DETERMINANTS OF EMOTIONAL DISTRESS IN BREAST CANCER SURVIVORS

BY

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A Dissertation submitted to the

Graduate School- Newark

Rutgers, The State University of New Jersey

In Partial fulfillment of the requirements

For the degree of

Doctor of Nursing

Graduate Program in

Written under the direction of

Charlotte Thomas-Hawkins

and approved by

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Newark, New Jersey

January 2020

ABSTRACT OF THE DISSERTATION

Determinants of Emotional Distress in Breast Cancer Survivors

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Rationale: There is no consensus regarding the definition and quantification of lymphedema. Moreover, most studies in breast cancer related lymphedema (BCRL) did not include lymphedema symptoms and its effect on outcome. Therefore, the results from the studies in BCRL have presented a wide gap in the findings. Moreover, despite its importance for health outcomes, there is a paucity of studies that have examined emotional distress (ED) over time in women with BCRL and little is known of the pattern of ED over time.

Study Purpose: This study aimed to identify and further understand the determinants of ED in breast cancer survivors.

Methods: This is a secondary analysis of de-identified data collected prospectively from 140 women who were diagnosed with breast cancer between December 2011 and April 2014.The inclusion criteria were women aged 21 years and over who were diagnosed with a first-time diagnosis of stage 1-III breast cancer and were scheduled for surgical treatment. Lymph volume was measured by the perometer, and 26 lymphedema symptoms and 12 ED symptoms were collected via the Breast Cancer & Lymphedema Symptom Experience (BCLE-SEI) instrument at pre surgery, four to eight weeks and 12 weeks post surgery.

Results: The level of ED over time did not decline spontaneously, but increased 12

months after surgical treatment. Situational factors examined were not associated. Two physiological factors, BMI and lymph volume were significantly associated with ED post-surgery. Lymphedema symptom intensity was significantly associated with ED post-surgery. A lymph volume increase of ≥ 5 % (*OR*= 3.9, 95 % *CI*; 1.469-10.452) and a high level of lymphedema symptom intensity score ≥ 9 (*OR*=8.7, 95 % *CI*; 3.362-22.356) were independently associated with a likelihood of high ED 12 months post-surgery in an adjusted model.

Conclusion: The findings from this study offer clinically relevant evidence-based knowledge regarding lymphedema, lymphedema symptoms and ED symptoms to inform the health care professionals to improve of the care in breast cancer survivors. The results can be used to assist in the early detection and assessment of ED and lymphedema symptoms in either the absence or presence of lymphedema in breast cancer survivors.

Dedication

I dedicate my dissertation work to my family. This journey would not be possible without of their support. A special thanks to my late parents, Youngsun and Jungae Suh, who encouraged me to pursue a career in nursing and my doctoral degree. Also, I dedicate my dissertation work to my husband, Yosik Chu, who has been a constant source of encouragement and support during the school, work and family life. I also dedicate this work to my sons, Bryan, James and Paul, and their families, who made me stronger, better and more fulfilled than ever I could dream of.

Acknowledgment

I am forever grateful to my PhD advisor and the committee chair, Dr. Charlotte Thomas-Hawkins for her endless time and dedication who helped me to think as a researcher.

To Dr. Mei, R. Fu, who is inspirational and a role model, who provided me such a valuable database for the analyses. Her expertise, support, and energy were most valuable in my dissertation work. I only can hope I can be as energetic and enthusiastic as she is.

To Dr. Gary Yu, who is an expert biostatistician. He made the analyses of the data fun and exciting.

To my committee members, Dr. Linda Flynn and Dr. Rita Musanti, each of you have given your time, expertise and guidance. I owe both of you a debt of gratitude.

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CHAPTER 1

The Problem

Recent medical advances in cancer treatments have made a tremendous contribution to longer survivals and fewer side effects in persons with cancer. While the improvements in treatment of cancer have made a long-term, disease-free survival possible, there has been a lack of attention paid to the nature of survivorships of cancer patients until recently. A recent study revealed that one in three persons (32%) with cancer experiences anxiety, depression, or feelings of stress or distress (Mehnert et al., 2014). In fact, cancer survivors often deal with a number of emotions and psychological responses during treatment and even long after cancer treatment is complete (Stanton et al., 2015). Often, a diagnosis of cancer requires a significant adaptive change for most survivors, particularly after diagnosis and at the end of treatment. Patients have difficulty coping with their cancer at diagnosis. Further, at the end of cancer treatment, they are often concerned with post treatment complications and the ever-present possibility of cancer recurrence (Koch et al., 2012). Yet, little is known of the pattern of emotional distress (ED) over time in persons with cancer, particularly in women who experience symptoms of lymphedema and who are at risk for lymphedema following treatment for breast cancer.

ED in Breast Cancer

Breast cancer is the most common type of cancer and the second leading cause of cancer death among women in the United States (U.S) (Centers for Disease Control and Prevention [CDC], 2018). Each year in the U.S., more than 237,000 women are diagnosed with breast cancer and more than 4,100 women die from it (CDC, 2018).

According to the American Cancer Society (ACS), about 3.1 million women residing in the U.S. are breast cancer survivors (ACS, 2018). Among the 3.1 breast cancer survivors, about 40% of them have lymphedema and the rest are at life-time risk for lymphedema (Fu et al., 2013). Successful adjustment to breast cancer includes managing ED. Although breast cancer patients may experience positive emotions, such as hope and gratitude, they may have more difficulty with negative emotions, including anxiety, sadness, anger, guilt, and fear. While these emotions can be common reactions to the illness process, negative emotions may be elicited by symptoms due to treatment side effects and ongoing symptoms because of the presence of cancer-related secondary chronic illnesses such as lymphedema or chronic pain syndrome.

ED describes what people feel when they are under mental, physical, or emotional pressure (National Cancer Institute [NCI], 2017). The prevalence of ED among cancer survivors is high. Approximately 20% to 40% of women with breast cancer experience negative emotional outcomes (Hewitt et al., 2004). Several risk factors for ED in cancer survivors have been identified such as age (Dominick et al., 2014), stage of cancer (Clough-Gorr et al., 2010), type of surgical intervention (Al-Ghazal et al., 2000), adjuvant chemotherapy (Kahn et al., 2012), perception of body image (Radina et al., 2008), lymphedema (Dominick et al., 2014), and pain and impaired mobility of the affected area (Dominick et al., 2014; Kahn et al., 2012).

Lymphedema and Breast Cancer

The incidence of breast cancer related lymphedema (BCRL) remains unclear due to a lack of a clear definition of this phenomenon, resulting in differences in diagnostic criteria. However, it is estimated that 8% to 56% of breast cancer survivors will develop

lymphedema (Norman et al., 2010; Kwan et al., 2010; Paskett, 2007; Shah, & Vinci, 2011), one of the most common complications among these individuals (Ezzo et al., 2015). BCRL may range from being mild, especially in the early stages, to a serious disabling condition and generally presents as a syndrome of abnormal swelling and multiple distressing symptoms (e.g., heaviness, tightness, firmness, aching or pain, numbness, stiffness, or impaired limb mobility) (Comier et al., 2010; Fu & Rosedale, 2009; Fu et al., 2010). Distressful lymphedema symptoms are often associated with lymph volume accumulation (Fu et al., 2016). Yet, the definition of lymphedema in breast cancer patients has not been standardized and remains a challenge in research and clinical practice (Fu et al., 2016). Traditionally, lymphedema has been diagnosed by healthcare providers' observations of swelling in the ipsilateral arm. In research, lymphedema assessments are operationalized in multiple ways including self-report, increases in limb girth, increases in limb volume, or bio-impedance ratio (Tsai et al., 2009). As such, there are consistent discrepancies in types of lymphedema measurement techniques and quantification among published reports (Armer & Stewart, 2005; Cormier et al., 2010; Fu et al, 2016; Ridner et al., 2012), making the comparison, interpretation, and generalizability of lymphedema data across studies difficult. Moreover, many researches support that an objective lymphedema measure, such as a 2 cm difference in arm circumference, can be arbitrary as 1) it does not include patient perception; or 2) does not take the functional impairment or symptoms (e.g., pain) into consideration (Fu et al., 2015[a]; Fu et al., 2016). Research reports clearly illustrate that only addressing lymphedema arm volume without managing other lymphedema-related symptoms may not be adequate (Fu et al., 2015 [a]; Oliveri et al., 2014).

Lymph Volume, Lymphedema Symptoms, and ED Over Time

Lymph volume and lymphedema related symptoms may be the factors most associated with increased ED and poorer quality of life among breast cancer survivors with this complication. Lymphedema symptoms can comprise visible lymphedema signs (i.e., enlarged limb, swelling, skin changes) (Fu, & Rosedale, 2009; Ridner et al., 2012) and subjective lymphedema symptoms (i.e., pain, heaviness of the arm/hand, firmness, tightness of the skin, tingling and/or weakness of the arm and/or hand, increased skin temperature of the affected area, fibrosis, arm fatigue) (Chachaj et al., 2010; Fu et al., 2016; Fu & Rosedale, 2009). Importantly, breast cancer survivors without traditionally defined lymphedema, as measured by an increase in limb volume, can also experience physical symptoms such as pain, numbness, tingling sensation, or impaired mobility (Fu et al., 2008). More importantly, lymphedema symptoms may indicate an early stage of lymphedema in which changes cannot be detected by current objective measures of limb volume. Most studies in breast cancer survivors with lymphedema only include lymph volume as a contributing factor to negative physical, social, and emotional outcomes, ignoring the impact of lymphedema symptoms on these outcomes (Fu et el, 2015[b]; Fu et al, 2016). Hence, it is important to include lymphedema symptoms in the study of lymphedema among breast cancer survivors.

Lymphedema symptoms can have a negative effect on physical and psychosocial functioning (Teo et al., 2015) and may lead to ED in breast cancer survivors. For example, findings from several studies reported significant associations between increased lymph volume, lymphedema symptoms, and reductions in physical, functional and emotional wellbeing (Chachaj et al., 2010; Fu et al., 2014; Kahn et al., 2012;

O'Toole et al., 2015; Shah et al., 2013). On the other hand, findings from other empirical studies in breast cancer survivors with and without lymphedema revealed no statistically significant differences in ED outcomes between the two groups (Oliveri et al., 2008; Vassard et al., 2010). These equivocal findings point to a need to gain a further understanding of the nature of the associations between lymph volume, lymphedema symptoms, and ED in women with breast cancer.

The characteristics of distress, including ED, in breast cancer survivors may change over time as these women live through diagnosis, treatment, treatment recovery, and into the years thereafter. Thus, there is a need to understand the nature of ED over time in breast cancer survivors with lymphedema. In addition, associations between lymphedema symptoms and ED in the context of trajectory over time are essential in breast cancer survivorship research. One to three months following cancer treatment is a transition period characterized by disruption and increased distress (Montazari et al., 2008). Generally physical functioning improves in a year post treatment and substantially by two to eight years after the treatment is completed (Burgess et al., 2005; Neyt & Albrecht, 2006). However, breast cancer survivors with lymphedema may continue to experience ED over time (Ahmed et al., 2008; Liu et al., 2014). Breast cancer survivors with lymphedema experience anxiety and depression typically at high levels at the time of cancer diagnosis, which is directly focused on coping with cancer diagnosis and treatment related matters (Epping- Jordan et al., 1999; Liu et al., 2014). However, for some patients, these symptoms may persist over periods of months or years subsequent to initial diagnosis and treatment. Breast cancer survivors with lymphedema may experience depression, hopelessness, helplessness, body image changes, and perceived disability

(Chachaj et al., 2010; Fu & Rosedale, 2009; Fu et al., 2013; Maxeiner et al., 2009; Oliveri et al., 2008; Woods, 1993). These experiences stem from the real potential that life will not go back to the way it was before the cancer diagnosis; that lymphedema is not curable; and that losses of function, independence and role changes are irreversible. Cross-sectional studies lack the ability to detect developments or changes in the characteristics of the target population over time. Current studies in women with breast cancer have not captured the pattern of emotional decline or improvements over time among breast cancer survivors with lymphedema. Moreover, the extent to which lymph volume and lymphedema symptoms explain variations in ED in breast cancer survivors has not been well studied.

Personal Factors and ED

Several personal factors may increase the risk for high levels of ED in breast cancer patients. For instance, younger age (Kahn et al., 2012; Mosher & Danoff-Burg, 2005), level of education (Vassard et al., 2010), marital status (Dominick et al., 2014), and obesity (Fu et al., 2015[a]; Vassard et al., 2010) have been reported as influencing factors on ED among patients with breast cancer. However, these findings are equivocal across studies in BCRL (Andreu et al., 2011). This gap may be due to the inconsistency of measuring lymph volume and establishing the diagnosis of lymphedema using a standardized method (Andreu et al., 2011). In addition, there is a dearth of longitudinal studies that follow newly diagnosed women to capture the incidence of lymphedema and determine the influencing factors over time. Hence, little is known of the extent to which factors predict initial ED in the post-treatment period and beyond. Specifically, the pattern of emotional change over time in breast cancer survivors with lymphedema is not

well understood and remains uncertain.

In summary, there is a gap in knowledge regarding the conceptualization and assessment of lymphedema and its symptoms in women with breast cancer over time, as well as the interrelationships among lymph volume, lymphedema symptoms and ED over time in these women. This may be due to; 1) inconsistency in defining lymphedema; 2) ignoring the lymphedema symptoms in the study of breast cancer survivors at risk for and with lymphedema (Fu & Yang, 2013); 3) a lack of using of a specific psychometric instrument for BCRL to study the phenomena for this population; and 4) the lack of longitudinal study designs that assess the distress over time. The proposed study is designed to address these limitations through a validated lymphedema measure, to assess lymphedema, lymphedema symptoms, and ED over time, and to examine the interrelationships among personal factors, lymph volume,-lymphedema symptoms, and ED over time in breast cancer survivors.

Purpose of the Study

The purpose of the study is to examine the determinants affecting ED in breast cancer survivors including symptoms related to lymphedema during the first year of cancer treatment. This study addressed the current gaps in the literature in a longitudinal study of women who have completed primary treatment for breast cancer. This study is intended to answer the following questions: In women, who have had breast cancer surgery,

a. What is the pattern over time of ED for women with breast cancer in the first year of cancer treatment?

b. What is the pattern over time of lymphedema symptoms for women with breast cancer in the first year of cancer treatment?
c. What is the pattern over time of lymph volume for women with breast cancer in the first year of cancer treatment?
d. What are the determinants or influencing factors for ED in the first year of cancer treatment?
    i. Are physiological factors (Body Mass Index [BMI], lymph volume, age impact ED in the first year of cancer treatment (*i.e.,* four to eight weeks and 12 months post-surgery)?
    ii. Are treatment or situational factors (marital status, level of education, type of surgery, type of therapy) associated with ED in the first year of cancer treatment (*i.e.,* four to eight weeks and 12 months post-surgery)?
e. Are influencing factors associated with lymphedema symptoms in the first year of cancer treatment (*i.e*., four to eight weeks and 12 months post-surgery)?
f. Are lymphedema symptoms associated with ED in the first year of cancer treatment (*i.e*., four to eight weeks and 12 months post-surgery)?

Significance of the Study

Over the past years, ED has gained importance in the evaluation of the patient-centered health outcomes among breast cancer survivors. ED in persons with BCRL is associated with negative health outcomes including reductions in physical and psychosocial functioning and overall quality of life. Despite its importance for health

outcomes in women with BCRL, there is a paucity of studies that have examined ED over time in women with BCRL. This gap in knowledge contributes to an incomplete understanding of the trend or trajectory of distress over time that breast cancer survivors who have received surgical treatment. , there is an absence of research that has examined interrelationships among lymph volume, lymphedema symptoms, personal factors and ED in the first year after women have had surgery for breast cancer. The proposed study addressed these gaps in knowledge.

CHAPTER 2

Review of The Literature

This chapter presents a discussion of the theoretical framework that guides this study and a synthesis and analysis of empirical literatures as it relates to ED in breast cancer survivors with lymphedema. The theoretical discussion in this chapter provides an overview of the Theory of Unpleasant Symptoms (TOUS), and its theoretical constructs that are postulated to associate with ED in breast cancer survivors with lymphedema. Following a discussion of the TOUS, a review of empirical literature in support of proposed relationships among these concepts is presented. The first section of the literature review presents a synthesis of empirical literature focused on ED in breast cancer including an analysis of studies that describe ED, variations in conceptualizations of ED as well as studies that provide empirical support for theorized relationships between situational and physiological influencing factors and ED in breast cancer survivors. The second section of the literature review presents studies that examine the lymphedema symptoms in breast cancer and analysis of studies that describe the interrelationships among lymphedema, lymphedema related symptoms and ED in female

breast cancer survivors. The third section presents a discussion of gaps in the literature to support the logic and plausibility of proposed relationships to be tested. The final section presents study hypotheses and theoretical and operational definitions.

Theoretical Framework

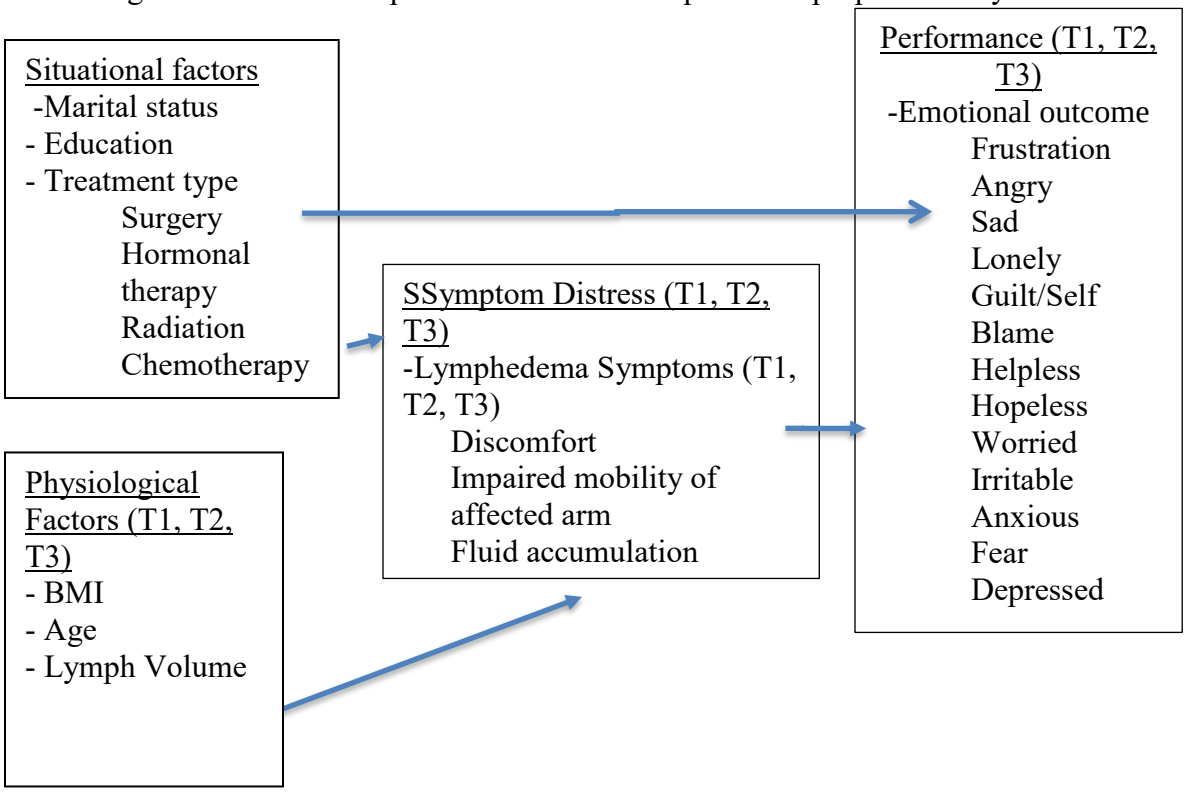
Theory of Unpleasant Symptoms (TOUS)

The TOUS is a middle-range theory that has three main components: the symptoms that an individual is experiencing, influencing factors that affect the nature of the symptom experience, and the consequences of symptom experience (Lenz et al.,1997). According to the TOUS (Lenz et al., 1997), symptoms have measurable dimensions: intensity, timing, distress and quality and may precede, lead to other symptoms, cluster together, reinforce each other, and influence outcomes. According to Lenz et al. (1997), symptoms are influenced by antecedent factors that are physiological, psychological and situational. Physiological antecedents are the normal or abnormal functions of bodily systems that may include age, dysfunction, physiological or anatomical abnormalities, comorbidities, abnormal lab values, stages or severity of illness (Lenz, & Pugh, 2003). Psychological factors may include mood or emotional state, response to illness, perceived uncertainty, and the meaning ascribed to the symptoms by the individual (Lenz, & Pugh, 2003). Situational factors refer to social and physical environment that may influence the experience and the reporting of symptoms including social support, marital status, occupation, ethnicity, family and work demand, medicine, treatment and available resources (Lenz, & Pugh, 2003). These factors are interactive and reciprocal as they relate to one another. Symptoms have a resultant effect on patient outcomes and performance that, in turn, have a reciprocal effect on both symptom

experience and antecedent factors (Lenz, & Pugh, 2003; Motl et al., 2009). Supported with theoretical perspectives of unpleasant symptoms, examining the emotional outcome in breast cancer survivors with lymphedema provides a theoretical basis for understanding the interrelationships between physiological factors, situational factors, unpleasant symptoms, and ED in female breast cancer survivors.

In summary, there is a gap in knowledge regarding the conceptualization and assessment of lymph volume and lymphedema symptoms in female survivors of breast cancer, as well as emotional outcomes in these women. The TOUS is a useful framework to understand how lymph volume, lymphedema symptoms and physiological and situational factors influence emotional outcome in breast cancer survivors with lymphedema over time. The theoretical relational propositions that was tested in this current study are depicted in Figure 1.

Figure 1. TOUS concepts and interrelationships for the proposed study



Literature Review

In order to understand the gap of the current knowledge in this population, the first section presents a review of empirical literature focused on ED in breast cancer survivors. The second section presents a review of empirical literature focused on associations between lymphedema symptoms and ED in patients with breast cancer. The third section presents a summary of the literature review and current knowledge gaps. The final section presents hypotheses for the proposed study.

ED in Breast Cancer Survivors

In this section, a synthesis and analysis of empirical literature that describes the prevalence ED in breast cancer, variations in the conceptualizations of ED in this population, and the associations between physiological and situational influencing factors and ED in breast cancer is presented. The literature search was delimited to studies published in the past twelve years that examined ED in samples of persons with breast cancer. The following search terms were used: breast cancer, emotional, mental, depression, psychological, quality of life, fear, and anxiety. Eleven exemplar studies are reviewed. For each study, author (s), title of study, design, sample characteristics, the instruments relevant to the proposed study, and relevant study findings are summarized in Table 1. First, the prevalence of ED in breast cancer survivors is presented. Second, the review of empirical literature focused on variations in the conceptualization of ED in breast cancer survivors is presented. Lastly, a synthesis of studies that provide empirical support for relationships between the influencing factors and ED in breast cancer survivors is presented.

Prevalence of ED

One aim of the proposed study is to examine the prevalence and patterns of ED over time in women with breast cancer. Emotions in patients with breast cancer change over time as they move through diagnosis to treatment to recovery. While cross-sectional studies revealed that 16% to 88% of women experience ED or impaired psychological wellbeing after cancer diagnosis or during treatment (Dominick et al., 2014;Kahn et al., 2012; Oliveri et al., 2008; pyszel et al., 2006; Schubart et al., 2014), the longitudinal studies reviewed offer some insight into changes in ED experiences over time in breast cancer survivors (Andreu et al., 2011; Clough-Gorr et al., 2010; Costa-Requena et al., 2013; Ng et al. 2017; Paskett et al., 2007; Vasard et al., 2010). Most breast cancer survivors reported that they experienced high levels of ED during the course of illness from diagnosis to treatment and thereafter (Andreu et al., 2011). Woman with breast cancer generally experience improvement of emotional wellbeing as they carry their lives further away from the diagnosis and the treatment experience (Ng et. al, 2017; Vassard et al., 2010). For example, in a longitudinal study (Ng et al., 2017), the percent of women who experienced psychological distress was high at diagnosis (50%) and 6 months later (51%), but declined somewhat one year after diagnosis (40%). However, there is a subset of woman who experience declines of ED over time. Little is known about the long-term negative emotional outcomes in these women and situational and physiological factors that influence their decline in ED over time (Kahn, et al., 2012; Ng et. al, 2017). The proposed study aims to address this gap in knowledge.

Variations in Conceptualization of ED.

The conceptualization and measurement of ED varied considerably across the studies. Emotional responses in the studies reviewed were represented largely as

depression and anxiety (Costa-Requena et al., 2013; Kahn et al., 2012; Schubart et al., 2014). However, other emotional responses assessed were anger (Schubart et al., 2014), stress (Kahn et al., 2012), emotional well-being (Costa-Requena et al., 2013), worry, sadness, fear, hopelessness and helplessness (Kahn et al., 2012; Schubart et al., 2014). These studies suggest that there is a variation of emotions over time among breast cancer survivors during the illness continuum. As ED in cancer patients encompasses a spectrum of emotions from sadness, fear, worry, hopelessness, depression, angry, frustration, guilt, helplessness, irritation, and loneliness to anxiety (Fu et al, 2013), it is important to pay attention to the variability of the different types of emotions over time and to accurately measure and quantify this variation. The proposed study addressed this knowledge gap.

Influencing factors and ED

Physiological Influencing Factors.

Lymph volume. Lymph volume is theorized as a physiological influencing factor associated with ED in the proposed study. Lymphedema is a condition of localized swelling caused by fluid collection due to an interrupted lymphatic flow. Several different methods have been used to measure lymph volume including absolute circumference change > 2 cm, absolute lymph volume difference > 10%, and relative lymph volume change > 10% (Taghian et al., 2014). The bio-impedance spectroscopy (BIS) measurement system represents an objective evaluation of lymph volume with a lesser degree of operator variability than other techniques and has been found to provide valid measurements (Fu et al., 2009; Stanton et al., 2015). Seven (Clough-Gorr et al., 2010; Dominick, et al., 2014; Kahn et al., 2012; Oliveri et al., 2008; Paskett et al., 2007; Pyszel et al., 2006; Vassard et al., 2010) of the eleven studies evaluated associations

between lymphedema and ED among breast cancer survivors. In the seven studies, only self-reports of lymphedema were used, and none employed objective measurements of lymphedema.

An aim of the proposed study is to examine the pattern of lymphedema over time in women with breast cancer. Of the eleven studies reviewed, only two studies assessed the trajectory of lymphedema over time (Oliveri et al., 2008; Paskett et al., 2007). In one study, 54% of study participants reported having arm swelling at 3 years after surgery (Paskett et al., 2007). Of those, 20 % noted the onset during the first six months after surgery, and 36 % had lymphedema by one year after surgery. Seventy percent of the cases of swelling were reported as being mild, 25% were moderate, and 5% reported severe swelling. The median time to swelling was 26 months after surgery. In the second study, Oliveri et al. (2008) examined arm and hand swelling in cross sectional design (range 9–16 years post-diagnosis) and reported 55% of the women noticed their first episode of swelling within 2 years since surgery for breast cancer. Of those, 76% reported they were currently experiencing swelling. While 51% of the women described their swelling as mild, 37% described their swelling as moderate, and 9% reported severe swelling. Lymphedema is a chronic progressive condition and a subgroup of patients experiences a severe persistent swelling (Oliveri et al., 2008). These findings of the studies suggest that, in addition to the presence of lymphedema, severity of lymphedema needs to be taken into consideration in the study of BCRL.

Of the eleven studies reviewed, seven studies examined the relationship between lymphedema and emotional outcomes (Clough-Gorr et al., 2010; Dominick et al., 2014; Kahn et al., 2012; Oliveri et al., 2008; Paskett et al., 2007; Pyszel et al., 2006; Vassard et

al., 2010). The types of emotional outcomes assessed were different across the studies and included assessments of emotional/psychological wellbeing (Paskett et al., 2007), depression, anxiety, mental functioning, and mood (Clough-Gorr et al., 2010; Dominick et al., 2014; Kahn et al., 2012; Oliveri et al., 2008; Vassard et al., 2010). Findings from five studies revealed that women with lymphedema report poorer emotional outcome compared with woman without lymphedema (Clough-Gorr et al., 2010; Dominick et al., 2014; Kahn et al., 2012; Paskett et al., 2007; Pyszel et al., 2006). In contrast, Oliveri et al. (2008) found no statistically significant difference in the level of depression or anxiety between woman with and without lymphedema. Similarly, Vassard et al. (2010) found no significant difference in mood disturbance between woman with and without lymphedema. While most studies reviewed revealed significant associations between lymphedema and poorer emotional outcomes, the studies did not explore the relationship between specific characteristics or severity of lymphedema and emotional outcomes in women with breast cancer. Moreover, the effects of persistent lymphedema over time on variations in emotional outcomes in women with breast cancer were not examined in the studies reviewed.

BMI. BMI is theorized as a physiological influencing factor in the proposed study. Obesity defined by BMI more than 30 kg/m^2 is one of the established risk factors for breast cancer occurrence and recurrence (World Health Organization [WHO], 2014) and has been reported that it affects disease free survival in patients with breast cancer (Chen et al, 2010). Moreover, obesity has been reported as a risk factor for developing post- operative BCRL (Fu et al., 2015[a]; Helyer et al., 2010). Additionally, the studies have shown a positive relationship between depression and obesity (Helyer et al., 2010;

Istvan et al, 1992; Woo, & Ho, 2001). Three (Dominick et al., 2014; Pyszel et al., 2006; Vasard et al., 2010) of the eleven studies reviewed examined BMI as a risk factor for poorer emotional or mental outcome in patients with breast cancer. Dominick et al. (2014) reported a BMI ≥30 kg/m^2 was significantly associated with poor mental health (p <. 001), but did not find a significant association with depressive symptoms (p = 0.23). On the other hand, Pysezel et al. (2006) and Vasard et al. (2010) reported BMI was significantly associated with emotional functioning (p =. 001), psychological health (p=<. 01) and mood and disturbance (p = .01).

Age. Age is theorized as a physiological influencing factor in the proposed study. Two studies reported age was not associated emotional outcome in breast cancer survivors ***(***Andreu et al., 2011; Costa-Requena et al., 2013). In contrast, four studies reported a significant association between younger age and poorer psychological wellbeing (Kahn et al., 2012), distress, anxiety, depression, anger (Schubart et al., 2010), depressive symptoms (Dominick et al., 2014), and lower psychological health (Vassard et al., 2010).

Situational influencing factors.

***Surgery*.** Surgery type is theorized as a situational influencing factor in the proposed study. Patients with breast cancer stage I to III undergo surgery. The types of surgery and recommendations are dependent upon the biology and the extent of breast cancer cells. Associations between surgery type and emotional outcomes were examined in three of the eleven exemplar studies, and the findings were contradictory across the studies. In one longitudinal study of breast cancer survivors (Andreu et al., 2011), psychological distress was highest at the time of surgery compared to other time points

including pre-surgery preliminary diagnosis, post-surgery definitive diagnosis, and treatment. Surgery type (lumpectomy v. mastectomy) was significantly associated with psychological distress in one study (Schubart et al., 2014) but unrelated to distress in another study (Kahn et al., 2012).

Chemotherapy, radiation therapy and hormonal therapy are theorized as situational influencing factors in the proposed study. Patient with breast cancer may undergo radiation and/or chemotherapy before or after surgery. Additionally, breast cancer patient may undergo hormonal therapy if their tumor type is hormonal receptor positive. Associations between treatment type and emotional outcomes were examined in two of the exemplar studies. In both studies (Kahn et al., 2012; Schubart et al., 2014), radiation and hormonal therapy were not associated with psychological distress, but there was a significant association between chemotherapy treatment and higher levels of psychological distress.

***Marital status/education*.** Marital status and education were theorized as situational influencing factors in the proposed study. One study (Dominick et al., 2014) examined associations between marital status and emotional outcome in breast cancer survivors and found that participants who were unmarried reported lower levels mental health ($p<.05$). Two studies (Adreu et al., 2011; Vassard et al., 2010) examined the level of education. Andreu et al. (2011) reported no association found between education and emotional outcome, whereas Vassard et al. (2010) reported higher levels of education was associated with poorer psychological health.

Table 1. Emotional outcome in breast cancer survivors

Author/Year/Title	Study Design	Relevant Findings
Andreu et al., 2011	Longitudinal T1: Preliminary diagnosis	Prevalence of emotional distress (BSI)

Author/Year/Title	Study Design	Relevant Findings
A longitudinal study of psychosocial distress in breast cancer: Prevalence and risk factors	T2: Surgery T3: Definitive diagnosis T4: Treatment Sample *n* = 102 non met Br Ca, Spain Age: M = 50.54 Tools ED measured - Psychosocial distress (General Severity Index) - Somatization, Depression and Anxiety (Brief Symptoms Inventory - BSI)	- T1: 24.5% of patients (M = 15.7, SD = 10.9) - T2: 16.7% of patients (M = 13.28, SD = 8.87) - T3: 16.7 % of patients (M = 13.27, SD = 9.91) - T4: 15.7 % of patients (M = 13.32, SD = 10.48) - About 5 in 10 women reported clinical distress at two or more times during the process of diagnosis and treatment, and 3 in 10 women at three or more times evaluated. Influencing factors on ED - Age *(r* = .28, *p* <. 01), education (*r*= 0.62, *p* <. 001), surgical treatment *(r* = 0.33, *p* <. 001), marital status (*r* = .72, *p* <. 001), employment status (*r*= - .36, *p* <. 0001), and stage of disease (*r* =. 37, *p* < .001) were associated with psychological distress at T4. - Correlations indicated that demographic and medical variables did not present a significant association with distress at T1, T2 and T3. Prevalence of LE - Not reported LE on ED - Not reported
Clough-Gor, Ganz, & Silliman, 2010 Older Breast Cancer Survivors:	Longitudinal T1: 3 months after surgery T2: 6 months after surgery T3: 15 months after surgery T4: 27 months after surgery	Prevalence of emotional distress - Not reported Influencing factors of emotional distress

Author/Year/Title	Study Design	Relevant Findings
Factors Associated with Self-reported Symptoms of Persistent Lymphedema Over 7 years of Follow-up	T5: 39 months after surgery T6: 51 months after surgery T7: 64 months after surgery T8: 75 months after surgery T9: 87 months after surgery Sample *n* = 400 Br Ca (stage I-IIIA), USA Age: 65–69 years (*n* = 116) 70–79 years (*n* = 234) 80+(*n* = 50) Tools ED measured - Mental Health Index (MHI5) - The Courtauld Emotional Control Scale (CECS) - The Mini-Mental Adjustment to Cancer Scale (Mini-MAC) * Lymphedema (LE): self - report	- Other factors except LE not reported Prevalence of LE - 36% reported persistent LE over 7 years of follow-up. - 4.5 % reported transient LE over 7 years of follow- up. LE on ED - Persistent LE was the single strongest statistically significant predictor of decreased scores mental health over follow- up (OR_{M-} HI5change = 2.86, 95% CI: 1.78–4.61). - Women with persistent LE consistently reported worse physical function and general mental health over follow-up. There was on average a 6-point significant difference (range 3–9 points) in MHI5 scores
Costa-Requena et al., 2013 Longitudinal assessment of distress and quality of life in the early stages of breast cancer treatment	Longitudinal T1: one week before starting treatment T2: in the middle of treatment T3: one month after the end of treatment Sample *n* = 62 Br Ca in Spain Age: M = 51.5, range = 31–87 m Tools ED measured - Emotional wellbeing (FACT-G)	Prevalence of ED - 51.6% (*n* = 32) of the women showed clinically significant symptoms of anxiety. - Anxiety was higher in the beginning (T1: M = 8.34) but decreased over time (T2: M = 6.89; T3: M = 6.66) *(p* =. 001) - HADS-Anxiety ($p < .01$) T1: M = 11.60, SD = 7.07 T2: M = 10.48, SD = 6.33 T3: M = 9.69, SD = 6.57 - No difference in depression over time: T1: M = 3.2; T2: M = 3.58; T3: M =3.02 (*p* = . 680)

Author/Year/Title	Study Design	Relevant Findings
	- Anxiety, depression (Hospital Anxiety and Depression Scale, HADS)	Influencing factors of ED - Age was not found influencing factor on distress (Mann-Whitney U test) at T1, T2 and T3. - Symptom distress accounted for 51.3 % of variance of QoL at T1 and T2 whereas accounted for 48.8 % at T3, psychological distress demonstrated a higher percentage of variance of the QoL compared to other treatment time-points * Other factors not reported. Prevalence of LE - Not reported LE on ED - Not reported
Dominick et al., 2014 The psychosocial impact of lymphedema-related distress among breast cancer survivors in the WHEL Study	Cross sectional M= 7.3 years Sample size *n* = 2431 Br Ca stage I – IIIA who had treatment for breast cancer within 4 years in USA Age: not reported Tools ED measured - Mental health (SF-36) - Depression (The Center for Epidemiologic Studies Depression Scale, CES-D) *LE assessment: self - report	Prevalence of ED - 48.9% reported moderate to extreme distress as a result of their LE Influencing factors of emotional distress - Being unmarried was significantly related to poor mental health ($p <. 05$). - Higher BMI was significantly related to poor mental health ($p <. 05$). - More comorbidity was significantly related to poor mental health ($p <. 05$). - Physically inactivity was significantly related to poor mental health ($p <. 05$) - Younger age was significantly associated with

Author/Year/Title	Study Design	Relevant Findings
		poor mental health and higher levels of depressive symptoms (p <. 05) - Lymph node removal was significantly associated with poor mental health and higher levels of depressive symptoms (p <. 05) - Current smoker status was significantly associated with poor mental health and higher levels of depressive symptoms (p <. 05). Prevalence of LE - 28.5% self-reported ever having lymphedema LE on ED - LE was a significantly related to depressive symptoms (p = .03) - LE related distress showed 73% higher odds of having poor mental health (p <. 01) when compared with women without
Kahn etal., 2012 Factors associated with long-term functional outcomes and psychological sequelae in women after breast cancer	Cross sectional 1 year to 24 years (M = 2.2 yrs, IQR = 1.4-4.9) Sample size n = 85 Br Ca, Australia Age: M = 57 year (IQR = 47.4-63.9) Tools ED measured - Depression, anxiety, stress (The Depression Anxiety Stress Scale, DASS) - Psychological wellbeing (The Perceived Impact of	Prevalence of ED - Depression: Normal/mild; 77.6%. Moderate/severe/extreme severe; 22.4% - Anxiety: Normal/mild: 81.2%, Moderate/severe/extreme severe: 18.8% - Stress: Normal/mild: 88.2%, Moderate/severe/extreme severe: 11.8% - Psychological wellbeing: moderate to extreme: 32 % (measured by PIPP, M = 2.2, IQR = 1.4- 3.4)

Author/Year/Title	Study Design	Relevant Findings
	Problem Profile, PIPP) * LE: Self report	Influencing factors of ED - The younger group showed poor Psychological wellbeing (p = .02). - Chemotherapy is associated with greater impact on psychological impact score (p = .005). - Surgery types were not associated with DASS or PIPP scores. - Reconstructive surgery was not associated with DASS or PIPP scores. - Lymph node involvement was not associated with DASS or PIPP scores. - Estrogen-receptor positive was not associated with DASS or PIPP scores. - Higher depression levels for the more recently diagnosed (p =. 02). Prevalence of LE - 28.5% reported to have LE LE on ED - LE was associated with higher psychological distress subscale (p = .003 and DASS Anxiety scale (p = .02).

Author/Year/Title	Study Design	Relevant Findings
Ng et al., 2017 Perceived distress and its association with depression and anxiety in breast cancer patients	Longitudinal T1. At the time of diagnosis T2: 6 m after diagnosis T3: 12 m after diagnosis Sample size *n* = 221 Br Ca stage I-IV, Malaysia * 8 % stage IV Age: Mean = 55.13 (SD =11.5) Tools ED measured - Anxiety and depression (HADS) - Psychological distress (Distress thermometer) * LE: not examined	Prevalence of ED (Distress thermometer) - T1: 50.2% (OR = 1.28, 95% CI = 1.13–1.44) - T2: 51.6% (OR = 1.27, 95% CI = 1.11–1.45) - T3: 40.3% (OR = 1.51, 95% CI = 1.29–1.76) *There was reduction in perceived level of distress, anxiety and depression scores at 12 months after the diagnosis. Influencing factors on emotional distress - Perceived distress was positively correlated with the change of anxiety score ($r = .25$, $p < .05$). - There was no significant correlation between the change of depression score and the change of distress. *Other factors not reported. Prevalence of LE: - Not reported LE on ED - Not reported
Oliveri et al., 2008 Arm/hand swelling and perceived functioning among breast cancer survivors 12 years post-diagnosis: CALGB 79804	Cross sectional 9–16 years post-diagnosis (M =12. 5 yr) Sample *n* = 245 Br Ca Age: M= 63 Tools ED measured - Depression: measured with the Center for Epidemiologic Studies Depression	Prevalence of ED - Not reported Influencing factors on emotional distress - Not reported Prevalence of LE (since surgery) - < 6 month; 36% - 6- 12 months: 7 % - 1 to < 2 years: 12% - 2 to < 5 years: 13 % - 10-15 years: 4 % - Constant *vs*. non constant

Author/Year/Title	Study Design	Relevant Findings
	(CES-D) - Breast Cancer Anxiety: assessed with a modified form of the Breast Cancer Anxiety and Screening Behavior Scale - General mental health: assessed by the Medical Outcomes Study Short Form 36 (SF-36) health status * LE: self-report	arm/hand swelling: 49 % *vs*. 41 % Location of LE - Hand (13 %). Upper arm (33 %), Lower arm (11 %), Hand and lower arm (5 %), Upper and lower arm (13 %), Entire arm and hand (21 %) Intensity of swelling - 51% Mild: 51% - Moderate: 37% - Severe: 9 % LE on ED - No difference in emotional outcomes with and without LE including depression (mean score = 9.95 *vs*. mean score = 9.37), anxiety (mean score = 0.79 *vs*. mean score = 0.80) and mental functioning (mean score= 76.11 *vs*. mean score= 77.04). - Women who reported severe swelling had significantly worse physical functioning (lower physical SF-36 scores) compared to women who reported mild or moderate swelling (p = .008), and there were non-significant trends toward worse depressive symptoms and poorer mental health (lower mental SF- 36 scores).

Author/Year/Title	Study Design	Relevant Findings
Paskett et al.,2007 The Epidemiology of Arm and Hand Swelling in Premenopausal Breast Cancer Survivors	Longitudinal T1: baseline T2: 6 m after surgery T3: 12 m after surgery T4: 18 m after surgery T5: 24 m after surgery T6: 30 m after surgery T7: 36 m after surgery Sample *n* = 622 Stage I-III invasive breast cancer within the previous 8 months at age, ≤ 45 years at diagnosis, USA Age: M = 38.5 year (20-45) Tools ED measured - Emotional wellbeing (FACT-B) - Mental health (the Short Form-12, SF-12) *LE: Self report	Prevalence of ED - Not reported Influencing factors on emotional distress - Not reported Prevalence of LE - At T2, 20 % reported having arm lymphedema. - At T3, 36 % reported having arm lymphedema. - At T7, 54% reported having arm lymphedema - Upper arm (43 %), Hand (34 %), Both arm and hand (22%) - Mild: 70 %: Moderate: 25%; Severe: 5 % LE on ED - Women with no LE had significantly better mental health SF-12 (44.8 *vs*. 43.1, $p < .01$) and FACT B (113.8 *vs*. 111.7, $p <. 01$).
Pyszel et al.,2006 Disability, psychological distress and quality of life	Cross sectional Sample n = 265 Br Ca, Poland Age: M=57 (31-80) Tools ED measured - Emotional functioning (EORTC QLQ-C30) - Psychological distress (General Health Questionnaire, GHQ) *LE: self- report	Prevalence of ED - Not reported Prevalence of LE - 31.69% reported having arm lymphedema Influencing factors of LE - Age ($p =. 60$) and marital status ($p =. 2$): not significantly associated. - Level of education ($p = 0.005$), occupation status ($p = 0.04$) and BMI ($p =. 002$): associated significantly LE on ED - Significantly associated

Author/Year/Title	Study Design	Relevant Findings
		with lower emotional functioning (0.47 *vs*. 0.57, *p* = .001)
Schubart et al., 2014 Screening for Psychological Distress in Surgical Breast Cancer Patients	Cross sectional M = 2.5 yr, 0.02–19.5 yr since diagnosis Sample size *n* =109 Br Ca Age: M = 57 years (range 29–92) Tools ED measured - Distress, depression, anxiety, and anger (Emotional upset thermometer) * LE: not examined	Prevalence of ED: - Distress: 22 % - Anxiety: 28 % - Depression: 18 % - Anger: 14 % - Burden: 16 % - Need for help: 10% Influencing factors of ED (ET score) - Younger age was associated with distress (*p* = .04), anxiety (*p* = .01), depression (*p* = .01), and anger (*p* =. 04) - More extensive surgery (bilateral mastectomy *vs*. unilateral mastectomy *vs*. lumpectomy) was correlated with higher levels of psychosocial distress *(p* =. 02). - Time since diagnosis was not correlated - Chemotherapy was not associated - Hormonal therapy was not associated - Cancer stage: not statistically significant differences Prevalence of LE - Not examined Influencing factors on LE Not examined
Vassard et al., 2010 Psychological consequences of lymphedema associated with	Longitudinal T1: 3 weeks before rehab T2: 6 months after rehab T3: 12 months after the rehabilitation * From 1 month to 5 years	Prevalence of ED - Not examined Influencing factors of ED - Higher BMI was associated with poorer psychological

Author/Year/Title	Study Design	Relevant Findings
breast cancer: A prospective cohort study	since surgery Sample *n* = 633 Br Ca (stage I-III, 125 with LE, 508 without LE), Denmark Age: M= not reported Tools ED measured - Psychological health: self - estimated - Emotional distress (Profile of mood states questionnaire (POMS-SF) *LE: Self report and then confirmed with first Author.	health ($p \leq .01$) and Mood and Disturbance score ($p = .01$). - Working compared with on sick leave unemployed or pensioner was associated with better psychological health ($p = <.01$) and Mood and Disturbance score ($p = .01$) - Higher education was associated with poorer psychological health ($p \leq .01$) and Mood and Disturbance scores ($p = .01$). - Married or cohabiting was associated with better psychological health ($p \leq .01$) and Mood and Disturbance scores ($p = .01$). - Age at time of surgery was associated with psychological health ($p \leq .01$). LE on ED - LE was associated with poorer psychological health ($p \leq .01$) only, was not associated with Mood and Disturbance score ($p = .32$) Prevalence of LE: 19.7% reported having verified LE. * Women with LE were 29% more likely to report less good or bad health than women without LE at the last follow-up (OR, 1.2; 95% CI, 1.1–1.3)

Lymphedema and Lymphedema Symptoms

In this section, a synthesis and analysis of empirical evidence that examined the

association between lymphedema and lymphedema symptoms in patients with breast cancer are presented. The literature search was delimited to studies that examined lymph volume or lymphedema symptoms following treatment for breast cancer. The following search terms were used: breast cancer, symptoms, lymphedema, lymphedema symptoms, functions, disability, mobility, impaired, pain, numbness, tingling, sensation, mobility, emotional, mental, depression, psychological, quality of life, fear, and anxiety. Ten exemplar studies are reviewed. For each study, author (s), title of study, design, sample characteristics, the instruments relevant to the proposed study, and relevant study findings are summarized in Table 2. First, the prevalence of lymphedema symptoms in breast cancer survivors is presented. Second, the review of empirical literature focused on the relationship between lymphedema symptoms and ED in breast cancer survivors is presented.

Prevalence of Lymphedema Symptoms

Four of the ten studies reviewed (Dominick et al., 2014; Kahn et al., 2012; Oliveri et al., 2008; Smoot et al., 2009) reported a prevalence of symptoms in patients who underwent surgery for breast cancer, however the symptoms were not identified as lymphedema-related in a majority of these studies. Kahn et al. (2012) reported a prevalence of breast related pain (75 %), upper limb weakness of affected side (42%), limited shoulder movement (33%), lymphedema (29%), phantom breast sensation (15%), and phantom breast pain (6%) in a sample of women with breast cancer. Dominick et al. (2014) reported swelling (57 %), puffiness (50%) and jewelry or clothing tightness on one side. In a third study, Oliveri et al. (2008) reported that 43 % of breast cancer survivors reported arm and/or hand pain. Only one study reported the prevalence of

symptoms in women with BCRL compared to those in woman without BCRL (Smoot et al., 2009). Smoot et al. (2009) reported 68% of woman with lymphedema reported pain, heaviness, ache, or strange sensations in the affected arm compared to 39 % of women without lymphedema in their cross sectional study. An obvious gap in the empirical literature is a scarcity of studies that examined the prevalence of lymphedema-related symptoms in patients with BCRL. None of reviewed studies explored lymphedema-related symptoms over time among breast cancer survivors. The likelihood for the development of debilitating lymphedema from breast cancer treatment remains a threat in breast cancer survivors. Yet, the trajectories of BCRL-related symptoms are not well studied. The proposed study addressed this gap.

Lymphedema and Lymphedema Symptoms

Two studies (Hayes et al., 2007; Smoot at al., 2009) of the ten studies measured lymph volume with the bio-impedance spectroscopy (BIS), an objective evaluation of limb volume. Mak et al. (2009) also employed objective assessments of lymphedema in their study by defining lymphedema as an increase in arm circumference at any level by 1.5 cm or more, compared to the contralateral side. Even though these studies utilized objective measurement of lymph volume, only one study examined the association between lymphedema and symptoms. Mak et al. (2009) reported severe lymphedema had a worse symptom severity sub-score compared to those with mild lymphedema (12.1 *vs*. 9.7, $p < .005$).

Seven studies of the ten studies examined lymphedema based on self-report, but only two of these studies examined associations between self-reported lymphedema and symptoms. Clough-Gorr et al. (2010) reported persistent lymphedema was the single

strongest statistically significant predictor of decreased mental health (OR_{M-} HI5change = 2.86, 95% CI: 1.78–4.61). Hayes et al. (2007) reported also 60% of women with lymphedema had transitory symptoms. The findings of these studies suggest that breast cancer survivors with lymphedema experience symptoms that are associated with increased lymph volume or self-reported lymphedema. However, the association between lymph volume and related symptoms over time has not been well studied, and this study addressed that gap in knowledge.

Lymphedema Symptoms and ED

Eight of the ten studies examined the association between symptoms and emotional outcome in breast cancer survivors. Findings from six studies revealed significant associations between symptoms and poor mental health, depression, psychological or ED (Clough-Gorr et al., 2010; Dominick et al., 2014; Kahn et al., 2012; Paskett et al., 2007; Pyszel et al, 2006; Vassard et al., 2010). In contrast, findings from two studies (Mak et al., 2009; Oliveri et al., 2008) found no association between symptoms and emotional outcome in breast cancer survivors. However, Oliveri et al. (2008) reported there was a subgroup of patients who reported a high rate of persistent symptoms including pain, swelling and interference with daily activities, and their study suggested that characteristics of symptoms such as severity or activity-limiting symptoms, not simply the presence of lymphedema, are associated with the trend towards poorer emotional outcome. Similarly, Clough-Gorr et al. (2010) reported that persistent swelling was the single strongest statistically significant predictor of decreased scores mental health. Breast cancer survivors report residual symptoms such as weakness of the affected side, impaired mobility of the affected arm, pain or lymphedema. Studies have

reported that breast cancer survivors with BCRL experience worse symptoms including swelling, sensory/neuro change and impaired mobility on the affected area compared to those without BCRL. There are few studies that have examined the trajectory of lymphedema symptoms over time and the effect of long-term symptoms on ED in breast cancer survivors. This study will address that gap in knowledge.

Table 2. Lymphedema symptoms on emotional outcome in patients with BCRL

Author/Year/Title	Study Design	Relevant Findings
Clough-Gorr et al., 2010 Older Breast Cancer Survivors: Factors Associated with Self-reported Symptoms of Persistent Lymphedema Over 7 years of Follow-up	Longitudinal T1: 3 months after surgery T2: 6 months after surgery T3: 15 months after surgery T4: 27 months after surgery T5: 39 months after surgery T6: 51 months after surgery T7: 64 months after surgery T8: 75 months after surgery T9: 87 months after surgery Sample *n* =163 Br Ca (stage I-IIIA, USA Age: 65–69 year: *n* = 116 70–79 year: *n* = 234 80+: *n* = 50 Tools symptom distress measured - Physical function (Physical Function Index 10, PFI10) - LE symptoms (Interview)	Prevalence of LE - 36% reported LE over 7 years of follow-up Prevalence of LE symptoms - Not reported Relationship between LE and LE symptoms - Not reported LE symptoms on ED - Persistent LE was the single strongest statistically significant predictor of decreased scores mental health over follow- up (OR_{M-} HI5change = 2.86, 95% CI: 1.78–4.61). - Women with persistent LE consistently reported worse physical function and general mental health over follow-up. There was on average a 6-point significant difference (range 3–9 points) in MHI5 scores ($p <. 05$)

Author/Year/Title	Study Design	Relevant Findings
	Tools ED measured - Mental Health Index (MHI5) - The Courtauld Emotional Control Scale (CECS) - The Mini-Mental Adjustment to Cancer Scale (Mini-MAC) * LE: self -report	
Dominick et al, 2014 The psychosocial impact of lymphedema-related distress among breast cancer survivors in the WHEL Study	Longitudinal T1. At the time of diagnosis T2: 6 m after diagnosis T3: 12 m after diagnosis Sample size *n* = 221 Br Ca stage I-IV, Malaysia * 8 % stage IV Age: Mean = 55.13 (SD =11.5) Tools LE symptoms measured - LE dataset (Norman et al., 2001) Tools ED measured - Anxiety and depression (HADS) - Psychological distress (Distress thermometer) * LE: self- report	Prevalence of LE - 28.5% self-reported ever having lymphedema Prevalence of LE symptoms - Swelling: 57 % - Puffiness: 50% - Having watches, rings, bracelets, or clothing becoming tight one side: 41 % - Numbers of LE symptoms At least one symptom: 71.7% Four or more: 44.2% Seven or more: 5 % Relationship between LE and LE symptoms - The number of current LE symptoms was associated with LE- related distress [χ^2 (3, N = 671) = 56.96, p < .01]. LE symptoms on ED - LE symptoms trend toward poor mental health (r = 0.582, p < .01). - LE-related distress associated with 73% higher

Author/Year/Title	Study Design	Relevant Findings
		odds of having poor MH when compared with women with no lymphedema. - LE symptoms were significantly associated with the CES-D scores (p <. 01).
Hayes, et al., 2007 Lymphedema After Breast Cancer: Incidence, Risk Factors, and Effect on Upper Body Function	Longitudinal T1: 6 months post op T2: 9 months post op T3: 12 months post op T4: 15 months post op T5: 18 months post op Sample n = 287 Br Ca who underwent surgery for Br Ca, Australia Age: M = 54 (10) Tools LE symptoms measured - Upper-body function (The Disability of the Arm, Shoulder and Hand Scale, DASH) - Upper-body symptoms Tools ED measured - Not examined *LE: measured by bio-impedance spectroscopy	Prevalence of LE - 60% of women had transitory symptoms, whereby the LE dissipated with or without treatment - 40% of patients experienced long term LE lasting for more than 3 months, and 63% of the women with long term LE experienced intermittent periods without symptoms. - 63% presented with symptoms at the first evaluation (6 months after treatment). Prevalence of LE symptoms - Poor range of arm movement: LE =45 %, Non LE= 35 % - Numbness: LE = 75 %, Non LE= 65 % - Tingling: LE =35 %, Non LE= 40 % - Weakness: LE =70 %, Non LE= 55 % - Stiffness: LE =60 %, Non LE= 45 % - Pain: LE =70 %, Non LE= 50% Relationship between LE and LE symptoms - UBF (Upper-body function): Association with

Author/Year/Title	Study Design	Relevant Findings
		lymphedema was not significant (OR 1.9; 95% CI, 0.8 to 4.6; p <. 15). - Having LE between 6 and 18 months after surgery was associated with having poorer upper-body function after surgery (OR=1.9; 95% CI, 0.8 - 4.6; p < .15) - Pain is the greatest differences between the groups (10%) (p = .05). LE and its symptoms on ED - Not reported
Kahn et al., 2012 Factors associated with long-term functional outcomes and psychological sequelae in women after breast cancer - Muscle, The Medical Research Council (MRC) - Visual Analogue Pain Scale - Functional Independence Measure (FIM) - Mobility, The Perceived Impact of Problem Profile, (PIPP) Tools ED measured - Depression, anxiety, stress (The	Cross sectional 1 year to 24 years (M = 2.2 years, IQR = 1.4-4.9) Sample size n = 85 Br Ca, Australia Age: M = 57 year (IQR = 47.4 - 63.9) Tools LE symptoms - wellbeing (The Perceived Impact of Problem Profile, PIPP) * LE: Self report	Prevalence of LE - 28.5% reported to have LE Prevalence of LE symptoms - Breast related pain (n = 63, 75%) - Phantom breast sensation (n = 13, 15%) and phantom breast pain (n = 5, 6%). - Limited shoulder movement *(n* =28, 33%). - Upper limb weakness of affected side (n = 36, 42%) Relationship between LE and LE symptoms - LE was associated with higher impact scores on the Mobility (p = .03). - Chemotherapy was associated with greater impact scores on the PIPP subscales (Psychological, p = .005; Mobility, p < .001; Participation, p = .002; Relationships, p = .02). - Women who received radiotherapy recorded slightly higher (better) FIM motor (better) total scores

Author/Year/Title	Study Design	Relevant Findings
Depression Anxiety Stress Scale, DASS) Psychological		(p = .02). LE symptoms on ED - Shoulder limitations due to pain (p < .007) and upper limb weakness (p =. 007) associated with higher anxiety and psychological distress (p < .03). - Limited range of shoulder movement was associated with higher scores on psychological wellbeing (p = .03).
Mak et al., 2009 Lymphedema and quality of life in Chinese women after treatment for breast cancer	Cross-sectional: Not reported Sample n = 202 Stage I-III Br Ca, Hong Kong Age: M = 51.2 (34-80) Tools LE symptoms measured - Physical function (FACT-B+4) - Symptom Distress (The self-devised Arm Symptom Distress): Swelling, Pain, Numbness or tingling, Limitations on movement or Infection Tools ED measured - Emotional wellbeing (FACT B+4) * LE: An increase in arm circumference at any level	Prevalence of LE: - N/A (Cases with only LE were recruited.) Prevalence of LE symptoms - Not reported Relationship between LE and LE symptoms - Arm symptoms were worse in LE (20.0 *vs*. 11.3; p < .0001). - Symptom-associated Interference on daily life was higher in patients with LE (9.1 *vs*. 3.8; p < .0001). - The Symptom Severity is associated with symptom-associated Interference (r = 0.87, p < .001). - Severe lymphedema had a worse Symptom Severity sub-score compared to those with mild LE (12.1 *vs*. 9.7, p < .005). LE symptoms on ED - No significant difference in emotional well- being between the group with LE

Author/Year/Title	Study Design	Relevant Findings
	by 1.5 cm or more compared to the contralateral side	and without LE.
Oliveri et al., 2008 Arm/hand swelling and perceived functioning among breast cancer survivors 12 years post-diagnosis: CALGB 79804	Cross sectional 9–16 years post-diagnosis Sample *n* = 245 Br Ca Age: M = 63 Tools LE symptoms measured - Physical health (SF-12) Tools ED measured - Depression: measured with the Center for Epidemiologic Studies Depression (CES-D - Breast Cancer Anxiety: assessed with a modified form of the Breast Cancer Anxiety and Screening Behavior Scale - General mental health: assessed by the Medical Outcomes Study	Prevalence of LE: - <6 months; 36% - 6- 12 months: 7 % - 1 to < 2 years: 12% - 2 to < 5 years: 13 % - 10-15 years: 4 % - Constant *vs*. non constant arm/hand swelling: 49 % *vs*. 41 % Prevalence of LE symptoms - Interference of daily life: 69% - Arm and/or hand pain: 43% Relationship between LE and LE symptoms - Not reported LE symptoms on ED - No difference in depression between pts with and without LE (mean score = 9.95, SD = 8.92 *vs*. mean score=9.37, SD = 8.41). - No difference in anxiety between pts with and without LE (mean score = 0.79, SD = 0.46 *vs*. mean score = 0.80 SD = 0. 47).

Author/Year/Title	Study Design	Relevant Findings
	Short Form 36 (SF-36) health status * LE: self-report	- No difference in SF mental health between pts with and without LE (mean score = 76.11, SD =16.60 *vs*. mean score = 77.04, SD = 16.63).
Paskett et al.,2007 The Epidemiology of Arm and Hand Swelling in Premenopausal Breast Cancer Survivors	Longitudinal T1: baseline T2: 6 m after surgery T3: 12 m after surgery T4: 18 m after surgery T5: 24 m after surgery T6: 30 m after surgery T7: 36 m after surgery Sample *n* = 622 Stage I-III invasive breast cancer within the previous 8 months at age, ≤ 45 years at diagnosis, USA Age: M = 38.5 year (20-45) Tools LE symptoms measured - Functional wellbeing (FACT-B) Tools ED measured - Emotional wellbeing (The functional assessment of cancer therapy-breast, FACT-B) - Mental health (the Short Form-12, SF-12) *LE: Self report	Prevalence of LE: - At T2, 20 % reported having arm lymphedema. - At T3, 36 % reported having arm lymphedema. - At T7, 54% reported having arm lymphedema - Upper arm (43 %), Hand (34 %), Both arm and hand (22%) - Mild: 70 %: Moderate: 25%; Severe: 5 % Prevalence of LE symptoms - Not reported Relationship between LE and LE symptoms - Not reported LE symptoms on emotional Distress - Pts with swelling had significantly poorer mental health SF-12 compared to pts with no swelling ($p <.$ 01).
Pyszel et al., 2006	Cross sectional	Prevalence of LE - 31.69% reported having

Author/Year/Title	Study Design	Relevant Findings
Disability, psychological distress and quality of life in breast cancer survivors with lymphedema	- Mean F/U or range is not reported Sample *n* = 265 Br Ca, Poland Age: M = 57 (31-80) Tools LE symptoms measured - Disability (WHO-DASII) - Physical functioning (EORTC QLQ-C30) - Breast symptoms, arm symptoms (The EORTC QLQ BR-23) Tools ED measured - Emotional functioning (EORTC QLQ-C30) - Psychological distress (General Health Questionnaire, GHQ) LE: self- report	arm lymphedema Prevalence of LE symptoms - Not reported Relationship between LE and LE symptoms - The group with LE had lower physical functioning (mean values, 0.55 *vs.* 0.65; *p* =. 001), worse arm disability (mean values, 45 *vs.* 38; *p* =. 001), worse arm symptoms (*p* < .00001) and worse breast symptoms (*p* <. 00001), compared to the group with LE. LE and its symptoms on ED - LE was significantly associated with lower emotional functioning (*p* =. 001). - An increase in breast and arm symptoms was associated with poorer psychological distress (*p* =. 004).
Smoot et al., 2009 Upper extremity impairments in women with or without lymphedema following breast cancer treatment	Cross sectional Not reported Sample *n* = 148 who completed Br Ca treatment within 6 months, USA Age: M = 56.33 (SD = 9.44) Tools LE symptoms measured	Prevalence of LE: - 50. 7% reported a previous diagnosis of LE Prevalence of LE symptoms - 68% of woman with LE reported pain, heaviness, ache, or strange sensations in the affected arm compared to 39 % woman with non-LE.

Author/Year/Title	Study Design	Relevant Findings
	- The upper extremity impairment (The Disabilities of Arm, Shoulder, and Hand, DASH) - Fine motor skills (The Finger Tapper Test) - Hand Strength (The hand- held dynamometers) - Ranges of motion (ROM) (goniometer) - Tactile sensitivity of the upper extremities (Semmes-Weinstein monofilaments) Tools ED measured - Not examined * LE: Lymph volume measured by circumferential assessment and bio-impedance	Relationship between LE and LE symptoms - Inter-limb differences in shoulder abduction were greater in women with lymphedema compared to those without (18° *vs*. 9°). - Range of motion in shoulder abduction on the affected side in the Lymphedema group was twice the loss of that seen in the Non-lymphedema group ($p <$. 05). - Strength was found significantly different between the two groups of women were found ($p <$. 001), * Elbow flexion strength was significantly correlated with the DASH item related to carrying objects over 10 lbs. - The women with lymphedema demonstrated reduced sensation in the medial arm ($p <$. 001). - The women with lymphedema more frequently reported upper extremity symptoms such as pain, ache, numbness, or heaviness in the arm. - Women with a previous diagnosis of lymphedema scored higher on the upper extremity activities: a statistically significant difference (10 points) between the Lymphedema and Non-lymphedema groups. - Statistically significant difference between pain

Author/Year/Title	Study Design	Relevant Findings
		and sensory loss between two groups ($p <. 05$) - Women with less medial arm sensation more frequently reported pain in the upper extremity. - No significant differences between lymphedema groups in Fine motor skills. - Tactile sensitivity was lower at the medial aspect of the arm, medial forearm, and index finger in the Lymphedema group ($p <. 05$). LE symptoms on ED - Not examined
Vassard, et al., 2010 Psychological consequences of lymphedema associated with breast cancer: A prospective cohort study	Longitudinal T1: 3 weeks before rehab T2: 6 months after rehab T3: 12 months after the rehabilitation * From 1 month to 5 years since surgery Sample *n* = 633 Br Ca (stage I-III), Denmark Age: M= not reported Tools LE symptoms measured - Not reported Tools ED measured - Psychological health: self-estimated - Emotional distress (Profile of mood states questionnaire (POMS-SF)	Prevalence of LE - 19.7 % reported having verified LE. Prevalence of LE symptoms - Not reported Relationship between LE and LE symptoms - Not reported LE symptoms on ED - LE was significantly associated with Psychological health ($p \leq .01$) and Mood and Disturbance score: significantly associated ($p =. 32$)

Author/Year/Title	Study Design	Relevant Findings
	*LE: Self report and then confirmed with first Author.	

Summary and Knowledge Gaps

Findings from the empirical literature indicate that not only lymph volume, but also lymphedema symptoms affect the physical, social and emotional wellbeing of breast cancer survivors with lymphedema as they cope with their cancer experience and its sequelae. Specifically, the studies reviewed indicated that lower levels of physical social functioning characterized by pain, impaired mobility, the swelling of the affected area was associated with negative emotional wellbeing and mental health. Findings from the empirical literature suggest that lymphedema and its symptoms have a considerable influence on QoL, even several years after treatment is completed. However, much of the published research about lymphedema has only addressed its physical and social functioning outcomes. Moreover, most of existing literature on BCRL has not included lymphedema symptoms. The proposed study used data that employed a validated psychometric tool designed for use in breast cancer survivors with BCRL that measures various emotions and BCRL-related symptoms including trunkal lymphedema.

Breast cancer survivors may also experience adverse effects from the treatment. Although these symptoms may overlap with the symptoms related to BCRL, studies have shown that breast cancer survivors experience more distressful symptoms compared to those without BCRL. Lymphedema-related symptoms may change in number and intensity as breast cancer survivors move through diagnosis to treatment and then to survival. Thus, the impact of variations in lymphedema-related symptoms over time on

emotional outcomes at different breast cancer trajectories likely differs as well. Yet, there is a paucity of studies that have examined the effect of lymphedema symptoms on ED over time in breast cancer survivors. Most studies employ cross-sectional designs and evaluate emotional outcomes largely in the context of quality of life (QoL) utilizing generic QoL instruments. Therefore, little is known about the types and variation of disease-specific emotions over time in breast cancer survivors. In order to understand the trajectory of changes in lymph volume, related symptoms, and ED over time, the proposed study examined these variables in a longitudinal design at three time points from the pre–operative period to one - year post-operative.

Currently, there is no consensus regarding the definition and quantification of lymphedema in order to establish and accurate diagnosis of this condition. Most studies that examined BCRL established the diagnosis of BCRL based on subjective self-report of swelling of the arm or hand. Swelling may develop not only on the arm or hand, but trunkal lymphedema may also occur on the chest, shoulder or back. Trunkal swelling may cause inflammation, infection or fibrosis, unpleasant sensation or impaired mobility that can affect breast cancer survivors with trunkal swelling physically and mentally. Thus, it is prudent to assess objective measures of lymph volume and trunkal lymphedema in research in order to sufficiently determine the impact of lymphedema on emotional outcomes in breast cancer survivors with BCRL. The proposed study addressed this gap through the use of existing lymph volume data that was measured objectively and quantified by using a validated instrument.

Lastly, the TOUS offers a theoretical approach to understanding and explaining theorized antecedents to variations in ED in breast cancer survivors. The proposed study

examined the effects of theorized influencing physiological and situation factors and unpleasant symptoms on ED in breast cancer survivors over time.

Study Hypotheses

1. Compared to the mean level of ED at Time 1 (T1), the mean level of ED increases significantly at Time 2 (T2) and at Time 3 (T3).
2. Compared to the mean level of lymph volume at T1, the mean level of lymph volume is significantly higher at T2 and T3.
3. Compared to the mean level of lymphedema symptom intensity at T1, the mean level of lymphedema symptom intensity is significantly higher at T2 and T3.
4. Physiological factors are significantly associated with the level of ED symptom intensity (*i.e.*, no ED, intermediate level of ED, high level of ED) at T2 and T3.
    i. Compared to baseline, younger age is significantly associated with higher levels of ED at T2 and T3.
    ii. Compared to baseline, higher BMI is significantly associated with higher levels of ED at T2 and T3.
    iii. Compared to baseline, higher lymph volume is significantly associated with higher levels of ED at T2 and T3.
5. Situational factors (marital status, level of education. type of surgery and type of therapy) is significantly associated with ED at T2 and T3.
    i. Compared to women who are not married or partnered, women who are married or partnered experiences lower levels of ED at T2 and T3.
    ii. Compared to woman with higher educational levels, woman with lower educational levels experiences lower levels of ED at T2 and T3.

iii. Compared to woman who underwent mastectomy, woman who underwent lumpectomy experiences lower levels of ED at T2 and T3.

iv. Type of therapy

a) Radiation: Compared to woman who received radiation therapy, woman who did not receive radiation therapy experiences lower levels of ED at T2 and T3.

b) Chemotherapy: Compared to woman who received chemotherapy, woman who did not receive chemotherapy experiences lower levels of ED at T2 and time T3.

c) Hormonal therapy: Compared to woman who received hormonal therapy, woman who did not receive hormonal therapy experiences lower levels of ED at T2 and T3.

6. The level of lymphedema symptom intensity at T2 and T3 is positively associated with the level of ED symptom intensity (*i.e.*, no ED, intermediate level of ED, high level of ED) at T2 and T3.

Theoretical and Operational Definitions

This section discussed the theoretical and operational definition for the proposed study. Each de-identified participant's data in the primary study was used and operationalized for hypotheses testing in the proposed study.

Physiological Factors

Physiological factors are "the normal or abnormal functioning of bodily system" (Lenz, et al., 2013, pp, 68). In the proposed study, physiological factors were operationalized as BMI, age, and lymph volume.

Lymph volume. Lymph volume refers to the increase of volume from baseline in the ipsilateral arm. Lymph volume in the primary study was operationalized as lymph fluid level assessed via a perometer and FDA approved Bioelectrical Impedance Analysis (BIA) device.

BMI. The BMI is a value derived from the weight and height of an individual. BMI is defined as the weight divided by the square of the body weight and expressed in units of kg

kg/m^2, resulting from weight in kilograms and height in meters, weight (kg)/height (m^2). De- identified participants' BMI in the primary study at pre-surgery, four to eight weeks post-surgery, and 12 months post-surgery was operationalized in the proposed study.

Age. Age was participant's self-reported age in years at the time of entering the primary study.

Situational Factors

The situational factors include the components of the physical and social environment that may influence on the patient's experience resulting from the symptoms and may comprise with socio-economic factors such as "marital status, social support, or therapies" (Lenz et al., 2013, pp, 68). In the proposed study, situational factors were operationalized as a participant's marital status, level of education, type of surgery, chemotherapy, radiation therapy, and hormonal therapy.

Marital status. Marital status was the participants' self-reported marital status at the time of entering the primary study.

Level of education. Level of education was participants' self-reported level of education at the time of entering the primary study.

Surgery type. The type of surgery was the type of surgical procedure the participants in the primary study underwent for the treatment of the first-time diagnosis of stage I-III breast cancer during the primary study period.

Treatment type. The type of treatment was the type of therapy (e. i., chemotherapy, radiation, hormonal therapy*)* the participants in the primary study received as treatment for the first time diagnosis of stage I-III breast cancer during the primary study period.

Unpleasant Symptoms. Unpleasant symptoms are defined as "the perceived indicators of change in normal functioning as experienced by patients" (Lenz et al., 2013, pp, 68). Lymphedema symptoms was defined as physical body symptoms related to the disease of lymphedema. In the proposed study, unpleasant symptoms were operationalized as participant scores on the Breast Cancer Lymphedema and Symptom Experience Index (BCL-SEI) in four areas: total symptom distress, fluid accumulation, discomfort, and impaired mobility.

ED. ED describes what people feel when they are under mental, physical, or emotional pressure (NCI, 2017) that is experienced and differentiated by an individual simultaneously with different emotions (Hay & Diehl, 2011). ED refers to the negative impact of symptom occurrence on one's emotions and psychological distress evoked by the symptom occurrence. In the proposed study**,** ED was operationalized as participants' scores on the Emotional Symptoms Scale in the BCL-SEI.

Breast cancer survivors. Breast cancer survivors are who remain alive from the time of diagnosis of breast cancer until the time of the end of life (NCI, 2018). In the proposed study, de-identified data from the primary study of 140 women with breast

cancer over 21 years of age who were diagnosed with a first-time diagnosis of stage 1- III breast cancer and were scheduled for surgical treatment of lumpectomy or mastectomy including sentinel lymph node biopsy (SLNB), SLND or ALND with or without neo-adjuvant or adjuvant therapy served as the analytic sample.

CHAPTER 3

Methodology

This chapter describes the research design and methods used for this study. The research setting, population characteristics, measurement and instrument, procedures for data collection and analysis was described in detail. This study was an analysis of secondary data from the primary study aimed to explore prospectively the phenotype of arm lymphedema defined by lymph volume and lymphedema symptoms in relation to inflammatory genes in women treated for breast cancer. The primary study employed a longitudinal, correlational design to investigate the ED in breast cancer survivors with lymphedema. This study was a retrospective secondary analysis of data from the primary study.

Study Sample

In the primary study, data from 140 women who were diagnosed with breast cancer were collected between December 2011 and April 2014 prospectively. Inclusion criteria were women aged 21 years and over who were diagnosed with a first-time diagnosis of stage 1-III breast cancer and were scheduled for surgical treatment of lumpectomy or mastectomy including sentinel lymph node biopsy (SLNB), SLND or ALND with or without neo-adjuvant or adjuvant therapy. De-identified data from this primary study was used for hypotheses testing in the proposed study. Women who were

diagnosed with metastatic cancer (Stage IV), a prior history of breast cancer and lymphedema, and bilateral breast cancer were excluded. In the primary study, after written consent was obtained for each participant, 140 women were enrolled and followed for 12 months after surgery at specific time points, that is, pre-surgery, four to eight weeks post-surgery, and 12 months post-surgery. In the primary study, perometer and bioimpedance devices were used to measure lymph volume, and the BCL-SEI was used to assess symptoms related to lymph fluid accumulation. Women who had an artificial knee or hip, and kidney or heart failure, cardiac pacemaker or defibrillator, artificial limbs or pregnancy were also excluded as the manufacturer suggests analysis by the BIA device may not be accurate under these conditions. Characteristics of participants in the primary study are shown in Table 3.

Table 3. Characteristics of Parent Study Sample

	Total sample (*n*=136)	
	M	SD
Age	52.1	11.1
Weight (lbs)	159.4	35.6
BMI	27.7	6.3
	n	%
Education		
Associate degree or less	45	33.1
Bachelor's degree	62	45.6
Graduate degree	29	21.3
Marital Status		
Married/partnered	80	58.8
Divorced/Widowed	20	14.7
Single, never partnered	36	26.5
Ethnicity		
Black/African American	27	19.9
White non –Hispanic	82	60.3
Asian	13	9.6
Hispanic/Latino	12	8.8
Other	2	1.5
Surgery		
Mastectomy	15	11
Lumpectomy	66	48.5

	Total sample (*n*=136)	
	M	SD
Mastectomy w/reconstruction	55	40.4
Chemotherapy		
No	61	44.9
Neoadjuvant	22	16.1
Adjuvant	53	39.0
Radiation		
No	38	29.9
Yes	89	70.1
Hormonal therapy		
No	63	46.3
Yes	73	53.7

Sample Size

Power analysis for chi-square, correlational, and multiple linear regression analyses were calculated to determine the appropriate sample size to yield sufficient power for these statistical techniques. For a 2-tailed correlation analysis using a moderate effect (r =. 25), a sample size of 123 is needed to yield a power of 0.80 at a 0.05 significance (Cohen, 1988). For chi-square analysis, based on a moderate effect, a sample size of 87 is needed to yield a power of 0.80 at a 0.05 level of significance (McHugh, 2013). For linear regression including eleven independent variables using a moderate effect size (f^2 = 0.15), a power of 0.80 at a 0.05 level of significance requires an estimated sample size of 125 (Cohen, 1988). For the proposed study, the de-identified data set comprised of 140 nurse responses to all survey items was sufficient to yield the statistical power for the planned data analyses.

Measures

Demographic information of each participant was collected via a demographic questionnaire in the primary study. In addition, clinical data was collected from

participants' medical record in the primary study. These de-identified data were analyzed as situational, physiological, and symptoms distress variables in the proposed study.

Independent Variables. A total of eleven independent variables was assessed in this study including seven physiological factor variables and four lymphedema symptom experience variables.

***Physiological factors*.** The following variables collected in the primary study were represented as physiological factors in the proposed study: age (in years), BMI, and lymph volume.

***Situational factors*.** Demographic variables in the primary study that were analyzed as situational factors include participants' marital status (single, married, separated, divorced, partnered), level of education (no school, less than high school, high school graduate, technical school, partial college, associate degree, bachelor's degree, master degree, doctoral degree, professional degree), type of surgery (mastectomy *vs*. lumpectomy), and presence or absence of radiation, chemotherapy or hormonal therapy.

***Symptom experience*.** In the primary study, the BCL-SEI was utilized for lymphedema symptom assessment, and participants completed the BCL-SEI questionnaires at pre-surgery, four to eight weeks post-surgery, and 12 months post-surgery. The BCL-SEI measures the occurrence of symptoms that are related to breast cancer, lymphedema and distress from the symptoms. The BCL-SEI is a two-part, 34 item self-report instrument. Data from Part I of the BCL-SEI were used examine the lymphedema symptom experience in the proposed study. This scale assesses the presence of 24 lymphedema symptoms, and items are arranged on a five-point Likert type scale (ranging 0=no to 4=very severe or a lot). A total symptom distress score is computed as

the sum of each symptom distress item score, and a higher score reflects more severe symptom distress. In the primary study, three BCRL symptom clusters were identified including impaired limb mobility, fluid accumulation, and discomfort. Factor analysis provided evidence for these clusters, and the three-factor solutions explained 49.7% to 52.5% of the variance in reported symptoms at 4-8 weeks and 12 months post- surgery. Therefore, in addition to total lymphedema symptom distress, impaired limb mobility, fluid accumulation, and discomfort symptom clusters were computed and examined.

The BCL-SEI demonstrates high internal consistency reliability with an alpha coefficient of 0.92 (Fu et al., 2012) and was able to distinguish breast cancer survivors with and without lymphedema symptom occurrence and distress ($p < .05$) (Fu et al., 2012). Convergent validity was demonstrated by significant correlations with dimensions of symptom distress (r= 0.35 to 0.93).

Dependent Variable.

***ED*.** Emotional and psychological distress data from Part II of the BCL-SEI collected in the primary study was examined in this study. The ED dimension (Item #29 a-h, range 0-32) assesses the negative impact of symptom occurrence on one's emotions, and the psychological distress dimension (Item #30 i-l, range 0-16) assesses the psychological distress evoked by the symptom occurrence. A higher score reflects more severe emotional and psychological distress.

Plan for Data Protection and Security

For the proposed study, Statistical Package for the Social Science (SPSS) data files from the primary study was examined. The computer and database files were password protected. Only the investigators had access to the password. De-identified

data collected for this study were entered into SPSS and only coded unique identifiers was used to identify participants' responses. Prior to analysis, de-identified data was examined for completeness and accuracy. Computer files was backed up on an external drive and secured in a locked file cabinet of which only the investigators had access.

Data Analysis Plan

A statistical database was created by the investigator using SPSS version 25. The investigator uploaded age, the level of education, marital status, weight, lymph volume, radiation, chemotherapy, mastectomy, lumpectomy, and hormonal therapy variables and participants' de-identified responses to study instruments into the SPSS database. Data analysis included descriptive statistics, including means and standard deviations, to describe sample's continuous ordinal and categorical data. Frequency tables, histograms, and scatterplots were used to assess distribution of study variables for normality. Tests for skewness and kurtosis were conducted. Data were inspected for inconsistencies, outliers, and wild data entry codes. A codebook, which includes copies of the original data set and the cleaned data set, basic descriptive data, correlations, regressions, syntax and output as well as the investigator notes, was generated to document analyses.

To test study hypotheses, a repeated measures ANOVA over time and one through three, paired t-tests (if data normally distributed) or Wilcoxin signed-rank tests, Kruskal-Wallis test or chi square test (if data not normally distributed or dichotomized) was employed to test differences in lymph volume, lymphedema symptoms, and ED between time points (baseline to T2; baseline to T3; T2 to T3).

To test study hypotheses 4 through 6, a series of unadjusted and adjusted linear regression models was examined to determine effects of independent variables on ED at

T2 and T3. Linear regression has four key assumptions. To test the adjusted effects of the independent variables, all independent variables was entered simultaneously into the regression model. Prior to regression analysis, assumptions for linear regression was tested (Tabachnick, & Fidell, 2013). The first assumption was that there was a substantial ratio of cases-to-IVs. The sample size for this study was based on power analysis for multiple regression, therefore, this assumption was met. The second assumption was that there was an absence of outliers. Univariate outlier analysis was conducted, and extreme outliers was deleted. The third assumption was that there was an absence of multicollinearity. For any two independent variables that were highly correlated (i.e., $r \geq .80$), only one was entered into the adjusted regression model. Final assumptions are that data were normally distributed, relationships between the independent variables and dependent variables were linear, and there was an absence of homoscedasticity. The pre-analysis data screening procedures, *i.e*., examination of residuals scatterplots, histograms, skewness and kurtosis of study variables, were examined.

Human Subjects Protection

The primary study was approved by the Investigational Review Board (IRB) of New York University. This was a secondary analysis of existing de-identified data. The study was submitted to the Institutional Review Boards (IRB) of Rutgers, The State University of New Jersey and exempt review was requested as the study does not involve human subjects and only de-identified data was analyzed. Data collected from this study are reported only in the aggregate whether verbally or in print. Following the mandatory six-year IRB data maintenance period, all associated electronic files will be deleted.

CHAPTER 4

Analysis of the Data

The purpose of the study was to identify and further understand the determinants of ED in breast cancer survivors with lymphedema. This study was an analysis of secondary data from a primary study that aimed to explore prospectively the phenotype of arm lymphedema defined by lymph volume and lymphedema symptoms in relation to inflammatory genes in women treated for breast cancer. In the primary study, data from 140 women who were diagnosed with breast cancer were collected between December 2011 and April 2014 prospectively at a hospital in New York City, NY. Inclusion criteria were; 1) women aged 21 years and over who were diagnosed with a first-time diagnosis of stage 1-III breast cancer; and 2) were scheduled for surgical treatment of lumpectomy or mastectomy including sentinel lymph node biopsy (SLNB), SLND or ALND with or without chemotherapy or radiation therapy. Participants who were hormonal receptor-positive continued with hormonal therapy after they completed surgery, chemotherapy or radiation. De-identified data from this primary study was used for hypotheses testing in the proposed study. Women who were diagnosed with metastatic cancer (Stage IV), a prior history of breast cancer or lymphedema, and bilateral breast cancer were excluded. In the primary study, after written consent was obtained for each participant, 140 women were enrolled and followed for 12 months after surgery at specific time points, that is, pre-surgery, four to eight weeks post-surgery, and 12 months post-surgery. For the proposed study, the Statistical Package for the Social Sciences (SPSS) v. 25 (IBM Corp., 2018) was used to examine data files from the primary study. The computer and database files were password protected. De-identified data collected for this study were entered into SPSS, and only coded unique identifiers were used to identify participants'

responses. Prior to analysis, de-identified data were examined for completeness and accuracy. Computer files were backed up on an external drive and secured in a locked file cabinet of which only the PI had access. Data quality was examined to assess variable scores for symmetry, an approximation to normal distributions, and extreme skewness. Data management consisted of a series of data checking methods. The data were cleaned and verified as recommended by Polit and Beck (2012). Data were inspected and checked for invalid and missing values, and identifiable patterns of expectancy, such as inconsistencies in the individual variable range. The distribution of scores for all study variables was examined by visually inspecting for skewness (evidence of central tendency) and kurtosis (evidence of tail heaviness relative to the total variance in the distribution). Means and standard deviations (SD) were used to summarize continuous variables; frequencies and percentages were used to summarize categorical variables. Chi-square analyses were performed to estimate the associations between categorical demographic and clinical predictors. Fisher's exact tests were conducted when data did not meet the assumptions of Pearson's chi-square (cells with expected counts < 5). Independent groups t-tests, paired t-test and ANOVAs were used to compare groups on normally distributed continuous variables, and Mann- Whitney, Chi, Wilcoxon Signed Rank and Kruskal-Wallis test of ranks were used for variables that were not normally distributed or categorized. Binary regression was used to estimate relationships. Analyses of the data are presented in this chapter.

Demographics of the Study Sample

The characteristics of participants in the primary study are shown in Table 3. Mean age of the sample population was 52 years and ranged from 26 to 81. The majority

of participants were married or partnered (57.9 %) with at least a bachelor's degree (65.7%). The participants reported their race/ethnicity as white (60.7%), Asian (10.0 %), black/African American (19. 3%), or Hispanic (8.6%). A majority of participants received radiation treatment (70. 5 %), and more than one-half of participants received chemotherapy (60.9 %).

Table 3. Characteristics of Study Sample at baseline

	Total sample (*N*=140)	
	M	SD
Age (26-81yr) (n=140)	52.1	11.0
	n	**%**
Education (n= 140)		
High school degree	17	12.1
Bachelor's degree	92	65.7
Graduate degree	31	22.1
Marital Status (n= 140)		
Married/partnered	81	57.9
Divorced/Widowed	21	15.0
Single, never partnered	38	27.1
Surgery (n=140)		
Mastectomy	71	50.7
Lumpectomy	69	49.3
Chemotherapy (n=128)		
No	50	39.1
Yes	78	60.9
Radiation (n=129)		
No	38	29.5
Yes	91	70.5
Hormonal therapy (n=108)		
No	51	47.2
Yes	57	52.8

Note. N = sample total; **n* may vary among variables based on number of missing items; % = percentage of the sample population.

Distribution of Study Variables

The distribution of scores for continuous variables (*i.e.*, age, BMI, lymph volume, lymphedema symptom intensity, ED symptom intensity) was examined for symmetry,

approximation to normal distribution using, histogram, Q-Q plots, and Shapiro-Wilk normality test. Normality test results are presented in Table 4.

Age was normally distributed. BMI was not normally distributed. Therefore, BMI was recoded into three categories: 1 = underweight/normal (< 24.9 Kg/m2); 2 = overweight (25-29 Kg/m2); and 3 = obese (≥ 30 kg/m2) for hypothesis testing. The lymph fluid volume variable was normally distributed only in the pre-op period (T1). Since a five percent lymph fluid volume increase enables detectable differences in QoL (Cormier et al., 2009; Fu et al., 2017), lymph fluid volume was recoded into two categories: 1 = < 5 %, and 2 = ≥ 5 %. Total lymphedema symptom intensity scores were not normally distributed across the three time-points. At four to eight weeks post- surgery (T2), while a little less than half of the participants (42. 6 %) had < 9 total lymphedema symptom intensity score, 56.7 % had ≥ 9 lymphedema symptom intensity score. At one-year post-surgery (T3), 74.5 % participants had < 9 total lymphedema symptom intensity score, 24.5 % had ≥ 9 total lymphedema symptom intensity scores. Thus, these scores were recoded into two categories: 1 = scores < 9 <, and 2 = scores ≥ 9 for hypothesis testing. Additionally, three phenotypes of lymphedema symptom intensity were arranged into three categories identified in the primary study (Fu et al., 2017) including 1) impaired mobility that consists of nine symptoms (limited movement of shoulder, limited movement of arm, a limited movement of elbow, firmness, tightness, heaviness, toughness, stiffness, hotness), 2) fluid accumulation that consists of nine symptoms (limited movement of wrist, limited movement of finger, swelling of hand, swelling of arm, swelling breast, swelling of chest, numbness, burning, redness) and 3) discomfort that consist of eight symptoms (tenderness, blistering, pain, stabbing, tingling, arm/hand

fatigue, arm/hand weakness, and seroma). Lastly, total ED symptom intensity scores were not normally distributed. At T2, about a quarter of participants (21.4 %) had ≥ 5 total ED symptom intensity score. At T3, similar to the findings at T2, 25 % of participants had ≥ 5 total ED symptom intensity score., Therefore total ED symptom intensity scores were recoded into three categories: 1 = no ED symptom intensity (score of 0); 2 = intermediate ED symptom intensity (scores 1-4), and 3 = high ED symptom intensity (scores ≥ 5) for hypotheses testing.

Table 4. Test of normality of continuous variables.

	Statistic	df	*p (*Shapiro-Wilk)
Age	.29	100	.546
BMI			
Pre-op	.949	100	.001
4-8 wks post-op	.940	100	.000
12 months post-op	.944	100	.000
Lymph Volume			
pre-op	.984	100	.284
4-8 wks post -op	.974	100	.048
12 months post-op	.699	100	.000
Lymphedema Symptoms			
Pre	.204	100	.000
4-8 wks post –op	.887	100	.000
12 months post- op	.733	100	.000
ED			
Pre	.119	100	.000
4-8 wks post –op	.678	100	.000
12 months post- op	.778	100	.000

*$p < 0.05$ indicates the null hypothesis that the data are normally distributed is rejected.

Description of Study Variables

Descriptive statistics for study variables are described in this section and presented in Table 5. The dependent variable was ED. The independent variables were physiological factors (*i.e..,* age, BMI and lymph fluid volume), situational factors (*i.e.,*

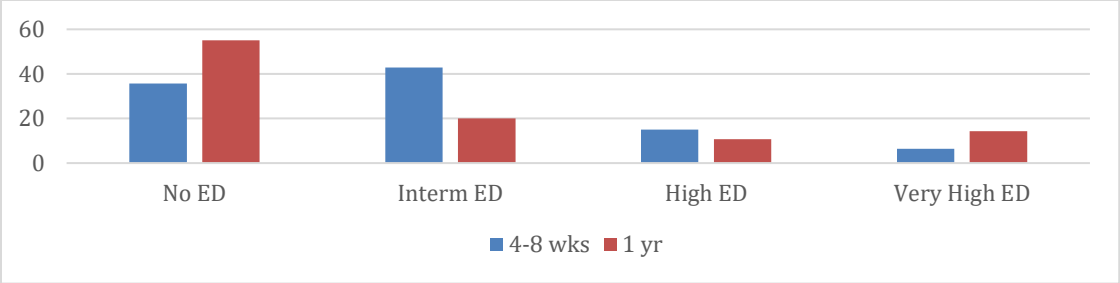
marital status, level of education, type of surgery, type of therapy), and lymphedema symptoms.

Dependent Variables

ED. At T1, 1.4 % of participants reported ED. However, 64.3 % and 45 % of participants reported they had ED at T2 and T3, respectively. Twelve ED symptoms were examined including feeling frustration, angry, depressed, guilty, worried, anxious, hopeless, helpless, sad, irritated, lonely and fear. The prevalence of these symptoms varied across the four to eight weeks post-surgery and 12 months post-surgery periods (see Figure 2). Of the 12 ED symptoms at T3, feeling irritable, anxious, fear, frustrated, helpless, guilt, guilt and hopeless were higher than they were at T2. At T2, the most prevalent ED symptom reported by participants was feeling worried (54.3%) followed by feeling sad (33.6 %). At T3, the most reported emotion was again feeling worried (39.3 %) followed by feeling irritable (32.1 %). The mean level of ED symptom intensity (possible range = 0-48) was .02, 2.93 and 3.27 at T1, T2 and T3, respectively. Interestingly, the percentage of participants who reported an ED symptom intensity score of ≥ 11 (very high) was higher (14.3 %) at T3, compared to (6.4 %) at T2 (see Figure 3).

Figure 2. % of participants experiencing ED symptoms at 4-8 weeks and 12 months post-surgery

Figure 3. The prevalence of ED symptom intensity at 4-8 weeks and 1- year post-surgery (%).



Independent Variables

Physiological Factors: Age, BMI, Lymph Fluid Volume. Mean age of the sample was 52 years (*SD*=11.0). The mean BMI ranged from 27.5 to 27.7 over the three time periods (see Table 5). At T1, 62.8% of participants were either obese (30.7 %) or overweight (32.1%), while 2.1% and 35% were under-weight and normal weight, respectively. This pattern of BMI was consistent at T2 and T3. At T2, a majority of the participants (72.1%) maintained pre-surgery weight and only 15.4% experienced a >5% weight loss whereas, at T3, 12.5% of the participants gained > 5% of their weight compared to T1. Mean lymph volume scores changed over time (see Table 5). Compared to baseline (T1), mean lymph volume was higher at T2 (*Mean increase=1 %)* and T3 (*Mean increase= 2 %).* The percentage of participants with lymph fluid volume ≥ 5% increased from T2 to T3. At T2, 16.7 % of participants had ≥ 5% lymph volume compared to 22. 8 % at T3.

Situational Factors: Marital status, Level of education, Surgery Type, Therapy Type. A majority of participants had a bachelor's degree (65.7 %), 12.1 % had a high school, diploma or less, and 22. 1% had a graduate degree. More than one-half of the sample was either married or partnered, 15 % was either divorced or widowed, and 27.1% was either single or never partnered. About one-half of participants (50.7 %) underwent a mastectomy. More than 70% of participants had radiation therapy, 60.9 %

of participants received chemotherapy and 52.8 % of participants underwent hormonal therapy with various types: Novaldex (70.2%), Anastrazole (22.8 %), Letrazole (2.1%), Leuprolide acetate for depot suspension (.7 %) or others (4.2%).

Lymphedema Symptoms. Twenty-six lymphedema symptoms were evaluated. At T1, a majority of participants (86.2%) did not have any lymphedema symptoms. However, at T2, most participants (98.6%) reported having at least one lymphedema symptoms. At T3, 63.8 % of participants reported having at least one lymphedema symptom.

Mean lymphedema symptom intensity score was .5, 12.8 and 6. 28 at T1, T2 and T3, respectively. Mean impaired mobility lymphedema symptom intensity score was .2, 5.0 and 2.3 at T1, T2 and T3, respectively. At T2, the most frequently reported impaired mobility symptom was tightness (54. 3 %) followed by limited movement of the shoulder (50.7 % %). At T3, the most frequently reported impaired mobility symptom was, again, tightness (33.6%) followed by arm heaviness (27.1%). Mean fluid accumulation symptom intensity score was .07, 4.21, and 1.9 at T1, T2, and T3, respectively. At T2, the most frequently reported fluid accumulation symptom was breast swelling (57.9 %) followed by numbness (53.6%). At T3, the most frequently reported fluid accumulation symptom was numbness (30%) followed by breast swelling (22. 9 %). Mean discomfort lymphedema symptom intensity score was .2, 4.21 and 1.9 at T1, T2 and T3, respectively. At T2, the most reported symptom was tenderness (84.3%) followed by pain (61.4%). At T3, the most reported discomfort was heaviness (37.1 %) followed by tightness (33.6 %). Most of participants (96.5 %) did not have lymphedema symptoms ≥

9 at T1. More than a half (56.7%) and about 25 % reported having lymphedema symptoms ≥ 9 at T2 and T3, respectively.

Table 5. Descriptive Statistics for Independent and Dependent Variables

Variables	**Time 1 (n=140)**	**Time 2 (n =138)**	**Time 3 (n = 136)**
Physiological Factors	Mean (SD)	Mean (SD)	Mean (SD)
Age	52 (11)	n/a	n/a
BMI	27.7 (6.32)	27.53 (6.49)	27.7 (5.89)
	n (%)	n (%)	n (%)
Under /Normal (< 24.9)	52(37.1)	54(38.6)	53(37.9)
Overweight (25– 29.9)	45 (32.1)	42(29.3)	42(30.0)
Obesity (≥30)	43(30.7)	43(30.7)	41(29.3)
Lymph Volume	Mean (SD)	Mean (SD)	Mean (SD)
	.995 (0.37)	1.01 (0 05)	1.02 (0.08)
	n (%)	n (%)	n (%)
<5%	n/a	115(83.3)	105 (77.2)
≥5%		23(16.7)	31(22.8)
Situational Factors	n (%)	n (%)	n (%)
Education			
High school degree	17(12.1)	n/a	n/a
Bachelor's degree	92(65.7)		
Graduate degree	31(22.1)		
Marital Status			
Married/partnered	81(57.9)	n/a	n/a
Divorced/Widowed	21(15.0)		
Single, never partnered	38(27.1)		
Surgery (n=140)			
Mastectomy	71(50.7)	n/a	n/a
Lumpectomy	69(49.3)		
Type of Therapy			
Chemotherapy (n=128)			
No	50(39.1)	n/a	n/a
Yes	78(60.9)		
Radiation (n=129)			
No	38(29.5)	n/a	n/a
Yes	91(70.5)		
Hormonal therapy (n=108)			
No	51(47.2)	n/a	n/a
Yes	57(52.8)		
Lymphedema Symptoms		60(42.6)	
<9 symptom Intensity	136(96.5)	80(56.7)	105(74.5)
≥ 9 symptom Intensity	4 (2.8)		35(24.8)

Variables	**Time 1 (n=140)**	**Time 2 (n =138)**	**Time 3 (n = 136)**
ED	Mean (SD)	Mean (SD)	Mean (SD)
ED Symptom Intensity	.02(19)	2.93(4.39)	3.27(5.34)
	n (%)	n (%)	n (%)
No ED (0)	138(98.6)	50 (35.7)	77(55.0)
Intermediate ED (1-4)	2(1.4)	60(42.5)	28(20.0)
High ED (5-10)	0(0.0)	21(15)	15(10.7)
Very High ED (≥11)	0(0.0)	9(6.4)	20(14.3)

Study Hypotheses Testing

For Hypothesis 1 to 3, Wilcoxon signed rank tests were used to examine mean differences in study variables between the time periods (shown in Table 6). For Hypothesis 4-6, the Anova test was employed to examine the association between age and level of ED symptom intensity (shown in Table 8). Kruskal -Wallis tests were employed to examine associations between non-normally distributed continuous variables *(i.e.*, lymph fluid volume, lymphedema symptoms, BMI,) and ED symptom intensity. Chi-square analyses were employed to examine associations between categorical recoded variables *(i.e.*, lymph fluid volume, lymphedema symptoms, BMI, surgery, marital status, level of education, types of therapy) and ED symptom intensity. In addition, binary logistic regression was conducted to examine the effects of physiological and situational factors on high levels of ED (shown in Tables 8 and 9).

Hypothesis 1- Compared to the mean level of ED at T1, the mean level of ED increases significantly at T2 and at T3.

The difference in total ED from T1 to T2 was significant (z=-8.265, p=.000), and the difference from T1 to T3 was significant (z=-8.265, p=.000). Therefore, hypothesis 1 was supported.

Hypothesis 2- Compared to the mean level of lymph volume at T1, the mean level of lymph volume is significantly higher at T2 and T3.

The mean level of lymph volume was significantly higher at T2 compared to T1(*Mean*= 0 %, *SD* = 37) to T2 (*Mean* = 1%, *SD* = 5) was significantly higher (*z*=-3.289, *p*=.001), and significantly higher at T3 than at T1*(Mean*= 2 %, *SD*=8) (*z*=-3.695, *p*=.000). Therefore, hypothesis 2 was supported.

Hypothesis 3. Compared to the mean level of lymphedema symptom intensity at T1, the mean level of lymphedema symptom intensity is significantly higher at T2 and T3.

The change in mean total lymphedema intensity symptom scores from T1 to T2 was found significantly higher (*z*= -8.265, *p*=.000) and the change in mean total lymphedema symptom intensity score from T1 to T3 was found significantly higher (z= -6.912, *p*=.000). Therefore, hypothesis 3 was supported.

Table 6. Hypothesis 1–3 Findings

	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	T1 to T2 (*p*-value)	T1 to T3 (*p*-value)
*ED	.02(.19)	2.93 (4.39)	3.27 (5.34)	*z*=-8.265 (*p*=.000)	*z*=-6.912 (*p*=.000)
*Lymph Volume	.995 (0.37)	1.01 (0 05)	1.02 (0.08)	*z*=3.289 (*p*=.001)	*z*=-3.695 (*p*=.000)
*Lymphedema Symptoms	.5(2.5)	12.8 (10.5)	6. 28 (9.9)	*z*=8.265 (*p*=.000)	z= 6.912 (*p*=.000)

*Wilcox Singed Rank test

Hypothesis 4: Physiological factors are significantly associated with the level of ED symptom intensity (*i.e.*, no ED, intermediate level of ED, high level of ED) at T2 and T3.

Age is inversely related to ED symptom intensity at T2 and T3. As shown in Table 7, age was not associated with ED symptom intensity either at T2 (*F* (46.93) =1.205, *p* =. 223) or T3 (*F* (46.93) =.703, *p*=.906).

BMI is positively associated with ED symptom intensity at T2 and T3. As shown in Table 7, BMI was not significantly associated with the total level of ED symptom intensity at T2 ($\chi^2(2) = .216$, *p* =. 898), but was significantly associated with ED at T3 ($\chi^2(2) = 6.734$, *p*=.034).

Lymph volume increase is positively associated with ED symptom intensity at T2 and T3. As shown in Table 7, the mean lymph volume increase was not significantly associated with a higher level of ED symptom intensity at T2 ($\chi^2(2) = .400$, *p* =. 819), but was significantly associated with this outcome at T3 ($\chi^2(2) = 19.313$, *p* =. 001). Similarly, when lymph volume increase was dichotomized into < 5 % vs. ≥ 5%, a greater than 5% lymph volume was significantly associated with higher levels of ED symptom intensity at T3 ($\chi^2(2) = 15.377$, *p* =. 000). Therefore, hypothesis 4 was partially supported.

Table 7. Physiological factors on the level of ED (*i.e*., No ED vs. Intermediate level of ED vs. High level) of ED at 4-8weeks and 1-year post surgery

		4-8 wks Post				1 yr Post		
	No ED (n=47)	Interm (n=58)	High (n=35)	*p*	No ED (n=74)	Intem (n=31)	High (n=35)	*P*
Age (n=140) * Mean (SD)	51.9 (12.2)	53.1 (9.9)	50. (11)	*p=.265*	52.5 (11)	51.6 (11. 6)	51.1 (9.9)	*p=. 820*
BMI Mean (SD) ***	27.4 (5.9)	28 (6.9)	27.5 (6.5)	*p=.748*	26.7 (5.8)	28.4 (5.8)	28.9 (6.3)	*p=.034^*
** ≤24.9 kg/m2(n)	17	22	15	*p=.956*	35	10	9	*p=.199*
25.0–29.9 kg/m2(n)	13	17	11		18	10	13	
≥ 30 kg/m2(n)	15	19	9		19	11	13	
		Mean Rank		*p*		Mean Rank		*p*

		4-8 wks	Post			1 yr	Post	
	No ED (n=47)	Interm (n=58)	High (n=35)	*p*	No ED (n=74)	Intem (n=31)	High (n=35)	*P*
Lymph Volume Increase **	71.17	70.1	65.50	*p*=.819	58.8	62.2	93.63	*p*=.000^
< 5 %(n)	36	44	25	*p=. 541*	58	28	19	*p=.001^*
≥ 5 %(n)	8	14	9		12	3	16	

n may vary among variables based on number of missing items at each time point.
* Anova, ** Chi test, *** Kruskal-Wallis Test
^ p <.05.

To further examine the independent effects of overweight and obese BMI (compared to under- and normal-weight) and ≥ 5% lymph volume (compared to < 5% lymph volume) on the likelihood of high ED symptom intensity (≥ 5), binary logistic regression was conducted. ED symptom intensity was recoded into a dichotomous variable (0 = no ED, intermediate ED; 1 = high ED). Since BMI and lymph volume were significantly associated with the level of ED at T3, unadjusted and adjusted binary regression models were examined for the T3 period only. For the unadjusted model, BMI and lymph volume were entered individually. As shown in Table 8, overweight and obese BMI at T3 were not significant predictors of a higher likelihood of ED symptom intensity at T3, but ≥ 5% lymph at T3 was significantly associated with a 4.8 times higher likelihood of high ED symptom intensity at T3 compared to participants with < 5% lymph volume at this time period. For the adjusted model, BMI and lymph volume at T3 were entered into the model simultaneously to ascertain the independent effects of these variables on ED symptom intensity at T3. The adjusted model was statistically significant, X^2 (3) =14.943, p=.002. The model explained 15.3% (Nagelkerke R^2) of the variance in likelihood and correctly classified 74.3 % of cases. As shown in Table 8, participants with lymph volume ≥ 5% at T3 were 4.5 times more likely to have a high

level of ED symptom intensity, compared to participants with < 5% lymph volume at this time period. BMI was not an independent predictor in the adjusted model.

Table 8. Unadjusted and adjusted effects of higher BMI and > 5% lymph volume on high levels of ED symptom intensity at T3

	Unadjusted Model		Adjusted Model	
	Odds Ratio (p-value)	95% Confidence Interval	Odds Ratio (p-value)	95% Confidence Interval
Physiological factors				
Overweight BMI	2.270 (*p*=.099)	.858- 6.006	1.913	.693-5.280
Obese BMI	2.192 (*p*=.113)	.830- 5.785	(*p*=.210)	.679-5.235
Lymph volume ≥ 5%	4.828 (*p*=.000)	2.039-11.432	1.913 (*p*=.224) 4.467 (*p*=.001)	1.866- 10.691

Hypothesis 5- Situational factors are significantly associated with the level of ED symptom intensity (*i.e.*, no ED, intermediate level of ED, high level of ED) at T2 and T 3. As shown in Table 9, marital status, level of education, type of surgery, radiation therapy (yes/no), chemotherapy (yes/no), and hormonal therapy (yes/no) were not significantly associated with the level of ED symptom intensity at either T2 and T3. Therefore, hypothesis 5 was not supported.

Table 9. Associations between situational factors and lymphedema symptom intensity and of ED symptom intensity

		4-8 wks	Post			12 m	Post	
	No ED (n=47)	Interm (n=58)	High (n=35)	*p*	No ED (n=74)	Interm (n=31)	High (n=35)	*p*
Education**(n)				*p=.365*				*p=.302*
Associates degree or less	7	8	2		7	7	3	
Bachelor's degree	38	37	22		48	19	25	
Graduate degree or more	7	13	11		19	5	7	
Marital Status**(n)				*p=.056*				*p=.985*
Married/partnered	23	42	16		42	19	20	

		4-8 wks	Post			12 m	Post	
	No ED (n=47)	Interm (n=58)	High (n=35)	*p*	No ED (n=74)	Interm (n=31)	High (n=35)	*p*
Widowed/Separated/ Divorced	8	7	6		11	4	6	
Single, never partnered	16	9	13		21	8	9	
Surgery**				*p=.882*				*p=.604*
Mastectomy	24	31	16		42	13	16	
Lumpectomy	26	29	14		35	15	19	
Type of Therapy**								
Radiation	13	18	7	*p=.822*	24	6	8	*p=.210*
No	31	39	21		42	22	27	
Yes								
Chemotherapy	18	21	11	*p=.878*	27	11	12	*p=.777*
No	25	36	17		38	17	23	
Yes								
Hormonal Therapy	16	28	7	*p=.098*	28	13	10	*p=.170*
No	20	21	16		23	14	20	
Yes								
		Mean Rank		*p*		Mean Rank		*p*
Lymphedema symptoms*** (total)	52.83	74.04	92.87	*P=.000^*	41.81	95.89	107.71	*p=. 000^*
Impaired Mobility	56.97	74.48	85.08	*p=.006^*	47.95	90.63	101.4	*p=. 000^*
Fluid Accumulation	57.72	69.35	91.35	*p=.001^*	47.43	92.13	104.0	*p=. 000^*
Discomfort	47.41	73.40	86.03	*p=.000^*	77.03	48.87	101.0	*p=. 000^*
<9 symptoms**	28	23	9	*p=.048^*	73	18	14	*p=.000^*
≥ 9 symptoms	22	37	21		4	10	21	

n may vary among variables based on number of missing items at each time point.
** Chi test, *** Kruskal-Wallis Test
^ $p < .05$.

Hypothesis 6- The level of lymphedema symptom intensity at T 2 and T3 is positively associated with the level of ED symptom intensity (*i.e.*, no ED, intermediate level of ED, high level of ED) at T2 and T3.

As shown in Table 9, a higher lymphedema symptom intensity score was significantly associated with higher levels of ED intensity both at T 2 ($\chi^2(2) = 19.113$, $p = .000$) and T 3 ($\chi^2(2) = 84.276$, $p = .000$). The phenotype categories of lymphedema symptom intensity were also examined. A higher impaired mobility score was significantly associated with higher levels of ED symptom intensity both at T2 ($\chi^2(2) = 10.205$, $p = .006$) and T 3 ($\chi^2(2) = 59.465$, $p = .000$). A higher fluid accumulation score was significantly associated with higher levels of ED symptom intensity both at T2 ($\chi^2(2) = 13.217$, $p = .001$) and T 3 ($\chi^2(2) = 69.952$, $p = .000$). A higher discomfort score was significantly associated with higher levels of ED symptom intensity both at T2 ($\chi^2(2) = 20.694$, $p = .000$) and T3 ($\chi^2(2) = 62.642$, $p = .000$). Therefore, hypothesis 6 was supported.

To further examine the individual effects of lymphedema symptom intensity ≥ 9 on the likelihood of high ED symptom intensity at T2 and T3, unadjusted binary logistic regression model was examined for both time periods. As shown in Table 10, a lymphedema symptom intensity score ≥ 9 was not associated with odds on a high level of ED symptom intensity at T2, but this intensity score at T3 was associated with a 9.7 times higher likelihood of high ED symptom intensity at T3. Since BMI and lymph volume were significantly associated with high ED at T3 (Table 7), an adjusted binary logistic regression model was examined to determine the independent effect of lymphedema symptom intensity ≥ 9 on ED intensity at T3, controlling for the individual bivariate effects of BMI and lymph volume. The adjusted model was statistically significant, $X^2(4) = 36.349$, $p = .000$. The model explained 34.5 % (Nagelkerke R^2) of the variance in the odds of ED symptom intensity at T3 and correctly classified 79.4 % of cases. As shown

in Table 10, participants with lymphedema symptom intensity ≥ 9 at T3 were 8.7 times more likely to have a high level of ED symptom intensity at T3 compared to participants with a lymphedema symptom intensity score < 9 at this time period. Lymph volume ≥ 5% at T3 remained significant in the adjusted model and was associated with a 3.9 times higher likelihood of a high level of ED symptom intensity at T3 compared to participants with a lymph volume of < 5% at this time period. BMI was not a significant predictor in the adjusted model.

Table 10. Unadjusted and adjusted effects of higher BMI and > 5% lymph volume on high levels of ED symptom intensity

	Unadjusted Model			Adjusted Model	
	Odds Ratio (*p*-value)	95% Confidence Interval		Odds Ratio (*p*-value)	95% Confidence Interval
T2 Lymphedema Symptom Intensity≥9	2.017 (*p*=.112)	.848-4.796	T3 Obese	1.357(*p*=.591)	.445-4.140
			Overweight	1.209(*p*=.747)	.381-3.833
			≥5 % lymph volume	3.918(*p*=.006)	1.469-10.452
T3 Lymphedema Symptom Intensity ≥9	9.750 (*p*=.000)	4.045-23.50	Lymphedema symptom intensity≥9	8.670(*p*=.000)	3.362-22.356

Summary of Hypothesis Testing

As listed in Table 11 of the six hypotheses tested, three were fully supported, two were partially supported, and one was not supported.

Table 11. Summary of Hypothesis Testing

Hypotheses	Findings
F. Compared to the mean level of ED at T1, the mean level of ED increases significantly at T2 and T3	Supported.
G. Compared to the mean level of lymph volume at T1, the mean level of lymph volume is significantly higher at T2 and T3.	Supported
H. Compared to the mean level of lymphedema symptom intensity at T1, the mean level of	Supported

Hypotheses		Findings
	lymphedema symptom intensity is significantly higher at T2 and T3	
I.	Physiological factors are significantly associated with the level of ED symptom intensity	Partially Supported
J.	Situational factors are significantly associated with the level of ED symptom intensity	Not supported
K.	The level of lymphedema symptom intensity at T 2 and T3 is positively associated with the level of ED symptom intensity (*i.e*., no ED, intermediate level of ED, high level of ED) at T2 and T3	Supported

CHAPTER 5

Discussion of the Findings

This chapter provides a summary and interpretation of findings of ED in women who underwent surgery for breast cancer stage I-III. A TOUS theoretical proposition stipulates that symptoms have measurable dimensions (*i.e.,* intensity, timing, distress and quality) and may precede, lead to other symptoms, cluster together, reinforce each other, and influence outcomes (Lenz et al., 1997). Using the framework of the TOUS, a discussion of findings related to the theorized relationships among ED, physiological factors (*i.e*., age, BMI and lymph fluid volume), situational factors *(i.e.,* level of education, marital status, type of surgery, type of therapy) and lymphedema symptoms was presented.

ED in Breast Cancer Survivors

Few studies have examined the pattern of ED over time in breast cancer survivors. Some studies report decreases in ED over time in a majority of breast cancer survivors (Bloom et al., 2003; Carlson et al., 2013; Liu et al., 2014). On the other hand, other researchers have reported a sustained level of ED over time (Bidstrup et al., 2015). In this

study, the level of ED did not decrease over time. Notably, ED increased from the immediate post-surgery period to 12 months post-surgery. One out of four breast cancer survivors reported high levels of ED (≥ 5) at 12 months post-surgery and the percentage of participants who reported an ED level ≥ 11 was higher (14.3 %) at one-year post-surgery compared four to eight weeks post-surgery (6.4%). These findings are consistent with a published report that indicates 20% to 30% of woman with breast cancer experience ED distress (Janz et al., 2014). The findings of persistent ED over time in this study are also consistent with another study that revealed persistent severe ED trajectories up to six to eight months after diagnosis of breast cancer in a subgroup of 15% to17% of breast cancer survivors (Fobair et al., 2006).

In general, the findings from this study support empirical findings that indicate, in breast cancer survivors, acute emotional responses to breast cancer diagnosis and subsequent treatment in the immediate post-surgery phase may change to chronic emotional responses as time elapses beyond this period (Agarwal et al., 2013; Boinon, et al., 2014). Additionally, the findings of this study indicate that a substantial numbers of breast cancer survivors may also experience a high level of chronic ED. The pattern of ED in this study has implications for long-term assessments of and treatment for ED in women with breast cancer who have received surgical treatment.

Physiological Factors

The effects of physiological factors (*i.e.*, age, BMI, and lymph volume) on the level of ED was examined. Age was not significantly related to ED in this study. Notably, findings from previous studies are mixed regarding this relationship. Some studies report that younger women may be more likely to experience distress (Andreu et al., 2011;

Domanick et al, 2012; Kahn et al., 2012; Park et al., 2017). On the other hand, findings from other studies revealed no significant relationship between ages and ED (Costa-Requena et al., 2013; Pyszel et al., 2006). Park et al. (2017) noted in their study that the age category of ≤ 40 years was associated with high level of distress. In this study, only 12.9 % were 40 years of age or less, and it is likely that the small number of participants in this age group may have accounted for the negative theorized relationship between younger age and high levels of ED. More research is needed to further explore any effects of age on ED in breast cancer survivors.

BMI was associated with high ED at 12 months post-surgery in bivariate analysis, but was not an independent predictor in multivariate analysis. Similar to age, studies that have examined relationships between BMI and ED revealed disparate findings. While some studies reported no association between BMI and ED (Accortt et al., 2015; Donovan et al., 2014; Kim et al., 2013), others have reported an association between increasing BMI and ED (Lee et al., 2011). In this study, a majority of the participants (72.1%) maintained pre-surgery weight throughout the study year. Therefore, a lack of variation in BMI over time may have accounted, in part, for the negative findings when lymph volume was controlled for in multivariate analysis.

In this study, lymph volume was measured objectively using a perometer at pre-surgery, four to eight-weeks post-surgery and 12 months post-surgery. Lymph volume varied over time; 16.7 % and 22.3 % of participants had a lymph volume increase of ≥ 5 % at four- to eight-weeks and 12 months post-surgery, respectively. These findings are consistent with a systemic review of 72 studies that revealed the incidence of lymphedema in breast cancer survivors ranged between 8.4% and 21.4%, and the

incidence increased up to 2 years after diagnosis (Disipio et al., 2013). Lymph volume increases of ≥ 5 % were significantly associated with ED at 12 months post-surgery and not during the immediate post-surgery period. Moreover, participants with lymph volume increases of ≥ 5 % were 4.5 times more likely to have the high level of ED at 12 months post-surgery compared to women with < 5% level of lymphedema at this time period. These findings are consistent with published reports that lymph volume increases of ≥ 5 % enable detectable differences in QoL (Cormier et al., 2009; Fu et al., 2017). Even though, traditionally, lymph volume differences of ≥ 10% are considered a cutoff point for a lymphedema diagnosis (Moffat et al., 2006), the findings from this study revealed that participants with lymph volume increases of ≥ 5 % may not experience ED in the acute phase of breast cancer surgery recovery, but may experience this outcome in the chronic recovery phase. These findings also stipulate a need for clinical screening for ED in women who experience a lymph volume increase ≥ 5 %. More research is needed to further examine associations between objective measures of lymph volume and ED over time in this population of women.

Situational Factors

The effects of situational factors (*i.e.,* marital status, level of education. type of surgery and type of therapy) on the ED were also examined. Study findings revealed no significant association between marital status and the level of ED, and these findings were not consistent with several studies that reported a positive association between marital status and ED (Bierman, 2006; Hewitt et al., 2011). Even though living alone or without a partner may lead to more distress in individuals with breast cancer (Ridner et al., 2012; Towers et al., 2008), the link between living alone and distress may occur in

the context of more advanced cancer. This study was limited to persons with stage I-III breast cancer, and marital status may not be an important predictor of ED for these individuals. More research that examines this association is warranted.

There was also no association between the level of education and ED in this study, and findings from the empirical literature varies relative to this association. Vassard et al. (2010) reported higher education was associated with poorer psychological health in their 5-year longitudinal study of women with breast cancer. On the other hand, some studies reported patients with more education became less depressed (Schroevers et al., 2003), while others reported no association (Andreu et al., 2011). A majority of women in this study had a bachelor's degree or higher, and only 12% had only a high school education. The distribution of education in the study sample may account for the insignificant association with ED over time.

The effects of surgery (*i.e.,* mastectomy vs. lumpectomy) on the level of ED over time was examined in this study, and no significant association was found. This negative finding is consistent with a negative association between surgery type and ED found in other studies (Cook et al., 2018; Kahn et al., 2012). On the other hand, Schubart et al. (2014) reported more extensive surgery (bilateral mastectomy *vs*. unilateral mastectomy *vs*. lumpectomy) was correlated with higher levels of psychosocial distress over time. Conversely, Den Oudsten et al. (2009) examined predictors of depressive symptoms 12 months after surgical treatment of early-stage breast cancer and reported that lumpectomy rather than mastectomy or no surgery predicted depression 12 months after diagnosis.

Similarly, the effects of treatment modality (*i.e.,* radiation, chemotherapy and hormonal therapy) on ED was also examined in this study, and no association was found.

This finding is consistent with findings from a recent systemic review of ten studies that examined treatment type in breast cancer that revealed no effect of the type of therapy on distress outcomes in eight of these investigation studies found (Cook et al., 2018).

Lymphedema Symptoms

In this study, the intensity experienced from 26 lymphedema symptoms and three symptom intensity phenotypes (*i.e.,* impaired mobility, fluid accumulation, discomfort) were examined over time. The total level of lymphedema symptom intensity, including the total intensity all three phenotypes of lymphedema symptoms, was significantly associated with the level of ED both at four- to eight-weeks and 12 months post surgery. Interestingly, the likelihood of having a high level of ED for those with a lymphedema symptom intensity score ≥ 9 was not significant (OR=2.017, p=.112) at four- to eight-weeks post-surgery. However, participants with a lymphedema symptom intensity of ≥ 9 at 12 months post-surgery had almost a ten times higher likelihood of experience high levels of ED compared to women with lymphedema symptom intensity < 9. This suggests that lymphedema symptoms in the acute phase of surgery recovery may not affect the level of ED, but the persistence of these symptoms at 12 months post-surgery leads to high levels of ED. These findings are consistent with findings from several studies that reported significant associations between increased lymphedema symptoms and reductions in emotional wellbeing (Chachaj et al., 2010; Fu et al., 2012; Kahn et al., 2012; O'Toole et al., 2015; Shah et al., 2012; Teo et al., 2015). The findings also underscore the need for long-term assessment and treatment of lymphedema symptoms in women after breast cancer surgery.

In summary, despite improvements in breast cancer prognosis, the diagnosis of breast cancer and its treatments can have a profound emotional impact. In this study, the level of ED over time did not decline spontaneously and increased long after after surgical treatment. Situational factors examined in this study were not associated with ED over time. Two physiological factors, BMI and lymph volume were significantly associated with ED post-surgery. Finally, lymphedema symptom intensity was significantly associated with ED post-surgery. Lastly, a lymph volume increase of ≥ 5 % and a high level of lymphedema symptom intensity score ≥ 9 were independently associated with a likelihood of high ED 12 months post-surgery.

Usefulness of the TOUS in Explaining the Trajectory of ED in Women with Breast Cancer after Surgical Intervention

According to Lenz et al. (1997), the TOUS postulates that physiological, psychological, situational influencing factors and unpleasant symptoms affect health outcomes, such as ED. Psychological antecedents to ED were not examined in this study. Two of the three physiological factors examined in this study, lymph volume and BMI, were significantly associated with the trajectory of ED over a one-year period. Similarly, the theorized relationship between lymphedema symptoms and ED were significant. None of the four situational factors were significantly related to ED as theorized. Thus, the theory constructs of physiological factors and lymphedema symptoms were useful in explaining the trajectory of ED over time in this study. The situational factors examined were not useful in explaining ED. In the future, other situational factors could be considered.

CHAPTER 6

Summary, Conclusions, Limitations, Implications, Directions for Future Research

Summary

This purpose of this study was to examine predictors of ED in breast cancer survivors with BCRL who underwent surgery for breast cancer stage I-III. The overarching aims of study were to determine the 1) pattern ED, lymph volume, and lymphedema symptoms, and 2) influencing factors associated with ED for women with breast cancer stage I-III in the first year of cancer treatment. Guided by the TOUS, the effects of physiological and situational factors, and lymphedema symptoms on the level of ED were examined.

This study was an analysis of secondary data from a primary, prospective, longitudinal study aimed at exploring the phenotype of arm lymphedema defined by lymph volume and lymphedema symptoms in relation to inflammatory genes in women treated for breast cancer. One hundred forty women who were diagnosed with a first-time diagnosis of stage 1-III breast cancer and were scheduled for surgical treatment were enrolled and followed for 12 months after surgery at pre-surgery, four -to eight-weeks post-surgery, and 12 months post-surgery. Lymph volume was measured by a perometer, and 26 lymphedema symptoms and 12 ED symptoms were collected using the BCL-SEI. Chi-square analyses were performed to estimate the associations between categorical demographic and clinical predictors. Independent groups t-tests, paired t-tests, and ANOVAs were used to compare groups on normally distributed continuous variables. Mann- Whitney, Chi-Square, Wilcoxon Signed Rank and Kruskal-Wallis test of ranks were used for variables that were not normally distributed or categorized. Binary

regression was used to examine independent predictors of ED for variables significantly related to this outcome in bivariate analyses.

Mean age of the sample was 52 years and ranged from 26 to 81. The majority of participants were married or partnered (57.9 %) with at least a bachelor's degree (65.7%). The participants reported their race/ethnicity as white (60.7%), Asian (10.0 %), black/African American (19. 3%), or Hispanic (8.6%). About a half of participants (50.7 %) underwent a mastectomy. More than 70% of participants had radiation therapy, 60.9 % of participants received chemotherapy and 52.8 % of participants underwent hormonal therapy. Mean BMI ranged from 27.5 to 27.7 over the three time periods. Mean percentage of increased lymph fluid volume was one percent (*SD*=0.05) and two percent (*SD*=0.08) at four- to eight- weeks and 12 months post-surgery, respectively. Mean lymphedema symptom intensity score was .5 (*SD*=2.47), 12.8 (*SD*= 10.49) and 6.3 (*SD*=9.9) at pre-surgery, four- to eight-weeks post-surgery and 12 months post-surgery, respectively. Mean ED symptom intensity score was .02 (*SD*=.19), 2.93 (*SD*=4.39) and 3.27 (*SD*= 5.34) at pre-surgery, at four- to eight-weeks post-surgery and 12 months post-surgery, respectively. Hypotheses examined and findings in this study were as follows.

1. **Compared to the mean level of ED at T1, the mean level of ED is significantly at T2 and at T3.**

   ED was significantly higher at four- to eight-weeks (T2) and 12 months (T3) post-surgery compared to baseline (T1).

2. **Compared to the mean level of lymph volume at T1, the mean level of lymph volume is significantly higher at T2 and T3.**

Lymph volume was significantly higher at four- to eight-weeks post-surgery (T2) and 12 months post-surgery (T3) compared to pre-surgery (T1).

3. **Compared to the mean level of lymphedema symptom intensity at T1, the mean level of lymphedema symptom intensity is significantly higher at T2 and T3.**

   The level of lymphedema symptom intensity was significantly higher at four- to eight-weeks post-surgery (T2) and 12 months post-surgery (T3) compared to pre-surgery (T1).

4. **Physiological factors are significantly associated with the level of ED symptom intensity (*i.e.*, no ED, intermediate level of ED, high level of ED) at T2 and T3.**

   BMI and a lymph volume increase ≥ 5% were significantly associated with the level of ED only at 12 months post surgery. In the adjusted binary logistic regression model, participants with lymph volume ≥ 5% at 12 months post-surgery were 4.5 times more likely to have a high level of ED, compared to participants with < 5% lymph volume at this time period. BMI was not an independent predictor.

5. **Situational factors are significantly associated with the level of ED symptom intensity (*i.e.*, no ED, intermediate level of ED, high level of ED) at T2 and T 3.**

Situational factors (marital status, level of education, the type of surgery, the type of therapy) were not associated with the level of ED both at four- to eight-weeks and 12 months post-surgery.

6. **The level of lymphedema symptom intensity at T 2 and T3 is positively associated with the level of ED symptom intensity (*i.e.*, no ED, intermediate level of ED, high level of ED) at T2 and T3.**

   A higher lymphedema symptom intensity score was significantly associated with higher levels of ED at both four- to eight-weeks and 12 months post-surgery. Each of three phenotypes of the lymphedema symptom intensity score (*i.e.,* impaired mobility, fluid accumulation and discomfort) was significantly associated with higher levels of ED at both four- to eight-weeks and 12 months post surgery. A lymphedema symptom intensity score ≥ 9 was independently associated with a 9.7 times higher likelihood of high ED symptom intensity at 12 months post-surgery.

Conclusion

This study revealed a pattern of increased lymph volume, lymphedema symptoms and ED symptoms in the acute surgical recovery phase (four to eight weeks post-surgery) and the chronic recovery phase (12 months post-surgery). Two factors significantly associated with the level of ED were found. A lymph volume increase ≥ 5 % and lymphedema symptom intensity score ≥ 9 were independent predictors of high ED at 12 months post-surgery. These findings highlight the importance of long-term screening for and treatment of lymphedema symptom and ED in women with breast cancer who have undergone surgical treatment.

Limitations

Inherent to the nature of the secondary analysis of existing data, the primary limitation of this present study that analyses and results were dependent on the data that had been collected in the primary study. The treatment strategy for breast cancer stage I-III is based on the extent and location of tumor, biology of tumor *(i.e*., pathology, biomarker, and gene expression), age and menopausal status at the time of diagnosis, comorbidities and preference of the patient. Woman with breast cancer, in addition to surgery, may undergo therapy that includes radiation therapy, neoadjuvant or adjuvant chemotherapy, adjuvant hormonal, Her2 neu targeted therapy or some combination of these. Generally, adjuvant chemotherapy lasts five months after surgery and intravenous Her2 neu targeted therapy lasts up to a year post surgery. Those with hormone receptor – positive in the lymph nodes who completed a year of intravenous Her2 neu targeted therapy may undergo an additional oral Her2 neu targeted therapy for another year. Some may undergo breast reconstruction after breast surgery, which may take many months. Even though the data in the primary study were comprehensive, examining the types of treatment details in relation to ED symptoms over time was not feasible. Therefore, the extent to which the trajectory of ED found in this study was also associated with concomitant treatments could not be determined. Lastly, the primary study was conducted in a single institution, and therefore, the findings in this study may have limited generalizability.

Implications

Given the improved survival of stage I-III breast cancer, serious consideration should be given to the evaluation of ED in this group. Lymphedema is one of the most

important factors that elicit daily stress in breast cancer survivors (Fu et al, 2014). Breast cancer survivors face a life-long risk of developing lymphedema and there is no cure for lymphedema. Our findings offer clinically relevant evidence- based knowledge regarding lymphedema, lymphedema symptoms and ED symptoms to inform the health care professionals to improve of the care in breast cancer survivors. Our results can be used to assist in the early detection and assessment of ED and lymphedema symptoms in either the absence or presence of lymphedema in breast cancer survivors.

Directions for Future Research

The followings are recommended for future research.

1. Additional studies are necessary to reproduce the findings in this study within a large group in a longer follow- up period to understand the trajectory of ED symptoms in relations to physiological and situational factors and lymphedema symptoms.
2. Currently, there is no consensus regarding the definition and quantification lymphedema in order to establish and accurate diagnosis of this condition. A consensus on the ideal measures for lymphedema, lymphedema symptoms, and ED symptoms would be valuable to further screen for early detection and consequent intervention.
3. Patient-reported signs and symptoms are often the first indication of clinically relevant lymphedema. However, there is a dearth of studies that compared an objective lymph volume increase to self-report of arm swelling and lymphedema symptoms to assess the diagnostic accuracy of self- report of lymphedema. The

development and validation of a self-report measure of lymphedema is necessary for clinical practicality and cost-effectiveness for early detection.

4. Trunkal lymphedema may also occur and affect lymphedema symptoms and the level of ED in breast cancer survivors. Thus, it is prudent to assess trunkal lymphedema in research in order to sufficiently determine the impact of lymphedema.
5. Breast cancer survivors experience various lymphedema symptoms that affect ED symptoms in breast cancer survivors. These symptoms may affect social functioning outcomes in breast cancer survivors. Therefore, the relationship between lymphedema and ED symptoms and social functioning outcomes should be explored.
6. Comprehensive evidence has accumulated associating ED symptoms with increased activity in the inflammatory processes (Howren et al., 2009). More research is needed to examine associations between inflammatory biomarkers and ED symptoms in breast cancer.

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