

PREDICTORS OF QUALITY OF LIFE WITH AXILLARY REVERSE MAPPING IN  
BREAST CANCER SURVIVORS

By

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## Abstract

Breast cancer is the second most common cancer among women in the United States. Sentinel lymph node biopsy for staging early breast cancer in clinically node negative patients is supported by the American Society of Clinical Oncology due to a greater morbidity associated with axillary lymph node dissection. Quality of life benefits of sentinel lymph node biopsy compared to axillary lymph node dissection are inconsistent and many studies have used quality of life questionnaires alone.

This descriptive correlational study was a primary analysis of factors that predicted quality of life over two years based on a modified Health Related Quality of Life Model. The sample consisted of 185 women, ages 29 to 88 who had the new axillary reverse mapping surgical procedure following an axillary lymph node dissection with sentinel lymph node biopsy or axillary lymph node dissection with or without sentinel lymph node biopsy. Descriptive analyses were conducted for occurrence of lymphedema and measures of physical function, general health perceptions, and health-related quality of life over two years. Individual characteristics, relationships of biological factors, symptoms, and functional status to general health perception and health-related quality of life were evaluated through separate regression analyses conducted at three time points over two years. Data were collected from the SF-36 and the axillary reverse mapping surgery form.

Up to 31% of the variance in *General Health Perception* was explained by seven variables (age, body mass index, surgery, pain, lymphedema, physical functioning, and strength) with physical functioning and pain contributing the most. As much as 37% of variance in mental component summary was explained by the same seven variables with physical functioning and pain contributing the most. Only 19% of the variance for physical component summary was

explained by five variables (age, body mass index, surgery, lymphedema, and muscle strength) with body mass index and muscle strength contributing the most at two years. Results provide information to help nurses formulate extended interventions and education for improving the perceptions and objective outcomes of women after undergoing axillary surgery for breast cancer.

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## **Chapter 1**

### **Introduction**

Breast cancer is the second most common cancer among women in the United States and the second leading cause of death in women (American Cancer Society, 2013). Nearly one in eight (12%) women in the United States will develop invasive breast cancer during their lifetime. The American Cancer Society estimates approximately 232,340 new cases of invasive breast cancer will be diagnosed in the United States during 2013. The overall five-year survival is 89%, thus the prevalence of women who have undergone breast cancer is very high (National Cancer Institute, 2013).

The clinical stage of breast cancer guides the surgical approach. American Joint Committee on Cancer uses the TNM (T-tumor, N-nodes, M-metastases) system for staging to determine breast cancer prognosis (Edge et al., 2010). The most common treatment for women with localized breast cancer is surgical excision and staging axillary lymph node evaluation with or without radiation therapy. Based on treatment guideline, staging and prognostic factors, and the cancer care provider's recommendations, a woman may receive neoadjuvant chemotherapy or hormonal therapy administered to shrink a tumor before definitive removal of the tumor. Other treatment options are adjuvant chemotherapy, hormonal therapy, or monoclonal antibody therapy with the goal of eliminating or delaying disease recurrence (Bradley, 2007). Prognostic factors are important indicators at the time of surgery to evaluate the associated disease-free or overall survival if no systemic adjuvant therapy is administered (Cianfrocca & Goldstein, 2004). Lymph node metastasis is an important prognostic factor for breast cancer. Sixty-one percent of women with invasive breast cancer are estimated to have localized disease (Stage 0-IIIB) with cancerous cells confined to the original cell layer or to breast lobes or ducts (with no metastatic

disease in the lymph nodes). Thirty-two percent have regional disease (i.e., spread to regional lymph nodes).

Breast-conserving surgery is considered the standard procedure in early breast cancer generally followed by radiotherapy (Kaufmann, Morrow, von Minckwitz, & Harris, 2010). Initially after treatment, breast-conserving surgery is credited for providing a better body image than mastectomy (Arndt, Stegmaier, Ziegler, & Brenner, 2008). Mastectomy is the treatment of choice when there is high risk for local recurrence.

In theory the sentinel lymph node(s) are the first draining lymph nodes from the primary breast tumor (National Cancer Institute, 2013). The sentinel lymph node (s) are removed and evaluated for cancer. Selective sentinel lymph node biopsy (SLNB) is used in early breast cancer tumors with clinically and ultra sound negative involvement of the axilla to determine node spread. When sentinel lymph node dissection is performed precise staging of the number of positive lymph nodes can be used to direct further treatment options (Glechner et al., 2013). Due to a greater morbidity associated with axillary lymph node dissection (ALND), SLNB for staging early breast cancer in clinically node-negative patients is supported by the American Society of Clinical Oncology (Lyman et al., 2005).

National Comprehensive Cancer Network (NCCN, 2013) guidelines recommend no further surgery in women with negative SLNB and ALND for selected women with a positive SLNB. Avoiding ALND is desirable since complications of the procedure such as lymphedema, numbness, and stiffness in the arm can impact quality of life. Lymphedema may occur early or late and frequently negatively affect function (Stout et al., 2012). Early intervention in patients with lymphedema may reduce the need for extensive rehabilitation and demonstrate a cost savings.

Some studies have compared SLNB and ALND, showing that SLNB is associated with shorter hospital stay, quicker return to normal activity, and reduced rates of short- and long-term morbidities, such as infection, seroma, shoulder mobility impairment, neuropathy, and upper limb edema (Belmonte et al., 2012). Quality of life benefits of SLNB compared to ALND are inconsistent. Quality of life studies have presented with problems such as absence of pretreatment assessment and reliable and valid quality of life tools. Goals in “Healthy People 2020” include not only disease and disability related conditions, but also those related to quality of life. According to Bredow, Peterson, and Sandau (2009) the term health-related quality of life is used to describe a more limited focus on areas of life most closely influenced by an individual’s health. As an interdisciplinary model health related quality of life includes measurement of variables that are traditionally important to nursing such as holistic consideration of an individual’s reactions to actual or potential illness.

This proposed study is a primary analysis of the secondary outcomes not yet evaluated from the “Axillary Reverse Mapping: A Prospective Study in Women with Clinically Node Negative and Node Positive Breast Cancer” (Connor et al., 2013). Axillary reverse mapping (ARM) is a surgical procedure that uses blue dye to locate axillary arm lymphatics, such as the lymphatic channels or blue dye lymph nodes.

The analyses of the secondary objectives were designed to evaluate occurrence of lymphedema and quality of life variables at set clinical follow up points and to compare quality of life measures between women with and without lymphedema. Quality of life and pain measured by (SF-36) were continuous and measured repeatedly over time (baseline, six months, one, two, and three years). Baseline demographics and screening information were recorded.

## **Background and Significance**

The status of the axillary nodes is still the most important prognostic factor for directing the impact of treatment. Reported in the ACOSOG-Z0011 phase III randomized trial of ALND in women with stage I or IIA breast cancer and positive lymph nodes (Lucci et al., 2007), SLNB has gained preference over ALND for the staging of early breast cancer due to less morbidity and the questionable survival benefits of ALND. These findings were part of a trend to move away from radical surgery for breast cancer. Rates of mastectomy declined in the 1980s after research showing survival rates following lumpectomy and radiation were comparable to those after a mastectomy (Fisher et al., 1989). According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2013) approximately 89% of these women may be eligible for surgery involving resection of the axillary lymph nodes.

Lymphedema is a recognized complication following axillary staging for breast cancer. Sentinel Lymph Node Biopsy has reduced the risk with a reported 5-8% with SLNB alone compared to at least 13% after ALND (Ashikaga et al., 2010; Mansel et al., 2006).

Lymphedema is an important consideration for nurses caring for breast cancer survivors due to its relatively high frequency and significant functional and quality of life implications for patients.

## **Quality of Life**

Some studies have shown that breast cancer survivors with arm lymphedema experience a poorer quality of life and more psychological distress than women without lymphedema (Pyszel, Malyszczak, Pyszel, Andrzejak, & Szuba, 2006; Ridner, 2005). Women who reported arm swelling also reported a significantly lower quality of life with multiple functional assessments (Paskett, Naughton, McCoy, Case, & Abbott, 2007). Shih et al. (2009) reported that

the psychosocial effects of breast cancer related to lymphedema to be as distressing as the primary diagnosis of breast cancer. Women with breast cancer-related lymphedema have been reported to have a poorer quality of life, greater level of anxiety or depression, higher risk of chronic pain, fatigue, and added difficulty functioning socially and sexually compared to women with no lymphedema (Shih et al., 2009).

### **Health and Illness Over Time**

According to Henly, Wyman, and Findorff (2011), change in health and illness over time is key to developing and evaluating interventions for individuals, families, and specific populations. The phrase health care trajectory is a concise and useful way to define change in health status over time. Understanding the path and cause of change in health over time allows anticipation of those at greatest risk for complicated trajectories and events, improves understanding of factors that impact change in health over time, and allows evaluation for outcome of interventions on the trajectory. Increased understanding about the course and causes of change in health status over time creates the possibility of control by impacting the trajectory.

With the use of random effects models for longitudinal data, advances in statistical modeling and computing have opened new avenues for designing longitudinal studies and analyzing results related to change (Laird & Ware, 1982; Muthen & Muthen, 2000). Valid health indicators should be used to measure change in values over time (Henly et al., 2011). At present nursing research has been perceived as variable focused and for the most part lacks use of repeated measures or longitudinal designs needed to support a personalized science approach.

A health trajectory science approach provides applicable knowledge for improving nursing care and optimal outcomes, at the time of care and beyond for individual patients. Whether evaluating the course of a health experience or assessing the impact of an intervention

on health over time, theory about change, temporal design of a study, and a statistical model to define the influence of time on health is essential to underscore the individual experience (Henly et al., 2011).

### **Theoretical Model**

The framework for this study is based on a modification of the Wilson and Cleary's (1995) original theoretical model of the Health-Related Quality of Life by Ferrans et al. (2005). Ferrans' model (2005) as presented in Figure 1 consists of five domains of the original model: biological function, symptoms, functional status, general health perception, and overall health-related quality of life. Overall Health-Related Quality of Life is described as subjective well-being related to how happy or satisfied an individual is with life (Wilson & Cleary, 1995). The biological component is described as a continuum with the ultimate molecular, cellular, and organ function at one end and serious life threatening at the opposing end of the spectrum. The biological components in the current study that may pose threats to the biological process were body mass index, type of axillary surgery, and chemotherapy. The symptom component is described as the individual's perception of abnormal physical and emotional states. Symptoms assessed included pain (subjective) and lymphedema (objective assessment). Functioning is defined by physical, psychological social, and role function. Physical functioning was measured by the SF-36 scores, muscle strength, and shoulder flexibility (recorded on the axillary reverse mapping form). General health perceptions signify a subjective scoring that includes all preceding health concepts. Overall quality of life is denoted as subjective well-being that is referring to how happy or satisfied an individual is with life as a whole. Each domain is related to the others and reciprocal links likely exist. Explicit definitions were provided to better explain individual characteristics (i.e., intrapersonal factors) and environmental characteristics (i.e.,



interpersonal factors, institutional factors, community factors, and public policy). Ferrans et al. (2005) model connects specific clinical factors to Health-Related Quality of Life. In general the Ferrans et al. model has been described as complex due to the multiple relationships.

Following the development of a substruction model (See Appendix A), a modification of the Health-Related Quality of Life model (Ferrans et al, 2005) was used as the foundation of this study to identify factors affecting the health related quality of life in women undergoing axillary surgery after the diagnosis of breast cancer. The variables included in this study are illustrated in Figure 1. The model was revised in an effort to simplify and clarify the critical elements of health related quality of life for women post axillary surgery and to establish causal relationships among them. The solid lines indicate the research questions to be tested in this study. The dotted lines indicate potential future use of the model.

Figure 1. Modified Model of Health-Related Quality of Life (HRQOL)

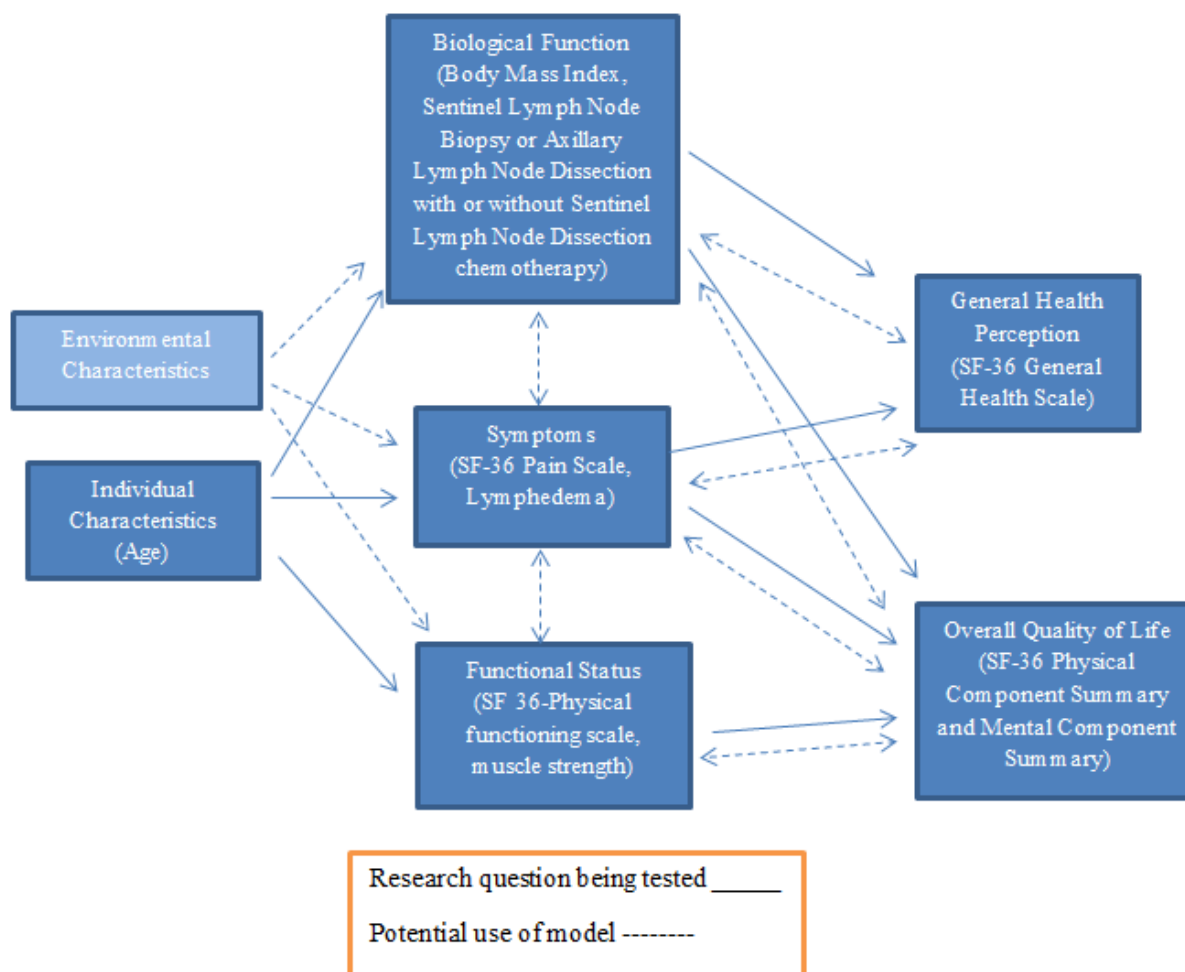


Figure 1. Adopted from “Conceptual Model of Health-Related Quality of Life,” by Ferrans, C. E., Zerwic, J. J., Wilbur, J. E., & Larson, J. L, 2005, *Journal of Nursing Scholarship*, 37, p. 338.

The quality of life factor domains in early breast cancer patients post SLNB with or without ALND may include biological function, symptoms, functional status, general health perceptions, and overall quality of life. Exploring quality of life domains most relevant to breast cancer survivors’ post-axillary lymph node surgery is critical in determining areas of intervention to help improve physical and mental components for health-related quality of life for two years

post-surgery. Demographics, muscle strength, shoulder flexibility, and the SF-36 were sources used to measure the various domains. The modified health-related quality of life proposed in this study was designed to examine the relationship of lymphedema (yes/no) and treatment (SLNB or ALND with or without SLNB) and (a) characteristic of the individual, (b) biological factors, (c) symptoms, and (d) functional status, to general health perceptions and overall health-related quality of life of breast cancer survivors who received a post axillary reverse mapping procedure with SLNB or ALND with or without SLNB. In the studied breast cancer sample individual characteristics biological function, symptoms, and physical function were evaluated as simultaneous and independent predictors for general health perception and overall quality of life.

### **Statement of Problem**

Approximately one-third of breast cancer survivors in general, the majority being African American women, presents with regional disease and positive lymph nodes; consequently, they require complete ALND (Sagen et al., 2009). The relationship of physiological indicators associated with breast post-axillary breast cancer surgery and measures of quality of life are not well characterized. Belmonte et al. (2012) reported that many studies evaluating quality of life have used quality of life questionnaires alone. A meta-analysis of six studies in more than 11,500 women reported a higher risk for harm with ALND than SLNB. Literature on relevant health outcomes over time is missing. According to Belmonte et al. (2012) controversy remains regarding quality of life benefits for SLNB compared to ALND in breast cancer patients. Estimates of the incidence and prevalence of lymphedema vary greatly (Poage, Singer, Armer, Poundall, & Shellabarger, 2008). Nurses and health care providers can use information from this study to provide tailored intervention and education to support women post breast axillary lymph node surgery throughout their health care trajectory.

## **Purpose of Study**

The purpose of the study was to identify components (i.e., individual characteristic [age], biological factors [body mass index, SLNB or ALND with or without SLNB, chemotherapy], symptoms [pain and lymphedema versus no lymphedema], and functional status [muscle strength, shoulder flexibility, and SF-36 physical function scale score] within the modified Health-Related Quality of Life model (Ferrans et al., 2005) that may predict general health perspective (SF-36 general health perception score) and overall quality of life (SF-36 physical and mental scores) of women with early breast cancer over time during the first 2 years after surgery (See Table 1, p. 38). The objective is to establish risk groups among women undergoing the newer axillary reverse mapping procedure for establishing those who may benefit from additional intervention.

**Research Questions.** The following research questions were explored:

1. What are the levels of pain, physical function, general health perceptions and health related quality of life over time (baseline, six months, one year, and two years) for women after axillary reverse mapping procedure?
2. Are there differences in physical function for women who had SLNB only or ALND with or without SLNB and women who did or did not receive chemotherapy measured over time (baseline, six months, one year, and two years)?
3. What is the occurrence of lymphedema (Yes/No) with measures of physical function, general health perception, and health-related quality of life over time (baseline, six months, one year, and two years)?
4. Controlling for an individual characteristic (age) what are the relationships of biological factors (body mass index, SLNB or ALND with or without SLNB), symptoms (pain), and

functional status (SF-36 function score, muscle strength, flexibility) to general health perception and health-related quality of life at three separate time points (six months, one year, and two -years).

### **Assumptions**

Subjects' self-reported quality of life reflected their actual quality of life. Understanding relationships between these components will support the future design of optimally effective clinical interventions.

### **Definitions of Terms**

The following are terms defined for the present study:

#### **Adjuvant Therapy**

Adjuvant therapy as a treatment for breast cancer is administered after primary therapy to improve the chance of long term survival (National Cancer Institute, 2013). Primary therapy for breast cancer generally includes surgery such as mastectomy or lumpectomy. Oncologist provides adjuvant therapy to destroy any cancer cells that may have spread, even if undetected by imaging or laboratory tests. Adjuvant therapy for breast cancer may include chemotherapy, hormonal therapy, targeted drug therapy, and/or radiation therapy.

#### **Axillary Lymph Node Dissection**

An axillary lymph node dissection is a surgical procedure to remove lymph nodes from the axillary region.

#### **Axillary Reverse Mapping (ARM)**

Axillary reverse mapping is an intraoperative technique designed to establish the lymphatic drainage in the upper extremity during a sentinel lymph node biopsy or axillary lymph node dissection. This procedure involves injection of dye to identify lymphatic drainage from the arm to enable preservation of lymphatic vessels. The technique had been examined for the

prevention of upper extremity lymphedema in patients undergoing surgery for breast cancer (Boneti et al., 2012).

### **Breast Conserving Surgery**

Breast-conserving surgery is performed to remove the breast cancer without removal of the entire breast. Examples of breast conserving surgery are lumpectomy (removal of the lump), quadrantectomy (removal of one quarter, or quadrant of the breast tissue), and segmental mastectomy (the cancer as well as some of the breast tissue and around the tumor and lining of the chest muscle beneath the tumor).

### **Clinical Staging**

Staging is a standardized way for physicians to evaluate findings related to how far the cancer has spread. The most common system to depict staging of breast cancer is the American Joint Committee on Cancer TNM (tumor, nodes, and metastasis) system. Breast cancer staging is determined by the results of physical exam, biopsy, and imaging tests (referred to as clinical staging), or on the findings of these tests in combination with the findings from surgery (pathological staging) (Edge et al., 2010).

### **Contralateral Lymph Node**

Lymph node located on the opposite side of the body as the breast cancer (National Cancer Institute, 2013).

### **Crossover**

A crossover event consists of identification of one or more lymph nodes that are both focally radioactive after Tc99m injection and noticeably stained blue after ipsilateral arm injection with Lymphazurin (Connor et al., 2011).

**Early Breast Cancer**

The term early stage breast cancer is used in reference to cancer that has not spread beyond the breast or axillary lymph nodes. It generally includes ductal carcinoma in situ and stages I, IIA, IIB, and stage IIIA breast cancers (National Cancer Institute, 2013; National Comprehensive Cancer Network, 2013).

**Ipsilateral Lymph Node**

Lymph node located on the same side of the body as the breast cancer (National Cancer Institute, 2013).

**Lymphedema**

Lymphedema is a condition that can occur when axillary lymphs are removed during breast cancer surgery (National Cancer Institute, 2013). Lymphedema is defined by Connor et al. (2011) as a change in arm circumference of greater than 2 cm when compared to the contralateral arm and with the baseline measurement.

**Modified Radical Mastectomy**

The operation involves removal of the entire breast, including skin, areola and nipple, as well as most of the axillary lymph nodes, sparing the muscle (Cotlar, Dubose, & Rose, 2003).

**Neoadjuvant Therapy**

Primary therapy for breast cancer generally includes surgery such as mastectomy or lumpectomy (National Cancer Institute, 2013). Neoadjuvant therapy is treatment administered before primary therapy.

**Sentinel Lymph Node**

The sentinel lymph node is the first lymph node to where cancer is probable to spread from the breast tumor (National Cancer Institute, 2013). There may be more than one sentinel

lymph node. When cancer metastasizes it may appear first in the sentinel node prior to spreading to other lymph nodes.

### **Lymph node status**

Lymph node status determines whether or not the lymph nodes in the underarm (axillary nodes) are cancerous. Lymph node-negative indicates the lymph nodes do not contain cancer and lymph-node positive indicates they lymph nodes do contain cancer. A physical exam (also referred to as clinical exam) can give an initial estimate of lymph node status (Komen, 2013).

### **Summary**

A large portion of women with a diagnosis of breast cancer undergo axillary staging with approximately 5% developing lymphedema with SLNB and 20 % ALND. Avoiding ALND is favorable due to complications such as lymphedema, numbness, and stiffness in the arm impacting quality of life. Quality of life benefits of SLNB compared to ALND are inconsistent with many studies having used quality of life questionnaires alone. Axillary reverse mapping is an emerging surgical procedure using blue dye to locate axillary arm lymphatics. A modified conceptual model was developed from the health related quality of life model to determine predictors of quality of life in breast cancer survivors undergoing axillary reverse mapping procedure.

This primary analysis of the secondary outcomes was proposed to address the lack of literature on quality of life measures over time in patients who have or have not had this new surgical procedure to reduce the possibility of lymphedema and other morbidities occurring. The descriptive correlational design provides a foundation to describe variables over a two year period and the relationship among the variables. Relationships of biological factors, symptoms, and functional status to general health perception and health-related quality of life will be evaluated through regression analysis at 3 time points over two years. Findings from this study



will contribute to knowledge that can lead to future nursing interventions to improve the quality of life of breast cancer survivors with and without lymphedema.

## **Chapter 2**

### **Review of Literature**

The purpose of this literature review was first to give an overview of health related quality of life models and the increased use of such models as a framework for the analysis of clinical variables and quality of life. The second and primary portion of the review addresses research that explores the elements of health-related quality of life and their determinants. The concepts presented are biological factors (body mass index, SLNB or ALND with or without SLNB, and chemotherapy,), symptoms (pain and lymphedema), functional status (SF-36 physical function scale score, muscle strength, and shoulder flexibility), general health perceptions, and overall quality of life in women post-axillary lymph node surgery. The review examined factors that may influence the five main components such as an individual characteristic (age). Finally, research studies or theoretical information related to determination of quality of life are presented.

The information gathered from the literature review includes both published and unpublished books, journals, periodicals, and webpages from 1980 through November, 2013. The search was conducted using PubMed and Cumulative Index of Nursing and Allied Health. An internet search was completed using the Google Scholar search engine at the World Wide Website. After articles were reviewed, a secondary review of references and bibliographies was conducted.

#### **History of Quality of Care in Oncology**

Nearly 30 years have passed since the founding of the National Coalition for Cancer Survivorship (Hoffman, 2004). When the National Coalition for Cancer Survivorship's founding members met in 1986 they rejected the historic definition of a cancer survivor as an individual

who had remained disease free for five years (Rowland, 2006). Since then they have been instrumental in embracing the right for individuals to label themselves as cancer survivors from the point of diagnosis through the remainder of their life, irrespective of whether death was eventually related to cancer. The intent for adopting the new language was to foster a change in the provider-patient communication in relation to cancer.

At the onset it was recognized that the bulk of patients diagnosed with cancer were living longer and discussion about long-term survival needed to be part of the early dialogue. The coalition acknowledged there were varying needs experienced by survivors across the cancer journey and recovery, articulately described by Fitzhugh Mullan (1985) as “seasons of survival”. The notion and advocacy by the National Coalition for Cancer Survivorship resulted in the concept of survivorship that is described as the period of health and well-being experienced by survivors after active cancer treatment (and possibly before a recurrence or a diagnosis of a new malignancy); it is considered a specific phase of the cancer control continuum being integrated into the oncology language.

Nursing’s interest in quality of life can be traced back to Florence Nightingale’s involvement with the British Military. Her contributions provided examples of how nurses could promote individual quality of life (Bredow, Peterson, & Sandau, 2009). The Oncology Nursing Society’s *Research Priority Survey* in 1991, found quality of life to be consistently ranked as a research priority (Mooney, Ferrell, Nail, Benedict, & Haberman, 1991).

The Office of Cancer Survivorship at the National Cancer Institute was established in 1996. The Office of Cancer Survivorship was a direct result of compelling and articulate consumer advocacy for more consideration to the unique and inadequately understood needs of the expanding population of cancer survivors. The directive of the Office of Cancer Survivorship

is to improve duration and quality of life of all individuals diagnosed with cancer (National Cancer Institute, 2013). The American Society of Clinical Oncology introduced a “Patient Survivor Care” track to its annual meeting in 2006 with the goal of recognizing the growing number of cancer survivors and the key role of oncologists in meeting their health care needs. Work on survivorship issues at the Institute of Medicine is ongoing with an in-depth evaluation of psychosocial care provided for cancer survivors. The study follows a 2004 report, *Meeting the Psychosocial Needs of Women with Breast Cancer* (Hewitt, Herdman, & Holland, 2004).

Post axillary-surgery quality of life has not been studied empirically to a large degree. The following literature review will examine references related to quality of life in breast cancer (specific to axillary lymph node surgery when available) in the five domains along with age as an individual characteristic that may influence the five domains.

### **Health Related Quality of Life Model**

Many health-related quality of life models have been applied between several health and illness conditions, across lifespan, and among individuals, families, and groups. A systematic review of health-related quality of life models by Bakas et al. (2012) identified that out of 100 articles published between 1999 and 2010 the most frequently used health related quality of life models were: Wilson and Cleary (1995a), Ferrans et al. (2005), or the World Health Organization (2007). Forty-six of the 100 articles were quantitative research (mainly descriptive studies), 16 were qualitative research, and the others were mixed methods, instrument development, literature review, model revision, and a consensus paper. Three of the 100 articles used Ferrans health-related quality of life as guidance (two related to traumatic brain injury and one related to instrument development for maternal post-partum quality of life measures). One article by Klassen, Pusic, Scott, Klok, and Cano (2009) described the impact of breast conditions

and surgery (breast reduction, augmentation, or reconstruction) to develop a quality of life framework specific to breast surgery. Due to the broad variety in disease states, health-related quality of life domains and specific characteristics could not be sufficiently analyzed.

Ferrans et al. (2005) health-related quality of life model, a revision of Wilson and Cleary (1995) model, was noted as having the greatest potential to guide future research and practice. In addition, authors recommend Ferrans and colleagues' model because they added individual and environmental characteristics to explain health-related quality of life. The WHO International Classification of Functioning and, Disability, and Health was seen as a less favorable option because it is viewed more as a model of mapping and clarification rather than a guide for hypothesis generation (Bakas et al., 2012).

Ferrans, Zerwic, Wilbur, and Larson (2005) revised Wilson and Cleary's (1995) model. The revised model maintained the five original domains. Changes included making explicit the definitions for individual and environmental characteristics, simplifying the portrayal of the model by removing non-medical factors and descriptions on the arrows illustrating the relationships in Figure 1. Furthermore, they contributed additional theoretical language regarding the basic concepts in the model and provided examples of instruments to enrich measurement such as the SF-36 (Bakas et al., 2012).

The model by Ferrans et al. (2005) can be considered parsimonious because it has seven main concepts to explain the construct of health-related quality of life; on the other hand it is complex due to the multiple relationships. To evaluate the relationships of biological factors (body mass index, SLNB or ALND with or without SLNB), symptoms (pain and lymphedema) and functional status (SF-36 function score, muscle strength, and flexibility) to general health perception and health-related quality of life a revision to Ferrans et al. (2005) were proposed

(See Figure 1). Characteristics of the individual were retained in the proposed model with an arrow from the concept to biological function, symptoms, and physical function. Environmental characteristics were not available to test for this study. Biological function, symptoms, and physical function have the potential for a reciprocal relationship with a linear or reciprocal relationship to general health and overall quality of life.

### **Characteristics of the Individual**

As described by Ferrans et al, (2005), epidemiological evidence suggests a connection between individual characteristics and biological function through detecting attributes or behaviors that increase or decrease the odds of developing a given health risk or problem. Examples of biological factors are: body mass index, skin color, or family history related to genetic risk factors. Demographic factors that may be associated with the incidence of illness are sex, age, marital status, and ethnicity. While some personal factors are unchangeable, they may be useful in targeting health intervention. Developmental status, an individual characteristic, can be important to contemplate when explaining health behavior and its impact on biological function. Interventions planned to change or modify behavior demand consideration of an individual's developmental status. For example, women with small children might be receptive to an at-home exercise program post-breast surgery to reap the rehabilitation benefits. Last, cognitive appraisal, affective response, and motivation are considered dynamic psychological factors that have the ability to influence one another.

**Age.** Increasing age is a risk factor for breast cancer (National Cancer Institute, 2013). In a study of women ( $n=93$ ) who were evaluated for quality of life impact of SLNB versus ALND had an average age of 59.2 years ( $SD= 8.6$ ) (Belmonte et al., 2012). A publication by Yi et al. (2010) identified 26,986 patients with disease positive lymph nodes, of which 4,425 experienced

SLNB only and 22,561 experienced SLNB with ALND. Women were significantly more likely to undergo SLNB alone if they were older (median age = 59 years) or if the cancer was low grade and estrogen receptor positive. Boneti et al. (2009) studied a sample of 220 women ( $M = 60.3$  years;  $SD = 11.3$ ) undergoing axillary reverse mapping to identify and preserve lymphatic draining the arm and the impact on lymphedema. This was consistent with the age ( $M = 60$  years) reported in the initial analysis by Connor et al. (2013).

Research supports that women of various ages diagnosed with breast cancer have different concerns and needs (Loerzel, McNeese, Powel, Su, & Meneses, 2008). Nonetheless, literature on the needs of women with breast cancer who are 65 years or older in the first year of survivorship is scarce; consequently, healthcare providers have little knowledge of the similarities and differences in older survivors and their younger equivalents. From a study of older women with early-stage breast cancer, Loerzel et al. (2008) reported positive quality of life in the first year of survivorship, but overall quality of life declined overtime. Exclusion criteria or absence of participation of older women in clinical trials has led to knowledge scarcity of quality of life among older women with breast cancer.

In a study of 266 women evaluating the time-course of lymphedema and potential risk factors for progression of lymphedema after breast conservation treatment, Bar Ad et al. (2012) reported age greater than 65 years of age at the time of breast cancer treatment was significantly related to higher rate of arm lymphedema when compared to women 65 years of age or younger.

### **Biological Function**

Biological function (formerly biological and physiological variables) is a comprehensive view that encompasses molecular, cellular, and the entire organ level processes (Ferrans et al., 2005). Biological functions can be assessed through such factors as laboratory tests, physical

assessment, and medical diagnosis. Shifts in biological function directly or indirectly influence all components of fitness, including symptoms, functional status, perceptions of health, and overall quality of life. Enhancing biological function is an essential part of holistic care. The interaction of individual and environmental characteristics likewise impacts biological function. For example, psychological characteristics, knowledge, and attitudes impact decisions individuals make about lifestyles eventually affecting biological function. Exposure to pathogens in the environment may increase the in risk of infection to a wound.

**Body Mass Index.** In a study of 133 women undergoing breast conserving surgery (SLNB with or without ALND), obesity was found to be a risk factor for developing postoperative lymphedema in breast cancer in patients (Helyer, Varnic, Le, Leong, & McCready, 2010). Women with a body mass index greater than 30 (obese) had twice the risk of developing lymphedema compared to those with a body mass index of less than 25. A small clinical trial ( $N=21$ ) examining weight reduction as a treatment for breast cancer-related lymphedema found weight loss may significantly decrease lymphedema (Shaw, Mortimer, & Judd, 2007). A prospective study tracked 138 breast cancer survivors for 30 months post diagnosis (Ridner, Dietrich, Stewart, & Armer, 2011). Women with a body mass index of 30 or greater at the time of diagnosis were 3.6 times more likely to develop lymphedema. Weight gain after diagnosis was not related to lymphedema. There is a lack of research to evaluate whether weight loss among women at risk for developing lymphedema would decrease risk (National Cancer Institute, 2013).

Empirical evidence suggests that upper-body exercise does not increase risk for lymphedema. Sagen, Karesen, and Risberg (2009) evaluated physical activity for the affected limb and arm lymphedema after breast cancer surgery. The authors concluded that women



undergoing breast cancer surgery with ALND should be encouraged to maintain physical activity in their daily lives without limitations or concern for arm lymphedema.

The association between body mass index and lymphedema is poorly understood. The researchers suggest that it could be a product of a heavier limb with extra subcutaneous tissue, adipose, and skin serving as a reservoir for lymphatic fluid or possibly due to the surgery being more extensive as a result of the existence of adipose tissue and hence more trauma to the lymphatics (Ozaslan & Kuru, 2004; Werner et al., 1991) .

Helyer et al. (2010) recognized research is limited regarding determinants of lymphatic flow and more studies on lymphatic drainage and impedance must be conducted to sufficiently explore the pathogenesis of lymphedema in the obese. Several researchers (Boneti et al., 2009; Thompson et al., 2007) have reported results of their experience with axillary reverse mapping. The focus of these studies has been to evaluate the ability of axillary reverse mapping to identify and preserve lymphatics draining the arm and its impact on lymphedema. There was no literature identified on determinants such as body mass index associated with lymphedema in axillary reverse mapping.

**Chemotherapy.** Evidence supports that women undergoing treatment of breast cancer may experience a number of symptoms that reduce their functional status and quality of life. Hofso, Miaskowski, Bjordal, Cooper, and Rustoen (2012) evaluated for differences in the symptom experience and quality of life of women with breast cancer who did and did not receive chemotherapy prior to radiation therapy. The five symptoms with highest association to poorer quality of life were lack of energy, worrying, difficulty sleeping, feeling drowsy, sweats, and pain. Women who received chemotherapy prior to radiation experienced two-fold the number of symptoms as women who did not receive chemotherapy. Poorer functional status, a greater

comorbidity score, and prior chemotherapy were all determinants of a greater number of symptoms. In a study of 772 patients with breast cancer, who had a primary surgery with ALND, 667 (88%) received adjuvant chemotherapy (Kim et al., 2013). Of those women receiving chemotherapy, 18% experienced lymphedema compared to only 2% in the group not receiving chemotherapy.

**Lymph Node Status.** Kim et al. (2013) also found lymphedema rates in women with  $\leq 10$  axillary dissected lymph nodes was 6% and those with  $> 10$  was 27% ( $p < .001$ ). A case-control study of 94 women to evaluate predictors of lymphedema after breast cancer surgery found no significant difference between negative versus positive lymph node status, but they did find the number of positive lymph nodes was significantly greater in women with lymphedema when compared to controls ( $p = 0.009$ ) (Swenson, Nissen, Leach, & Post-White, 2009). Liljegren and Holmberg (1997) reported in a study of 381 women undergoing a segmental mastectomy and ALND, that those with ten or more lymph nodes removed were less likely than women with fewer lymph nodes removed to develop lymphedema during the first year (53% vs. 33%) and during the next two years (33% vs. 20%).

**Axillary Surgery.** Lymphedema alone is known as a complication after axillary staging for breast cancer. SLNB has reduced but not eliminated the chance of this complication. The reported risk of lymphedema ranges from 5-8 % with SLNB alone and a minimum of 13 % after ALND (Ashikaga et al., 2010; Mansel et al., 2006). Axillary reverse lymph is an intraoperative technique developed to establish the lymphatic drainage in the upper limb during a sentinel lymph node biopsy or axillary lymph node dissection (Conner et al., 2013). The procedure involves injection of dye to identify lymphatic drainage from the arm to facilitate preservation of

lymphatic vessels. This technique was evaluated in all patients in this study for the prevention of upper limb lymphedema in women undergoing surgery for breast cancer.

## **Symptoms**

Instruments used to measure symptoms may be categorized as global, condition-specific measures, and symptom-specific measures. Global measures are broad and capture various symptoms where condition-specific measures are focused on symptoms related to certain conditions. Symptom-specific measures pertain to a particular symptom such as pain measured by a visual analog pain scale from 0-10 (Wong-Baker Faces Foundation, 1983). The dimension of symptoms measured are comprised of frequency, intensity, and distress in addition to quality, cause, treatment, consequences, location, and timing. An individual's experience, evaluation, and interpretation of symptoms are influenced by multifaceted interactions with both individual factors (i.e., knowledge and personal characteristics) and environmental factors (i.e., interactions with a rehabilitation specialist).

**Pain.** One study of 49 patients evaluated pain at 3.0 months and 3.4 years after recovery of upper limb function following axillary lymph node dissection (Devoogdt et al., 2011). The authors reported that women had equal levels of pain and discomfort, associated with arm movement, 3.0 months and 3.4 years after surgery with a median visual analog scale score of 2.0. At three months after surgery, 96% of women expressed pain and discomfort. This number decreased by 17% ( $p < 0.05$ ) to 79% at 3.4 years after surgery. Seventy-nine percent of women reported a visual analog score ranging between one and seven. Fifty-six percent of women reported a visual analog score between one and four (mild pain) and 23% had a visual analog score between five and seven (moderate pain). There was no report of severe pain. A positive correlation was found between the visual analog scale score at 3.0 months and 3.4 years follow

up. There was no significant difference in the incidence of pain between the mastectomy (33%) and breast-conserving surgery (67%) group.

According to a study by Swenson et al. (2002) breast cancer patients undergoing SLNB ( $n=169$ ) had less pain at one and six months post-surgery compared to those who had an ALND ( $n=78$ ). Additionally, researchers (Schrenk, Rieger, Shamiyeh, & Wayand, 2000) reported significantly higher rates of pain in patients after ALND compared to SNLB. Currently there is insufficient research data regarding incidence of post-axillary reverse mapping pain.

**Arm Circumference/Lymphedema.** According to Erickson, Pearson, Ganz, Adams, and Kahn (2001), lymphedema varies from 0% to 56%, and up to half of breast cancer survivors reported symptoms consistent with lymphedema with or without a clinical diagnosis (Ahmed, Prizment, Lazovich, Schmitz, & Folsom, 2008). Lymphedema is clinically described as a swelling (at minimum 200 mL by volume or 2 cm by circumference measurement) of the affected arm compared to the non-affected arm. There are a number of methods in the literature for assessing limb volume; however, lack of standardizations makes it challenging for professionals to evaluate the at-risk extremity (Ridner, Montgomery, Hepworth, Stewart, & Armer, 2007). Possibilities for limb volume are water displacement, tape measure, infrared scanning, and bioelectrical impedance measures. The most common method for diagnosis of lymphedema is circumferential upper-extremity measurement using specific anatomical landmarks (National Cancer Institute, 2013).

Lymphedema is identified as an independent predictor of decreased quality of life, even when other predictive factors such as socioeconomic status, decreased range of motion, age and obesity are adjusted for or used as covariates ( Petrek, 2004). The presentation of lymphedema may be insidious. Lymphedema may be abruptly triggered by local inflammation from causes

such as infection or limb injury and is characterized by non-pitting swelling of the arm often involving digits. Lymphedema also may progress to recurrent skin infections (Bicego et al., 2006). Symptoms accompanying lymphedema include: heaviness or fullness related to the weight of the arm, a tight sensation of the skin, or limited flexibility of the affected joint (National Cancer Institute, 2013). Activities of daily living, hobbies, and the capability to perform previous tasks, may be affected. Breast cancer survivors with arm lymphedema have been found to have more disability, poorer quality of life, and a greater psychological distress than women without lymphedema (Pyszal, Malyszczak, Pyszal, Andrzejak, & Szuba, 2006; Ridner, 2005).

Lymphedema has been reported to develop within days to 30 years after treatment of breast cancer (Shaw, Mortimer, & Judd, 2007). One study found that 80% of women develop onset within three years of surgery while the rest experience edema at a rate of 1% per year (Petrek, Senie, Peters, & Rosen, 2001). The incidence of arm lymphedema can span from 8% to 56% at two years post-surgery (Petrek et al., 2001). Data are inconsistent on the incidence and prevalence of lymphedema after breast cancer that may be due to the differences in patient characteristics.

In the Iowa Women's Health Study of 1,287 breast cancer survivors, 104 reported lymphedema and 475 reported arm symptoms (Ahmed et al., 2008). The authors reported women diagnosed with lymphedema or arm symptoms without lymphedema experienced lower physical and mental scores on the health-related quality of life.

### **Functional Status**

People typically do not function at full capacity on a daily basis (Ferrans et al., 2005). Even those with high capacity might only use a portion of their capacity on a day-to-day basis.

When health problems cause a decline in functional capacity, it might be necessary for an individual to use a higher percentage of capacity or to reduce daily activities.

Measures of functional capacity have been broadly reported in the scientific literature with several established measures available. For instance, testing muscle strength indicates functional capacity for strength. Scales from the SF-36 Health Survey (Ware & Sherbourne, 1992a) have been used often to measure physical and social function. The SF-36 is a generic tool that can be administered to healthy individuals or those with a chronic disease. The dimensions of capacity utilization and functional reserve are viewed as clinically meaningful and typically measured subjectively.

**SP-36 Physical Functioning Score.** Segal et al. (2001) evaluated the impact of exercise on physical function using the SF-36 physical functioning scale in women with stage I and II breast cancer during adjuvant therapy. The physical functioning scale consists of ten items that evaluate several aspects of physical functioning and span severe and minor limitations. Researchers reported a significant ( $p=0.04$ ) decrease in physical function in the control group by 4.1 points, and an increase by 5.7 and 2.2 points in the self-directed and supervised exercise groups, respectively (Segal et al., 2001).

**Muscle Strength and Flexibility.** Rietman et al. (2004) conducted a study to evaluate impairments, disabilities and health-related quality of life in 52 women after a modified radical mastectomy or segmental mastectomy with ALND, and to analyze the association between treatment modalities, disabilities, and health-related quality of life. The mean follow up was 2.7 years. Active shoulder range of motion, grip strength, arm volume, and pain were used to measure impairments. The Shoulder Disability Questionnaire was used to assess disabilities and the RAND-36 item Health Survey was used to measure health-related quality of life. The most

frequent impairments found were pain (60%) and reduction of grip strength (40%). The occurrence of impaired range of motion ( $>20^\circ$ ) was 9 to 16% and of edema was 15%. Mean scores on the RAND-36 contrasted significantly ( $p<.05$ ) on scores of physical functioning, vitality, and health perception to a female control group. Chemotherapy and radiation were determinants for impaired ROM. Pain and restricted range of motion explained 61% and 12%, respectively, of the disability. Pain, grip strength, and arm volume were significant ( $p<.05$ ) predictors of health-related quality of life.

Velloso, Barra, and Dias (2011) explored possible impairments and functional performance of the upper extremity on activities of daily living and health-related quality of life among breast cancer survivors treated through SLNB and investigated the association between variables. Results showed a 75% prevalence of symptoms impacting the affected upper extremity (pain or discomfort in arm or shoulder) or breast with the severity rated as mild. Only 4.4% of the 54 women evaluated experienced lymphedema and no range of motion restriction was detected. Researchers found minimal functional limitation of the upper arm and concluded that SLNB preserves upper extremity function with little impact on quality of life.

### **General Health Perceptions**

Two defining characteristics of general health perceptions are: (a) they integrate all components of the model, and (b) they are subjective in nature. This domain is a blend of all the various components of health in a comprehensive evaluation. According to a review by Bjorner et al (cited in Ferrans et al., 2005) of 39 studies, this concept is supported by the findings that the most powerful and consistent predictors of general health perceptions are physiological processes, symptoms, and functional ability. Ferrans et al. (2005) maintains that while general health perceptions are influenced by the previous components of the model, they are different

from others. Therefore, it is best to use tools that measure other components, such as symptoms or functioning, to evaluate general health perceptions. General health perception can be measured by a single global question regarding how individuals rate their health or through a series of questions on the SF-36 (Ware & Sherbourne, 1992).

According to Ferrans et al. (2005) when rating their health, individuals generally consider a variety of health aspects as well as the implied meaning of each. Differences have been found between men and women when evaluating health in general (Benyamini, Leventhal, & Leventhal, 2000). Women's health ratings are based on a wider range of health-related and non-health-related factors than are men's.

Another study in cancer patients showed a reflexology intervention had a positive impact on perception of impairment and functional status that included physical and psychological function, with implications for general health perception (Wright, Courtney, Donnelly, Kenny, & Lavin, 2002). O'Sullivan (2001) measured the self-perceived health status of a cohort of breast cancer survivors ( $N=120$  women) using the SF-36 questionnaire. The researchers found that the health status of the participants was significantly ( $p<.05$ ) better than that of the comparison group in four of the eight domains: social functioning, mental health, vitality, and general health perceptions. No studies were identified that specifically assessed women's general health perception following axillary lymph node surgery.

### **Overall Quality of Life**

The final component of the model, overall quality of life, was defined by Wilson and Cleary (1995) as subjective well-being linked to how happy or satisfied a person is with life overall. Subjective well-being is a construct that consists of pleasant and unpleasant affect, global judgment of life satisfaction, and satisfaction with personal domains of life (Deiner, Suh, Lucas,



& Smith, 1999). Wilson and Cleary (1995) underscored how individuals' values and preferences affect overall quality of life. Hence, the impact of values must be a part of an assessment of satisfaction with life. Life satisfaction can be measured by a solitary question or through a battery of questions about satisfaction with various characteristics of life. Using an instrument to measure values is beneficial because it allows the researcher to determine whether values have changed over the course of the study.

Quality of life benefits of SLNB compared to ALND are not as well documented as the benefits of SLNB (Belmonte et al., 2012). Limitations are absence of pretreatment assessment and reliable and valid quality of life tools. Kootstra et al. (2008) pointed out that two-year, post-stage I/II breast cancer patients' quality of life is comparable to quality of life shortly before surgery. Emotional function was rated as better than prior to surgery. SLNB was not associated with a superior quality of life when compared to ALND. However, as one would expect, undergoing systemic therapy and/or experiencing complications unfavorably affects quality of life.

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANC) randomized trial comparing SLNB to standard axillary treatment in the management of early breast cancer patients included a comprehensive and repeated quality of life assessment over 18 months (Fleissig et al., 2006). The significant differences in the treatment groups completing the Functional Assessment of Cancer Therapy-Breast (FACT-B+4) favored the SLNB group throughout the 18-month evaluation, with the benefit being arm functioning and better quality of life in the SLNB group.

## **Background and Overview for Primary Analysis**

The clinical stage of breast cancer guides the surgical approach. American Joint Committee on Cancer uses the TNM (T-tumor, N-nodes, M-metastases) system for staging to determine breast cancer prognosis (Edge et al., 2010). The most common treatment for women with localized breast cancer is surgical excision and staging axillary lymph node evaluation with or without radiation therapy. Based on treatment guideline, staging and prognostic factors, and the cancer care provider's recommendations, a woman may receive neoadjuvant chemotherapy or hormonal therapy administered to shrink a tumor before definitive removal of the tumor. Other treatment options are adjuvant chemotherapy, hormonal therapy, or monoclonal antibody therapy with the goal of eliminating or delaying disease recurrence (Bradley, 2007). Prognostic factors are important indicators at the time of surgery to evaluate the associated disease-free or overall survival if no systemic adjuvant therapy is administered (Cianfrocca & Goldstein, 2004). Lymph node metastasis is an important prognostic factor for breast cancer. Sixty-one percent of woman with invasive breast cancer are estimated to have localized disease (Stage 0-IIIB) with cancerous cells confined to the original cell layer or to breast lobes or ducts (with no metastatic disease in the lymph nodes). Thirty-two percent have regional disease (i.e., spread to regional lymph nodes).

Breast-conserving surgery is considered the standard procedure in early breast cancer generally followed by radiotherapy (Kaufmann, Morrow, von Minckwitz, & Harris, 2010). Initially after treatment, breast-conserving surgery is credited for providing a better body image than mastectomy (Arndt, Stegmaier, Ziegler, & Brenner, 2008). Mastectomy is the treatment of choice when there is high risk for local recurrence. Breast-conserving surgery may be contraindicated for woman with large tumors in a small breast, persistent positive nodes after a

resection, diffuse calcifications, potential poor cosmetic outcome, and contraindications to radiation therapy (Belmonte et al., 2012).

Over time, genetic testing of breast cancer tumors may be sufficient to determine the need for treatment and replace the need for node biopsies. The status of the axillary nodes is still the most important prognostic factor for directing the impact of treatment. Reported in the ACOSOG-Z0011 phase III randomized trial of ALND in women with stage I or IIA breast cancer and positive lymph nodes (Lucci et al., 2007), SLNB has gained preference over ALND for the staging of early breast cancer due to less morbidity and the questionable survival benefits of ALND. These findings were part of a trend to move away from radical surgery for breast cancer. Rates of mastectomy declined in the 1980s after research showing survival rates following lumpectomy and radiation were comparable to those after a mastectomy (Fisher et al., 1989).

The surgical approach in the primary study (Connor, et al., 2013) was based on findings that show identification of the two lymphatic systems in the axilla—those draining the breast and those draining the axilla—is possible through injection of a radioactive isotope in the breast for SLN identification and injection of blue dye (lymphazurin or methylene blue) into the arm for identification of arm lymphatics.

The primary aim of the study was to gain further knowledge and experience with lymph node surgery. The researchers investigated variations and patterns in arm lymphatic drainage that leads to disruption of arm lymphatics during SNLB and ALND. Findings from the primary analysis showed that axillary reverse mapping is a feasible procedure for identifying and preserving axillary arm lymphatics with an acceptable rate of SLN crossover (Connor et al., 2013). A secondary aim was to evaluate variables of quality of life, including pain, and

compare between individuals with and without lymphedema. The statistical analysis for efficacy was based on the occurrence of lymphedema rates (with SLNB and ALND) within the first year after surgery. The primary analysis used one year estimates as the historical control (i.e. null hypothesis) rates against which the observed rates on-protocol were compared. The sample size was determined based on the lymphedema outcomes, and was set to recruit 153 SLNB only procedures and 58 ALND procedures (Connor et al., 2013).

### **Summary**

Controversy around quality of life benefits of SLNB compared to ALND in women with early breast cancer remains. The four publications identified in the literature comparing SLNB with or without ALND using axillary reverse mapping are in the early stages (feasibility, phase I, and II trials) (Bedrosian et al., 2010; Boneti et al., 2009; Connor et al., 2013; Ponzzone et al., 2009). Connor et al. (2013) have collected quality of life data not yet analyzed through the MOS SF-36 (Medical Outcomes Study Short Form-36) that will be beneficial to the feasibility of axillary reverse mapping to provide direction for patient education and intervention pre- and post- axillary node surgery. To this author's knowledge there has been no quality of life data published comparing SLNB with and without ALND using axillary reverse mapping.

## Chapter 3

### Methodology

This section describes the study design, the sample of breast cancer participants in the study, the setting, procedures, measures, and data analysis for the primary analysis of secondary outcomes. The primary analysis is summarized with results of the early findings. Lastly, ethical considerations and limitations are discussed.

#### Study Design and Purpose

The current proposed study is a primary analysis examining the secondary outcomes not previously analyzed in the axillary reverse mapping study. The purpose of the study is to apply the modified model of Ferrans et al. (2005) (see Figure 1) to evaluate the impact of individual characteristics (age), biological factors (body mass index, SLNB or ALND with or without SLNB, chemotherapy), symptoms (pain and lymphedema), functional status (muscle strength, shoulder flexibility, and SF-36 physical function scale score), general health perspective (SF-36 general health perception score), and overall quality of life (SF-36 physical and mental scores) of women with early breast cancer over time during the first two years after surgery. The study will evaluate the benefits of the newer axillary reverse mapping procedure on the health-related quality of life.

**Research Questions.** The following research questions will be explored: Among 185 patients with clinical node negative or node positive breast cancer recruited for evaluation to this prospective non-randomized trial between December 2009 to February 2012:

1. What are the levels of pain, physical function, general health perceptions, and health related quality of life over time (baseline, six months, one year, and two years) for women after axillary reverse mapping?

2. Are there differences in physical function for women who have had SLNB or ALND with or without SLNB and women who did or did not receive chemotherapy measured over time (baseline, six months, one year, and two years)?
3. What is the occurrence of lymphedema (Yes/No) with measures of physical function, general health perception, and health-related quality of life) over time (baseline, six months, one year, and two years)?
4. Controlling for an individual characteristics (age), what are the relationships of biological factors (body mass index, SLNB or ALND with or without SLNB), symptoms (pain and lymphedema), and functional status (SF-36 function score, muscle strength, and flexibility) to general health perception and health related quality of life at three separate time points (six -months, one year, and two year). (See Figure 1)

The primary aim of the axillary reverse mapping study was to prevent lymphedema by preserving arm versus breast axillary lymphatics. Adoption of the technique has been limited due to concerns regarding feasibility and oncologic safety. The non-randomized, single-center, Phase II prospective study was undertaken to investigate axillary reverse mapping in clinically node negative and node positive breast cancer patients. Conner (2013) reported on 184 participants undergoing 212 axillary reverse mapping procedures (28 bilateral): 155 SLNB without ALND (Group 1) and 57 ALNDs with/without SLNB (Group 2). If they had a SLN, directly entered a SLN, or were within ALND boundaries during axillary reverse mapping, lymphatics were not preserved. The potential scenarios for injection of lymphazurin or methylene blue dye and radioactive isotope are depicted in the Appendix B flow chart (Connor, 2011). Authors concluded that axillary reverse mapping is a feasible procedure for identifying and preserving axillary arm lymphatics with an acceptable rate of crossover. The secondary aim of the axillary reverse mapping study was:

- 1) To evaluate variables of quality of life

- 2) To compare these variables between those individuals with and without lymphedema.

### **Sample and Setting**

All 185 patients were registered with a Midwestern Academic Medical Cancer Center Clinical Trials Office to participate in this prospective non-randomized clinical trial between December 2009 to February 2012. The Internal Review Board approved trial recruited 185 participants. Axillary reverse mapping was attempted during SLNB procedures and ALND with or without a SLNB. Subject participation in the study began at the time of their eligibility visit and lasted for three years. At the time this portion of the study was analyzed not all women had reached three years of follow up.

Eligible patients included women between the age of 18 to 89 years or older with a diagnosis of breast cancer requiring lymph node evaluation for ipsilateral or contralateral breast cancer or prophylactic mastectomy. Women who received neoadjuvant therapy and clinically node positive were allowed to participate. Patients were excluded if they were pregnant or nursing, had history of prior axillary procedure, breast augmentation, blue dye allergy, or history of lymphedema.

### **Procedures**

When a patient presented to the clinic the preliminary evaluation included the standard evaluation of the patient's breast cancer; this consisted of a full history and physical, a clinical breast exam, review of relevant imaging studies, and any known pathology (Connor et al., 2013). Once the patient met all of the inclusion criteria and if the patient and surgeon agreed on a SNLB and/or ALND, the patient was presented with the study protocol. The study then was described in detail to the patient who was allowed sufficient time to read over the study details and ask questions. If the patient chose to participate in the study, informed consent was obtained and a

HIPPA form was completed by the patient. A dedicated and experience research clinical data coordinator was assigned to the study.

The case report form consists of a set of forms for each participant that provided a record of the data obtained according to the study protocol. Case report forms were completed as scheduled during the course of the study (baseline, six months, one year, two years, and three years). Data needed to complete these forms were captured remotely in the web-based comprehensive research information system. The medical chart and any other clinical worksheets, and procedural reports were the source of verification of the data entered into the study database. Appropriate baseline demographic information, required eligibility checklists, required registration forms and a copy of the signed informed consent were sent to principal investigator for review to confirm eligibility. The individual then could be enrolled in the study.

### Measurements

An overview of the measures operationalized for this study are found in Table 1.

Table 1

#### *Measures for Testing Single-Domain and Multiple-Domain Indicators*

<b>Domain</b>	<b>Measured Variable</b>
Individual Characteristics	Age
Biological function	Body Mass Index, sentinel lymph node biopsy, and axillary lymph node dissection, chemotherapy
Symptom status	SF-36 Pain Scale, lymphedema
Physical function	Short-Form health survey (SF-36) physical functioning scale score, muscle strength, shoulder flexibility
General Health Perception	SF-36 general health scale score
Overall Quality of Life	SF-36 physical and mental scores



**Age.** Age was recorded during review of the appropriate baseline demographic information and on the required eligibility checklists. Date of birth was extracted from the health record at a Midwestern medical center. Date of birth was converted to a continuous age variable.

**Height and Weight.** Height in inches was collected from the patient record. Weight in pounds was recorded at baseline, six months, one, and two years. Body mass index was automatically calculated by the electronic health record (kilograms/meters<sup>2</sup>). Body mass index is viewed as an accurate way to determine the effect of weight on an individual's health and can be used as an indicator for health status and disease risk (Casey, 2013).

**Chemotherapy.** Chemotherapy history was recorded by the coordinator on the lymphedema assessment axillary reverse mapping case report form (Appendix C) completed at baseline, six months, one, two, and three years. The categories for chemotherapy were: Chemotherapy (Yes/No), Neoadjuvant Chemotherapy (Yes/No), and Adjuvant Chemotherapy (Yes/No). There is no documentation describing specific chemotherapy regimen on the form. Adjuvant chemotherapy rates and total number of patients receiving chemotherapy were factored in during the descriptive analysis based information recorded on the lymphedema assessment form and the axillary reverse mapping case report form (data not analyzed). For the purpose of avoiding reduction of statistical power in analysis patients was categorized as chemotherapy yes/no.

**Lymphedema.** According to the protocol patients were scheduled to undergo a total of seven arm edema assessments throughout the study. The information for this analysis was recorded at baseline, six months, one year, and two years. No special appointments were requested for this monitoring as these assessments coincided with the standard follow-up for

surgical patients. The edema assessment and other measurements were completed by a qualified and trained member of the study investigators' personnel (Connor et al., 2011).

The edema assessment was performed by measuring the arm circumference in centimeters (cm). Measurements were taken on both arms at the level of the metacarpophalangeal joints, wrist, 10 cm above the wrist, at the elbow and 10 cm above the elbow. These measurements were recorded at the stated intervals and compared to baseline. In a study evaluating arm lymphedema following breast cancer surgery, Taylor, Jayasinghe, Koelmeyer, Ung, and Boyages (2006) reported the reliability was 0.97 to 0.98 for circumferential measurements. There was a high correlation ( $r = 0.98$ ) for circumferential measurements and water displacement for measuring in upper-limb volume.

For the purpose of these analyses, measurements of the bilateral upper extremities were considered at baseline, six months, one, and two years. If an increase of circumferential measurement of 2 cm or more compared to baseline occurred, the patient was referred to a lymphedema specialist at the Midwestern academic medical center Physical Therapy Department for lymphedema evaluation and treatment. A girth difference of more than 2 cm in the involved arm versus the uninvolved arm was an accepted criteria for a positive diagnosis of lymphedema in clinical practice (Armer & Stewart, 2005). Suspected lymphedema was confirmed by the lymphedema specialist in order to be considered as having occurred.

**Muscle Strength.** Assessment of grip strength is commonly used to assess hand function. Assessment of hand grip strength was conducted by using the DETECTO Digital Handgrip Dynamometer (DHS) (DETECTO, 2008), that registers force in pounds per square inch. The manufacturer claimed the device was reliable and accurate, although no evidence to support the claim was found. The subject squeezed the dynamometer with maximum isometric effort while

keeping the arm at a right angle with the elbow at the side of the body. The best of three trials for each hand was recorded, with at least 15 seconds recovery between each effort. It was documented which hand was the dominant hand, as this could affect the results. Documentation was recorded on the Lymphedema Assessment axillary reverse mapping case report form (Appendix C). This information was recorded at each assessment.

**Shoulder Flexibility.** Range of motion was assessed by evaluating shoulder movement; flexion, abduction, and rotation. Results were recorded on the lymphedema assessment axillary reverse mapping case report form (Appendix C). The scoring is based on a scale from one to six, with one representing almost no movement and six representing full comfortable motion (Morimoto et al., 2003). These measurements were recorded at baseline, six months, one and two years and recorded in comprehensive research information system.

**SF-36 Physical and Mental Health Scores.** Patients completed a standard measure of health-related quality of life, the MOS 36-Item Short-Form Health Survey (SF-36) (Ware & Sherbourne, 1992); this was completed at each arm assessment throughout the study period. For the purpose of analyzing secondary outcomes the baseline, six month, one and two year scores were evaluated. Scores were transferred to the Research Electronic Data Capture (RedCap), a secure, web-based application developed to support data capture for clinical trials at a Midwestern academic medical center.

**The SF-36** is a 36-item, self-administered generic health-related quality of life assessment designed to measure eight health attributes (<http://www.sf-36.org/demos/SF-36.html>). The SF-36 has been administered successfully in the U.S. general population and other countries to various age groups and in specific diseases such as breast cancer (Ware & Gandek, 1998). The survey can be administered in five to ten minutes. The eight subscales that are part of

these general areas of health-related quality of life are: (a) physical functioning, (b) role function-physical, (c) bodily pain, (d) social functioning, (e) role-emotional well-being, (f) vitality (energy/fatigue), (g) mental health, and (h) general health perceptions. All items, subscales and clusters within the SF-36 scale are designed to be scored on a scale of 0-100 with 100 indicating the most favorable score. The number of responses for each question varies. Self-reported health transition is the only item out of the 36 not used to score the eight SF-36 scales. The eight scales form two separate clusters resulting from the physical and mental health variance they share. Factor analytic studies indicate that physical and mental health factors account for 80-85% of the reliable variance.

The identification of the two factors led to the construction of the psychometrically-based physical and mental health summary measures (Ware & Gandek, 1998). Physical functioning, role-function physical and bodily pain correlates highly with the physical component and are the backbone for the scoring of the physical component summary tool. The highest correlation for the mental component is with mental health, role-emotional well-being, and social functioning scales that contribute to the majority of the mental component summary measure. Vitality, general health, and social functioning have notable correlations for both components. General health loads higher on Physical Component Summary and vitality and social functioning load higher on Mental Component Summary; therefore, they are placed in these respective components. Reliability for the physical component summary is 0.92 and for the Mental Component Summary 0.88. The primary scales used in the parent study for analysis were the Physical and Mental Component Summary Scores. The scores were recorded on the lymphedema assessment axillary reverse mapping case report form (Appendix C).

The interpretation of physical component and mental component summary results are made easier with the standization of mean scores and standard deviations (Ware, 2002). For example, norm-based scoring is useful to monitor disease groups over time. Linear transformations were conducted to transform scores to a mean of 50 and standard deviations of 10 in the general population. Scores higher or lower (0 to 100) indicate better or worse quality of life compared to the general United States population.

**SF-36 Pain Scale.** The SF-36 is a 36-item self-administered generic health related quality of life assessment designed to measure eight health attributes (Ware & Sherbourne, 1992). Pain is one of the eight attributes in the SF-36. Each of the scales has a score that ranges from 0 to 100 with a higher score representing a more favorable health status. The SF-36 retained the SF-20 question regarding the frequency of bodily pain or discomfort and added an item regarding the extent of interference with normal activities because of pain. There are a total of two questions in the in the pain scale. . The pain scale reliability is 0.90 (Ware & Gandek, 1998).

**SF-36 Physical Functioning Scale.** Physical function is another one of the eight attributes in the SF-36 (Ware & Sherbourne, 1992). Each of the ten items within the subscale has a range of 0 to 100 with a higher score representing a more favorable physical functioning. The Physical Functioning Scale consists of ten items that evaluate several components of physical functioning and a range of severe to minor physical limitation. The physical functioning alpha coefficient value for internal consistency reliability is 0.93 (Ware & Gandek, 1998).

**SF-36 General Health Perception.** General Health Perception consists of five items (Ware & Gandek, 1998). It correlates highly ( $r= 0.96$ ) with the 22-item General Health Rating Index. The scale evaluates health as poor and likely to get worse versus excellent health. A sixth item, asks participants to score the amount of change in their general status over one year. The

item is not used to score any of the eight multi-item scales. Reliability alpha is reported at 0.81. (Ware & Gandek, 1998).

### **Sample Size Justification**

The sample size for this study was set based on the primary lymphedema outcomes as noted in chapter 2 (p. 34).

### **Data Analysis**

Data were analyzed by Statistical Package for Social Science (SPSS) version 21. Descriptive statistics include means and standard deviations were reported for the variables in each of the research questions along with sample demographics. Coefficient alphas were reported for each scale score for this study sample. P values of  $\leq .05$  were the cut-off value for statistical significance in all analyses.

Specific data analyses were conducted for each of the following research questions:

1. What are the levels of pain, physical function, general health perceptions and health related quality of life over time (baseline, 6-months, 1-year, 2-year) for women after axillary reverse mapping procedures? To explore research question one, descriptive statistics that include means and standard deviations are reported, along with graphing group means. Pain, functional status, general health perception and health related quality of life are continuous variables (See Table 2).

Table 2

*Type of Variables, Scales, Measures, and Ranges Research Question 1*

Variables/Domain	Scale	# of Items	Measurement	Range
Lymphedema/Symptom	Lymphedema assessment axillary reverse mapping form	2	Categorical	0-1
Functional status/Physical Function	SF 36 questions 3-12	10	Continuous	0-100 Lowest=Very limited in performing all PA including bathing or dressing Highest=Performs all types of PA including the most vigorous without limitations due to health
General Health Perception	SP 36 questions 1,33,34,35,36	5	Continuous	0-100 Lowest=evaluates health as poor and likely to get worse Highest=Evaluates personal health as excellent
Health Related Quality of Life/Overall Quality of Life	SF- 36 Physical Component Summary (PCS)	21	Continuous	0-100 Lowest=Limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness, health rated "poor" Highest= No physical limitations, disabilities, or decrements in well-being, high energy level, health rated excellent.
	SF- 36 Component Summary (MCS)	14	Continuous	0-100 Lowest =Frequent psychological distress, social and role disability due to emotional problems, health rated "poor". Highest=Frequently positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated "excellent".

2. Are there differences in physical function for women who have had SLNB or ALND with or without SLND and women who did or did not receive chemotherapy measured over time (baseline, six months, one year, and two years). GPower (Faul, Erdfelder, Lang, & Buchner, 2007), was used to conduct analysis of variance (ANOVA) repeated measures to answer the research question. Using a power of 0.80 (alpha 0.05), medium

effect size, two groups and eight measures, the sample size is calculated to be 22.

According to Raul et al. (2007) an  $f$  of 0.25 is a medium effect.

Table 3

*Type of Variables, Scales, Measures, and Ranges Research Question 2*

Independent Variable	Scale	# of Items	Type of Measurement	Range
Surgical Treatment-SLNB or ALND	Documented per medical records	2	Categorical	0-1
Chemotherapy Therapy	Documented on axillary reverse mapping work sheet	2	Categorical	0-1
Dependent Variables	Scale	# of Items	Type of Measurement	Range
Functional status/Physical function	SF 36 questions 3-12	10	Continuous	0-100 Lowest=Very limited in performing all PA including bathing or dressing Highest=Performs all types of PA including the most vigorous without limitations due to health

3. What is the occurrence of lymphedema (Yes/No) with measures of physical function, general health perception, and health-related quality of life over time (baseline, six months, one year, and two years)? For research question three, descriptive analyses consisted of graphs of individual values by lymphedema group (yes/no); individual data were graphed followed by means and standard deviations that were tested statistically using *t-tests*. Table 4 gives information about each of the variables used for this analysis.

Table 4

*Type of Variables, Scales, Measures, and Ranges Research Question 3*



Variables/Domain	Scale	# of Items	Measurement	Range
Lymphedema/Symptom	Lymphedema assessment axillary reverse mapping form	2	Categorical	0-1 0= No lymphedema. 1= lymphedema
Functional status/Physical function	SF 36 questions 3-12	10	Continuous	0-100 Lowest=Very limited in performing all PA including bathing or dressing Highest=Performs all types of PA including the most vigorous without limitations due to health
General Health Perception	SP 36 questions 1,33,34,35,36	5	Continuous	0-100 Lowest=evaluates health as poor and likely to get worse Highest=Evaluates personal health as excellent
Health Related Quality of Life/Overall Quality of Life	SF- 36 Physical Component Summary (PCS)	21	Continuous	0-100 Lowest=Limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness, health rated "poor" Highest= No physical limitations, disabilities, or decrements in well-being, high energy level, health rated excellent.
	SF- 36 Component Summary (MCS)	14	Continuous	0-100 Lowest =Frequent psychological distress, social and role disability due to emotional problems, health rated "poor". Highest=Frequently positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated "excellent".

4. Controlling for individual characteristics (age) what were the relationships of biological factors (body mass index, SLNB or ALND with or without SLNB), symptoms (pain and lymphedema), and functional status (SF-36 function) to general health perception and health-related quality of life at three separate time points (six months, one year, and two years)? Six multiple regression equations were tested. Separate multiple regressions for each of the three time points were conducted and separate multiple regressions for each of the two dependent variables: General health perceptions and health-related quality of

life. The independent variables were the one individual characteristic (Step 1), and biological factors, symptoms, and functional status variables (Step 2) (See Table 5). Based on calculations outlined by Cohen (cited in Green, 1991) a sample size of 89 is required to evaluate multiple correlation coefficients with a power of 0.80, (alpha 0.05), medium effect size, and five predictors. A sample size of 103 is required for a medium effect size and seven predictors. Using Cohen's equation  $f = R^2 / (R^2 - 1)$ ,  $f$  was calculated to be 0.15. Chi-square was used to determine whether there was a statistically significant difference in lymphedema between a SLNB only and ALND with or without SLNB and lymphedema and the SF-36 scale scores.

Table 5

*Type of Variables, Scales, Measures and Ranges Research Question 4*

Independent Variable	Scale	# of Items	Type of Measurement	Range
Individual Characteristics: Age	Medical Records		Categorical	TBD
Biological factors: Body Mass Index	Medical Records		Continuous	TBD
Functional status: Physical function	SF 36 questions 3-12	10	Continuous	0-100 Lowest=Very limited in performing all PA including bathing or dressing Highest=Performs all types of PA including the most vigorous without limitations due to health
Symptoms: Pain	SF 36 questions	2	Continuous	0-100 Lowest=Very severe and extremely limiting pain. Highest= No pain or limitation due to pain.
Lymphedema	Lymphedema assessment axillary reverse mapping form	2	Categorical	0-1 0= No lymphedema. 1= lymphedema
Dependent Variables	Scale	# of Items	Type of Measurement	Range
General Health Perception	SP 36 questions 1,33,34,35,36	5	Continuous	0-100 Lowest=evaluates health as poor and likely to get worse Highest=Evaluates personal health as excellent
Health-Related Quality of life/ Overall Quality of Life	Physical Component Summary (PCS)  Component Summary (MCS)	21  14	Continuous  Continuous	0-100 Lowest=Limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness, health rated "poor" Highest= No physical limitations, disabilities, or decrements in well-being, high energy level, health rated excellent. 0-100 Lowest =Frequent psychological distress, social and role disability due to emotional problems, health rated "poor". Highest=Frequently positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated "excellent".

## **Ethical Considerations**

This investigator was added as a sub-investigator to the parent study. The Human Research and Protection Program and Human Subjects Committee were contacted for direction on approval of research questions that are a primary analysis of the secondary outcomes. All electronic and paper files are stored in secure, password protected electronic files/systems or in locked cabinet files according to the parent protocol. The extent of access to participant data within the informatics system was restricted to an as needed basis. Data were entered into a excel data base by trained study personel. Every tenth entry was checked by this investigator for accuracy and if errors were identified every fifth entry was reviewed for accuracy.

## **Summary**

An analysis examining the secondary outcomes of the primary study was conducted using a descriptive correlational design to explore the research questions. Answering the proposed questions provided knowledge for future nursing interventions to improve the quality of life of breast cancer survivors with and without lymphedema post axillary reverse mapping prodecure. The possible correlation of biological status, symptoms, and functinal status to quality of life may provide insight for tailored intervention among the expanding number of breast cancer survivors.

## Chapter 4

### Results

The sample demographics as well as the results for each research question are presented in this chapter. The purpose of this primary analysis examining secondary outcomes was to describe pain levels, functional status, general health perceptions, and health-related quality of life over two years for women after axillary reverse mapping. Differences in functional status for women who did or did not receive chemotherapy were assessed using a mixed model method. A descriptive analysis was conducted for occurrence of lymphedema and measures of functional status, general health perceptions, and health-related quality of life over two years. Because the correlation between age and all independent variables was found to be insignificant simultaneous regression was performed. The relationship of individual characteristics, biological factors, symptoms, and functional status to general health perception and health-related quality of life was evaluated at three time points over two years.

#### Sample Characteristics

The final sample size for this study was 185. Due to the focus on longitudinal time points participants included in the analysis were those seen at three of the four time points (i.e., before surgery, six months, one year, and two years post-surgery). The majority of participants were white (91%). The age in study participants included in the primary analysis of secondary end points ranged from 29 to 88 years old ( $M = 56$ ;  $SD = 11.4$ ). The mean body mass index was 29.3 ( $SD = 6.8$ ) with a range from 18.2 to 55. Seventy percent of women had a body mass index (BMI) of  $\geq 25$  kg/m<sup>2</sup> and 40% had a body mass index of  $\geq 30$  kg/m<sup>2</sup>. Approximately two thirds underwent a SLNB on one or both sides of the axilla compared to one-third undergoing an

ALND. Nearly 65% of participants received chemotherapy. Sample demographics are provided in Table 6.

Table 6

*Sample Demographics*

	<i>Frequency</i>	<i>Percentage</i>
<b>Surgery</b>		
Axillary Lymph Node Dissection	56	30.3
Sentinel Lymph Node Biopsy (unilateral)	107	57.5
Sentinel Lymph Node Biopsy (bilateral)	22	11.8
Total	185	
<b>Chemotherapy</b>		
Yes	56	30.3
No	121	65.4
Known	8	4.3
Total	185	
<b>Race</b>		
White	169	91.4
African American	13	7
Hispanic or Latino	2	1.1
Asian	1	0.5
Total	185	

Lymphedema was also analyzed by ethnicity. The results in Table 7 are a cross tabulation of whether lymphedema occurred (or not) and race in order to see if lymphedema differed with race. The cross tabulation showed that up to 33% and 37.5% of African American women experience lymphedema at one and two years respectively compared to 3.6% and 3.4% of Caucasian women at one and two years respectively. No Latino women experienced lymphedema.

Table 7.

*Lymphedema Frequency by Race*

Race	No LE	LE	Frequency	Chi-square
<b>Six Months</b>				
White	155	7	4.3%	3.61
African American	11	2	15%	
Latino	0	0		
<b>One Year</b>				
White	160	6	3.6%	18.96**
African American	4	8	33%	
Latino	0	0		
<b>Two Years</b>				
White	139	5	3.4%	13.64 **
African American	5	3	37.5%	
Latino	0	0		

Note. \*\*= $p < 0.001$  ; LE= Lymphedema

## Sample Descriptives

Health-related quality of life was evaluated before surgery and six months, one year, and two years post-surgery. The SF-36 (Ware & Sherbourne, 1992) was used. Scores for the subcategories were calculated using standardized procedure where scores higher or lower (0 to 100) indicate better or worse quality of life, respectively, compared to the general United States population.

## Research Question One

The first research question was: What are the levels of pain, physical function, general health perceptions and health related quality of life (mental component summary and physical component) over time (baseline, six months, one year, and two years) for women after axillary reverse mapping procedures? Table 8 lists the summary statistics for level of pain, functional status, general health, physical component status, and mental health status.

Table 8

### *Descriptive Statistics for SF-36 Scale Measures at Four Time Points*

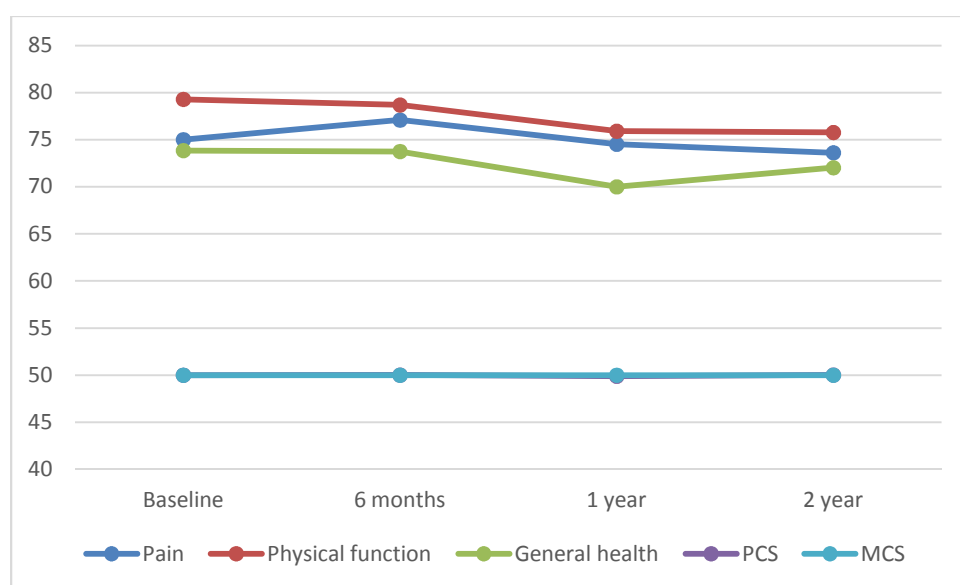
Time	Pain	Physical Function	General Health	Total PCS	Total MCS
	<i>M(SD)</i>	<i>M(SD)</i>	<i>M(SD)</i>	<i>M(SD)</i>	<i>M(SD)</i>
Baseline	75.01 (23.80)	79.29 (23.84)	73.85 (18.74)	50.00 (9.54)	50.00 (10.00)
6 Months	77.09 (21.04)	78.69 (24.84)	73.75 (18.13)	50.01 (9.98)	50.00 (9.99)
1 Year	74.52 (23.90)	75.91 (26.04)	70.00 (19.51)	50.00 (9.99)	49.89 (10.00)
2 Year	73.62 (23.53)	75.77 (26.39)	72.03 (19.89)	50.02 (12.60)	50.00 (10.00)

Note. *M* = mean; *SD* = standard deviation; PCS = physical component summary score; MCS = mental component summary score.



The mean level of pain, physical function, and general health, are consistently more favorable at baseline and six months post-surgery. Scores were lower at one year and two years post-surgery (see Figure 2). Standardized physical component and mental component summary scores show no variance over time.

*Figure 2.* Mean Levels of Pain, Physical Function, General Health, and Physical Component Status (PCS) and Mental Component Status (MCS) by Time Periods (baseline, 6 months, 1 year, and 2 year).



## Research Question Two

Research question two was to determine if there were any differences in physical function for women who had SLNB or ALND with or without SLNB and women who did or did not receive chemotherapy measured over time (baseline, six months, one year, and two years)? Table 9 shows the means and standard deviations for functional status at the four time point for those receiving chemotherapy and those not receiving it.

Table 9

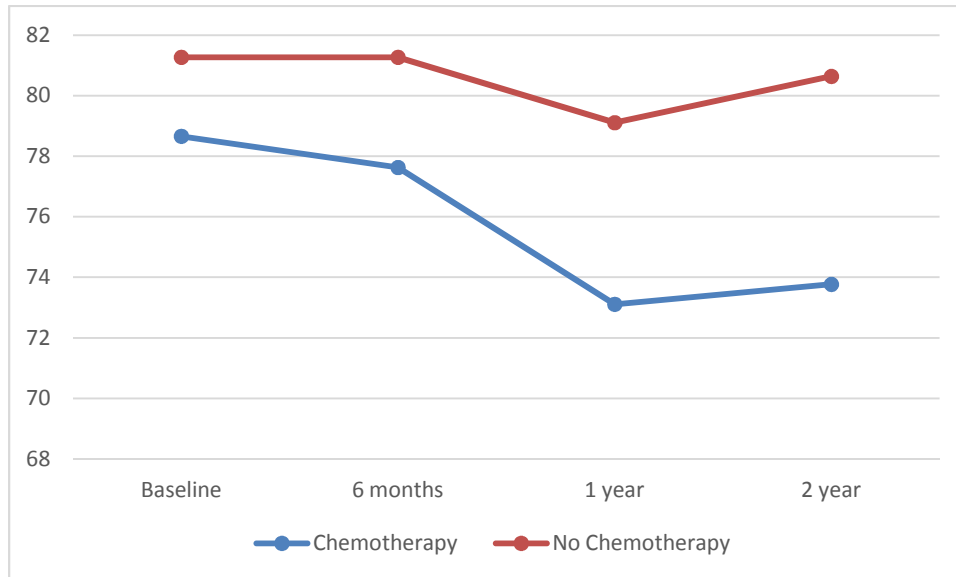
*Means and Standard Deviations of Physical Function at Four Time Points in Chemotherapy (yes/no) Participants*

	Chemotherapy	No Chemotherapy
Time	<i>M (SD)</i>	<i>M (SD)</i>
Baseline		
Physical Function	78.66 (24.84)	81.27 (21.07)
Six months		
Physical Function	77.64 (26.00)	81.27 (23.30)
One year		
Physical Function	73.11 (26.70)	79.12 (25.51)
Two year		
Physical Function	73.78 (25.90)	80.65 (25.97)

Note. *M* = mean; *SD* = standard deviation

A repeated-measures ANOVA assessed whether there was a difference between the average functional status scores at four time points for those receiving chemotherapy versus no chemotherapy and surgery (SLNB or ALND with or without SLNB). Testing the assumptions for repeated measures, the assumption of normality was met; however, the assumption of sphericity was violated. Results for the functional status levels in the chemotherapy (yes/no) group indicated that participants did rate the same over the four time periods. Using Huynh-Feldt correction because  $\epsilon$  was  $> .75$  (Leech, Barrett, & Morgan, 2008, p 160), the within subject effect (time) was not significant. While the means in Table 8 and Figure 3 appear higher in the no chemotherapy group there was no significant difference between the chemotherapy and no chemotherapy groups in a between group analysis.

*Figure 3.* Differences in Mean for Physical Function in Participants Receiving Chemotherapy Versus no Chemotherapy.



Findings for the physical function levels in the surgery (SLNB or ALND) group indicated that participants did not rate the same over the four time periods (see Table 10).

Table 10

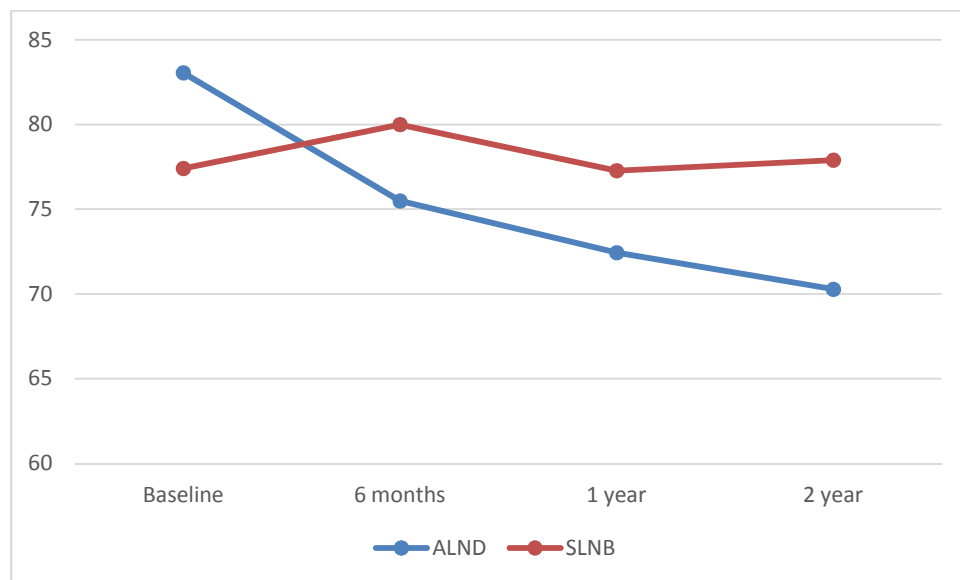
*Means and Standard Deviations of Physical Function at Four Time Points According to Type of Surgery*

	Axillary Lymph Node Dissection	Sentinel Lymph Node Biopsy
Time	<i>M (SD)</i>	<i>M (SD)</i>
Baseline		
Physical Function	84.53 (18.77)	79.39 (23.55)
Six months		
Physical Function	75.37 (22.23)	80.50 (25.64)
One year		
Physical Function	71.19 (27.36)	78.13 (24.89)
Two year		
Physical Function	67.97 (30.60)	80.08 (23.72)

Note. *M* = mean; *SD* = standard deviation

Huynh-Feldt was used again because Epsilon was  $> .75$ . The within subject effect (time) was significant ( $F_{(2.54, 354.01)} = 3.06, p < .05$ ). Examination of the means (see Figure 4) indicate a significant decrease in mean scores from baseline compared to six months in the ALND group ( $F_{(1,139)} = 6.06, p < .05$ ). There was no significant difference between surgery groups in the between group analysis  $F_{(1,139)} = 2.9, p = 0.91$ . However the time main effect was qualified by a significant interaction between time and surgery,  $F_{(2.55, 354.1)} = 3.06, p < .05$ .

*Figure 4.* Differences in Functional Status for Participants with Sentinel Lymph Node Biopsy or Axillary Lymph Node Dissection with or without Sentinel Lymph Node Biopsy



### Research Question Three

Research question number three was to assess the occurrence of lymphedema with the measures of physical function, general health perception, and health-related quality of life over time (six months, one year, and two years)? Individuals with baseline lymphedema were excluded from the study. Lymphedema in the SLNB group diminished over time in contrast to an increase over time in the ALND with or without SLNB group (see Table 11). Total lymphedema ranges from 5.1% to 5.6% during the two years after axillary surgery.

Table 11

*Clinical Findings in the SLNB, ALND, and Group Totals During the Two Years after Surgery*

	SLNB	ALND	Total	
	%	%	%	<i>P</i>
Objective lymphedema				
Six months	3.3	9.4	5.1	0.13
One year	3.2	11.1	5.6	0.68
Two years	1.8	14.0	5.2	0.01**

Note. \*\* $p \leq 0.01$ ; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection

Descriptive statistics for variables— pain, physical function, general health, mental component summary, and physical component— in participants with and without lymphedema at three time points are shown in Table 12. The number of individuals with lymphedema is considerably less than those with lymphedema.

Table 12

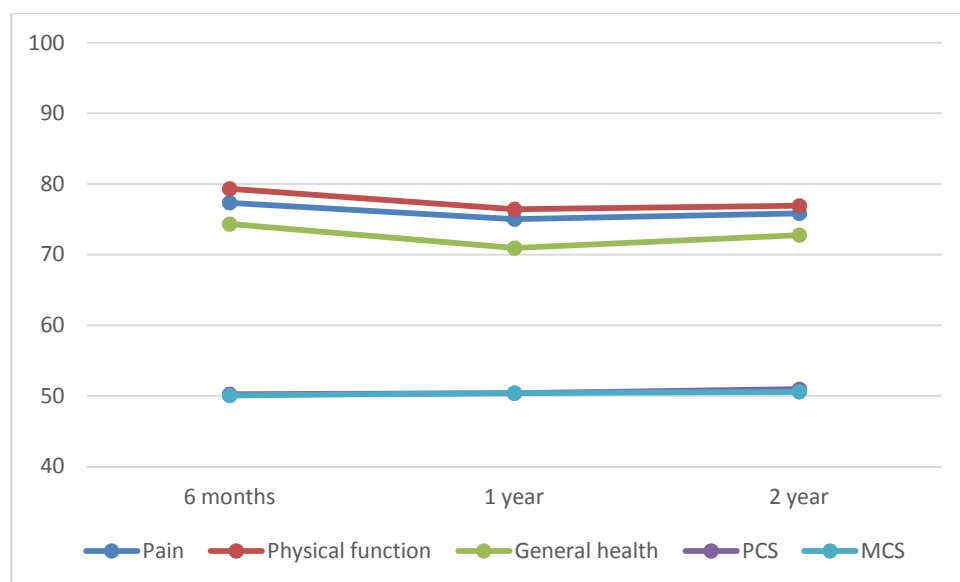
*Statistics from SF-36 Scale in Participants with or without Lymphedema*

	No Lymphedema		Lymphedema	
	<i>M (SD)</i>	<i>n</i>	<i>M (SD)</i>	<i>n</i>
<b>Six Months</b>				
Pain	77.35 (21.40)	151	89.58 (13.45)	6
Physical Function	79.32 (24.67)	154	76.67 (27.51)	6
General Health	74.33 (17.92)	152	70.83 (13.20)	6
Physical Component Summary	50.24 (9.95)	162	48.05 (12.65)	7
Mental Component Summary	50.05 (10.01)	152	48.66 (13.18)	9
<b>One Year</b>				
Pain	75.02 (22.84)	150	61.56 (39.64)	8
Physical Function	76.42 (25.61)	151	62.22 (35.45)	9
General Health	70.93 (18.27)	151	53.89 (28.26)	9
Physical Component Summary	50.39 (9.62)	152	42.79 (14.12)	9
Mental Component Summary	50.40 (9.79)	152	42.55 (11.66) *	9
<b>Two Years</b>				
Pain	75.85 (22.60)	142	54.64 (15.91)	7
Physical Function	76.91 (24.76)	145	68.75 (31.71)	8
General Health	72.77 (19.15)	143	61.88 (23.44)	8
Physical Component Summary	50.95 (11.59)	146	41.31 (11.73) *	8
Mental Component Summary	50.58 (9.63)	146	46.56 (7.08)	8

\* $p = \leq 0.05$ ; *M* = Mean; *SD* = Standard Deviation

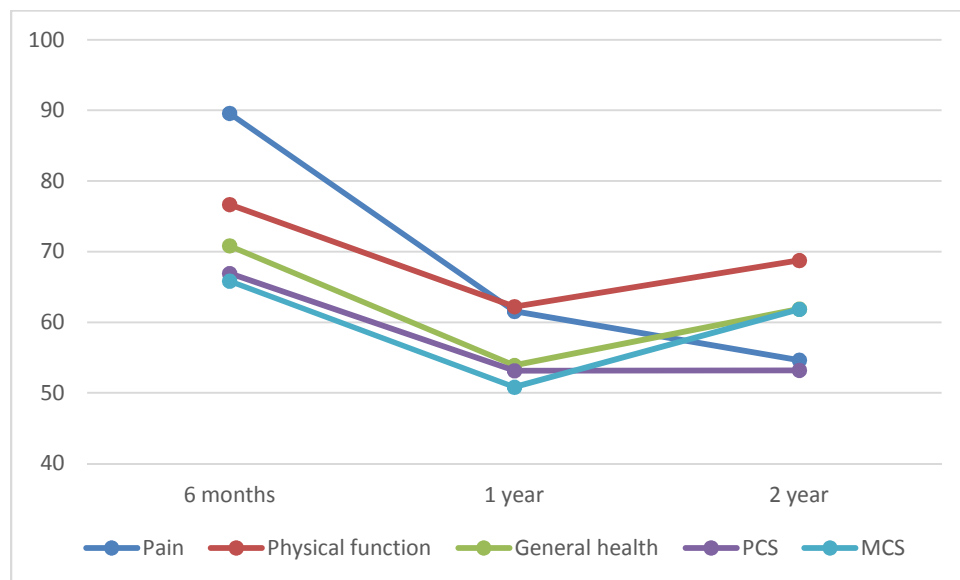
The means of the variables at three time points are depicted for the women with no lymphedema (see Figure 5) and for women with lymphedema (see Figure 6). At the six month analysis pain scores were higher (favorable) in the lymphedema group compared to the non-lymphedema group although not statistically significant. General health, mental component summary, and physical component summary scores were most favorable in the non-lymphedema group compared to the lymphedema group. There is a statistically significant difference between the lymphedema and non-lymphedema groups with mental component summary at one year,  $t_{(159)} = 2.31, p = 0.02$  and with physical component summary at two years,  $t_{(154)} = 2.29, p = 0.02$ . At one and two years, physical function, pain, general health, mental component summary, and physical component summary scores were most favorable in the non-lymphedema group.

*Figure 5.* Physical Function, General Health Perception, and Health Related Quality of Life (physical component summary and mental component summary) in Women with no Lymphedema During the Two Years after Surgery





*Figure 6. Physical Function, General Health Perception, and Health Related Quality of Life (physical component summary and mental component summary) in Women with Lymphedema During the Two Years after Surgery*



#### **Research Question Four**

Research question number four was: Controlling for an individual characteristic (age), the relationships were explored of biological factors (body mass index, SLNB or ALND with or without SLNB), symptoms (pain and lymphedema), and physical function to general health perception and health-related quality of life at three separate time points (six months, one year, and two years). Separate multiple regressions for each of the three time points were conducted with separate regressions for each of the dependent variables: general health perceptions and health-related quality of life (mental component summary and physical component summary). The independent variables were age, body mass index, surgery, pain, lymphedema, and physical function. There was no variability on any of the flexibility scores, and consequently, these were not entered into the regression analysis. Prior to interpreting the regression analysis each model

was evaluated for the main assumptions of regression. The residuals for normality were assessed using PP plots, the constant variance assumption by examining scatter plots of the residuals by predicted values. All PP plots approached line of normality and no pattern was identified in the scatter plot indicating the data meet the assumptions of errors being normally distributed and variances of the residuals were constant.

**General Health.** Multiple regression was conducted to determine the best linear weighted combination of age, body mass index, surgical procedure, pain, lymphedema, and functional status for predicting *general health*. The correlation between age and all independent variables was found to be insignificant therefore simultaneous regression was performed. According to Leech, Barrett & Morgen (2008, p 95) a high correlation is 0.50 or 0.60 and above causing concern with multicollinearity problems. The correlation matrix showed the highest correlation between six month pain and general health to be 0.46, one year general health and pain was 0.46, and two year general health and physical function was 0.41. The combination of all seven variables significantly predicts general health at six months, one, and two years (see Table 13). The variance at six months, one year, and two years is 27%, 27%, and 23% respectively, explained by the linear weighted combination of all variables. According to Cohen (cited in Green, 1991, p. 501), there was a large effect at all three time points. The beta weights (see Table 13) suggest that lower pain levels and a higher physical function score contribute most to predicting favorable general health scores at all three time periods. The zero order, partial, and part correlations are in descending order. The flexibility variables were not correlated with the dependent variable and removed from the analysis.

Table 13

*Simultaneous Multiple Regression Analysis Summary for General Health*

Variable	6 Months			1 Year			2 Years		
	<i>b</i>	<i>SEB</i>	$\beta$	<i>b</i>	<i>SEB</i>	$\beta$	<i>b</i>	<i>SEB</i>	$\beta$
Age	0.26	0.13	0.16	0.19	0.15	0.11	0.19	0.16	0.10
BMI	-0.44	0.21	-0.04	-0.34	0.23	-0.12	-0.5	0.25	-0.16
Surgery	2.45	2.81	0.06	-1.15	3.10	-0.03	-1.02	3.50	-0.02
Pain	0.32	0.07	0.39**	0.27	0.07	0.33**	0.20	0.08	0.23*
Lymphedema	-11.01	7.15	-0.12	-12.03	6.70	-0.14	-0.96	8.27	-0.01
Physical Function	0.16	0.06	0.22**	0.15	0.07	0.19**	-0.22	0.08	0.26**
Muscle Strength	0.45	0.21	0.17	-0.20	0.28	0.01	0.51	0.31	0.14
Summary Statistics for the Three Time Period Models									
6 Months			1 Year			2 Years			
	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>
	0.31	0.27	8.68	0.30	0.27	8.64	0.27	0.23	6.70

Note.  $p^* \leq 0.05$   $p^{**} \leq 0.01$ ,  $p^{***} < 0.01$  in all models, *b*= unstandardized coefficient, *SEB*= standard error of *b*,  $\beta$ = standardized coefficient

**Mental Component Summary.** Three separate multiple regressions were again conducted to establish the best linear weighted combination of age, body mass index, surgical procedure, pain, lymphedema, functional status and muscle strength for predicting the mental component summary. The correlation matrix showed the highest correlation between six month pain and mental component summary is 0.53, one year mental component summary and pain is 0.50, and two year mental component summary and pain is 0.58. The seven variable linear weighted combination significantly ( $p < 0.01$ ) predicted MCS as indicated in the model summary at six months, one year, and two years (see Table 14). The findings indicate that 33%, 31% and 37% of variance was explained at six months, one year, and two years, respectively, in the mental component summary model. The beta weights, presented in Table 13 indicate that pain

and functional status contributed the most to predicting the mental component summary scores. The zero order, partial, and part correlations are in descending order and the adjusted  $R^2$  is not substantially smaller than the  $R^2$  therefore no suppression is suspected.

Table 14

*Simultaneous Multiple Regression Analysis Summary for Mental Component Summary*

Variable	6 Months			1 Year			2 Years		
	<i>b</i>	<i>SEB</i>	$\beta$	<i>b</i>	<i>SEB</i>	$\beta$	<i>b</i>	<i>SEB</i>	$\beta$
Age	0.01	0.00	0.00	0.10	0.07	0.12	-0.13	0.06	-0.02
BMI	-0.47	0.09	-0.04	-0.01	0.11	0.01	0.03	0.10	-0.02
Surgery	-0.26	1.19	-0.02	0.68	1.54	0.03	0.11	1.37	0.01
Pain	0.15	0.03	0.41**	0.13	0.03	0.33**	0.17	0.03	0.44*
Lymphedema	-1.27	3.02	-0.03	-5.07	3.33	-0.11	2.87	3.25	0.06
Physical Function	0.09	0.03	0.29**	0.20	0.03	0.31**	0.11	0.03	0.30**
Muscle Strength	-0.02	0.09	-0.02	0.33	0.14	0.20	-0.03	0.12	-0.02
<b>Summary Statistics for the Three Time Period Models</b>									
	6 Months			1 Year			2 Years		
	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>
	0.36	0.33	12.63	0.34	0.31	10.24	0.41	0.37	12.27

Note.  $p^* \leq 0.05$   $p^{**} \leq 0.01$ ,  $p^{***} < 0.01$  in all models, *b*= unstandardized coefficient, *SEB*= standard error of *b*,  $\beta$ = standardized coefficient

**Physical Component Summary.** Next, three separate multiple regressions were conducted to establish the best linear weighted combination of age, body mass index, surgical procedure, pain, lymphedema, physical function, and muscle strength for predicting the physical component summary. The correlation matrix showed pain and physical component summary had a correlation ranging between 0.798 and 0.803 among the three time points. The correlation between physical function and physical component summary ranged from 0.72 to 0.79 at three

time points. Physical function and pain were removed from the combination as they were scored as a component of the physical component summary (dependent variable). A five variable linear weighted combination significantly ( $p < 0.01$ ) predicted physical component summary as shown in the model summary of Table 15 at one year and two years only. No single or combination of variables predicted physical component symptoms at six months. The findings indicate that 16%, and 9% of variance was explained at one year and two years, respectively, in the physical component summary model. Increased body mass index, surgery and muscle strength were the best predictors of physical component symptoms at one year and increased body mass index and muscle strength at one and two years.

Table 15

*Simultaneous Multiple Regression Analysis Summary for Physical Component Summary*

Variable	6 Months			1 Year			2 Years		
	<i>b</i>	<i>SEB</i>	$\beta$	<i>b</i>	<i>SEB</i>	$\beta$	<i>b</i>	<i>SEB</i>	$\beta$
Age	-0.66	0.08	-0.07	-0.34	0.18	0.16	0.33	0.19	0.16
BMI	-0.17	0.13	-0.11	-0.73	0.28	-0.21**	-0.98	0.31	-0.27**
Surgery	-0.45	1.86	-0.02	9.36	3.93	0.18	4.59	4.38	0.09
Lymphedema	-2.21	4.42	-0.04	0.59	8.34	-0.01	-10.65	9.94	-0.10
Muscle Strength	0.16	0.12	0.01	1.30	0.33	0.34**	0.75	0.38	0.18*
Summary Statistics for the Three Time Period Models									
6 Months			1 Year			2 Years			
	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>	<i>R</i> <sup>2</sup>	<i>Adjusted R</i> <sup>2</sup>	<i>F</i>
	0.20	-0.01	0.57	0.19	0.16	6.82	0.13	0.09	3.85
	0.20	-0.01	0.57	0.19	0.16	6.82	0.13	0.09	3.85

Note.  $p^* \leq 0.05$   $p^{**} \leq 0.01$ ,  $p^{***} < 0.01$  in all models, *b*= unstandardized coefficient, *SEB*= standard error of *b*,  $\beta$ = standardized coefficient

## Summary

An important finding from this study was that the mean level of pain, physical function, general health, and physical component status were most favorable at six months post-surgery and least favorable one year post surgery. Levels improved at two years post-surgery, but did not recover to baseline levels. The mean level of mental components summary was highest (more favorable) at baseline and lowest (less favorable) at one year post surgery returning to near baseline levels at two years post-surgery. Mental component summary scores and physical component summary scores were similar. There was no statistical difference in physical function levels between women who had SLNB only or ALND or between those receiving chemotherapy versus no chemotherapy. There was a significant difference in the within subject effect (time) for surgery. Mean scores for functional status were significantly higher at six months compared to baseline regardless of the type of surgery. Women with lymphedema have a significantly lower mental component summary score at one year than those without lymphedema.

Multiple regression analyses showed that lower pain scores and higher physical function contribute the most to the prediction of more favorable general health scores at all three time points. Pain and functional status scores contributes the most to predicting mental component summary scores at all three time points. Lower body mass index, surgery, (SLNB or ALND with or without SLNB) and greater muscle strength were the best predictors of higher physical component summary scores at one year and a lower body mass index and greater muscle strength at two years was the best predictor for a favorable physical component summary score.

## **Chapter 5**

### **Discussion**

Chapter five presents a discussion for the findings from the primary analysis examining secondary outcomes using a descriptive correlational design to determine factors that predict quality of life after axillary reverse mapping with sentinel lymph node biopsy or axillary lymph node dissection with or without sentinel lymph node biopsy. Theoretical relevance and clinical application are reviewed. The strengths and limitations of the study are discussed and recommendations for future research are presented.

### **Summary of Study Findings**

Quality of life benefits of SLNB compared to ALND with or without SLNB are inconsistent in the literature. Many studies have used quality of life questionnaires alone with patient reports of lymphedema. Little is known about the quality of life benefits of a newer procedure, axillary reverse mapping. The researcher has worked as a clinician with breast cancer patients for over 15 years and frequently provided education on lymphedema prevention and related complications. As a nurse practitioner the researcher saw patients with complications extending from a few months to many years post axillary surgery.

The current study is one of the first to conduct a descriptive analysis of pain levels, functional status, general health perceptions, and health related quality of life in breast cancer survivors for two years after axillary reverse mapping in lymph node positive and negative breast cancer and to examine variables that predict quality of life components. The findings from this study suggest women may need the greatest support from health care providers at one year post surgery irrespective of their surgical procedure or therapy. Results also suggest that education and guidance around lymphedema prevention is increasingly important at baseline and continues

as time goes on particularly for those women undergoing axillary reverse mapping in combination with ALND with or without SLN biopsy. General health, mental component summary, and physical component summary were most favorable in the non-lymphedema group although a group of individuals with lymphedema is not well represented in this study.

### **Characteristics of the Individual**

**Age.** The mean age of 56 years in this study was younger than in other studies referenced (Belmonte, et al.,2012; Boneti et al., 2009). Twenty percent of women were  $\geq 65$  years old. There is a similar mean age amongst SLNB participants of 55.5 years ( $SD = 12.72$ ) and ALND participants of 55.7 years ( $SD = 10.82$ ) with or without SLNB that differs from other studies where older women were more likely to undergo SLNB (Yi et al.,2010). Controlling for age had no impact in determining the best predictive model for the dependent variable of interest. While age contributed variance to the predictive models of general health, physical component summary, and mental component summary it was not a significant predictor.

### **Biological Function**

**Body Mass Index.** Nearly 60% of the United States population are overweight or obese, and similarly 66% of women are overweight or obese at the time of a breast cancer diagnosis. Obesity is defined as a body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup> and overweight as body mass index of  $\geq 25$  kg/m<sup>2</sup> (World Health Organization, 2011). The rate of overweight or obese at the time of breast cancer diagnosis in this group of women was 70% ( $M = 29.3$ ,  $SD 6.8$ ) potentially placing them at higher risk for co-morbidities and other complications. In this study increased body mass index (BMI) significantly contributed to the lower physical component summary scores at one and two years suggesting women who are heavier post-surgery may have more physical challenges.



**Chemotherapy.** A good portion of women in the study received neo-adjuvant or adjuvant chemotherapy (65%). Specific type of chemotherapy was not collected for the analysis. Anticipated short-term side effects of chemotherapy are hair loss, nausea and vomiting and are likely dependent on the drug therapy (Komen, 2013). Long-term more common side effects of chemotherapy may include early menopause, weight gain, fatigue, cognitive dysfunction, and neuropathy that may impact quality of life in a breast cancer survivor. The incidence of the potential side effects related to chemotherapy was not collected. While the mean scores in this study were higher (more favorable) in the no chemotherapy group there was no significant difference in functional status between the chemotherapy and no chemotherapy groups. Albeit non-significant, clinically the findings suggest that patients receiving chemotherapy may need greater support and evaluation at one year post-surgery and beyond.

### **Symptoms**

**Pain.** The mean pain levels are highest (most favorable) at baseline and six months post-surgery. Scores were lower (less favorable) at one year and continued to deteriorate at two years post-surgery. The mean and standard deviation scores in the United States general population are 75.2 and 23.7, respectively, indicating that scores are in range with the general United States population (Ware, 1994). With that said, decline after six months suggests the need for health care providers to monitor and address change in pain levels. Hormonal therapy is prescribed to hormone receptor positive women in the adjuvant setting after surgery or chemotherapy. In trials comparing the overall quality of life in women receiving various hormonal medications compared to those not receiving treatment, there were no differences found in the quality of life between groups (Ochayon, Zelker, Kaduri, & Kadmon, 2010). On the other hand, there were variations in the different symptoms experienced depending on the

hormone they were taking. Hence, joint and muscle aches can be symptoms with hormonal therapies and can unfavorably impact quality of life. It would be reasonable to think that women with hormone receptor positive breast cancer may be starting hormonal therapy following their six month post-surgery visit. It is hypothesized that this may add to the increased pain levels at one and two years.

Swenson, Nissen, Leach, & Post-White (2009) reported that women with lymphedema and their matched controls did not differ significantly in quality of life when taking hormone therapy. Based on the literature review and the fact that the history of hormonal therapy was not recorded on the case report form, it was not evaluated as a factor for determining quality of life in this group. A lower pain level significantly contributed to more favorable general health and mental summary component scores at six months, one year, and two years suggesting it is important symptom to assess in patients at every clinical visit

Schrenk, Reiger, Shamiych, & Wayand (2000) compared arm circumference, subjective lymphedema, and pain in women with SLNB and ALND ( $n= 35$ ). The length of follow up post operatively was 15.4 months in the SLNB group and 17.0 months in the ALND group (range, 4-28 months). Results showed a higher rate of objective lymphedema in woman undergoing an ALND when compared to a SLNB, but it was only significantly higher at two years. The findings from this study are partially consistent with that of Swenson et al. (2002). Pain was greater in the ALND group compared to the SLNB group at one month, six months, and 12 months post-surgery. On the other hand pain intensity decreased with an increased amount of time patients were out from surgery.

**Arm Circumference/Lymphedema.** The lower rate of lymphedema in the SLNB group and the decline in occurrence in this study are consistent with the literature (3.3%, 3.2%, and

1.8% respectively at six months, one year, and two years) (Swenson, et al., 2002). Contrary to this, the rates of lymphedema increased in the ALND group at 9.4%, 11.1%, and 14% at six months, one year, and two years, respectively and are consistent with reports in the literature (Ashikaga et al., 2010; Mansel et al., 2006). In this study the mean of SF-36 variables (pain, physical function, general health, physical component summary and mental component summary) are considered at three time points for women with no lymphedema and for those with lymphedema (Table 12). Mental component summary scores at one year and physical component summary scores at two years are significantly higher in the non-lymphedema group. The number of women with lymphedema is low and typically the variance in this group is larger which likely contributes to the lack of statistical difference between groups. Clinically SF-36 scores appear more favorable in the non-lymphedema group compared to the lymphedema group with the exception of pain scores in the six month group. No lymphedema contributes to favorable scores in the general health perception, mental component summary, and physical component summary models.

### **Functional Status**

**SF-36 Physical Function Score.** According to Ware and Gandek (1998) the mean SF-36 physical function score for the general U.S. adult population is 84.2 ( $SD = 23.3$ ). Women in this study have a mean physical function score lower than the general U.S. population. The physical function score gradually declines from base line to two years post-surgery. There is no significant difference in physical functioning score between chemotherapy and no chemotherapy or between time periods. There was a significant difference in baseline mean scores between the surgical procedures. Women undergoing an ALND had more favorable scores at baseline than those undergoing SLNB and ultimately experienced a significant decrease in the mean physical

functioning scores. The mean scores for the SLNB group showed a slight improvement. The findings indicate that women with a higher functioning score tended to receive the more aggressive surgical procedure.

**Muscle Strength.** This study evaluated the muscle strength in a regression as an independent variable and did not compare the difference between the affected and non-affected arm strength. Rietman et al (2004) found no significant difference in grip strength between the affected and non-affected side. Grip-strength was an important factor in the following three SF-36 subscales: physical functioning, role limitation physical and role limitation emotional. The contribution of muscle strength to the general health model, mental component summary, or physical component summary in this study is minimal. The three subscales (physical functioning, role limitation physical and role limitation mental) were not studied separately, but as a component of mental component summary and physical component summary.

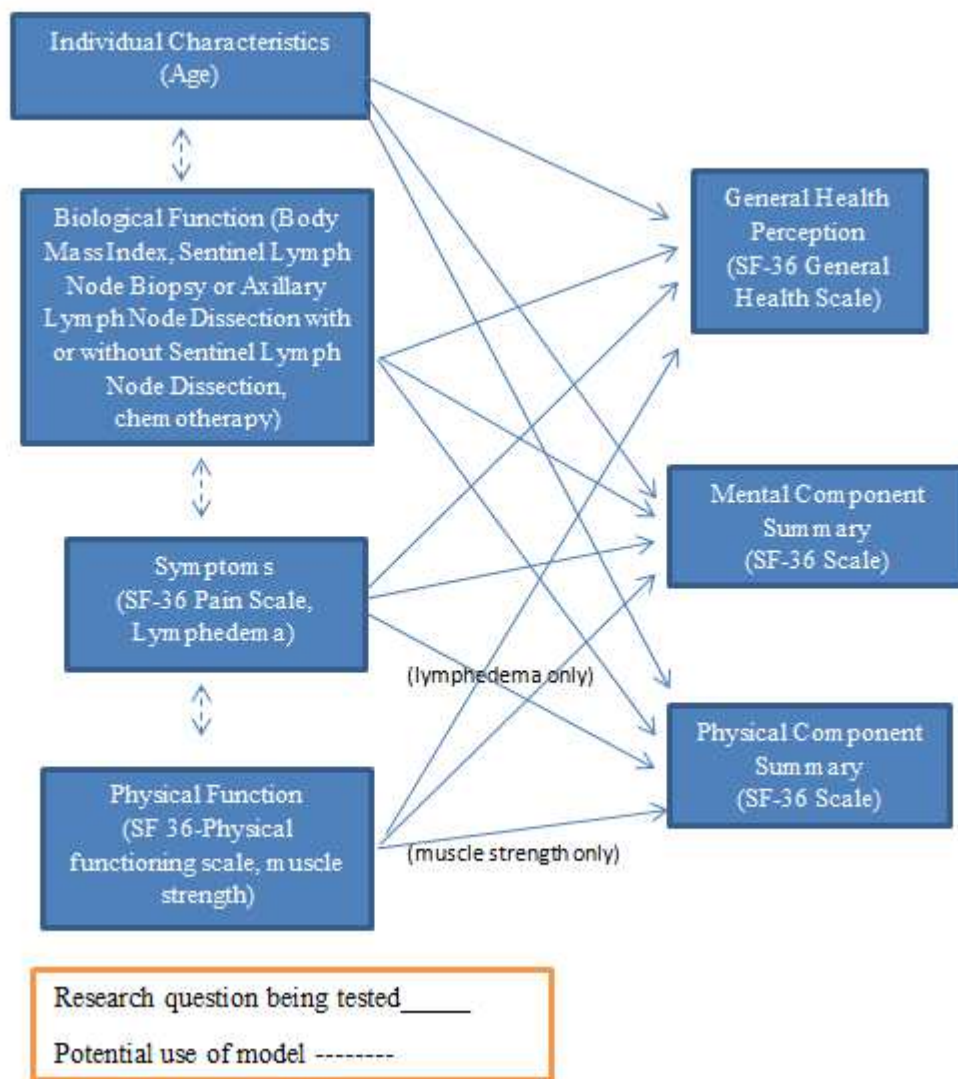
**SF-36 General Health Perception.** The mean general health score for the general US population is 71.9. The general health score for this study are highest at baseline and lowest at one year (see Table 7). Findings are comparable to that of O'Sullivan (2002) reporting a SF-36 general health perception score of 71.5 in a cohort of breast cancer survivors. No studies were found that specifically examined general health perception in breast cancer patients after axillary lymph node surgery. General health perceptions have been shown to be connected to biological and physiological factors according to Wilson & Cleary (1995). Due to the large number of factors affecting health perception it important to consider the variability of each individuals unique situations.

**SF-36 Physical and Mental Health Scores.** The mean scores for physical component summary and mental component summary are 50 and standard deviations of 10 in the general

population after a linear transformation (Ware, 2002). Mean scores in this study at the four time points were very near 50 for physical component summary and mental component summary. The baseline physical component summary are nearly identical in a similar study of women undergoing ALND or SLNB (Belmonte et al., 2012) while the mental component summary and physical component summary scores from the similar study at six and 12 months are below the mean of 50 (ranging from 47.52-42.76). The differences in physical component summary and mental component summary scores among women with and without lymphedema at one and two years are displayed in Table 12. Belmonte et al. found a significant decline ( $p = \leq 0.001$ ) in mental component summary and physical component summary scores at one month, six months and twelve months when compared to baseline. A Belgium long-term evolution of quality of life study of women beyond 5 years found that the longer the survival time the more quality of life of breast cancer treated patients improved and the less breast cancer had an impact on the quality of life (Neyt & Albrecht, 2006).

**Theoretical Relevance.** The research model was revised based on results of this study and the associations with recent literature (See Figure 7).

Figure 7. Domains Predicting Quality of Life Post-Axillary Lymph Node Surgery



In this study the domains were examined as simultaneous and independent predictors for general health perception, physical component summary, and mental component summary. Because predictive factors for mental component summary and physical component summary differ they were separated in the final model. Age was removed as a linear component and repositioned as a simultaneous factor. Individual characteristic, biological function, symptoms, and physical function all contributed to general health perception, physical component summary

and mental component summary. The level of contribution for each domain varies somewhat with each dependent variable. In general higher physical functioning and lower pain scores contributed the most to the prediction of general health perception and mental component summary. Lower muscle strength and higher body mass index significantly predicted lower physical component summary scores.

### **Implications for Practice**

In this study it could be concluded that health care professionals are doing a reasonable job of managing the breast cancer patients' perception of issues affecting quality of life (pain, physical functioning, general health, physical component summary and mental component summary) within the first six months post-surgery. The diminishing quality of life scores at one year and two years compared to baseline and six months may be a result of less frequent contact and encouragement from providers post completion of therapy and/or side effects with the start of hormonal therapy. It may be that women need additional follow up calls for assessment of symptoms and the option for more frequent visits after their six month post-surgery visit.

Pain is common symptom experienced from cancer diagnosis through survivorship (Oncology Nursing Society, 2013). As a result of the breast cancer or treatment, pain causes significant physical and psychosocial challenges. Pain uniquely impacts the quality of an individual's life, increases vulnerability and creates dependence on healthcare providers to assess for acceptable management. Because oncology nurses embrace holistic care and have ongoing contact with women throughout the continuum of care, they are in a position to identify undertreated or untreated physical or mental conditions and advocate for its relief.

Discussion from the breast cancer survivorship care plan should review suggestions to reduce risk of lymphedema such as maintaining a healthy weight, avoiding tight fitting clothes,

and avoiding injections and intravenous infusions in the affected arm. Tools such as the American Cancer Society's (2014) guideline to physical activity and nutrition should be used for education on core exercise and upper body strengthening and healthy eating.

Study findings will be useful to establish priorities for nursing interventions to enhance quality of life in breast cancer survivors' post-axillary surgery. Implementation of survivorship care plans related to adverse effects of surgery, chemotherapy, overweight or obesity, physical fitness level and should receive more attention and regular evaluation of quality of life in breast cancer patients (American Society of Clinical Oncology, 2014).

It is important for women to know what to anticipate after treatment. Patient recorded information on progression of quality of life can be of great value to healthcare providers in the management of breast cancer survivors perceptions. Results can be used to encourage patient who are newly diagnosed with breast cancer or for those who are lacking confidence in towards making progress with quality of life components. When informing women undergoing axillary surgery education must include the fundamental differences in various aspects of quality of life overtime. The epidemic of obesity must also be considered in planning patient procedures and care. Health care providers may obtain patient resources through replicable organizations for example the American Cancer Society (2014), Livestrong Foundation (2014), Oncology Nursing Society (2014), and Susan G. Komen (2013). Cancer Survivorship Training (CST) (Klemp, 2014) is an e-learning education and training tool to help healthcare providers meet their professional needs and improve the lives of cancer patients in areas such as energy balance, psychosocial issues, physical and late long term effects of cancer and its treatment. For the two year period evaluated the higher risk for threat to quality of life may be at the one year time period and is most prevalent in women. As a member of interdisciplinary teams involved in



practice, education, administration, and research oncology nurses must take a vital position quality of life management.

### **Study Strengths and Limitations**

The study was a preplanned prospective analysis which eliminates bias of a retrospective trial. Collection of pre-surgery baseline data allowed for interpretation of changes in quality of life over time. The present study used valid and reliable measurement tools and objective measurements to evaluate quality of life in breast cancer survivors' post-axillary lymph node surgery.

Some limitations should be taken into account. A risk of bias or threat to internal validity exists because there was no control group, no blinding, and no random assignment. Because weight measurement was not a primary objective of the study there was no protocol or standard procedure for measuring height and weight such as removal of shoes, standardized scale, measuring the patient in street clothes or a gown. Data on social and physical components were not gathered therefore control of environmental characteristics was possible. The sample size was based on the primary objective, therefore women undergoing SLNB ( $n=129$ ) without ALND compared to those with ALNDs ( $n=56$ ) with/without SLNB limits the ability to evaluate for complications with the higher risk group (i.e. ALND and those with lymphedema in each group). While ethnicity was not reported in the initial publication by Connor et al. (2013) the lack of diversity in clinical trials is often a limitation at this Midwestern Cancer Center. The domains within the modified health-related quality of life model could not be fully evaluated due to limitations in the data collected and recorded in the database. Many of the suspected risk factors, individual and environment characteristics such as income, education, social support, number lymph nodes removed, and complications with wound healing were not collected on case report

forms. Because some of the environmental characteristics are modifiable or may influence overall quality of life they are important to collect in future studies.

While quality of life scores were typically more favorable in women who did not have lymphedema, a statistically significant difference in quality of life scores was not always detected. This finding was similar in women undergoing ALND who had lower quality of life scores but likely due to the smaller sample size in this group a statistically significant difference was not identified. Researchers (Belmonte et al., 2012) conclude that a disease specific questionnaire may be better at identifying clinically relevant differences between treatment groups and time points in breast cancer than the SF-36 physical functioning scale focused on lower extremity mobility. Another limitation is that the participant's history of radiation therapy was excluded from the analysis for parsimony and small sample size. Lymph node status was not a part of the surgery axillary reverse mapping assessment form and also excluded for the same reasons.

### **Recommendations for Future Research**

Future research needs to be conducted to explore the quality of life in breast cancer survivors as axillary surgery techniques advance. The study needs replication in women undergoing axillary reverse mapping procedures with SLNB and ALND with or without SLNB as the feasibility of this procedure evolves. The addition of a tumor site-specific tool such as FACT-B-4 to that assesses upper arm impairment may be useful in detecting relevant clinical differences (Belmonte et al., 2012). Studies are needed specifically in those individuals experiencing lymphedema to gain additional knowledge of their quality of life challenges. Controlling for environmental and individual characteristics is recommended in future studies. Findings from Table 7 suggest that lymphedema in African Americans is more than twice that in

the Caucasian women at six months, one year and two years. Future studies need to target African American women and other races to broaden the knowledge base for complications. Inclusion of hormonal therapy as a biological function measure is recommended in future studies. While data collection is planned for three years post-surgery for this study only two years of data were analyzed. With the increasing number of breast cancer survivors living longer lives there is ongoing need to study and manage quality of life issues beyond five years post diagnosis and treatment.

### **Conclusion**

In summary, there was no significant difference in physical functioning for women receiving chemotherapy or no chemotherapy in a between group or within group (time) analysis. Physical functioning was significantly higher at baseline compared to six months in the ALND group. There was no significant difference in functional status between surgical groups. Incidence of lymphedema in women undergoing the axillary reverse mapping procedure in the SLNB group diminished over time and increased over time in the ALND group. At one year women with no lymphedema demonstrated significantly higher mental component summary scores compared to those with lymphedema. At two years women with no lymphedema had a significantly higher physical component summary score compared to those without lymphedema. As much as 31% of the variance in general health was explained by seven variables (age, body mass index, surgery, pain, lymphedema, physical functioning, and strength) with physical functioning and pain contributing the most. Up to 37% of variance in mental component summary was explained by the same seven variables with physical functioning and pain contributing the most. Only 19% of the physical component summary variance was explained by five variables (age, body mass index, surgery, lymphedema, and muscle strength) with body

mass index and muscle strength contributing the most. Quality of life benefits for SLNB are not clearly demonstrated. Based on this study they seem to become more apparent at two years.

Further studies of quality of life issues beyond two years and in a larger more diverse heterogeneous population are recommended.

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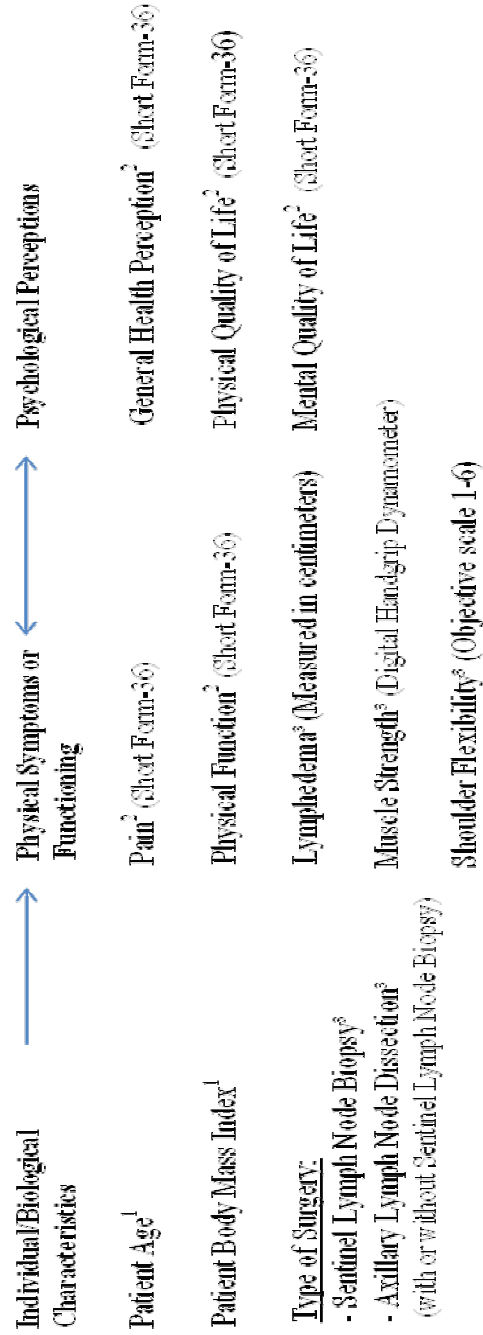


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Appendix A

*Health-Related Quality of Life Substructure Model*

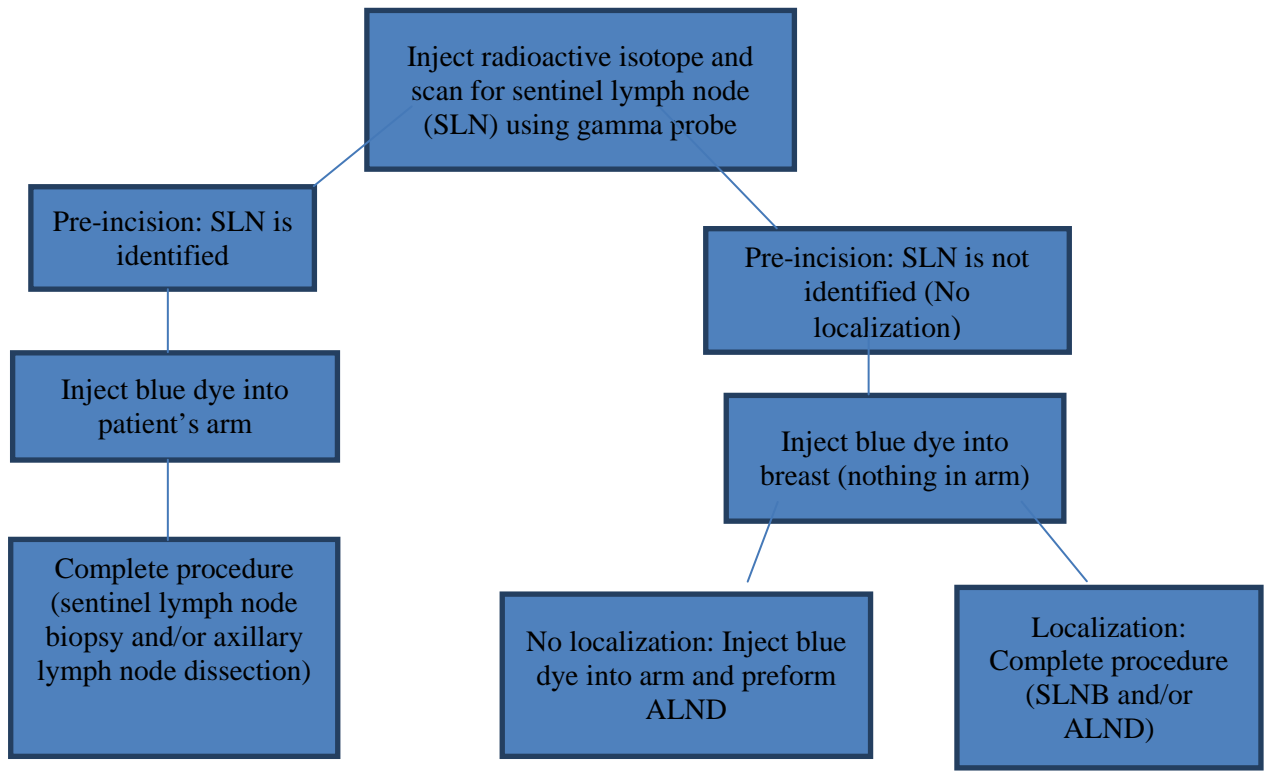



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Note. Operational Variables Derived From: 1=Demographic chart data, 2=Short Form (SF)-36, 3= Axillary Reverse Mapping Case Report Form and Surgery Form

Appendix B

*Axillary Reverse Mapping Procedure Flow Chart*



Appendix C

Lymphedema Assessment Axillary Reverse Mapping Case Report Form

Patient ID: [redacted] Patient Study ID: 11737 Age: [redacted] years Gender: Female of Kansas Cancer Center (KUCC)

Study Number: 11737
Study Title: ARM: Axillary Reverse Mapping
Study Calendar: null
Version Number: 2

Lymphedema Assessment (ARM)

Section 1

Data Entry Date 11/18/2013

LYMPHEDEMA ASSESSMENT

Timepoint \_\_\_\_\_

Table with columns: Arm Circumference, Left, Right. Rows: Meta-carpophalangeal Joints, Wrist, 10 cm above the wrist, Elbow, 10 cm above the elbow.

Muscular Strength

Medical Handgrip Dynamometer ? Dominant
Left
Right

Weight \_\_\_\_\_ lbs.

Blue Tattoo [radio] Yes [radio] No [radio] N/A

Shoulder Flexibility - Range of Motion

## Appendix C

*Lymphedema Assessment Axillary Reverse Mapping Case Report Form (continued)*

Right Shoulder Flexibility \_\_\_\_\_

Left Shoulder Flexibility \_\_\_\_\_

Lymphedema

 Yes No

Lymphedema Location

 Right Left Both**Employment Status**

Currently Employed

 Yes No

Average Number of Hours Per Week \_\_\_\_\_

Change in Employment Since Diagnosis (Explain Below)

 Yes No

Notes \_\_\_\_\_

**Quality of Life Measures**

Visual Analog Pain Scale \_\_\_\_\_

SF-36 Completed

 Yes No

Mental Health Subscale

Score \_\_\_\_\_

Physical Health Subscale

Score \_\_\_\_\_

Notes \_\_\_\_\_

Lymphedema Assessment completed by:

 Lori Ranallo Stephanie Roling Other

Completed by: \_\_\_\_\_

**Treatment History**

Chemotherapy

 Yes No

Neo-Adjuvant

 Yes No

Adjuvant

 Yes No

Radiation Therapy

 Yes No