarina Nunes Matias

Júri:

Presidente

Professor Doutor José Henrique Fuentes Gomes Pereira

Vogais

Professora Doutora Analiza Mónica Lopes de Almeida Silva

Professora Doutora Diana de Aguiar Santos

Mafalda Maria Travado Reis

2016

Acknowledgments

I would like to express my gratitude to the following:

Professor Analiza Mónica Silva she was very enthusiastic from the beginning, helping me organizing this project with her knowledge and very rare work ability. I truly appreciate her support in this journey and her total availability to answer my e-mails or to meet me to discuss some doubts. She gave me wings to fly, she let me manage my project as I wish and gave me full support whenever I needed it, making me more confident.

Professor Catarina Matias who made possible all the practical component of my thesis. She helped me to learn the procedures of bioelectrical impedance and Jamar dynamometer, she was always available to teach me over and over and to meet with me to explain it at any time. Without her help, patience and availability I would not have finish this thesis in time. Thank you for always being there, even during her vacations when my SPSS was crashing and I did not know what to do, she gave me opening to be in contact with her almost 24/7 and I truly appreciate it. She is an unbelievable person with an amazing heart.

Viva Mulher Viva Associação especially Dra. Cidália, Dr. Araújo and Sofia. They were amazing, Dra Cidália was always worried if everything was ok, if the room where I was doing the measurements was good enough, if the mattress was the one I needed, if I had enough alcohol and compresses, if the number of participants was ok and so on, she was really amazing! Dr. Araújo helped me with information regarding the patients and Sofia made herself responsible for the phone calls and finding the participants for the study. Without Sofia availability to call to all the survivors of the Association I would not have had enough participants.

Thank you Viva Mulher Viva Associação for making it possible.

I also want to thank to **Rita Pinto,** former colleague, for all her assistance with endnote and SPSS.

I would like to thank to all my friends for their support.

To **Ana Sofia Alves,** my amazing best friend, for her tremendous support, love, patience, good advices, and ability to help me and calm me during this process.

At last, the ones that are always with me, my **family**! I would like to thank to my mom for her contacts and knowledge regarding breast cancer, to my dad for always being very enthusiastic and supportive, to my grandmother for all her love and hugs and for always showing me how proud she is, to my brother for his patience with my bad moods.

Table of Contents

6

Tables and figures

Figures List

Tables List

Chart List

Abbreviations

ASHT	American Society of Hand Therapists
BC	breast cancer
BCS	breast cancer survivors
BCM	body cell mass
BI	bioelectric impedance
BIA	bioelectrical impedance analysis
BIS	bioelectrical impedance spectroscopy
BMI	body mass index
CFR	cancer related fatigue
ECW	extracellular water
FFM	fat free mass
HC	hip circumference
HGdom	handgrip dominant side
HGL	handgrip left side
HGR	handgrip right side
HIV	human immunodeficiency virus
ICW	intracellular water
IPAQ	International Physical Activity Questionnaire
IPAQ-SF	international physical activity questionnaire short form
MF-BIA	multiple-frequency bioelectrical impedance analysis
MVPA	moderate-vigorous phisical activity
PA	physical activity
PhA	phase angle

QOL	quality of life
R	resistance
SF-BIA	single frequency bioelectrical impedance analysis
SM	skeletal muscle
TBW	total body water
TNM	tumor-node-metastasis
TPO	time post operation
WC	waist circumference
WHR	wait-to-hip ratio
Xc	reactance
Z	impedance

Abstract

Background: Accurate prognostic tools are determinant for decision-making in cancer care planning. Objective measures such as bioelectrical impedance spectroscopy (BIS) may improve the accuracy of prognostic. In this cross-sectional study the goal was to determine if the water compartments and the phase angle were predictors of muscular strength in breast cancer survivors (BCS).

Methods: A total of 41 BCS (age 54.6 ± 9.2) were evaluated. Water compartments and phase angle were assessed with BIS and muscular strength was assessed with handgrip dynamometer. Moderate-to-vigorous physical activity (MVPA) was assessed using the International Physical Activity Questionnaire (IPAQ). Measurements were performed in the morning after an overnight feast.

Results: Linear regression analysis showed that phase angle explained 22% ($r^2 = 0.216$) of the variance of the handgrip. Independently of MVPA and time post-operation, phase angle remained a significant predictor (B=2.269, p=0.085). No associations were found between water compartments and handgrip strength (p>0.05).

Conclusions: The findings of this study suggest that phase angle is an important predictor of muscular strength in breast cancer survivors.

Key words: **breast cancer, phase angle, muscular strength, water compartments, bioelectrical impedance spectroscopy, extracellular water, intracellular water, waist circumference, hip circumference, physical activity.**

Resumo

Introdução: É necessário definir medidas de prognóstico precisas para que haja uma melhor tomada de decisão relativamente ao planeamento do tratamento de cancro da mama. Medidas objetivas como a bioimpedância elétrica multiespectral (BIS) podem melhorar a precisão de prognóstico. Neste estudo transversal o objetivo será determinar se os compartimentos hídricos e o ângulo de fase são preditores da força muscular em sobreviventes de cancro da mama.

Métodos: A amostra consistiu em 41 sobreviventes de cancro da mama (idade 54.6 ± 9.2 anos). Os compartimentos hídricos e o ângulo de fase foram medidos com a BIS e a força muscular com um dinamómetro. A atividade física moderada a vigorosa (MVPA) foi avaliada através do Questionário Internacional de Atividade Física (IPAQ). As medições foram realizadas durante a manhã com os participantes em jejum.

Resultados: A análise da regressão linear mostra que o ângulo de fase explica 22% (r^2 = 0.216) da variação da força muscular. Independentemente da MVPA e tempo pós-operatório, o ângulo de fase manteve-se um preditor significativo (B=2.269, p=0.085). Não foram encontradas associações entre os compartimentos hídricos e força muscular (p>0.05).

Conclusão: Os resultados deste estudo sugerem que o ângulo de fase é um importante preditor da força muscular em sobreviventes de cancro da mama.

Palavras-chave: **cancro da mama, ângulo de fase, força muscular, compartimentos hídricos, bioimpedância elétrica multiespectral, água extracelular, água intracelular, perímetro da cintura, perímetro da anca, atividade física.**

Introduction

Humans and animals have had cancer throughout recorded history. Some of the earliest evidence of cancer was found in ancient Egyptian manuscripts describing cases of tumor, or ulcers, of the breast that were removed by cauterization that date back to 3000BC. At this time, they were describing this disease as not treatable.[1]

Cancer is a term used for cells that start to grow out of control in a certain part of the body, because of damaged DNA. These cells are different from normal cells, instead of dying or repair the damage, they continue to grow and form new abnormal cells that the body does not need. Most DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in our environment.[2] Cancer cells can also invade other tissues, throughout the bloodstream or lymph vessels of our body, where they begin to grow and form new tumors that replace normal tissue. This is a process called metastasis.[2]

Breast cancer (BC) is the most common cancer among women in developed countries.[3] In recent years, the BC incidence rates have been increasing throughout the world.[3] With respect to Portugal, data from the report of the International Agency for Research on Cancer (IARC) from 2012[4] show that the number of new cancer cases per year (incidence) was 49,200 and the number who died (mortality) was 24,100. In terms of incidence and mortality, colorectal cancer is both the leading cause of cancer in our country, with 7,129 new cases diagnosed per year, as well as the leading cause of cancer mortality, with 3,797 reported deaths. This is followed by prostate cancer with 6,622 incident cases and 1,582 deaths and breast cancer with respectively 6,088 (incident cases) and 1,570 (deaths).

In Portugal, BC ranks in first among cancers affecting women, with an age-standardized incidence rate of 60.0/100 000 females.[3] Due to early detection and more advanced treatment options, the mortality rates of breast cancer worldwide have decreased in the last decade, with an estimated annual percentage charge of -2% year in Portugal.[3,5]

However, despite the decrease in mortality rates, BC incidence continues to rise, with a concerning increase of 20% newly diagnosed cases since 2008.[6] This increase has been attributed to economic growth and societal changes associated with poor

13

dietary choices and lack of physical activity, both been considered major risk factors for the development of the disease.[6]

1.1 Background

1.1.1. What is Breast Cancer

A woman's breast is made up of lobules (glands that can make milk), ducts (small tubes that carry milk from the lobules to the nipple), fatty and connective tissue, blood vessels, and lymph vessels (Figure 1). Most breast cancers begin in the cells that line the ducts.[7]

The lymph system is one of the main ways breast cancer spreads. Normally, lymph nodes, which are filters connected by vessels that carry a clear fluid called lymph, are small, bean-shaped tissues that contain a certain kind of immune system cells that try to catch and trap cancer cells before they reach other part of the body.[8]

Most of the lymph vessels of the breast drain into lymph nodes under the arm (axillary nodes); lymph nodes around the collarbone (supraclavicular and infraclavicular lymph nodes); and lymph nodes inside the chest near the breastbone (internal mammary lymph nodes).
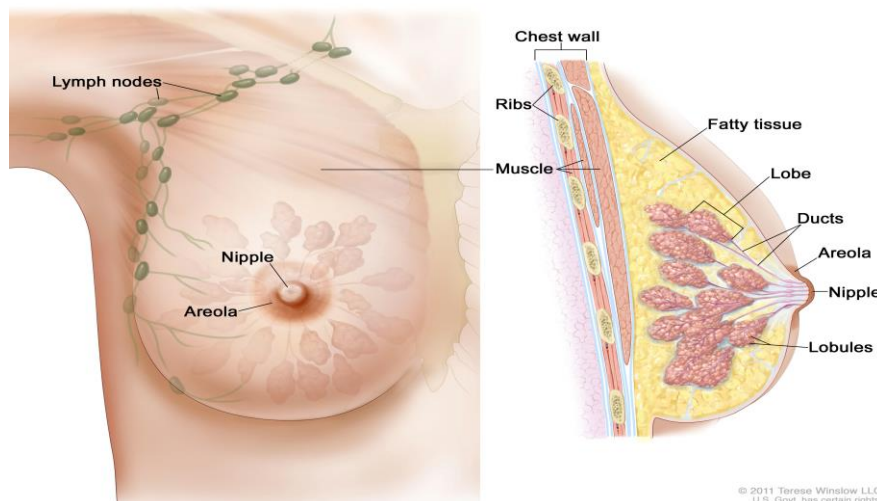
Figure 1: on the left side - lymph nodes distribution; on the right side - inside of a breast (http://www.cancer.gov/types/breast)

When a lump or spot is discovered in the breast, a complete physical exam

(bimanual palpation of the breasts and locoregional lymph nodes assessment) and an imaging test (bilateral mammography, ultrasound of the breast and regional lymph nodes and MRI) are performed to look more closely to the chest and to help finding abnormalities.[7,9]

After the diagnosis of breast cancer, disease stage should be assessed to help organize the different factors and some of the personality features of the cancer into categories, in order to best understand prognosis, to guide treatment decisions and to provide a common way to describe the breast cancer so that results of the treatment can be compared and understood.[8,10] The tumor-node-metastasis (TNM) staging system is the most common system used to describe the different stages and it was first implemented by Pierre Denoix in 1942.[10] It is based on whether the cancer is invasive (cancer has grown into normal tissues and cancer cells have spread to other parts of the body through the blood or lymph system) or non-invasive (cancer that stay within the milk ducts or milk lobules in the breast), the size of the tumor (T), how many lymph nodes (N) are involved, and whether it has spread to other parts of the body (M for metastasis).[7]

1.1.2. Breast Cancer Staging

So, accordingly with TNM system BC is divided into **Stage 0** used to describe non-invasive breast cancers. There is no evidence of cancer cells or non-cancerous abnormal cells breaking out of the part of the breast, in which they started, or getting through to or invading neighboring normal tissue.

Stage I the tumor has <2cm and it can be found in small groups of cancer cells in the lymph nodes**.** It is divided into subcategories known as IA and IB.

Stage II the tumor has <2cm and it has spread to the axillary lymph nodes or the tumor has between 2-5cm but it hasn't spread to the axillary lymph nodes. It is divided into subcategories known as IIA and IIB.

Stage III the tumor can be any size and it has spread to the chest wall and/or skin of the breast; or it has spread to 10 or more axillary lymph nodes; or the cancer has spread to lymph nodes above or below the collarbone; or the cancer has spread to axillary lymph nodes or to lymph nodes near the breastbone. It is divided into subcategories known as IIIA, IIIB and IIIC.

Stage IV the tumor has spread beyond the breast to other organs of the body, such as bones, distant lymph nodes or skin, lungs, liver and brain. The words used to describe stage IV breast cancer are advanced and metastatic.

It is not known what exactly causes BC but it is known that some risk factors such as diet (associated with obesity), alcohol, age, genetic predisposition and physical activity contribute to the rising incidence of the disease. However, the presence of a risk factor, or even several, does not mean that a woman will get breast cancer. Although many risk factors may increase the chance of having breast cancer, it is not yet known just how some of these risk factors cause cells to become cancer.[7,9]

1.1.3. Breast Cancer treatment

The most common treatments for BC are surgery, radiation therapy, chemotherapy, hormonal therapy and biological therapy.

When developing a treatment plan there are factors to consider such as the type of BC, age, menopausal status, overall health and personal preferences or situation. Other factors, regarding the tumor, need to be taken into consideration such as the stage of cancer (size of tumor and if it has spread); grade of cancer (how cancer cells look and behave); hormone receptor status (if cancer cells have receptors for estrogen and progesterone); HER2 status (HER2 is a protein on the surface of the breast cells that promotes growth).[11]

After considering for this factors, the patient will then be treated with the following options: a) **surgery**, the most common treatment where the main goal is to remove completely the tumor from the breast. There are two different types, breast-conserving surgery and mastectomy (remove the whole breast). This treatment may be combined with radiation therapy, chemotherapy and hormonal therapy; b) **radiation therapy**, where high doses of radiation are applied to destroy cancer cells. Works by damaging the cancer cells repeatedly leaving no time to repair themselves in between daily treatments; c) **chemotherapy**, which is the administration of drugs, usually through a tube into the vein, to destroy cancer cells. Drugs slow or stop cancer cells from growing, multiplying or spreading to other parts of the body; d) **hormonal therapy**, as mentioned before, some BC tumors have hormone receptors. When the estrogen or progesterone attach to the tumor they can stimulate growth. This therapy

reduces the levels of these hormones in the body or blocks their effect on cancer cells. This therapy is often given after surgery, radiation and chemotherapy to reduce the risk of cancer coming back; e) **biological therapy** works with the immune system to help protect the body from the disease.[11]

1.1.4. Follow up care

The transition from active treatment to post treatment care is critical to long-term health. When treatment ends some women feel lost, anxious and worried that cancer might come back. Some women may also have low self-esteem due to loss of breast, hair, scars and lack of mood for sex. The inclusion in support groups for women who survived is of extreme importance to help regain confidence, improve response to treatment, speed recovery, reduce risk of recurrence and improve quality of life.[11,12]

Cancer related fatigue (CFR) is a highly prevalent and multifactorial symptom classically defined as 'a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning'. This symptom does not get better with rest and is very common in breast cancer survivors (BCS).[13]

A survivor is anyone who has been diagnosed with cancer, from the time of diagnosis through the rest of life.[12] For some survivors, this kind of fatigue lasts a long time after treatment and can make it hard for them to exercise. A study conducted by Winters-Stone et al[14] reported that women with lower extremity muscle weakness, high body fat and lower physical activity levels had greater fatigue. The specific etiology of CRF is still unknown but it is frequently associated with a wide variety of psychosocial factors (e.g. clinical depression), and exacerbating symptoms (e.g. chronic pain, nausea) as well as treatment side effects.[13,15] Studies have shown that patients who follow an exercise program tailored to their needs feel better physical and emotionally and it helps reduce fatigue.[7,16]

The post-surgery period is also crucial due to the possibility of developing complications, such as lymphedema, reduction in muscle function, decrease in upper limb functionality and muscular strength.[17]

Although adjuvant therapy combinations and advances in early detection have improved survival rates (5 year survival rates of approximately 90%)[17-21], BCS often report side effects such as weight gain, unfavorable changes in body composition and

exhibit reduction in muscle strength (impaired shoulder function with decrements in shoulder muscular strength, shoulder mobility and functional capacity) associated with cancer related symptoms.[17,20] Limitations in upper body strength such as pushing, lifting, reaching were reported as especially problematic in this population.[22] Such limitations may be due to surgical trauma and activity avoidance.[20]

It is important to introduce BCS in exercise programs to help them recovering their strength and reduce their weight so they can recover their self-esteem and quality of life.

1.2. Muscular Strength and Breast Cancer

The skeletal muscle (SM) is the largest organ in the human body, constituting 40-50% of total body mass in healthy non-obese humans.[23] It is responsible for performing muscular contractions, generating external mechanical force, which enables the realization of daily activities and exercise and plays an important role in primary and secondary disease prevention as an essential regulator of metabolic and inflammatory homeostasis.[23,24] It is also an influential organ in hormonal, immune and metabolic function.[25]

Cancer treatments have acute and chronic effects on the muscle system. The loss of lean muscle mass results in muscle weakness, decreased functional work capacity, decreased flexibility and reduced mobility. These series of events occur due to a decline in protein synthesis in conjunction with enhanced protein catabolism caused by cancer treatment and consequent deconditioning, leading to a diminished quality of life.[17,19] The contractile and metabolic proteins that are lost are responsible for muscle contraction, force generation, extensibility and the production of energy (ATP).[19]

The muscle has a very important role in whole body protein metabolism in the response to stress and therefore prevention of many pathologic conditions and chronic diseases.[24] Maintenance of the protein content of certain tissues and organs such as the skin, brain, heart and liver is essential for survival. These tissues and organs, in the post absorptive state, rely on a steady supply of amino acids via the blood to serve as precursors for the synthesis of new proteins to balance the persistent rate of protein breakdown that occurs in all tissues. However, the stressed induced by advanced cancer or traumatic injury, imposes greater demands for amino acids from muscle protein

breakdown. Physiologic responses necessary for recovery lead to the accelerated synthesis of protein due to the greater demand of amino acids. Studies suggest that a protein intake >3g.kg.d is required to provide the necessary precursors for the synthesis of protein for normal healing of, for example, a burn injury in 50% of whole body. This means that individuals with limited reserves of muscle mass respond poorly to stress.[24]

Despite the efficacy of cancer treatments in improving survival, BCS usually suffer from substantial impairments that affect their level of physical activity such as increased body fat, reduced aerobic exercise capacity and muscle weakness.[26] These are well known risk factors responsible for loss of muscular strength, which leads to a poor quality of life.[14,25,27-31] Also, deconditioning during active treatment may contribute to declines in upper and lower extremities strength,[13,18,32] regardless of disease stage.[18,23,30]

The role of muscular strength in the performance of activities of daily living and exercise, as well as in the prevention of chronic diseases, is increasingly being recognized. Important findings suggest that poor muscle strength is a predictor of death from all causes, cardiovascular disease and cancer.[27,33-36]

Reduced muscle strength is associated with loss of physical functionality and with negative impact on recovery after surgery or illness, which partly explains the high predictive power of muscle function tests.[35] In addition, muscular strength has been recognized as an important health related component of fitness and has been shown to be positively related to cardiorespiratory fitness.[36,37]

The loss of muscle mass is detrimental for cancer survival. A significant portion of patients return for rehabilitation treatment after several months to even years after discharge, with several complaints of upper limb dysfunction that incapacitate performance of daily tasks.[38] Evidence suggests that the ability to perform physical tasks in daily life is determined by a threshold level of muscular strength.[31] Increasing the physical activity level during and after the treatment may improve the muscle strength and control the atrophy as well as improving quality of life outcomes.[30,31] A study performed with BC patients by Vardar-Yagli et al[30] found a positive association between physical activity levels and peripheral muscle strength. Another study[31] performed with cancer patients found that muscle strength was strongly related to physical functioning before treatment and changes in muscle strength were correlated

with changes in physical functioning. In addition to this studies, Harrington et al.[26] found that all strength measures assessed in his study were decreased in the BCS when compared to healthy subjects.[39]

Skeletal muscle has a greater adaptability when given appropriate training stimuli, even in cases of severe muscle atrophy and fatigue. Enhancing lean body mass size and function will improve survival after cancer treatment.[25,31]

In order to determine the severity of SM loss, muscle strength needs to be assessed. The exertion of muscle contraction is measured as muscle strength.[23]

1.2.1. Measures of Strength

There are several methods for the measurement of voluntary and involuntary muscle function. One method used to determine involuntary muscle contraction is electrical stimulation at various frequencies but constant isometric length. Although this method is considered the superior procedure in regard to objectivity, it is not suitable for clinical routine. Regarding measurements of voluntary strength (handgrip, knee extension and hip flexion strength) the handgrip is the most common measure of muscle function and functional capacity for clinical purposes due to its easy use, reliability, validity, feasibility, generalization of overall strength, since it correlates with elbow flexion strength, knee extension strength and trunk extension strength and because it is a significant predictor of health related quality of life in cancer patients.[17,18,27,32,35,36,40]

Grip strength has been shown to be a predictor of postoperative complications, functional limitations, functional decline, disability and mortality.[18,27,36,41] However, as recently shown by Norman et al.[42] mortality prediction of handgrip strength is dependent on which further parameters are included in the regression models. Handgrip strength predicted 6 months mortality in cancer patients but lost its significance when bioelectrical phase angle was introduced in the model.[35] Also, several factors are negatively associated with handgrip strength in BC such as mood, fatigue, pain, hypersensitivity and neck shoulder mobility.[17] Depressed mood is a potential confounder of the association between handgrip strength and mortality because it is associated with increased risk of mortality and risk of accelerated decline in muscle strength.[43] Fatigue in cancer can also have a negative impact on generating a maximal

voluntary handgrip contraction, meaning that women with lower strength have more fatigue compared with women with higher strength.[14,32]

Several studies have shown that having low muscular strength is a predictor of all-cause mortality, as well as mortality due to cardiovascular diseases and cancer in healthy and diseased people[23,32-34,36,44] and so it seems important to assess handgrip strength and to determine whether and to what extent the measured values are abnormally low.[37] Handgrip strength is strongly correlated with post-operative complications and has been reported to be predictive of length of hospital stay, loss of functional status, body cell mass depletion, post-surgery complication, short-term survival in hospitalized patients as well as associated with probability of premature mortality and earlier onset of disability.[32,35,45,46]

In conclusion, higher levels of strength will have a protective effect from disability and mortality.[18,36,47]

1.2.2. Handgrip Test

The gold standard for assessment of muscle strength is the force exerted in a maximum voluntary contraction with force output measured by a dynamometer.[23,36,40]

The strongest evidence in relation to mortality has been reported for the handgrip strength test.[36,37] This test reflects the maximum strength derived from combined contraction of extrinsic and intrinsic hand muscles, which leads to the flexion of hand joints. It was originally developed for hand surgery but quickly become the focus of interest in numerous studies due to its feasibility and prognostic relevance.[35]

Therefore, handgrip strength test has been recommended as an assessment of muscle function for oncology rehabilitation and it is an important indicator of health-related quality of life in BCS.[18,32,36,48] Grip strength test is commonly used to evaluate the integrated performances of muscles by determining maximal grip force produced in one muscular contraction.[40] It likely reflects the combined influences of genetic predisposition, acquired modifications of physical constitution, aging processes and chronic diseases.[47] It has been used in a variety of clinical areas and for multiple purposes such as the assessment of upper limp impairment, evaluation of work capacity for those with hand injury and other work-related injuries, the evaluation of people with other impairments and disabilities such as chronic fatigue syndrome and muscular

dystrophy, determining the efficacy of different treatments for people with a range of disabilities, part of an overall fitness assessment and determining the level of effort exerted.[49]

A wide range of instruments is available to measure grip strength. There are four basic categories for the measurement of handgrip strength: a) **hydraulic** which is a sealed system that records grip strength in kg or pounds of force. This includes the Jamar dynamometer, a measure with static grip with handles that can be adjusted to 5 different positions (2.5, 3.8, 5.1, 6.4 and 7.6 cm apart). This is the most widely used instrument; b) **pneumatic** instruments which uses the compression of an air-filled bulb or bag to determined grip pressure. Commonly used by individuals who have painful hands or fragile skin, as they are viewed as being more comfortable to grasp and softer. A criticism is that this method can only measure the pressure of grip and not its force;[50] c) **mechanical** instruments that record grip strength based on the amount of tension produced in a steel spring; d) **strain gauges**: commonly measure grip strength in Newtons of force.[49]

The California Medical Association Committee studied some dynamometers and found that the Jamar dynamometer was "*perfect to the extent that its sealed hydraulic system is a nearly leak proof as any mechanical appliance can be made*", recommending it as the best measure of grip strength.[50] This Committee summarized three basic factors of grip measurements: grip is a force, grip is not a pressure and the measurement of grip must be in force units such as pounds or grams.[50]

Therefore, the Jamar dynamometer has been reported to be the most reliable, valid, fast and easy to perform instrument with the highest calibration accuracy for the measurement of grip strength, as well as better repeatability than other equipment and has been recently validated in advanced cancer patients.[32,37,48-51]

Although there is not any consensus in measurement protocols, consistency is crucial since posture, arm side and handle position of the dynamometer easily alter maximum grip strength.[35,50] The American Society of Hand Therapists (ASHT) purposes a methodology associated to high intra- and inter-test reliability. According to them, the assessment of grip strength should be made sitting in a straight-backed chair with the feet flat on the floor, shoulder adducted and neutrally rotated, elbow flexed at 90º with forearm in a neutral position.[17,35,49,51] This protocol was developed to

be used with the Jamar dynamometer.[49] Most of the studies follow the ASHT protocol in an attempt to control known risk of errors[48] however, the handgrip strength values depend on many other factors such as the model of the dynamometer in use, inadequate calibration, sample characteristics (physical activity level, etc.) and probably ethnical differences.[46]

Regarding the handle position, every individual should use the most comfortable, however, it seems advantageous to standardize the method as much as possible and reports suggest that the second position is the most comfortable and has the higher grip strengths.[48-50,52] It was also reported that a 3 second time of contraction should be used as it is sufficient to obtain a maximum reading without exposing the patient to adverse effects such as increased blood pressure or heart rate, which accompanies prolonged isometric contraction.[32,49,51]

This technique has allowed for large cohorts of handgrip strength data to be obtained and to make predictions concerning key health indicators, especially in aging and clinical populations where malnutrition and cachexia are prevalent.[32]

A study held by Kilgour et al.[32] was the first to link handgrip strength with survival in advanced cancer. They also found that an overall reduction in handgrip strength was related with the appearance of sarcopenia.[32]

A systematic review conducted by Neil-Sztramko et al[18] pooled grip strength data from 26 studies in BC population and reported that in women off treatment the mean value was 22.8 kg (95% CI 20.6 to 25.1).[18]

Normative values are essential if informed decisions are to be made about the individual's status relative to the general population.

Even though the distribution of a given measure for a specific population does not necessarily mean the health state of the population, it is reasonable to assume that handgrip strength values in the lower end of the distribution may be indicative of several outcomes.[45,46]

1.2.3. Muscle Dysfunction and Obesity

Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.[53,54] The loss of

skeletal muscle arises from a fall in protein synthesis and an increase in protein degradation, which is a side effect of cancer treatment.[17,23,53,55-57] It is often misdiagnosed as a condition of weight loss but it is actually a highly complex metabolic disorder and one of the most frequent effects of malignancy, which is why within oncology, interest in muscle function has traditionally been confined to the clinical entity of cancer cachexia.[23,58]

Cancer cachexia is characterized by severe muscle wasting, systemic inflammation and malnutrition leading to both acute and chronic impairments in various aspects of physical function[18,23,58] such as extensive loss of muscle mass, strength and metabolic function[24] and reduced fitness levels[17], and contributes to nearly one third of all cancer deaths.[58]

The cachectic state is particularly problematic in cancer, typifying poor prognosis and often lowering the responses to chemotherapy or radiation treatment.[58] In a study conducted by Wolfe et al[24] it was found that the amount of body protein, which is related to the amount of muscle mass, predicted recurrence in lung cancer patients that were receiving radiation therapy.

Although cancer cachexia is associated with loss of SM, gain of adipose tissue can occur, culminating in the condition of sarcopenic obesity.[17,54] Martin et al[54] found that most of the cancer patients of his study were more commonly overweight or obese and often had occult severe pre-existing muscle depletion. Sarcopenia (progressive loss of muscle mass and function)[24] itself is an independently prognostic of lower survival in obese patients with cancer.[54] According to Cantarero-Villanueva et al[15] the lack of strength associated with an increased body mass index (BMI) may be related to sarcopenia and a decreased grip strength.

One common side effect that occurs in over 50% of BCS is the gain of weight, which can be related to the development of comorbid conditions that affect survival[15,59-62] as well as risk of cancer recurrence due to increasing endogenous estrogen production,[63] with most explanations focusing on adiposity rather than body weight per se.[61,64,65] Evidence[62] suggests that reported weight gain happens during the first two years after diagnosis, with the weight gained ranging from few grams to several kilograms. In a study conducted by Arpino et al[62] it was shown that weight gain is also associated with changes of body fat composition, namely an increase of waist

circumference and hip circumference. Although weight is the simplest anthropometric index of excess adiposity, it does not distinguish between fat free tissues (comprised primarily of muscle, bone and extracellular water) and adipose tissue.[63] Waist and hip circumference and waist-to-hip ratio (WHR) are additional measures of body fat distribution that provide an index of both subcutaneous and intra-abdominal adipose tissue.[62,66-68] The evidence on abdominal obesity on BC survival highlights the need of using general obesity (body mass index) as well as fat distribution (waist circumference and WHR) to evaluate prognosis.[69]

It is well established that obesity has an impact on BC occurrence and it is important to distinguish 2 types of obesity: android (WHR>0.8) in which fat is mainly distributed in the upper body (shoulders and abdomen) and gynoid (WHR<0.8) where fat accumulates in the lower part of the body (buttocks, thighs).[66] According to Pacholczak et al[66] women with BC present an android type of silhouette with the distribution of fat tissue present in the central and upper parts of the body. They also mention that this type of obesity cause more pronounced abnormalities in metabolic and hormonal systems[66] perhaps because of its relation with visceral adiposity.[70] Women with increased WHR have a twofold higher risk of all-cause mortality compared with women with a lower WHR, in models adjusted for physical activity and BMI.[69] Therefore, women with central adiposity may be at higher risk of BC than women whose fat is primarily distributed subcutaneously over hips and buttocks[70] because abdominal obesity, is associated with an elevated level of circulating insulin that is mitogenic, anti-apoptotic, and pro-angiogenic, and has been found to be associated with worse BC prognosis.[68] Several adipokines produced by adipose tissue are related to hyperinsulinemia and angiogenesis promotion, which is a major contributor to the aggressive behavior of BC.[69]

Cancer patients with a body mass index (BMI) > 35kg/m^2 have worse disease free survival than those of normal weight, independent of age, race, treatment and sex.[15] BMI is a measure of weight adjusted for height that provides a better approximation of the proportion or total amount of adipose tissue in the body than does weight alone.[63] The validity of BMI as a measure of adiposity is further supported by its association with obesity-related risk factors such as total cholesterol and blood glucose.[63] It's calculated as weight in kilograms (kg) divided by height in meters squared (m^2).[62] The classification goes as follows: underweight (BMI < 18.5), normal weight (BMI 18.5 to

24.9), overweight (BMI 25-29.9) and obese (BMI > 30) and is used in adults > 20 years old.[71] When the BMI is over 25 kg/m^2 that person is at increased risk of developing health problems due to abnormal or excessive fat accumulation.[68,71] Central obesity promotes a concomitant increase in WHR at the same level of BMI therefore, and with increasing evidence of health risks associated with abdominal fat, WHR and waist circumference have been commonly used in epidemiologic studies as measures of central adiposity.[63,68] World Health Organization cutoff points of waist circumference and WHR for substantial increased risk of metabolic complications in women are >88 cm and ≥ 0.85, respectively.[69]

A sedentary lifestyle combined with an unhealthy BMI increases the risk of cardiorespiratory diseases in BCS, which is among the most frequent concomitant comorbidity in women with BC.[15] In addition to this, abdominal obesity is a predisposing factor[67] which means that having a waist circumference superior than 88 cm is associated with and increased risk of this comorbidity. This value of waist circumference is exceeded by almost 100% of the obese BC patients and is linked with increased mortality.[15]

Due to all these factors it is expected that muscular strength is reduced in obese patients due to a decreased level of fitness.[15]

All cancer patients are subjected to a wide range of degenerative factors, which are all potent causes of muscle dysfunction including aging, malnutrition, physical inactivity and factors directly related to disease pathophysiology and therapy toxicity.[23] Lintermans et al[72] reported a negative impact of taking aromatase inhibitors – medication that suppresses the plasmatic concentration of estrogen, such as Anastrazol - on the SM system with more than half of patients complaining of this with loss of grip strength. The loss of SM explains why patients with cachexia have a reduced mobility and quality of life, together with a shorter life span.[57]

1.3. Physical Activity

In long-term cancer survivors, physical activity (PA) has gained interest as a modifiable lifestyle factor that may improve mortality.[73]

According to some authors[30,31,64,74-77] exercise interventions in cancer patients and survivors are associated with favorable outcomes such as achievement of a healthy

body weight, reduced recurrence risk, mitigating cancer treatment side effects (i.e. fatigue), improvements in quality of life (QOL), psychological well-being, body image as well as improvements in physical functioning (i.e. oxygen capacity, flexibility, strength measures), anthropometric measures (i.e. body weight) and health related biomarkers (i.e. blood pressure, heart rate). Therefore, it should be a priority to have an appropriate weight, a healthful diet and a physically active lifestyle aimed at preventing recurrence, second primary cancers and other chronic conditions.[12]

A report from Europe's largest survey assessing outcomes in people living with and beyond cancer show that <25% met the current physical activity guidelines, 43% had trouble with fatigue and 45% experience fear of disease recurrence.[77] Another study[78] mention that up to 70% of BCS do not meet recommendations of 150 minutes per week of moderate to vigorous intensity PA (e.g. brisk walking, jogging, swimming).

The combined high prevalence of inactivity and sedentary time may be particularly concerning for BCS given their already heightened risk for poor health and disabilities.[78] Several studies[79-82] show that women who engaged in PA after a diagnosis of BC had a statistically significant 20-50% lower risk of death from BC, especially if this PA was within the guidelines. Hormonal changes induced by exercise, such as a reduction of circulating estrogen concentrations mediated by a reduction in adipose tissue or PA independent increase in the amount of sex hormone-binding globulin and improvement in insulin sensitivity may explain the relationship between PA and survival among BCS.[73,80,81] Additionally, PA may also improve the immune response, possibly by promoting killer cell, macrophage and cytokine activity, as well as up regulating antioxidant enzyme activity, which may protect against DNA damage.[73]

Studies show that regular exercise after BC diagnosis is significantly associated with improved overall and disease free survival following a dose response pattern[81] and that PA influence extends to women regardless of age at diagnosis, stage of disease at diagnosis and post-diagnosis BMI.[80]

In a study conducted by Bradshaw et al[73] the beneficial effect of PA appear slightly stronger in the time period following diagnosis and also among women who were not overweight in the year before diagnosis for both all cause and BC specific mortality. This study was able to follow PA over several years allowing to evaluate the associations of activity near or after diagnosis.[80,81,83]

Monitoring physical function during and after treatment may help health professionals to identify declines in order to increase muscle strength and control the atrophy, which will improve morbidity, mortality and quality of life.[17,18,25,30,53]

To monitor trends and evaluate public health or individual interventions aiming at increasing levels of PA, reliable and valid measures of habitual PA are essential.

Several routine instruments are available to measure PA, including self-report questionnaires, indirect calorimetry, direct observation, heart rate telemetry and movement sensors.[84,85] All these methods have well known limitations and for PA there is currently no perfect gold standard criterion.[86]

In large-scale cohort studies questionnaires are more frequently used due to their low cost and easy administration.[84] There are at least 85 self-administered PA questionnaires for adults but the International Physical Activity Questionnaire (IPAQ) is the most widely used.[85] The IPAQ was developed in an attempt to standardize assessment of the prevalence of PA in different countries and cultures around the world.[87] Its reliability and validity was tested in 14 centers in 12 countries during the year 2000 with the support of World Health Organization and centers for Disease Control.[84,88] From this study it was suggested that the last 7-day short form of IPAQ could be used for national and regional prevalence studies.[88] IPAQ has two versions available: 31-item long form (IPAQ-LF) and the 9-item short form (IPAQ-SF). The short form records the activity of 4 intensity levels: 1) vigorous-intensity such as aerobics, 2) moderate-intensity such as leisure cycling, 3) walking and 4) sitting.[85] The short version is specific to the 'last 7 day recall' because the burden on participants to report their activity is smaller[85] and there is no difference between the reliability and validity of the short and long form.[88]

Although IPAQ-SF is recommended and widely used, some studies[85,87] found that this method tends to overestimate the amount of PA reported compared to an objective device. Hence, the evidence to support the use of IPAQ-SF as an indicator of relative or absolute PA is weak. However, a study conducted in BCS assessed PA with the IPAQ-SF and found a positive association between PA levels and peripheral muscle strength, showing the significant protective effect of PA on BC risk.[30]

As mentioned before, BCS and cancer patients have less muscle strength compared with healthy people.[15] Growing evidence suggests that exercise has the

capacity to mitigate and/or reverse muscle dysfunction in patients with cancer[23,30] as shown by Christensen et al[23] BC patients who performed resistance training during chemotherapy had an increase of 0.8kg of muscle mass. Another study[19] suggested that moderate-intensity exercise can provide a sufficient physiological stimulus to improve muscular performance in cancer survivors, whether exercise is performed during or after cancer treatment. But it is important to note that, according to Doyle et al[12] low to moderate intensity for healthy population may be of high intensity for cancer survivors.

The ability to perform physical tasks in daily life is determined by a threshold level of muscular strength and that's why strength training in cancer patients would seem to be a potent physiological intervention for regaining lost muscles and improving QOL.[31]

1.4. Water Compartments and Breast Cancer

Being the major constituent in the human body, water comprises about 40-70% of the entire body mass and constitutes approximately 72-74% of free fat mass (lean tissues) and approximately 10% of fat mass (relatively nonaqueous).[89-91] The total amount of water in the body referred as total body water (TBW) is divided in two main compartments: intracellular water (ICW) corresponding to the fluid within the cells and it is ~66% (2/3), and extracellular water (ECW) which includes all fluid outside the cells ~33% (1/3). These fluid compartments are separated by plasma membranes that surround the cell.[92]

When conditions outside the body change, these changes are reflected in the composition of ECW, which surrounds the individual cells of the body. Uncorrected deviations in factors such as oxygen and carbon dioxide exchange, can lead to disease and/or death. Therefore it is crucial to maintain concentration gradients and the movement of solutes and water across barriers to preserve normal body function.[92] In some clinical conditions, alterations in body hydration and fluid distribution cause differences in the ratio ECW to ICW, and with certain drugs, the body can retain or lose significant amounts of water and therefore present different proportions of TBW.[92,93]

Adequate water volume is essential for optimal thermoregulation, cardiovascular and metabolic function. A 3-4% reduction in hydration is likely to cause a reduction of 2% in muscular strength.[94]   In a recent study conducted in judo

athletes by Silva et al.[94], it was found that independently of changes in body weight and arm lean soft tissue, athletes that decreased the intracellular water (ICW) compartment were more likely to reduce grip strength.[94]

Additionally, TBW estimations have been used to monitor nutritional status and identify disease states, such as dehydration and chronic kidney disease.[95]

In healthy individuals the hydration of fat-free mass (FFM) and the ratio between ECW and TBW are tightly regulated. In malnourished patients and under a variety of other diseases there is usually a relative increase in ECW, which often results in an increase of TBW.[96]

The most significant confounding variable in BCS is edema of the distal extremities, which may result from lymphedema, and will affect impedance measurements.[93]

Lymphedema is the most problematic and dreaded complication of BC treatment, particularly after surgery or lymph node removal,[17,97,98] characterized by the accumulation of protein-rich extracellular fluid, resulting from damaged or blocked vessels[99] leading to a significant increase in the volume of the affected limb, resulting of an impairment in the ability of the lymphatic system to drain the proteins and macromolecules of the interstitium.[17] It is an incurable, progressive, disfiguring and disabling disorder that is often misdiagnosed and treated too late or not treated at all.[100] It may present immediately or years after treatment.[97] Incidence may vary from 6-30%.[21] Early treatment due to early diagnosis may prevent progression to the chronic phase.[100] Despite the causes of lymphedema, such as stiffness and decreased range of motion of the affected limb joints, handgrip strength test, mentioned in the previous chapter was unchanged regardless the presence or absence of lymphedema.[17]

Measurements of TBW and ECW involve the use of invasive tracer-dilution techniques. These techniques are expensive and time consuming for routine procedures. Until recently it has not been feasible to use field body composition methods, such as bioelectrical impedance analysis (BIA), to assess routinely the nutritional status of hospitalized patients.[96]

Data from the last decade indicate that BIA was able to predict the onset of lymphedema 10 months before clinical diagnosis.[99,100] At low frequencies,

lymphedema assessment through BIA detects ECW changes. Increases in the volume of this fluid reflects the contribution of lymph accumulation when the subject being at study is at risk of developing lymphedema.[100]

Intracellular fluid is unaffected by the advert or progression of the disease. Hence, an ECW/ICW ratio is constructed to help detecting the early onset of lymphedema. This ratio is a validated method and appears to have equal or better sensitivity than other techniques in detecting lymphedema.[100,101] However, if assessed too early, as within 3 months of surgery, normal postoperative swelling could be misconstrued as evidence of lymphedema.[97] A participant was classified as having lymphedema when impedance ratio was more than 3 standard deviations above population mean.[97]

1.4.1. Bioelectrical impedance

The principles of bioelectric impedance (BI) have been established for more than 40 years but methods for estimating components of body composition, specifically total body water, intra and extracellular water, and fat-free mass, are comparatively recent.[102]

The use of BI to estimate body composition is based on the principle that an electrical current flows at different rates through the human body and is resisted by body tissues and water.[93] It is also based on the greater electrolyte content and conductivity of free fat mass (FFM) compared to that of adipose tissue or bone and upon the geometrical relationship between impedance and volume of the conductor.[102,103]

Therefore, impedance (Z) is the frequency dependent opposition of a conductor to the flow of an alternating current and is composed by two vectors: resistance (R) and reactance (Xc).[93,102]

The R is described as pure opposition of the conductor (intracellular fluids, body fluids and electrolytes) to the flow of an electric current and is related to the amount of water present in the tissues.[104] The Xc is the resistive effect produced by tissues interface and cell membranes, is the inverse of capacitance, where capacitance is the storage of energy in a circuit by a capacitor.[61,105] In human body, capacitance occurs when regions of high conductivity (i.e. ECW and ICW) are separated by regions of low

conductivity (i.e. cell membranes).[105] Therefore, ECW and ICW act as resistors in parallel while the cell membrane behaves as an imperfect capacitor and introduces a reactive and hence frequency dependent component to the total impedance.[106]

At 5kHz signal pathway is only conducted through ECW because there is very little capacitive penetration of the signal into the intracellular volume and it's assumed that measured impedance is totally resistance.[106,107] At midrange frequencies (e.g. 50kHz) a small amount of intracellular penetration occur due to some capacitors being electrically charged. Therefore, at 50 kHz the resistance is lower than at 0 kHz because there is a greater cross sectional area and a shorter path to destination electrode.[105] At high frequencies (>500kHz), the current is able to penetrate the cell membrane of the intracellular compartment[107], taking a more direct pathway through the body, therefore including both water compartments[105,106] assuming resistance index is linearly correlated with TBW.[107]

Therefore, the $0/\infty$ kHz parallel model (Cole-Cole) is the most accurate model for the analysis of water compartmentalization. The success of this method can be attributed to the fact that ECW and ICW are the major electrical conductors in the body and they reside adjacent to each other, with ICW being isolated from ECW by low conductivity membranes.[108] This model is very useful for the assessment of body water in diseased populations in which the ratio ECW to TBW is altered.[107]

BI depends on static assumptions and dynamic relationships regarding electrical properties of the body. Anthropometric measurements (e.g. height, weight, age, sex, race, etc.) are often used in many of the BI prediction equations.[106,109] These parameters are included to reduce the effects of interindividual variance in R and Z values, related to differences in body size and in shape and to increase the prediction accuracy of body composition estimates.[109] It is also important to control some aspects to guarantee the validity, reproducibility, and precision of the measurement in similar populations. Therefore, some standardizations have been suggested in order to replicate results, such as the subject body position, length of time in supine position before measurement, correct stature measurement, skin preparation with alcohol before electrode placement, electrode position, hydration and menstrual cycle, consumption of food and beverages before test, ambient air and skin temperature, recent physical activity and conductance of the examination table.[106,109-111]

BI is considered to be a feasible filed method as it is an easy, portable, inexpensive, noninvasive, and less time consuming method,[61,93,105,112-114] especially if compared with laboratorial methods such as deuterium dilution, tritiated water dilution, bromide dilution, and even dual energy x-ray absorptiometry.[104] BI results are available immediately and measurements can be repeated as often as desired without side effects for the participant.

Malnutrition is a frequent manifestation in patients with advanced cancer and is a major contributor to morbidity and mortality. Malnutrition is characterized by changes in cellular membrane integrity and alterations in fluid balance with an increase in ECW, which often results in an increase in TBW.[96] As a result, measurement of body composition is an important component of overall nutritional evaluation in cancer patients.[61]

At 50 kHz the current does not completely penetrate the cell membranes but in normal subjects this is not particularly important because the intracellular volume represents a relatively constant proportion of the TBW. In patients, there may be significant variations in the proportions of ICW and ECW and it is more important that the frequency is high enough to allow the current to completely penetrate the intracellular space.[115] Clinical advantage to monitor both ECW and ICW makes BI the preferred technique for future clinical research.[109]

A decrease in ECW/ICW ratio would result in a relatively lower resistance per unit of body water and higher TBW.[114,116]

To estimate a certain body compartment based on bioelectrical impedance methods it is important to choose the type of device that will be used. The single frequency bioelectrical impedance analysis (SF-BIA) device and multiple-frequency bioelectrical impedance analysis (MF-BIA) have the measured resistance and/or reactance incorporated into empirical prediction equations, developed by regression analysis.[104] The bioelectrical impedance spectroscopy approach (BIS), estimates body composition through a mathematical modeling technique[108,117] on a range of resistance values measured at different frequencies to extrapolate the resistance of the ECW and ICW.[104]

1.4.1.1. Single Frequency Bioelectrical Impedance Analysis

Single-frequency bioelectrical impedance analysis is by far the most widely available impedance methodology, which involves the application of an electrical current for the measurement of impedance at a single frequency, typically 50 kHz.[118] The current passes between surface electrodes placed on hand and/or foot. Some instruments use foot-to-foot or hand-to-hand electrodes.[110]

SF-BIA strictly measures a weighted sum of ECW and ICW resistivity. Impedance data is entered into predictive equations derived through statistical regression in order to determine TBW, from which FFM is calculated according to the assumption that FFM is constantly hydrated at ~0.73.[118] However, SF-BIA cannot determine differences in ICW. Therefore, a problem of using a single-frequency measurement to predict TBW is that the sensitivity of a single high-frequency measurement to changes in ECW and ICW is different due to their different resistivities, a simple change in the ratio ECW/ICW will alter TBW resistivity and cause error.[119] As so, the SF-BIA is not valid under conditions of significantly altered hydration, but this does not negate its use to predict absolute FFM or TBW in normally hydrated subjects.[110,120] In malnourished patients or under a variety of other diseases such as edema, there is usually an increase in ECW, which often results in and increase of TBW,[96,110,118] when this occurs, Cole-Cole model should be used.[107]

In SF-BIA the assumption that FFM is constantly hydrated is a major limitation of this technique in the assessment of body composition, as FFM hydration may not be constant for all populations.[105]

1.4.1.2. Multiple Frequency Bioelectrical Impedance Analysis

At 50kHz, the electrical pathway is primarily extracellular because there is very little capacitive penetration of the signal into the intracellular volume, which means, the cell membrane acts as an insulator, and it is assumed that the impedance is principally a function of ECW, responsible for the measured R at R_0.[105,107,110,119] Thus, one can conclude that SF-BIA is limited in the ability to distinguish the distribution of body water into its intra- and extracellular compartments.[121]

At infinite or very high frequencies, as it occurs in MF-BIA and BIS, the conduction through the ICW increases and becomes fully conductive. Impedance, or

the total body R (R_∞) is a function of both ICW and ECW (TBW), which is caused by cell membrane capacitance.[106,110,119]

Therefore, TBW assessment by SF-BIA was replaced by MF-BIA devices that apply the current at limited and defined frequencies (e.g. 5, 50, 100, 200 or 500kHz) and offer the potential of measuring TBW, ECW and ICW separately.[103,118]

Due to its efficacy in accurately predict TBW, MF-BIA was used to monitor the efficacy of treatment for lymphedema in patients following surgery for BC. This method was shown to be significantly more sensitive than others to detect small differences in the extracellular volumes between the arms of any individual. ECW was elevated after clinical diagnosis of lymphedema. This index does not require normalization to another body segment and can be used to detect all types of peripheral edema including both uni- and bilateral lymphedema.[101]

There are two approaches to the use of MF-BIA data:

1. Multiple Frequency Bioelectrical Impedance Analysis

MF-BIA first introduced by Thomasset el al.[103] used impedance data at two frequencies: one at very low frequencies (usually 5kHz) and the other at very high frequencies (typically 50, 100, 200 to 500kHz). The impedance data are applied to regression-derived equations in order to predict TBW, ECW, and ICW.[118]

Unlike the SF-BIA, this model correctly assumes that the specific resistivities of intra- and extracellular fluid are different. It assumes that R at low frequencies is the resistance of the extracellular fluid (Re) because virtually no conduction occurs due to high cell membrane capacitance. On the other hand, R at high frequencies is the resistance of whole fluid (Rt) because there is total conduction through the cell membrane.[118] The resistance of the intracellular fluid (Ri), is a function of both low and high frequency.[105]

However, the use of more than one frequency gives a variability of results and no conclusions can be made regarding the validity of one frequency over another, in the prediction of body fluid compartments.[105]

2. Bioelectrical Impedance Spectroscopy

In contrast to SF-BIA and MF-BIA, BIS uses physical and mathematical

modeling and mixture equations (e.g. Cole-Cole and Hanai formula)[108,117] to generate relationships between R and body fluid compartments, instead of regression equations.[110] BIS measures the impedance across a spectrum of frequencies and can accommodate interindividual variation due to the mathematical modeling generated factors. As so, BIS provides a more direct, individualized measurement of ECW and ICW than other impedance approaches.[118]

In commercial BIS instruments using the Cole-Cole model[108], multifrequency impedance data are mathematically modeled to reduce the influence of artifacts at low and high frequencies. In this model, the body is viewed as an electrical circuit with intracellular and extracellular pathways in parallel and having cell membranes serve as capacitors for the intracellular pathway.[105]

Cole model is computed by using nonlinear curve fitting to extrapolate data to the low and high frequency limits. This procedure generates Cole model terms, including R_e (resistance associated with the ECW); R_i (resistance associated with the ICW); C_m (cell membrane capacitance); and exponent α. Cole model terms are then applied to equations derived from the Hanai mixture theory, which is essentially based on the notion that the body is a conducting medium of water, electrolyte-rich tissues (e.g. blood and muscle) in addition to nonconducting material within it (eg, bone, fat and air filled spaces).[120] This theory was applied to improve the Cole-Cole linear model as (1) it accounts for the effects of non-conducting substances in the body water, (2) removes the apparent population-specificity found with Cole-Cole linear equations, and (3) improves sensitivity to body water changes [122].

The TBW is assumed to be the sum of ECW and ICW [118,123,124], and the FFM is calculated based on the mean density of the intra- and extracellular water and its associated material.

Therefore, Cole-Cole model and Hanai theory[108] will be useful for the assessment of body water compartmentalization in diseased populations in which ratio ECW to TBW is altered.[107,119]

1.4.2. Validation in Clinical Populations

BI has been validated to assess body composition and nutritional status in a

variety of patients, including cancer.[61,96,105,112,125-127] The existent data is, so far, inconclusive, nevertheless, BIS seem to present itself as a valid alternative to assess body composition and body water compartments, in clinical populations.

In Netherlands, BIA is routinely used in surgical and oncological patients, where quick measurements of body compartments are needed.[104] According with Earthman et al.,[118] BIS is the only field technology available that has the potential to measure body water volumes and body cell mass (BCM) in the clinical setting. The BCM has clinical relevance because it has been defined as the total mass of metabolically active, living, functioning cells. A loss of BCM can cause a decrease in physical strength and immune function, with an increase in susceptibility to infections, as observed in human immunodeficiency virus (HIV) patients.[118] BIA also predicts short-term survival in HIV patients.[109]

Therefore, from a clinical perspective, the ability of BIS to accurately estimate BCM by quantifying ICW, as well as the ability to monitor fluid distribution between the ICW and ECW compartments, would greatly enhance nutrition assessment, as well as the overall clinical care of the patient.[118]

However, according with the review of 11 studies in oncological and surgical patients made by Haverkort et al.,[104] BIA measurements underestimated TBW and FFM irrespective of the equation or device used. The results of these studies indicate that the application of the Heitmann equation contributes, to some extent, to a valid estimation of TBW in patients with incurable cancer. They concluded that BIA estimations in the individual patient care with regard to oncological and surgical patients can be useful when performed longitudinally and under strict conditions.[104]

Fredix et al.,[128] also concluded that BI is a promising method for the assessment of body composition in clinical practice provided that population specific prediction formula are used.[128]

According to Moon et al.,[120] an increase in ECW, which can be due to a high BMI, very common in BCS, have been shown to influence BIS estimations, causing an overestimate in TBW. These authors suggest the application of TBW equations instead of predefined values automatically calculated by equipment's, and apply those in an appropriate equation to predict hydration.

1.4.3. Phase Angle

In healthy subjects, age, sex and BMI are the major determinants of phase angle (PhA). Aging is associated with a decrease in tissue mass (reduced Xc) and in TBW (increased R) resulting in decreased PhA. A higher PhA is observed in persons with an increased BMI because PhA is directly related to cell membranes (amount and functional status) and persons with increased BMI have more fat cells resulting in higher PhA values. For BMI > 40 kg/m^2 an inverse relationship is observed, this has been attributed to a higher tissue hydration or a pathological fluid overload.[129-131]

Patients often exceed normal BMI range and a differentiation between PhA as an indicator of body composition and cellular function altered by disease may require BMI-specific reference values to exclude an influence of body composition,[132] since increased BMI is a common feature of BC patients.[17,30,57]

As mentioned before, measurement of body composition is an important component of overall nutritional evaluation in cancer patients and in association with cell membrane functional analysis it is able to reflect cell function and integrity.[133] Changes in cell integrity are characterized by malnutrition, which is a major contributor to morbidity and mortality and so, a predictor of shortened survival.[42,134]

Nutritional status has been evaluated through objective measures such as anthropometric and laboratory methods. This methods are not ideal in the clinical setting because they are time consuming and require well-trained staff.[61] The use of impedance methods as a measurement of assessment of body composition and nutritional status overcomes the aforementioned issue and other challenges that might appear with the assessment in the clinical setting.[131]

We now know that cell membranes produce capacitance (Xc) by storing parts of the charge as a capacitor. The storage of the current creates a phase shift that can be regarded as the ratio of R and Xc and is expressed as phase angle .[135] Bioelectrical PhA has consistently been shown to have great prognostic relevance with regard to morbidity and mortality in several conditions such as HIV/AIDS, liver cirrhosis, sepsis, hemodialysis, lung, colorectal and pancreatic cancer.[42,131-134] PhA is the angle the impedance vector forms relative to the R vector, as shown in Figure 2, and is calculated through the following equation:

$$\text{Phase Angle} = (\text{Resistance}/\text{Reactance})*(180/\pi).[102]$$

Although the biological meaning of PhA is not well understood, it is considered a novel marker of cellular function,[44] as reflects in one hand, the capacitance behavior of tissues (reactance) and is associated with cellularity, cell size and integrity of the cell membrane and, on the other hand, on its pure resistive behavior (resistance), which is dependent on lean tissue mass and tissue hydration between intra- and extracellular spaces.[42,61,113,129,131,132,134-136] PhA is positively associated with Xc and negatively associated with R.[61]
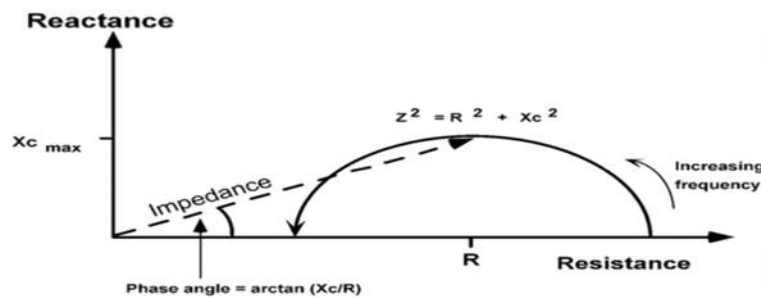
Figure 2: *Diagram of the graphical derivation of the phase angle and its relationship with R, Xc and Z.*[136]

Changes in the extracellular to body cell mass ratio are probably associated with changes of the PhA. This ratio is a known sensitive marker of malnutrition, characterized by both increased ECW and decreased BCM (mainly muscle mass), typical features of systemic illness, and PhA appears to reflect its prognostic significance.[42,129,136,137] Castanho et al.[133] discovered a direct association between ECW/BCM ratio and tumor volume in lung cancer patients.

A low PhA is associated with cell death or decreased cell integrity (reduced Xc)[135], a loss of ICW reflects BCM loss, which is frequently accompanied by an increase in ECW in mainly clinical populations characterizing edema/extracellular accumulation and poor health[42,118,138] while a higher PhA is an indicator of wellness, low ECW:ICW ratio,[137] associated with large quantities of intact cell membranes of skeletal mass and BCM reflecting stronger cell function.[42,61,113,130,136,139,140] Due to this feature, PhA is positively correlated with muscle mass as well as with muscle strength (assessed by handgrip strength test) in many diseases such as cancer,[42,112,113,135,136,139] representing objective functional measures with prognostic potential in these patients.[44]

Disease, inflammation, malnutrition or prolonged inactivity can result in disturbed electric tissue properties (cellular membrane integrity and alterations in fluid balance)[132] that directly affect PhA. A low PhA has been associated as a useful predictor of impaired nutritional and functional status, decreased quality of life, increased morbidity and shortened survival in tumors such as pancreatic, lung, colorectal, and breast cancer.[42,61,131,134,138-140] It may also be a predictor for the risk of severe complications after surgical procedures in patients with advanced cancer.[44]

The problem of the PhA is that most authors generated PhA cutoffs based on their study population and those cutoffs are not necessarily transferable to other populations. However, reference values from a healthy population offer the possibility of assessing individual deviations of a patient in relation to the population average in order to help an early identification of patients at risk of impaired functional and nutritional status and increased mortality.[42] Previous studies have proposed age- and sex- specific percentile cutoffs for PhA which have been shown to be clinically useful in cancer patients.[42] More recently Hui et al.[44] defined cutoff PhA values for the prognostic of survival in cancer patients as follows:

2º >PhA< 3º survival time < 3months;

4º >PhA< 5º survival time between 3 and 6 months;

PhA ≥ 6º represents a survival time > 6 months.

Cancer can affect the nutritional status to different degrees of severity. The prognostic role of PhA is easier to assess if standardized values are used.[129,132] Sick individuals, such as cancer patients, are expected to have negative standardized PhA, which become increasingly lower with a worsening prognosis.[131] According to some authors,[42,129-131] studying standardized PhA according to sex-, age- and BMI- stratified mean reference values enhances its prognostic relevance because individual deviations from population norms provide better information than absolute values and only malnutrition and inflammation will be identified as significant risk factors. According to Norman et al.[42] the standardized PhA is the strongest predictor for impaired functional and nutritional status and a better indicator of 6 months mortality than are malnutrition and disease severity in cancer. They also suggest that the fifth percentile of sex-, age-, and BMI- stratified reference values is a suitable and clinically relevant indicator of cancer cachexia related symptoms and decreased survival and allows

identification of patients at risk who are in particular need of intensified medical and nutritional attention. These authors also showed that patients with a PhA below the 5th percentile had significantly lower handgrip strength.[42]

It is generally agreed that a PhA below 5º means that the person needs medical management.[139] Gupta et al.[134], Hui et al.[44] Lee et al.[139] demonstrated longer survival time in cancer patients with a PhA higher than 4.5º. Selberg et al.[136] demonstrated that patients with liver cirrhosis that have an abnormally low (<4.4º) and borderline (4.5º and 5.4º) PhA have clearly reduced survival times. These studies indicate that PhA is a predictor of poor outcome and according to Kyle et al.[135] patients with low PhA have significantly lower FFM and significantly higher percentage of FM.

A study conducted by Gupta et al.[61] in 259 breast cancer patients concluded that those with a PhA ≤ 5.6º had a median survival of 23.1months, while those with a PhA > 5.6º had 49.9 months. They also concluded that PhA was a strong predictor of survival after controlling for the effects of stage at diagnosis and prior treatment history. The cutoff point of this study was in agreement with those reported by other studies.[136]

2. Relevance of the Study

It is known that physical activity is very important in breast cancer patients (BC) and breast cancer survivors (BCS) because [74,141] it helps to improve cancer related symptoms such as muscular and cardiorespiratory fitness, physical functioning, fatigue, psychological well-being, body image, body composition, and health-related biomarkers[74], improving quality of life.[141,142] An important health related component of fitness is muscular strength, which has been shown to be positively related to cardiorespiratory fitness.[143] Although muscular strength has received far less attention than cardiorespiratory fitness, recent studies support the hypothesis that low muscular strength in adulthood also predicts all-cause mortality, as well as mortality due to cardiovascular disease and cancer in healthy and diseased people.[33,34,40,41,43,47,86,144-146]

As the majority of cancer patients do not engage in physical activity programms[23], muscle dysfunction, characterized by an impairment in muscle strength or muscle composition, may occur.[23] Growing evidence suggests that exercise has the capacity to moderate and/or reverse muscle dysfunction in patients with cancer. As shown by Christensen et al[23], early stage BC patients increased muscle strength 25-35% after a 17-week resistance training program.

A method to assess muscle function is through the handgrip test proven to be one of the most reliable, valid, health related to muscular strength. [17,36]

Recent studies in BCS show that surgical procedure and cancer cachexia, defined by severe muscle wasting, systemic inflammation and malnutrition [23,27] were causes for the reduction in muscle strength as well as risk factors for all-cause mortality. [17,23,27]

Another complication of breast cancer treatment, due to surgery or radiotherapy of the axillary area, is lymphedema[97] characterized by accumulation of protein-rich extracellular fluid resulting from damaged or blocked vessels.

A very reliable method to measure this fluid accumulation is through bioelectrical impedance (BIA) characterized as a non-invasive, inexpensive, portable and easy to use method that gives reliable measurements of body composition.[61,93,112,113] BIA is based on the principle that an electric current flows at different rates through the body. Body impedance is an opposition of the conductor to that flow and consists of two vectors: resistance R and reactance Xc. [93,106] R is the major opposition to the flow of an electric current, related to the amount of water present in the tissues and Xc is the

resistive effect produced by tissues interface and cell membranes.[61,93,147] The body is mostly composed of water with ions, divided into two compartments: intracellular (ICW) and extracellular (ECW), and at low frequencies <50kHz current is only conducted through extracellular water (ECW and measured impedance is totally resistive).[93,94,106] It would be important to explore the association of water compartments in patients with cancer, as it seems to exist an association between cellular hydration and strength, though in other populations.[94,113] So far, no study was conducted in cancer patients aiming to analyze cellular hydration with strength.

As it was mentioned before, at low frequencies ECW is measured but when high frequencies are applied, the current penetrates the cell membrane, increasing the reactance vector, causing the phase angle (PhA) to open.[106] PhA is obtained by arctangent of the directly measured reactance-to-resistance ratio.[113] It is associated positively with most of the nutritional markers and is an indicator of cell integrity and water distribution between intra and extracellular spaces.[61,113] It is also a prognostic marker in several clinical conditions, including cancer,[61] as it represents either cell death or malnutrition, characterized by changes in cellular membrane integrity. Due to this characteristic, PhA is a useful predictor of impaired muscle function.[61,113]

Gupta et al,[61] concluded that PhA is a strong predictor for survival in BC patients after controlling for the effects of stage at diagnosis and prior treatment history. Also, it seems to exist an association between PhA and muscle strength in cancer patients[44] as both represent measures with prognostic potential.[44,112]

This study emerged because there is a need to define prognostic tools easy to apply, noninvasive and that are valid for the clinical setting. Studies with these variables have been performed in clinical settings but none explored the relationship between PhA and water compartments with muscular strength in breast cancer survivors, adjusting for potential confounders.

3. Objectives

This study aims to determine if the water compartments and the phase angle are predictors of the muscular strength in breast cancer survivors adjusting for habitual physical activities, age and time post operation.

4. Methodology

In this chapter an overall description of the methods used in this thesis will be provided, including study design and sample.

4.1. Study Design and Sample

Study Design and Sample Size

Forty-one breast cancer survivors were assessed in this observational cross sectional study. The measurements of phase angle, muscular strength and water compartments were performed at Hospital de São José in partnership with Viva Mulher Viva Associação, in a room that was prepared in advance in order to avoid errors. Before giving written informed consent to participate, each participant was informed about the goals of the study and its benefits.

All procedures were approved by the Ethics Committee of the Faculty of Human Kinetics, University of Lisbon, and were conducted in accordance with the declaration of Helsinki for human studies of the World Medical Association.[148]

Inclusion/Exclusion Criteria

The inclusion criteria were patients who survived from breast cancer and were currently being followed up.

The exclusion criteria was having performed a recent surgery for removing mammary tissue (< 6 months), because according to Gomes et al.[17] breast cancer survivors show changes in body composition and handgrip strength 6 months after surgery.

We assured that the participants recruited were not involved in other studies or under any dependent relationship with the investigators of the study.

4.2. Body composition measurements

The protocol involved preparation/instructions to subjects, anthropometrics, international physical activity questionnaire, measurement of handgrip and bioelectrical impedance. Each session lasted approximately 30 minutes.

4.2.1. Preparation

Each participant was instructed to do overnight fast before coming for a morning visit at Hospital São José and to wear minimal clothing. They were further asked to remove all objects that could interfere with bioelectrical impedance assessment. The following measurements were conducted:

4.2.2. Anthropometry

<u>Measurement of Body Mass and Stature using Anthropometry</u>

The participants weight and height were measured using a stadiometer with a scale incorporated (SECA, Hamburg, Germany), respecting standardized procedures. The measurement was taken after subject removed the shoes and using minimal clothes. Weight and height were measured to the nearest 0.01kg and 0.1cm, respectively.

Body mass index (BMI) was calculated as body mass (kg) divided by the square of the stature (m).

<u>Measurement of waist and hip circumferences</u>

Waist circumference was measured according to the United States National Institute of Health protocol, at the top of the iliac crest.[67] Hip circumference measurement was taken at the widest portion of the buttocks.[66,149] Both measurements were taken with the measuring tape parallel to the floor and snugged around the body, without constricting it. The participants were in the erect position and weight distributed evenly. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.[62,149]

4.3. Bioelectrical Impedance Spectroscopy (BIS)

The present study used BIS analyzer model 4200B Xitron Technologies (San Diego, CA, USA).

Anthropometric variables, gender and age of individuals were inserted into the interface of BIS software and only then the examination was initiated.

A few requirements prior the test were taken into consideration in order to guarantee the validity, reproducibility and precision of the measurement: position of the body, length of time in supine position before measurement, correct stature measurement, skin preparation with alcohol before electrode placement, electrode position, hydration status, menstrual cycle, consumption of food, beverages and diuretic drinks before test, ambient air and skin temperature, recent physical activity, the use of metals and conductance of the examination table.

Participants adopted a supine position with their arms and legs abducted at an angle of 45º. After cleaning the skin with alcohol, four electrodes were placed on the dorsal surfaces of the right hand and right foot. The source electrodes were placed on the hand, in the middle of the dorsal surface proximal to the metacarpal-phalangeal joint, and on the foot, in the middle of the dorsal surface proximal to the metatarsal-phalangeal joint. The detector electrodes were placed on the wrist at the midline between the distal prominences of the radius and ulna and in the ankle joint at the line between the malleoli. The source and detector electrodes must be placed with a 5cm distance between each other. After placement of electrodes we connected the black cable to the distal surface and the red cable to the proximal surface. The alternating current is passed through the outer pair of electrodes, while the voltage drop across the body is measured using the inner pair of electrodes.
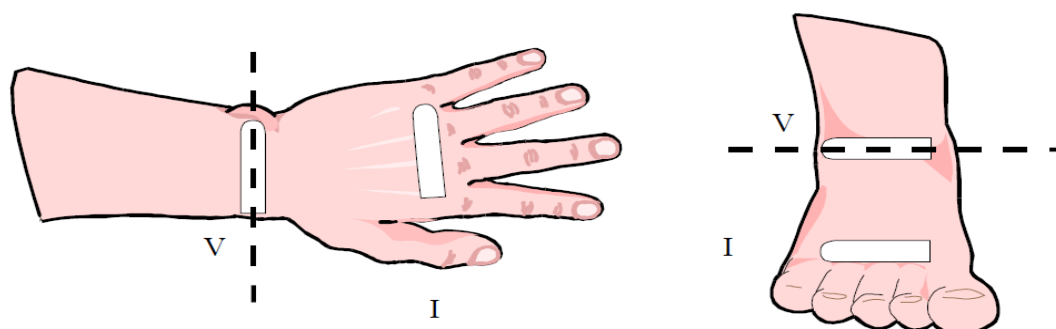
Figure 3: Example of how the electrodes must be placed in the right hand and foot for BIS assessment.

The measurements were performed 10 minutes after the participants have been lying down and whole body resistance (R) and reactance (Xc) was determined from a 5KHz to 1MHz spectrum, from which impedance (Z) is derived, according to the Cole-Cole cell suspension model.[108] This procedure derives a theoretical impedance at zero and infinity frequencies, based on a non-linear curve fitting from the measured resistance and reactance.

4.4. Water Compartments

The R values at the ideal measurement frequencies are predicted using Cole-Cole plot, with R_0 representing the R of the ECW and R_∞ representing the R of intra- and extracellular fluid (TBW).[110]

The BIS software is programmed to perform biophysical modeling on the impedance data according to Cole-Cole cell suspension model[108] to generate Cole model terms: Re – resistance associated with the ECW; Ri – resistance associated with the ICW; Cm – cell membrane capacitance; and exponent α. The ECW and ICW volumes are predicted from the modeled Re and Ri using equations formulated by the Hanai mixture model[117]. The TBW is calculated as the sum of ECW and ICW.

Gudivaka et al.[107] found that the Cole-Cole model accurately predicted changes in TBW, ECW and ICW in diseased populations, where the ratio ECW to TBW is altered.[110]

4.5. Phase Angle (PhA)

The relationship between capacitance and R is interesting because it reflects different electrical properties of tissues that are affected in various ways by disease, nutritional status, and hydration status.

When R and capacitance are plotted graphically after standardizing for height, sex, race, etc., different disease/conditions appear to form different clusters. The PhA, which is one measure of the relationship described above, and other interrelated indices, including R_0/R_∞, has been used to predict clinical outcome[110] since is one of the best indicators of cell membrane function related to the ratio of ECW and ICW.

Capacitance causes a phase shift quantified geometrically as the arctangent of the ratio of reactance to resistance, or phase angle. The phase angle was calculated using

the following equation:

$$\text{Phase Angle (degrees)} = (\text{Resistance/Reactance})*(180/\pi).$$

The most common frequency to extrapolate the phase angle is 50kHz since the current passes through both intra- and extracellular fluids.[110]

4.6. Handgrip Strength

<u>Measurement of forearm maximal strength</u>

Forearm maximal strength will be determined using a handgrip dynamometer (Jamar, Sammons Preston, Inc., Bolingbrook, IL, USA) with visual feedback. The assessment was made sitting in a straight-backed chair with the feet flat on the floor, shoulder adducted and neutrally rotated, elbow flexed at 90º with forearm in a neutral position, according to the methodology purposed by the American Society of Hand Therapists (ASHT).[48] Dynamometer was adjusted to each subject's hand with each trial lasting approximately 3 seconds. The best of 3 maximal trials was used for data analysis. Measurements of right and left side were taken in all the subjects and dominant side was noted. The same adjustment of the dynamometer was used for all tests for each subject.

This method was developed for the use with the Jamar dynamometer.[49] Most of the studies follow the ASHT protocol in an attempt to control known risk of errors.[48]

4.7. Physical Activity

Physical activity was evaluated with short form of International Physical Activity Questionnaire (IPAQ). The IPAQ short form is a seven-item measure of four domains of activity: vigorous-intensity physical activity; moderate-intensity physical activity; walking and sitting. Participants reported frequency (during the last seven days) and duration of physical activity (minutes/hours usually spent on one of those days). Participants also reported the total time they've spent sitting on a week day during the last seven days. Physical activity was calculated as the summation of the days, hours and minutes of vigorous-intensity and moderate-intensity physical activity, presented in minutes.

4.8. Statistical Analysis

Sample size was calculated considering a moderate (>0.15) Cohen's $f2$ effect size (which is appropriate for calculating the effect size within a multiple regression model in which the independent variable of interest and the dependent variable are both continuous) with a type I error of 10%, power 80% and 4 predictors (the independent variable: phase angle or ICW or ECW and three confounding variables: age, time post-operation, moderate-to-vigorous physical activity) a total of 32 participants was required. To assure that equipment failure or any missing variable would not affect the calculated effect size we over-sized the required sample by 25%, and therefore, ~40 participants were recruited.

Statistical analysis was performed using IBM SPSS Statistics for Mac OS version 22.0, 2010 (SPSS Inc., IBM Company, Chicago IL, USA). The statistical significance was set as $p < 0.1$, specifically for the variables that were tested as independent predictors of muscular strength.

Descriptive statistics (means ± standard deviation) were performed for all outcome measurements.

Bivariate correlations were conducted in a preliminary analysis.

A potential confounding variable in BCS is edema of the distal extremities, which may result from lymphedema, and will affect impedance measurements.[93]

In order to examine whether lymphedema interact with the relationship between impedance variables and strength, Univariate General Linear Model test was conducted to test if the lymphedema by each bioimpedance variables was significant. If this is nonsignificant (p<0.05) the sample will be further analyzed as a whole.

Multiple regression model was used to determine if our dependent variable Y (HGR, HGL, HGdom) was predicted by one or more of the independent variables X (BIS variables, moderate-vigorous physical activity (MVPA), age and time post operation (TPO)). As expressed in the following equation:

$Y_{HG} = \beta_0 + \beta_1 X_{Bis\ variables} + \beta_2 X_{MVPA} + \beta_3 X_{age} + \beta_4 X_{TPO} + \varepsilon$

where $\beta_0, \beta_1,.. \beta_k$ are the regression coefficients and ε the error.

The coefficient of determination r^2 was also determined for all outcome variables. This parameter measures the quality of the adjustment of the model and

represents the variability of the dependent variable that is explained by the regression model. The explanatory power will be better if this value is close to 1.

5. Results

In this chapter it will be presented the main results of this study.

5.1. Characteristics of the Sample

In table 1 means and standard deviations regarding the characteristics of the sample (n=41) such as age, anthropometric (body mass, stature, BMI, waist circumference, hip circumference, WHR), BIS (PhA, ECF, ICF, FFM), handgrip (HGR, HGL, HGdom) and physical activity (MVPA) measurements are summarized.

Univariate general linear test was performed to understand if phase angle was explanatory of the handgrip regardless of a participant having or not lymphedema. Because there was no interaction found, the sample was analyzed as a whole.

5.2. Preliminary Tests

Bivariate correlations were performed to observe if there was any association between phase angle, and other BIS related variables with handgrip measurements.

Direct associations were observed between phase angle and handgrip measured on the right side. No associations were found with regard to handgrip measured on the left side and dominant side.

Since the analysis of the interaction term lymphedema by each bioimpedance variables was nonsignificant ($p > 0.05$) in explaining muscular strength, the whole sample was used to test the predictive power of phase angle in explaining muscular strength.

5.3. Multiple Regression Analysis

Multiple regression analysis was performed controlling PhA, step by step, for, age, MVPA and time post operation (TPO). As presented in table 2 and 3 the phase angle emerged as an explanatory variable of the handgrip measured on the right side, independently of MVPA, age and TPO.

Linear regression analysis, table 2, showed that phase angle explained 22% ($r^2 = 0.216$) of the variance of the handgrip.

Chart 1 represents the association between the dependent variable (handgrip) and the independent variable (phase angle).

Table 1: Participants characteristics

Variables	Mean ± Std. Deviation
Age (yrs)	54.6 ± 9.2
Body Mass (kg)	68.0 ± 11.7
Stature (cm)	159.9 ± 6.7
BMI (kg/m^2)	26.6 ± 4.6
Waist Circumference (cm)	87.1 ± 10.9
Hip Circumference (cm)	100.3 ± 8.9
WHR	0.9 ± 0.1
PhA (º)	5.5 ± 0.7
ECF (L)	13.9 ± 1.7
ICF (L)	16.1 ± 3.0
FFM (kg)	39.9 ± 6.3
HGR (kg)	24.9 ± 5.5
HGL (kg)	22.0 ± 5.9
MVPA (min/week)	99.4 ± 118.7

Abbreviations: BMI: body mass index; WHR: waist hip ratio; BIS: bioelectrical impedance analysis; PhA: phase angle; ECF: extracellular fluid; ICF: intracellular fluid; FFM: fat free mass; HGR: handgrip right side; HGL: handgrip left side; HGdom: handgrip dominant side; MVPA: moderate-vigorous physical activity

Table 2: *Predictive power of phase angle in explaining muscular strength*

Model	R*	R Square#	Adjusted R Square	Standard. Error of Estimate
1	0.47[a]	0.22	0.20	4.90
2	0.59[b]	0.35	0.31	4.53
3	0.59[c]	0.35	0.30	4.57
4	0.61[d]	0.37	0.30	4.58

a. Preditors: (Constant), Phase angle

b. Preditors: (Constant), Phase angle, age

c. Preditors: (Constant), Phase angle, age, moderate to vigorous physical activity (MVPA)

d. Preditors: (Constant), Phase angle, age, MVPA, time post operation

* coefficient of correlation

#coefficient of determination
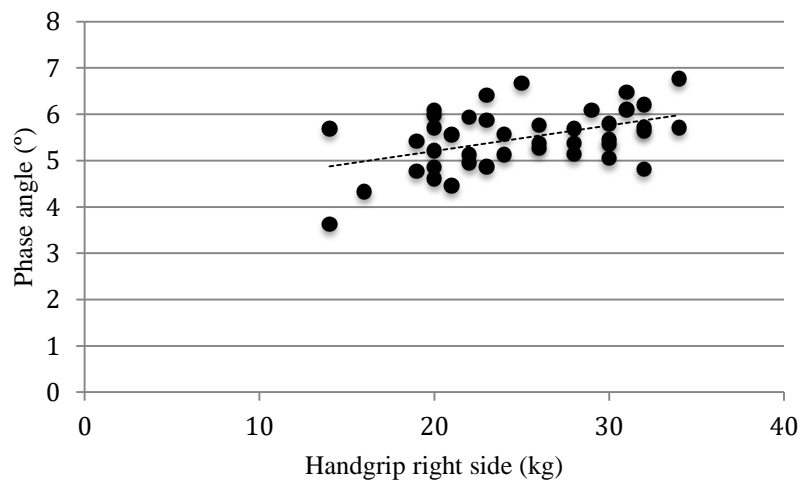
Chart 1: *Regression plot between phase angle and handgrip measured on the right side*

***Table 3**: Adjusted and unadjusted coefficients for the phase angle in determining muscular strength*

| Model | Coeficients[a] | | | |
| | Unstandardized Coefficients | | Standardized Coefficients | Sig |
	B	Std. Error	Beta	
(Constant)	3.51	6.57		0.60
PhA (º)	3.91	1.19	0.47	0.00
(Constant)	22.60	9.23		0.02
PhA (º)	2.71	1.19	0.32	0.03
Age	-0.23	0.08	-0.39	0.01
(Constant)	24.39	9.77		0.02
PhA (º)	2.48	1.26	0.30	0.06
Age	-0.25	0.09	-0.42	0.01
MVPA (min/week)	0.00	0.01	0.09	0.55
(Constant)	25.71	9.90		0.01
PhA (º)	2.27	1.28	0.27	0.09
Age	-0.26	0.09	-0.45	0.01
MVPA (min/week)	0.00	0.01	0.06	0.66
TPO (month)	0.02	0.02	0.13	0.37

Abreviations: PhA: phase angle; MVPA: moderate-to-vigorous physical activity; TPO: time post operation; Std error: Standard error

6. Discussion

We found that the phase angle explained 22% of the variability in muscular strength and remained in the model even after adjusting for age, habitual physical activity and time post operation. However, no association was found between water compartments and muscular strength.

As mentioned before, PhA is one of the best indicators of cell membrane function related to R (hydration) and Xc (membrane area & integrity), which are both associated with handgrip strength.

Phase angle represents a novel marker of cellular function. A higher PhA represents good cell integrity and a low PhA represents cell death or decreased cell integrity.[61]

In comparison to healthy subjects, a low phase angle frequently occurs in sick patients correlating with disease severity.[130] It has consequently been shown to be predictive of impaired prognosis (mortality, disease progression, incidence of postoperative complications, length of hospital stay) in pancreatic, colorectal, breast and lung cancer, as well as in HIV/AIDS, liver cirrhosis, renal insufficiency on peritoneal- or haemo-dialysis, amyotrophic lateral sclerosis, systemic sclerosis, bacteraemia/sepsis and surgical patients.[130,131]

However, despite its prognostic value, there is still the need to define valid cut-off values in order to use it as clinical indicator for disease related malnutrition in various disease settings.[130] The problem with PhA is that most authors generate PhA cut-offs based on their study population which makes them specific and non transferable to other populations.[42] Gupta et al.[61], Hui et al.[44] and Lee et al.[139] demonstrated longer survival time in cancer patients with a PhA higher than 5.6º. In the current study, the PhA mean value (5.48 ± 0.65) can be of concern if we follow the cut-off values presented in the studies mentioned before. Gupta et al[61] went further and established that patients with BC that had a PhA < 5.6º had a median survival of 23.1 months while those with a PhA > 5.6º had a median survival of 49.9 months. However, an important note must be considered, all of this studies were performed in patients with cancer.

Phase angle is also one of the best indicators of cell membrane function related

to the ratio between extracellular and intracellular water. Significant alterations in body fluid hydration, fluid distribution and differences in the ECW/BCM ratio caused by medical condition can affect impedance measurements and are probably associated with changes in the PhA.[136] According to Schwenk et at[137] in systemic illness a low PhA corresponds to a high ECW-ICW ratio due to the ECW expansion and loss of ICW. One of the most significant confounding variable is edema of the distal extremities which may result in lymphedema.[93] In the current study, to understand the significance of this variable a univariate general linear model was performed, showing that lymphedema was not an interactive factor. Edema represents an accumulation of protein-rich extracellular fluid resulting from damaged or blocked vessels, leading to swelling.[99] Any edema, whatever the underlying cause, is due to an imbalance between capillary filtration and lymph drainage. Lymphedema strictly occurs when swelling is due to a failure of lymph drainage in circumstances in which capillary filtration is not increased[150] due to node removal or adjuvant treatment such as radiation.[97]

Because of the existing link between lymphedema and body fluids we compared if ECW would be higher in the group of women with lymphedema (N=5), using Mann-Whitney test. Women in this sample that showed lymphedema presented higher ECW values compared to those without lymphedema. This findings are in line with what has been discovered in other studies,[99,100] that lymphedema is characterized for an expansion of ECW.

In this study, there was no association between ECW and ICW and the handgrip strength. Possible causes may be due to the fact that in disease, the ECW/BCM ratio is altered. According to a study conducted in athletes, a 3-4% reduction in hydration leads to a 2% reduction in muscular strength.[94] However, to our knowledge, there are no studies conducted in BCS relating hydration status with handgrip strength. According to Haussinger et al.[151] a cell swelling theory states that cellular shrinkage, leads to catabolism. Because in systemic illness, there is a decrease in ICW, our goal was to see if there was an association between this cell shrinkage and the lack of strength in the population in study. According to Earthman et al.[118] it was observed in HIV patients that a loss of ICW, which reflects BCM loss, can cause a decrease in physical strength and immune function.

So far, investigations with water compartments in breast cancer patients have

58

been related to associations between lymphedema and ECW. One study conducted by Gomes et al.[17] reported that handgrip strength was the same regardless the presence or absence of lymphedema (ECW). Further studies are needed to understand if a decrease in muscle strength of BCS is related to a decrease in ICW.

Loss of function and muscle strength occurs with both disease and malnutrition and it is of major clinical significance.

Data from the current study suggest that phase angle is a predictor of strength assessed by handgrip measured on the right side (Table 3). In a study conducted by Norman et al.[112], significant association between PhA and handgrip strength were also found. Another study[44] conducted in advanced cancer patients found that phase angle was a significant predictor of survival and that lower handgrip strength demonstrated a trend toward shorter survival.

This test is the most reliable, valid and easy to perform within the oncologic setting. Its ability to characterize overall strength has been given the possibility to predict postoperative complications, functional limitations, disabilities and mortality. It has been used as a health-related quality of life in BCS.

A systematic review conducted by Neil-Sztramko et al.[18] pooled grip strength data from 26 studies in BC population and reported that the mean value was 22.8 kg (95% CI 20.6 to 25.1) in women off treatment. Bohannon et al.[52] presents age, gender and side specific reference values for handgrip strength, measured with Jamar and in accordance with the ASHT protocol, derived from a meta-analysis of multinational data. Individual patients whose grip strength is less than the lower limit of the confidence intervals can be considered to be impaired.

In the present study, mean value of the handgrip measured on the right side was 24.90 kg, a value below what is expected based on the mean age of this sample.

These values demonstrate the need to monitor physical function after treatment (as well as during treatment) in order to help health professionals to identify declines and improve functional outcomes.

Physical activity has been used as a therapeutic aid in the treatment of various pathophysiological conditions.[19] It has been found, in healthy populations, decreases in

muscular endurance after only 2 weeks of physical inactivity. In disease, physical inactivity results in more exacerbated reductions.

Findings from a study performed by Schneider et al[19] suggest that moderate-intensity exercise can provide a sufficient physiological stimulus to improve muscular performance in cancer survivors.

One of the findings of the present study was that most of BCS do not engage in enough physical activity programs (MVPA 99.39 ± 118.67 min) not meeting the minimal recommendations for physical activity (150 minutes). This can be one of the causes, besides cancer treatment itself, responsible for the loss of muscular strength. Our findings are in agreement with a study conducted by Holick et al[78] where it was reported that up to 70% of BCS did not meet recommendations of 150 minutes per week of moderate to vigorous intensity PA (e.g. brisk walking, jogging, swimming).

According to Bosetti et al[152], around 50% of patients with cancer have an existing chronic condition and are at increased risk of developing new comorbidities such as heart failure, diabetes, osteoporosis and others, during the survivorship period. This and the fact that most of the BCS do not engage in enough physical activity leads to many other factors such as an increase in body mass, waist circumference and WHR. This variables are associated with several outcomes that can lead to mortality and BC recurrence.[63,66,76,153]

According to some authors, when the BMI is over 25 that person is at increased risk of developing health problems due to abnormal or excessive fat accumulation.[68,71] In the present study, among the 41 women assessed, 26 presented a BMI > 25 kg/m^2, 16 have a WC > 88cm and 25 have a WHR > 0.85. World Health Organization cutoff points of waist circumference and WHR for substantial increased risk of metabolic complications in women are > 88 cm and ≥ 0.85, respectively.[69]

BMI is a number based on a person's weight and height. The higher the number, the more body fat a person has. WC and WHR are variables that correlate with central obesity and are also associated with weight gain,[62,68] specifically fat distribution in the abdominal area.

60

As so, overweight and obesity are associated with low levels of PA which can lead to lower muscle strength.[154] However, in our study, there was no association between MVPA and handgrip strength.

7. Limitations

Despite the encouraging findings of this study, some limitations must be addressed.

Firstly, given the global scale of this disease, our sample (n=41) is small, which does not allow for a generalization of the results. Also, the power to detect any association may be compromised with this current sample size.

Secondly, the sample is not equitable in terms of age. The youngest participant was 36 years old and the oldest was 76 years old, which influences body composition parameters assessed from BIA, such as PhA, as the older the person, the lower the PhA (due to a reduction in reactance which parallels the loss of muscle mass).[110,130] Nevertheless, we adjusted our analysis for age as aconfounder variable between the association of PhA with strength.

Finally, given the cross sectional design this study does not allow a casual effect relationship.

8. Conclusions

Our findings indicate that regardless of age, MVPA and TPO, phase angle was a significant predictor of muscular strength as assessed by the handgrip test. However, water compartments were not associated with muscular strength.

9. Future work

Although there was no relationship found between handgrip and water compartments, namely ICW, in our population, future studies should explore possible associations of cell hydration and strength.

Also, performing a longitudinal study must be of interest in order to understand the behavior of these variables (phase angle, handgrip, ICW and ECW) over time.

It would also be newsworthy to conduct a study comparing BIA related parameters and muscular strength between breast cancer patients (in different stages of BC) and survivors, adjusting for counfonders, since there is no study, to date, that has shown the behavior of these variables according to the stage of the disease, including those that survived.

10. Bibliography

1. American Cancer Society. The History of Cancer. 2014:16. http://www.cancer.org/acs/groups/cid/documents/webcontent/002048-pdf.pdf. Accessed 18/11/2015

2. American Cancer Society. What is Cancer? 2014:43. http://www.cancer.org/acs/groups/cid/documents/webcontent/003086-pdf.pdf. Accessed 18/11/2015.

3. André MR, Amaral S, Mayer A, Miranda A, Group RSW. Breast cancer patients survival and associated factors: reported outcomes from the Southern Cancer Registry in Portugal. *Acta Med Port.* 2014;27(3):325-330.

4. GLOBOCAN 2012: Estimated cancer Incidence, Mortality and Prevalence Worldwide in 2012. In. World Health Organization.

5. Battaglini C, Bottaro M, Dennehy C, et al. The effects of an individualized exercise intervention on body composition in breast cancer patients undergoing treatment. *Sao Paulo Med J.* 2007;125(1):22-28.

6. Battaglini CL, Mills RC, Phillips BL, et al. Twenty-five years of research on the effects of exercise training in breast cancer survivors: A systematic review of the literature. *World J Clin Oncol.* 2014;5(2):177-190.

7. American Cancer Society. Breast Cancer Overview. 2014. Accessed 16/11/2015.

8. Your Guide to the Breast Cancer Pahtology. 2016.

9. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v8-30.

10. Singletary SE, Connolly JL. Breast cancer staging: working with the sixth edition of the AJCC Cancer Staging Manual. *CA Cancer J Clin.* 2006;56(1):37-47; quiz 50-31.

11. Society CC. Understanding Treatment for Breast Cancer: a guide for women. In: cancer.ca: Avon; 2012.

12. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin.* 2006;56(6):323-353.

13.   Kilgour RD, Vigano A, Trutschnigg B, et al. Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer. *J Cachexia Sarcopenia Muscle.* 2010;1(2):177-185.

14.   Winters-Stone KM, Bennett JA, Nail L, Schwartz A. Strength, physical activity, and age predict fatigue in older breast cancer survivors. *Oncol Nurs Forum.* 2008;35(5):815-821.

15.   Cantarero-Villanueva I, Galiano-Castillo N, Fernández-Lao C, et al. The influence of body mass index on survival in breast cancer patients. *Clin Breast Cancer.* 2015;15(2):e117-123.

16.   Hewitt M, Greenfield S, Stoval E. From Cancer Patient to Cancer Survivor. 2006.

17.   Gomes PR, Freitas Junior IF, da Silva CB, et al. Short-term changes in handgrip strength, body composition, and lymphedema induced by breast cancer surgery. *Rev Bras Ginecol Obstet.* 2014;36(6):244-250.

18.   Neil-Sztramko SE, Kirkham AA, Hung SH, Niksirat N, Nishikawa K, Campbell KL. Aerobic capacity and upper limb strength are reduced in women diagnosed with breast cancer: a systematic review. *J Physiother.* 2014;60(4):189-200.

19.   Schneider CM, Hsieh CC, Sprod LK, Carter SD, Hayward R. Cancer treatment-induced alterations in muscular fitness and quality of life: the role of exercise training. *Ann Oncol.* 2007;18(12):1957-1962.

20.   Fong SS, Ng SS, Luk WS, et al. Shoulder Mobility, Muscular Strength, and Quality of Life in Breast Cancer Survivors with and without Tai Chi Qigong Training. *Evid Based Complement Alternat Med.* 2013;2013:787169.

21.   Kärki A, Simonen R, Mälkiä E, Selfe J. Impairments, activity limitations and participation restrictions 6 and 12 months after breast cancer operation. *J Rehabil Med.* 2005;37(3):180-188.

22.   Satariano WA, Ragland DR. Upper-body strength and breast cancer: a comparison of the effects of age and disease. *J Gerontol A Biol Sci Med Sci.* 1996;51(5):M215-219.

23.   Christensen JF, Jones LW, Andersen JL, Daugaard G, Rorth M, Hojman P. Muscle dysfunction in cancer patients. *Ann Oncol.* 2014;25(5):947-958.

24.   Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr.* 2006;84(3):475-482.

25. McDonald C, Bauer J, Capra S, Waterhouse M. Muscle function and omega-3 fatty acids in the prediction of lean body mass after breast cancer treatment. *Springerplus.* 2013;2:681.

26. Harrington S, Padua D, Battaglini C, Michener LA. Upper extremity strength and range of motion and their relationship to function in breast cancer survivors. *Physiother Theory Pract.* 2013;29(7):513-520.

27. Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc.* 2003;51(5):636-641.

28. Winters-Stone KM, Dobek J, Nail L, et al. Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial. *Breast Cancer Res Treat.* 2011;127(2):447-456.

29. Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. *J Cancer Surviv.* 2012;6(2):189-199.

30. Vardar-Yagli N, Sener G, Saglam M, et al. Associations among physical activity, comorbidity, functional capacity, peripheral muscle strength and depression in breast cancer survivors. *Asian Pac J Cancer Prev.* 2015;16(2):585-589.

31. De Backer IC, Van Breda E, Vreugdenhil A, Nijziel MR, Kester AD, Schep G. High-intensity strength training improves quality of life in cancer survivors. *Acta Oncol.* 2007;46(8):1143-1151.

32. Kilgour RD, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care Cancer.* 2013;21(12):3261-3270.

33. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *BMJ.* 2008;337:a439.

34. Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. *Int J Epidemiol.* 2007;36(1):228-235.

35. Norman K, Stobäus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. *Clin Nutr.* 2011;30(2):135-142.

36.   Ortega FB, Silventoinen K, Tynelius P, Rasmussen F. Muscular strength in male adolescents and premature death: cohort study of one million participants. *BMJ.* 2012;345:e7279.

37.   Spruit MA, Sillen MJ, Groenen MT, Wouters EF, Franssen FM. New normative values for handgrip strength: results from the UK Biobank. *J Am Med Dir Assoc.* 2013;14(10):775.e775-711.

38.   Assis MR, Marx AG, Magna LA, Ferrigno IS. Late morbidity in upper limb function and quality of life in women after breast cancer surgery. *Braz J Phys Ther.* 2013;17(3):236-243.

39.   Harrington S, Padua D, Battaglini C, et al. Comparison of shoulder flexibility, strength, and function between breast cancer survivors and healthy participants. *J Cancer Surviv.* 2011;5(2):167-174.

40.   Al Snih S, Markides KS, Ray L, Ostir GV, Goodwin JS. Handgrip strength and mortality in older Mexican Americans. *J Am Geriatr Soc.* 2002;50(7):1250-1256.

41.   Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. *Am J Med.* 2007;120(4):337-342.

42.   Norman K, Stobäus N, Zocher D, et al. Cutoff percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer. *Am J Clin Nutr.* 2010;92(3):612-619.

43.   Rantanen T, Harris T, Leveille SG, et al. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol A Biol Sci Med Sci.* 2000;55(3):M168-173.

44.   Hui D, Bansal S, Morgado M, Dev R, Chisholm G, Bruera E. Phase angle for prognostication of survival in patients with advanced cancer: preliminary findings. *Cancer.* 2014;120(14):2207-2214.

45.   Mendes J, Alves P, Amaral TF. Comparison of nutritional status assessment parameters in predicting length of hospital stay in cancer patients. *Clin Nutr.* 2014;33(3):466-470.

46.   Schlüssel MM, dos Anjos LA, de Vasconcellos MT, Kac G. Reference values of handgrip dynamometry of healthy adults: a population-based study. *Clin Nutr.* 2008;27(4):601-607.

47. Rantanen T MK, He Q, Ross GW, Willcox BJ, White L. Midlife muscle strength and human longevity up to age 100 years: a 44year prospective study among a decent cohort. *Age (Dordr).* 2012;34:564-570.

48. Peolsson A, Hedlund R, Oberg B. Intra- and inter-tester reliability and reference values for hand strength. *J Rehabil Med.* 2001;33(1):36-41.

49. Innes E. Handgrip strength testing: a review of the literature. *Australian Occupational Therapy Journal.* 1999;46:120-140.

50. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. *J Hand Surg Am.* 1984;9(2):222-226.

51. Trutschnigg B, Kilgour RD, Reinglas J, et al. Precision and reliability of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance analysis) measurements in advanced cancer patients. *Appl Physiol Nutr Metab.* 2008;33(6):1232-1239.

52. Bohannon RW PA, Massy-Westropp N,Desrosiers J, Bear-Lehman J. Reference values for adult grip strength measured with a Jamar dynamometer: a descriptive meta-analysis. *Physioterapy.* 2006;92:11-15.

53. Fox KM, Brooks JM, Gandra SR, Markus R, Chiou CF. Estimation of Cachexia among Cancer Patients Based on Four Definitions. *J Oncol.* 2009;2009:693458.

54. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol.* 2013;31(12):1539-1547.

55. Tisdale MJ. Cachexia in cancer patients. *Nat Rev Cancer.* 2002;2(11):862-871.

56. Lundholm K, Bylund AC, Holm J, Scherstén T. Skeletal muscle metabolism in patients with malignant tumor. *Eur J Cancer.* 1976;12(6):465-473.

57. Tisdale MJ. Mechanisms of cancer cachexia. *Physiol Rev.* 2009;89(2):381-410.

58. Acharyya S, Ladner KJ, Nelsen LL, et al. Cancer cachexia is regulated by selective targeting of skeletal muscle gene products. *J Clin Invest.* 2004;114(3):370-378.

59. Poterucha T, Burnette B, Jatoi A. A decline in weight and attrition of muscle in colorectal cancer patients receiving chemotherapy with bevacizumab. *Med Oncol.* 2012;29(2):1005-1009.

60. Tisdale MJ. Are tumoral factors responsible for host tissue wasting in cancer cachexia? *Future Oncol.* 2010;6(4):503-513.

61. Gupta D, Lammersfeld CA, Vashi PG, et al. Bioelectrical impedance phase angle as a prognostic indicator in breast cancer. *BMC Cancer.* 2008;8:249.

62. Arpino G, De Angelis C, Buono G, et al. Metabolic and anthropometric changes in early breast cancer patients receiving adjuvant therapy. *Breast Cancer Res Treat.* 2015;154(1):127-132.

63. Calle EE, Thun MJ. Obesity and cancer. *Oncogene.* 2004;23(38):6365-6378.

64. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol.* 2007;25(28):4396-4404.

65. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. *Cancer Epidemiol Biomarkers Prev.* 2005;14(7):1672-1680.

66. Pacholczak R, Klimek-Piotrowska W, Kuszmiersz P. Associations of anthropometric measures on breast cancer risk in pre- and postmenopausal women-a case-control study. *J Physiol Anthropol.* 2016;35(1):7.

67. World Health Association. Waist Circumference and Waist Hip Ratio: Report of a WHO Expert Consultation. 2008.

68. Amadou A, Hainaut P, Romieu I. Role of obesity in the risk of breast cancer: lessons from anthropometry. *J Oncol.* 2013;2013:906495.

69. Chan DS, Norat T. Obesity and breast cancer: not only a risk factor of the disease. *Curr Treat Options Oncol.* 2015;16(5):22.

70. Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. *Am J Epidemiol.* 1999;150(12):1316-1324.

71. American Cancer Society. Body Weight and Cancer Risk, Excess Body Weight: A Major Health Issue in America. 2015.

72. Lintermans A, Van Asten K, Wildiers H, et al. A prospective assessment of musculoskeletal toxicity and loss of grip strength in breast cancer patients receiving adjuvant aromatase inhibitors and tamoxifen, and relation with BMI. *Breast Cancer Res Treat.* 2014;146(1):109-116.

73. Bradshaw PT, Ibrahim JG, Khankari N, et al. Post-diagnosis physical activity and survival after breast cancer diagnosis: the Long Island Breast Cancer Study. *Breast Cancer Res Treat.* 2014;145(3):735-742.

74. Pinto BM, Floyd A. Methodologic issues in exercise intervention research in oncology. *Semin Oncol Nurs.* 2007;23(4):297-304.

75. Bluethmann SM, Vernon SW, Gabriel KP, Murphy CC, Bartholomew LK. Taking the next step: a systematic review and meta-analysis of physical activity and behavior change interventions in recent post-treatment breast cancer survivors. *Breast Cancer Res Treat.* 2015;149(2):331-342.

76. Balneaves LG, Van Patten C, Truant TL, Kelly MT, Neil SE, Campbell KL. Breast cancer survivors' perspectives on a weight loss and physical activity lifestyle intervention. *Support Care Cancer.* 2014;22(8):2057-2065.

77. Bourke L, Homer KE, Thaha MA, et al. Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. *Br J Cancer.* 2014;110(4):831-841.

78. Phillips SM, Dodd KW, Steeves J, McClain J, Alfano CM, McAuley E. Physical activity and sedentary behavior in breast cancer survivors: New insight into activity patterns and potential intervention targets. *Gynecol Oncol.* 2015;138(2):398-404.

79. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity, risk of death and recurrence in breast cancer survivors: A systematic review and meta-analysis of epidemiological studies. *Acta Oncol.* 2015;54(5):635-654.

80. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2008;17(2):379-386.

81. Chen X, Lu W, Zheng W, et al. Exercise after diagnosis of breast cancer in association with survival. *Cancer Prev Res (Phila).* 2011;4(9):1409-1418.

82. Ibrahim EM, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. *Med Oncol.* 2011;28(3):753-765.

83. Nelson SH, Marinac CR, Patterson RE, et al. Impact of very low physical activity, BMI, and comorbidities on mortality among breast cancer survivors. *Breast Cancer Res Treat.* 2016;155(3):551-557.

84. Saglam M, Arikan H, Savci S, et al. International physical activity questionnaire: reliability and validity of the Turkish version. *Percept Mot Skills.* 2010;111(1):278-284.

85. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. *Int J Behav Nutr Phys Act.* 2011;8:115.

86. Artero EG, Lee DC, Ruiz JR, et al. A prospective study of muscular strength and all-cause mortality in men with hypertension. *J Am Coll Cardiol.* 2011;57(18):1831-1837.

87. Ekelund U, Sepp H, Brage S, et al. Criterion-related validity of the last 7-day, short form of the International Physical Activity Questionnaire in Swedish adults. *Public Health Nutr.* 2006;9(2):258-265.

88. Craig CL, Marshall AL, Sjostrom M, et al. International Physical Activity Questionnaire: 12-Country Reliability and Validity. *Medicine & Science in Sports & Exercise.* 2003:1381-1395.

89. Sawka MN, Coyle EF. Influence of body water and blood volume on thermoregulation and exercise performance in the heat. *Exercise and sport sciences reviews.* 1999;27:167-218.

90. Moore FD, Boyden CM. Body Cell Mass and Limits of Hydration of the Fat-Free Body: Their Relation to Estimated Skeletal Weight. *Annals of the New York Academy of Sciences.* 1963;110:62-71.

91. Katch F, McArdle W. *Water in Nutrition, Weight Control and Exercise.* Boston1977.

92. Matias AC. *Hydrometry and Body Composition: Methods Development and Validation in Athletes*. Faculdade Motricidade Humana: Exercício e Saúde, Universidade de Lisboa; 2013.

93. Dehghan M, Merchant AT. Is bioelectrical impedance accurate for use in large epidemiological studies? *Nutr J.* 2008;7:26.

94. Silva AM, Fields DA, Heymsfield SB, Sardinha LB. Relationship between changes in total-body water and fluid distribution with maximal forearm strength in elite judo athletes. *J Strength Cond Res.* 2011;25(9):2488-2495.

95. Moon JR. Body composition in athletes and sports nutrition: an examination of the bioimpedance analysis technique. *Eur J Clin Nutr.* 2013;67 Suppl 1:S54-59.

96. van Marken Lichtenbelt WD, Westerterp KR, Wouters L, Luijendijk SC. Validation of bioelectrical-impedance measurements as a method to estimate body-water compartments. *Am J Clin Nutr.* 1994;60(2):159-166.

97.   Hayes SC, Janda M, Cornish B, Battistutta D, Newman B. Lymphedema after breast cancer: incidence, risk factors, and effect on upper body function. *J Clin Oncol.* 2008;26(21):3536-3542.

98.   Ridner SH, Bonner CM, Doersam JK, Rhoten BA, Schultze B, Dietrich MS. Bioelectrical impedance self-measurement protocol development and daily variation between healthy volunteers and breast cancer survivors with lymphedema. *Lymphat Res Biol.* 2014;12(1):2-9.

99.   Cornish BH, Chapman M, Hirst C, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. *Lymphology.* 2001;34(1):2-11.

100.   Rockson S. Bioimpedance analysis in the assessment of lymphoedema diagnosis and management. *Journal of lymphoedema.* 2007;2(1):44-48.

101.   Cornish BH, Thomas BJ, Ward LC, Hirst C, Bunce IH. A new technique for the quantification of peripheral edema with application in both unilateral and bilateral cases. *Angiology.* 2002;53(1):41-47.

102.   Baumgartner RN, Chumlea WC, Roche AF. Bioelectric impedance phase angle and body composition. *Am J Clin Nutr.* 1988;48(1):16-23.

103.   Thomasset MA. Bioelectric properties of tissue. Impedance measurement in clinical medicine. Significance of curves obtained. *Lyon Med.* 1962;94:107-118.

104.   Haverkort EB, Reijven PL, Binnekade JM, et al. Bioelectrical impedance analysis to estimate body composition in surgical and oncological patients: a systematic review. *Eur J Clin Nutr.* 2015;69(1):3-13.

105.   Buchholz AC, Bartok C, Schoeller DA. The validity of bioelectrical impedance models in clinical populations. *Nutr Clin Pract.* 2004;19(5):433-446.

106.   Hills A, Byrne N. Bioelectrical impedance and body composition assessment. *Malays J Nutr.* 1998;4(1):107-112.

107.   Gudivaka R, Schoeller DA, Kushner RF, Bolt MJ. Single- and multifrequency models for bioelectrical impedance analysis of body water compartments. *J Appl Physiol (1985).* 1999;87(3):1087-1096.

108.   Cole KS, Cole RH. Dispersion and absorption in dielectrics. *Journal of Chemical Physiology.* 1941;9.

109.   Ellis KJ, Bell SJ, Chertow GM, et al. Bioelectrical impedance methods in clinical research: a follow-up to the NIH Technology Assessment Conference. *Nutrition.* 1999;15(11-12):874-880.

110. Kyle UG, Bosaeus I, De Lorenzo AD, et al. Bioelectrical impedance analysis-part I: review of principles and methods. *Clin Nutr.* 2004;23(5):1226-1243.

111. Kyle UG, Bosaeus I, De Lorenzo AD, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. *Clin Nutr.* 2004;23(6):1430-1453.

112. Norman K, Pirlich M, Sorensen J, et al. Bioimpedance vector analysis as a measure of muscle function. *Clin Nutr.* 2009;28(1):78-82.

113. Matias CN MC, Santos DA, Martins F, Silva AM, Laires MJ, Sardinha LB. Magnesium and phase angle: a prognostic tool for monitoring cellular integrity in judo athletes. 2015;xx(x):1-7.

114. Simons JP, Schols AM, Westerterp KR, ten Velde GP, Wouters EF. The use of bioelectrical impedance analysis to predict total body water in patients with cancer cachexia. *Am J Clin Nutr.* 1995;61(4):741-745.

115. Hannan WJ, Cowen SJ, Plester CE, Fearon KC, deBeau A. Comparison of bio-impedance spectroscopy and multi-frequency bio-impedance analysis for the assessment of extracellular and total body water in surgical patients. *Clin Sci (Lond).* 1995;89(6):651-658.

116. Nwosu AC, Mayland CR, Mason SR, Khodabukus AF, Varro A, Ellershaw JE. Hydration in advanced cancer: can bioelectrical impedance analysis improve the evidence base? A systematic review of the literature. *J Pain Symptom Manage.* 2013;46(3):433-446.e436.

117. Hanai T. Electrical properties of emulsions. In: Sherman P, ed. *Emulsion Science.* New York: Academic Press; 1968:354-477.

118. Earthman C, Traughber D, Dobratz J, Howell W. Bioimpedance spectroscopy for clinical assessment of fluid distribution and body cell mass. *Nutr Clin Pract.* 2007;22(4):389-405.

119. Matthie J, Zarowitz B, De Lorenzo A, et al. Analytic assessment of the various bioimpedance methods used to estimate body water. *J Appl Physiol (1985).* 1998;84(5):1801-1816.

120. Moon JR, Smith AE, Tobkin SE, et al. Total body water changes after an exercise intervention tracked using bioimpedance spectroscopy: a deuterium oxide comparison. *Clin Nutr.* 2009;28(5):516-525.

121. Chumlea WCaS, S.S. *Bioelectrical Impedance Analysis in Human Body Composition.* Human Kinetics: Champaign, IL2005.

122. Matthie JR, Withers P. Impedance measurements of body-water compartments. *Am J Clin Nutr.* 1995;61(5):1167-1169.

123. Xitron Technologies. Hydra ECF/ICF Model 4200 Operating Manual. 2007.

124. Xitron Technologies. 4000B Bio-impedance spectrum analyzert system Operating Manual. 2002.

125. Fein PA, Gundumalla G, Jorden A, Matza B, Chattopadhyay J, Avram MM. Usefulness of bioelectrical impedance analysis in monitoring nutrition status and survival of peritoneal dialysis patients. *Adv Perit Dial.* 2002;18:195-199.

126. Desport JC, Preux PM, Bouteloup-Demange C, et al. Validation of bioelectrical impedance analysis in patients with amyotrophic lateral sclerosis. *Am J Clin Nutr.* 2003;77(5):1179-1185.

127. Pencharz PB, Azcue M. Use of bioelectrical impedance analysis measurements in the clinical management of malnutrition. *Am J Clin Nutr.* 1996;64(3 Suppl):485S-488S.

128. Fredrix EW, Saris WH, Soeters PB, et al. Estimation of body composition by bioelectrical impedance in cancer patients. *Eur J Clin Nutr.* 1990;44(10):749-752.

129. Stobäus N, Pirlich M, Valentini L, Schulzke JD, Norman K. Determinants of bioelectrical phase angle in disease. *Br J Nutr.* 2012;107(8):1217-1220.

130. Norman K, Stobaus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. *Clin Nutr.* 2012;31(6):854-861.

131. Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN, Jr. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. *Am J Clin Nutr.* 2005;82(1):49-52.

132. Bosy-Westphal A, Danielzik S, Dorhofer RP, Later W, Wiese S, Muller MJ. Phase angle from bioelectrical impedance analysis: population reference values by age, sex, and body mass index. *JPEN J Parenter Enteral Nutr.* 2006;30(4):309-316.

133. Castanho IA, Lopes AJ, Koury JC, Tessarollo B, Silva AC, Nunes RA. Relationship between the phase angle and volume of tumours in patients with lung cancer. *Ann Nutr Metab.* 2013;62(1):68-74.

134. Gupta D, Lammersfeld CA, Vashi PG, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in stage IIIB and IV non-small cell lung cancer. *BMC Cancer.* 2009;9:37.

135. Kyle UG, Genton L, Pichard C. Low phase angle determined by bioelectrical impedance analysis is associated with malnutrition and nutritional risk at hospital admission. *Clin Nutr.* 2013;32(2):294-299.

136. Selberg O, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. *Eur J Appl Physiol.* 2002;86(6):509-516.

137. Schwenk A, Beisenherz A, Römer K, Kremer G, Salzberger B, Elia M. Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment. *Am J Clin Nutr.* 2000;72(2):496-501.

138. Kyle UG, Soundar EP, Genton L, Pichard C. Can phase angle determined by bioelectrical impedance analysis assess nutritional risk? A comparison between healthy and hospitalized subjects. *Clin Nutr.* 2012;31(6):875-881.

139. Lee SY, Lee YJ, Yang JH, Kim CM, Choi WS. The Association between Phase Angle of Bioelectrical Impedance Analysis and Survival Time in Advanced Cancer Patients: Preliminary Study. *Korean J Fam Med.* 2014;35(5):251-256.

140. Gupta D, Lis CG, Dahlk SL, et al. The relationship between bioelectrical impedance phase angle and subjective global assessment in advanced colorectal cancer. *Nutr J.* 2008;7:19.

141. Velthuis MJ, May AM, Koppejan-Rensenbrink RA, et al. Physical Activity during Cancer Treatment (PACT) Study: design of a randomised clinical trial. *BMC Cancer.* 2010;10:272.

142. Charlier C. *Understanding and promoting physical activity in breast cancer survivors*. Heerlen: phsycology, Open University; 2012.

143. Ortega FB, Ruiz JR, Castillo MJ, et al. [Low level of physical fitness in Spanish adolescents. Relevance for future cardiovascular health (AVENA study)]. *Rev Esp Cardiol.* 2005;58(8):898-909.

144. Fujita Y, Nakamura Y, Hiraoka J, et al. Physical-strength tests and mortality among visitors to health-promotion centers in Japan. *J Clin Epidemiol.* 1995;48(11):1349-1359.

145. Katzmarzyk PT, Craig CL. Musculoskeletal fitness and risk of mortality. *Med Sci Sports Exerc.* 2002;34(5):740-744.

146. Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med Sci.* 2002;57(10):B359-365.

147. Małecka-Massalska T, Chara K, Gołębiowski P, et al. Altered tissue electrical properties in women with breast cancer--preliminary observations. *Ann Agric Environ Med.* 2013;20(3):523-527.

148. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310(20):2191-2194.

149. Lohman TG, Roche AF, Martorell R. *Antrophometric standardization reference manual.* 3-8 ed. Champaign, IL.: Human Kinetics Publishers; 1988.

150. Mortimer PS. The pathophysiology of lymphedema. *Cancer.* 1998;83(12 Suppl American):2798-2802.

151. Häussinger D, Roth E, Lang F, Gerok W. Cellular hydration state: an important determinant of protein catabolism in health and disease. *Lancet.* 1993;341(8856):1330-1332.

152. Bosetti C, Bertuccio P, Levi F, Chatenoud L, Negri E, La Vecchia C. The decline in breast cancer mortality in Europe: an update (to 2009). *Breast.* 2012;21(1):77-82.

153. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. *J Clin Oncol.* 2005;23(7):1370-1378.

154. Hulens M, Vansant G, Lysens R, Claessens AL, Muls E, Brumagne S. Study of differences in peripheral muscle strength of lean versus obese women: an allometric approach. *Int J Obes Relat Metab Disord.* 2001;25(5):676-681.