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Lymphedema in Breast Cancer Survivors : : Risk Factors, Distress and Quality of Life, and Patient Compliance with a Physician Referral

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UNIVERSITY OF CALIFORNIA, SAN DIEGO
SAN DIEGO STATE UNIVERSITY

Lymphedema in Breast Cancer Survivors: Risk Factors, Distress and Quality of Life, and Patient Compliance with a Physician Referral

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Public Health (Health Behavior)

by

Sally Ann Dominick

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2013

The Dissertation of Sally Ann Dominick is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Co-Chair

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Chair

University of California, San Diego

San Diego State University

2013

DEDICATION

I dedicate this dissertation to my family:

To my parents, Dave and Julie,

to my siblings, Tim and Jane,

and to my grandparents, Ed and Mary,

without your love and support this dissertation would not have been possible.

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LIST OF ABBREVIATIONS

BMI, body mass index

HBM, Health Belief Model

HRQOL, health-related quality of life

MET, metabolic equivalent

MH, mental health

MHW, MET-hours per week

OT, occupational therapy

PH, physical health

PSM, prospective surveillance model

WHEL, Women's Healthy Eating & Living

UC, University of California

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ACKNOWLEDGEMENTS

I would like to extend my gratitude to each and every person who has supported me along my academic journey and the completion of this dissertation. First and foremost, I would like to thank my doctoral committee for their support and contribution to this research project. To my dissertation chair and mentor, Dr. Lisa Madlensky, I am deeply thankful for your guidance, encouragement and commitment to my professional development. Thank you for always being available to meet with me and for providing valuable feedback on my numerous manuscript drafts. I would also like to thank my dissertation co-chair, Dr. John Pierce, whose wisdom, research expertise, and mentorship, has been invaluable throughout the course of my doctoral studies. Thanks also to Dr. Loki Natarajan for all your statistical expertise and guiding me in the right analytical direction. I would like to thank my other dissertation committee members, Drs. Elva Arredondo, Hala Madanat and Tony Reid, for providing their support and expertise.

I would like to thank the WHEL Study staff and participants for their time and participation in this study. Also thank you to Resenia Collins, Patricia Kormanik, Kenneth Nunes, Jr., and the UC San Diego Health System health care providers and patients for your participation in this research. Also I would like to express my appreciation to Shirley Flatt, Susan Wancewicz, Hollie Ward, Aimee Humphrey and other members of the UCSD Cancer Prevention and Control team.

I would also like to acknowledge and thank my family for supporting each and every endeavor I have made; I am profoundly grateful for everything you have done for me. Also thank you to my friends, colleagues, and professors who have encouraged and supported me throughout this research.

VITA AND PUBLICATIONS

VITA

2013	Doctor of Philosophy in Public Health (Health Behavior), University of California, San Diego and San Diego State University, San Diego, CA
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PUBLICATIONS

Dominick SA, Madlensky L, Natarajan L, and Pierce, JP. (2013). Risk factors associated with breast cancer-related lymphedema in the WHEL Study. Journal of Cancer Survivorship, 7(1), 115-23.

Dominick SA, Irvine AB, Beauchamp N, Seeley JR, Nolen-Hoeksema S, Doka KJ, and Bonnano GA. (2009-2010). An Internet tool to normalize grief. Omega Journal of Death and Dying, 60(1), 71-87.

ABSTRACT OF THE DISSERTATION

Lymphedema in Breast Cancer Survivors: Risk Factors, Distress and Quality of Life, and Patient Compliance with a Physician Referral

by

Sally Ann Dominick

**Doctor of Philosophy
in Public Health (Health Behavior)**

**University of California, San Diego, 2013
San Diego State University, 2013**

**Professor Lisa Madlensky, Chair
Professor John P. Pierce, Co-Chair**

Background: While the incidence of breast cancer-related lymphedema has decreased with advancements in breast cancer treatments, it is still a common late effect of treatment and more research is needed to better understand its physical and psychosocial impact among breast cancer survivors. The Women's Healthy Eating and Living (WHEL) Study (a randomized trial to test the effect of a plant-based diet among breast cancer survivors) provided a dataset for this research. Additionally, medical charts from breast cancer patients at a large academic medical center were reviewed for this dissertation.

Aims: Aims of this dissertation were to: 1) identify the risk factors of lymphedema among breast cancer survivors in the WHEL Study, 2) examine the psychosocial impact of breast cancer-related lymphedema among participants in the WHEL Study, and 3) examine breast cancer patient compliance with a health care provider referral for an occupational therapy (OT) lymphedema consult.

Methods: This study employed quantitative research methods to investigate lymphedema among breast cancer survivors. For aims 1 and 2, risk factors of lymphedema and the psychosocial impact of lymphedema among WHEL Study participants were assessed using bivariate analyses and logistic regression modeling. For the third aim, a retrospective chart review was conducted to examine patient compliance with attending an OT lymphedema consult.

Results: This dissertation project found that 28.5% of WHEL Study participants self-reported lymphedema. Risk factors of lymphedema identified were body mass index greater than 25 kg/m^2, the removal of 11 or more lymph nodes, and breast cancer surgery plus radiation therapy. Also this dissertation provided new evidence that women with lymphedema-related distress had higher odds of reporting lower physical and mental health scores than women without lymphedema. Additionally, 20.5% of breast cancer patients were not compliant with attending an OT lymphedema consult after receiving a referral; non-attenders were more likely to have fewer lymph nodes removed compared to attenders.

Conclusions: This dissertation project provided an in-depth investigation into breast cancer-related lymphedema. The knowledge gained by this study provides public health professionals and health care providers critical information to guide decisions and interventions related to the prevention and treatment of lymphedema.

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CHAPTER 1

Introduction

INTRODUCTION

Background & Significance

As of January 1, 2009, approximately 2.7 million breast cancer survivors, accounting for 22% of all cancer survivors, were alive in the United States [1]. Over the next few decades, the number of breast cancer survivors is expected to grow due to the aging of the population and the decline in breast cancer mortality [1].

With the anticipated growth in the number of breast cancer survivors, research in the area of breast cancer survivorship is a priority due to the occurrence of late effects of treatment, such as lymphedema, and the challenges associated with transitioning from cancer patient to survivor. Previous studies, related to quality of life, late effects of treatment, and cancer recurrence and mortality, have shown that a myriad of physical, psychological, and social complications can occur among breast cancer survivors [2–5]. One such difficulty facing breast cancer survivors is the risk of secondary lymphedema as a side effect of breast cancer treatment. Lymphedema is an uncomfortable and chronic condition that usually arises as a result of damage to the lymphatic system near the affected breast region, impeding the flow of lymphatic fluid throughout the affected region and into the arm and/or hand. Depending on the severity of the lymphatic system damage, the build-up of lymphatic fluid can cause a variety of symptoms. Common symptoms of breast cancer-related lymphedema are arm or hand swelling, tenderness, numbness, puffiness, pain, and arm or hand heaviness [6–8]. It is estimated that between 6 and 30% of breast cancer survivors develop lymphedema after undergoing breast cancer treatment [9].

Studies have been conducted to investigate the many facets of lymphedema among breast cancer survivors. For example, studies focused on identifying the risk

factors of lymphedema have found lymph node removal, radiation therapy, chemotherapy, infections, injury, body weight, older age, inflammation, and poor hygiene as common risk factors [8,10–18]. Additionally, studies have found that women with breast cancer-related lymphedema have a diminished quality of life [8,14,18–22]; however, these studies have not distinguished whether the poorer quality of life is due to the survivors' distress related to lymphedema, breast cancer, or other issues. Other studies have examined lymphedema education and found that providing patients with lymphedema education can prevent the development of lymphedema as well as improve health outcomes among those living with lymphedema [23–25]. Since patient education is important for lymphedema prevention and management, studies are needed to determine if patients are compliant with attending appointments that provide lymphedema prevention information.

Since breast cancer-related lymphedema is a complex problem, more research is warranted to fully understand the occurrence and effect of lymphedema among breast cancer survivors. Lymphedema can be difficult to monitor and fully describe because it can develop any time (months or years) after breast cancer treatment. Additionally, distinguishing between the impact of lymphedema versus breast cancer itself on the overall health of breast cancer survivors can be challenging. The primary objective of this dissertation project was to address some of the gaps in breast cancer-related lymphedema research using data from the WHEL Study and medical records of breast cancer patients at a large academic medical center in San Diego, CA.

Study Populations

Studies #1 and #2 describe the secondary data analysis conducted using data collected from the Women's Health Eating and Living (WHEL) Study, a dietary

intervention trial that assessed the effect of a diet high in fruits and vegetables on breast cancer recurrence and mortality. The WHEL Study enrolled 3088 women diagnosed with early stage breast cancer between 1995 and 2000 [26]. The study results found no significant differences in breast cancer recurrence or mortality among participants [27]. Since there were no differences between the intervention and control groups, the study population was treated as a cohort for this dissertation project.

For Study #3, the study population was breast cancer patients at a large academic medical center who received a health care provider referral for an occupational therapy (OT) lymphedema consult between June 2010 and December 2011.

Dissertation Theme and Aims

The theme of this dissertation was lymphedema among breast cancer survivors. The three dissertation manuscripts each focused on a unique aspect of breast cancer-related lymphedema.

- Study #1 Aim: To identify the risk factors associated with lymphedema among breast cancer survivors in the WHEL Study.

- Study #2 Aim: To assess how lymphedema-related distress is associated with quality of life (i.e., physical and mental health) and depressive symptoms among participants in the WHEL Study.

- Study #3 Aim: To investigate breast cancer patient compliance with attending an OT lymphedema consult after receiving a provider referral at a large academic medical center.

Taken together, this dissertation seeks to discover 1) who develops lymphedema, 2) if lymphedema-related distress impacts psychosocial functioning, and 3) who attends an OT lymphedema appointment. As shown in Figure 1.1, these study outcomes are influenced by a variety of factors.

Theoretical Framework

For Study #1, we chose to examine variables previously shown to be associated with lymphedema in the literature as potential risk factors of lymphedema among the WHEL Study population.   Since Study #1 focuses on examining risk factors for developing lymphedema, a framework based on health behavior theories is not readily applicable. However for the other two studies, the Transactional Model of Stress and Coping based on the work of Lazarus, Folkman, and Moskowitz [28] is a suitable framework to use when examining the outcomes of psychosocial functioning and attendance at an OT consult. In this model, the individual's perceptions/appraisals of stressors and ability to cope combine with her application of coping skills to result in an outcome. The process of coping is on-going and cyclic, thus outcomes can impact re-appraisals, which in turn can influence the application of coping strategies, creating a new or different outcome [28]. For example, for Study #2 the primary appraisal is the individual's evaluation of the significance of lymphedema-related distress. The secondary appraisal is the person's perception of control and efficacy to cope with lymphedema-related distress. The primary and secondary appraisals lead to the individual's coping strategies, such as problem-focused, emotion-focused, or meaning-based coping. These coping strategies used by the individual result in positive or negative psychosocial functioning.

In addition to the Transactional Model of Stress and Coping, the Health Belief Model (HBM) is an applicable theory to use when examining patient compliance. The HBM constructs include perceived susceptibility, perceived severity, perceived benefits of the health behavior, perceived barriers concerning the behavior, cues to action, and self-efficacy [29,30]. For example, a part of Study #3 will focus on identifying barriers related to breast cancer patient attendance at an OT lymphedema consult. Since this dissertation project involves secondary data analyses and a retrospective chart review, some of the constructs in these theoretical frameworks may not directly apply. Yet these frameworks set up this dissertation project to identify potential areas to target with future theoretically grounded intervention research.

Dissertation Outline

This dissertation is composed of an introduction (Chapter 1), three distinct manuscripts (Chapters 2 through 4) and a discussion (Chapter 5). Chapter 1 describes the background and significance as well as the theme and objectives of the dissertation. The first manuscript (Chapter 2) assesses the risk factors of lymphedema identified among breast cancer survivors in the WHEL Study. Chapter 3 (the second manuscript) investigates the association between lymphedema-related distress and psychosocial functioning (i.e., quality of life and depressive symptoms) among WHEL Study participants. The third paper (Chapter 4) is a retrospective chart review that examines breast cancer patient attendance at an OT lymphedema consult after receiving a health care provider referral. The final chapter (Chapter 5) includes a discussion of the key findings, suggestions for future research, and recommended health behavior interventions targeting factors associated with breast cancer-related lymphedema.
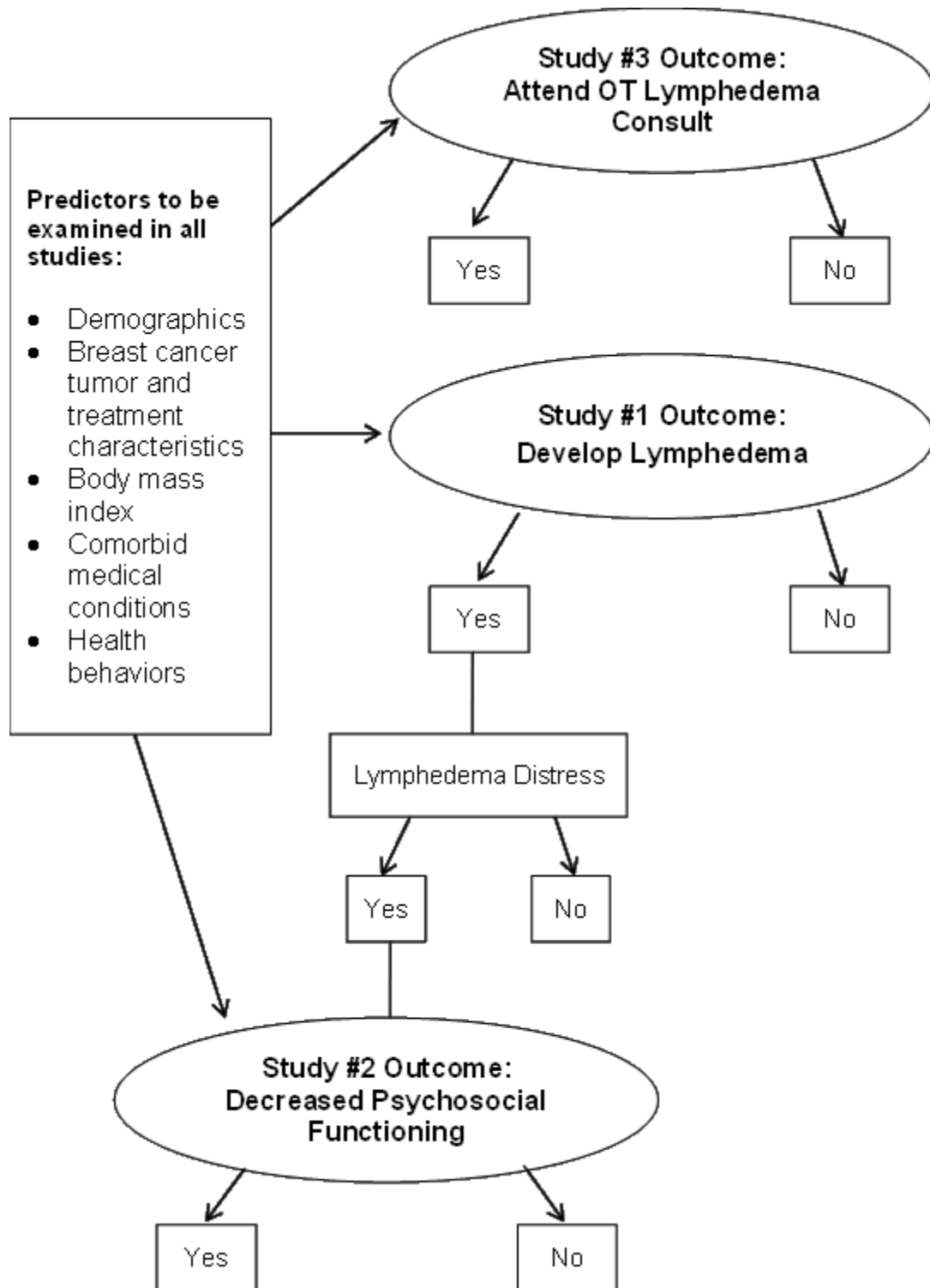
Figure 1.1. Overall diagram of the dissertation project.

REFERENCES

1. Howlader, N, Noone, AM, Krapcho, M, Neyman, N, Aminou, R, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations) 2012. Bethesda, MD: National Cancer Institute. Bethesda, MD: National Cancer Institute.

2. Browall M, Ahlberg K, Karlsson P, Danielson E, Persson LO, Gaston-Johansson F. Health-related quality of life during adjuvant treatment for breast cancer among postmenopausal women. Eur J Oncol Nurs. 2008;12(3):180–9.

3. Luecken LJ, Compas BE. Stress, coping, and immune function in breast cancer. Ann Behav Med. 2002;24(4):336–44.

4. Perry S, Kowalski TL, Chang CH. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. Health Qual Life Outcomes. 2007;5:24.

5. Schou I, Ekeberg Ø, Sandvik L, Hjermstad MJ, Ruland CM. Multiple predictors of health-related quality of life in early stage breast cancer. Data from a year follow-up study compared with the general population. Qual Life Res. 2005;14(8):1813–23.

6. Morrell RM, Halyard MY, Schild SE, Ali MS, Gunderson LL, Pockaj BA. Breast cancer-related lymphedema. Mayo Clinic. 2005;80(11):1480–4.

7. Norman SA, Localio AR, Potashnik SL, Simoes Torpey HA, Kallan MJ, Weber AL, et al. Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. J Clin Oncol. 2009;27(3):390–7.

8. Sakorafas GH, Peros G, Cataliotti L, Vlastos G. Lymphedema following axillary lymph node dissection for breast cancer. Surg Onc. 2006;15(3):153–65.

9. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. Cancer. 1998;83(12 Suppl American):2776–81.

10. Kwan ML, Darbinian J, Schmitz KH, Citron R, Partee P, Kutner SE, et al. Risk factors for lymphedema in a prospective breast cancer survivorship study: the Pathways Study. Arch Surg. 2010;145(11):1055–63.

11. Goldberg JI, Wiechmann LI, Riedel ER, Morrow M, Van Zee KJ. Morbidity of sentinel node biopsy in breast cancer: the relationship between the number of excised lymph nodes and lymphedema. Ann Surg Oncol. 2010;17:3278-86.

12. Ridner SH, Dietrich MS, Stewart BR, Armer JM. Body mass index and breast cancer treatment-related lymphedema. Support Care Cancer. 2011;19:853-7.

13.   Meeske KA, Sullivan-Halley J, Smith AW, McTiernan A, Baumgartner KB, Harlan LC, et al. Risk factors for arm lymphedema following breast cancer diagnosis in black women and white women. Breast Cancer Res Treat. 2009;113:383–91.

14.   Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. Cancer Epidemiol Biomarkers Prev. 2007;16:775–82.

15.   McLaughlin SA, Wright MJ, Morris KT, Sampson MR, Brockway JP, Hurley KE, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: patient perceptions and precautionary behaviors. J Clin Oncol. 2008;26:5220–6.

16.   Norman SA, Localio AR, Kallan MJ, Weber AL, Torpey HAS, Potashnik SL, et al. Risk factors for lymphedema after breast cancer treatment. Cancer Epidemiol Biomarkers Prev. 2010;19:2734–46.

17.   Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast Cancer Res Treat. 2011;130:981–91.

18.   Paskett ED, Dean JA, Oliveri JM, Harrop JP. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. J Clin Oncol. 2012;30(30):3726–33.

19.   Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. J Clin Oncol. 2008;26(35):5689–96.

20.   Nesvold I-L, Reinertsen KV, Fosså SD, Dahl AA. The relation between arm/shoulder problems and quality of life in breast cancer survivors: a cross-sectional and longitudinal study. J Cancer Surviv. 2010;5(1):62–72.

21.   Oliveri JM, Day JM, Alfano CM, Herndon JE, Katz ML, Bittoni MA, et al. Arm/hand swelling and perceived functioning among breast cancer survivors 12 years post-diagnosis: CALGB 79804. J Cancer Surviv. 2008;2(4):233–42.

22.   Ridner SH. Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. Support Care Cancer. 2005;13(11):904–11.

23.   Cheifetz O, Haley L. Management of secondary lymphedema related to breast cancer. Can Fam Physician. 2010;56(12):1277–84.

24.   Fu MR, Chen CM, Haber J, Guth AA, Axelrod D. The effect of providing information about lymphedema on the cognitive and symptom outcomes of breast cancer survivors. Ann Surg Oncol. 2010;17(7):1847–53.

25. Sherman KA, Koelmeyer L. The role of information sources and objective risk status on lymphedema risk-minimization behaviors in women recently diagnosed with breast cancer. Oncol Nurs Forum. 2011;38(1):E27–36.

26. Pierce JP, Faerber S, Wright FA, Rock CL, Newman V, Flatt SW, et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials. 2002;23(6):728–56.

27. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA. 2007;298(3):289–98.

28. Wenzel L, Glanz K, Lerman C. Stress, coping and health behaviors. In: Glanz K, Rimer B, Lewis F, editors. Health Behavior and Health Education: Theory, Research and Practice. 3rd ed. San Francisco: Jossey-Bass; 2002. p. 210–39.

29. Janz NK, Becker MH. The Health Belief Model: A decade later. Health Educ Q. 1984;11(1):1–47.

30. Janz, NK, Champion, VL, Stretcher V. The Health Belief Model. In: Glanz, K, Rimer, BK, Lewis F, editor. Health Behavior and Health Education: Theory, Research and Practice. 3rd ed. San Francisco: Jossey-Bass; 2002. p. 45 – 66.

CHAPTER 2

Risk Factors Associated with Breast Cancer-related Lymphedema in the WHEL Study

ABSTRACT

Introduction Lymphedema is a significant health problem faced by a large percentage of breast cancer survivors. The Women's Healthy Eating and Living (WHEL) Study has a unique data set collected after the completion of breast cancer treatment, which allowed a focused analysis of risk factors for breast cancer-related lymphedema.

Methods Participant characteristics, treatment modalities, and health behaviors were examined as potential predictors of lymphedema among breast cancer survivors with univariate analyses and multivariate logistic regression.

Results Lymphedema status was assessed for 83% of the study cohort (2431 of the 2917 WHEL participants). Among these respondents, 692 (28.5%) women reported yes to either a physician's diagnosis of lymphedema or a question on arm/hand swelling. When compared to other participants, women with lymphedema were diagnosed at a younger age, more likely to have a higher body mass index, had a larger tumor size, had more lymph nodes removed, more likely to have a mastectomy with radiation therapy, and more likely to have chemotherapy. In the final multivariate-adjusted model, body mass index greater than 25 kg/m2 ($p<0.01$), the removal of 11 or more lymph nodes ($p<0.01$), and breast cancer surgery plus radiation therapy ($p<0.01$) showed a strong independent association with developing breast cancer-related lymphedema.

Conclusions The results of this study highlight the importance of educating breast cancer survivors about the modifiable risk factors (e.g., body mass index) associated with the development of lymphedema.

INTRODUCTION

Over 2.6 million women are estimated to be breast cancer survivors in the United States [1]. One difficulty facing breast cancer survivors is the risk of secondary lymphedema of the ipslateral arm/hand. Breast cancer-related lymphedema can occur months or years after breast cancer treatment (e.g., surgery, radiation) and is estimated to affect approximately 6 to 30% of women who receive such treatment [2]. Erickson and colleagues' (2001) review reports the overall incidence of arm edema in breast cancer survivors as 26% (with a range of 0 to 56%) [3].One of the main risk factors for breast cancer-related lymphedema is lymph node removal [3–6]. In the past decade, the incidence of breast cancer-related lymphedema has decreased with the use of sentinel lymph node biopsy (SLNB); however, lymphedema is still a considerable problem [7–9]. McLaughlin and colleagues (2008) reported that the development of lymphedema occurred among 5% of the 600 patients who underwent SLNB alone [8]. Among older breast cancer survivors, Yen and colleagues (2009) found that lymphedema developed in 5.7% of women who had no axillary surgery, 7% who underwent SLNB, and 21% who underwent axillary lymph node dissection (ALND) [7]. These studies indicate that while lymph node removal is a key risk factor, it is not the only risk factor for breast cancer-related lymphedema. Other potential risk factors include tumor stage, radiation therapy, chemotherapy, infections, injury, body weight, age, inflammation, and poor hygiene [6, 8, 10–15]. While breast cancer treatment-

related risk factors for lymphedema may be unavoidable, other risk factors may be modifiable.

The main objective of this study was to examine participant baseline characteristics (e.g., age, body mass index, treatment type, and level of physical activity) as potential predictors of lymphedema among early stage breast cancer survivors enrolled in the Women's Healthy Eating and Living (WHEL) Study. The WHEL Study's unique data set was collected after the completion of breast cancer treatment and allows focused analyses of a variety of topics relating to breast cancer survivorship, including lymphedema.

METHODS

Study Population

The WHEL Study tested the effect of a plant-based diet on breast cancer recurrence and mortality among breast cancer survivors. The WHEL Study enrolled 3088 women within 4 years of diagnosis of early stage breast cancer categorized using American Joint Committee on Cancer (edition IV) criteria as stage I (≥1cm), stage II, or stage IIIA [16]. Participants were recruited at seven study sites in California, Arizona, Oregon and Texas through physicians, tumor registries and community breast cancer events between March 1995 and November 2000. Over a median 7.3 years of follow-up, 16.9% of the women in the comparison group and 16.7% of women in the intervention group experienced an additional breast cancer event, and 155 women in the intervention group died compared to 160 women in the comparison group [17].

Procedures

Participants in the WHEL Study were asked to complete a series of questionnaires at 5 study time points [baseline, 1 year, 2 or 3 years (randomly determined), 4 years, and 6 years]. These study assessments were completed by self-administered questionnaires and in-person interviews. Participants were also contacted twice per year by WHEL staff to collect information on health status, hospitalizations, medical procedures and other breast cancer and health related topics (one of which was lymphedema). Additional study protocols have been described elsewhere [16]. Procedures for this study were approved by the institutional review boards of each participating institution.

Baseline Dataset

Upon enrollment into the WHEL Study and prior to randomization, participants completed a series of baseline assessments described in detail below.

Demographics

Demographic data, including age at diagnosis, marital status, ethnicity, and education, were collected at baseline by a telephone screening interview and intake forms. Height and weight were measured during the first clinic visit and used to calculate body mass index (BMI), which was categorized as underweight/normal weight (BMI < 24.9 kg/m^2), overweight (BMI = 25 to 29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2).

Tumor and Treatment Characteristics

Medical records including pathology reports were reviewed for each participant. Axillary lymph node dissection was an eligibility inclusion criterion for all WHEL

participants. Variables that were documented included tumor grade and size, number of lymph nodes removed, type of breast cancer surgery (i.e., lumpectomy or mastectomy), administration of chemotherapy and/or radiation therapy, and use of anti-estrogen therapy. The present analysis uses three categories to describe breast cancer treatment: mastectomy with no radiation therapy, lumpectomy plus radiation therapy, and mastectomy plus radiation therapy.

Health Behaviors

At each of the 5 study time points, participants completed a questionnaire on their personal health habits, including smoking status and a validated 9-item physical activity scale[18]. The present analysis uses only the baseline assessment of the personal health habits questionnaire. Physical activity frequency, duration and intensity were converted into metabolic units (METs) using a standard compendium in accordance with Ainsworth et al. [19]. Following other studies [18, 20, 21], we classified mild physical activity as equivalent to 3 METs, moderate activity to 5 METs, and strenuous activity to 8 METs. Slow, average, fast, and very fast walking were assigned values of 2, 3, 4, or 6 METs, respectively. Total energy expenditure was calculated by weighting time (in minutes) spent per week by METs.   As per Hong et al., 2007, we created a physical activity variable based on total MET-hours per week (MHW) values with four categories: inactive (MHW < 3.3), mildly to moderately active (3.3 ≤ MHW < 10.0), active (10.0 ≤ MHW < 20.0) and highly active (MHW ≥ 20.0) [20].

Comorbid medical conditions

Participants completed a health status questionnaire that assessed the prevalence of some diagnosed diseases and conditions. Some of these conditions

were combined into general systems (i.e., cardiovascular conditions) to increase the sample sizes in each category and to avoid the potential for overlapping diagnoses. For example, cardiovascular conditions include high blood pressure, angina, any use of cholesterol-related medications, peripheral arterial disease, and other heart-related conditions.

Lymphedema Special Dataset

Starting in March 2003 through August 2006 as part of the semi-annual calls, WHEL staff conducted telephone interviews with participants to assess lymphedema status. The interview questions were adapted from Norman and colleagues' (2001) validated telephone lymphedema questionnaire [22]. Prior to starting the questionnaire, participants were informed that lymphedema is a swelling of the arm or hand due to fluid buildup following surgery. To assess lymphedema status, women were asked two questions: 1) "Since your breast cancer treatment, was there ever a time when your arms or hands were different sizes from each other?", and 2) "Since your breast cancer treatment, has a health care professional ever told you that you have lymphedema?". The responses for both items were "yes", "no", or "not sure/don't know". Women were grouped into two categories based on their responses to the above two questions. The lymphedema group consists of women who answered "yes" to one or both of the above questions. Women who responded "no" or "not sure/don't know" to both questions were categorized as not having lymphedema.

Statistical Methods

Univariate analyses were conducted to examine if participant demographics (e.g., age, ethnicity, BMI), tumor and treatment characteristics (e.g., tumor size,

number of lymph nodes removed, treatment modality), health behaviors (e.g., smoking and physical activity) and comorbid medical conditions (e.g., arthritis, osteoporosis) were significantly associated with lymphedema status. Categorical variables were analyzed using χ^2 tests and continuous variables with independent samples T-tests and Wilcoxon Rank Sum test. Lastly, logistic regression modeling was used to examine the association between baseline participant characteristics and self-report of lymphedema. Independent variables that were statistically significant in the univariate analyses were entered into the model using a stepwise entry procedure. In addition, we examined interaction terms between each of the variables included in the logistic regression model. Significance for all analyses was set at $P<0.05$. All analyses were conducted using SPSS v.16.0 (Chicago, IL).

RESULTS

By March 1, 2003, 2917 WHEL participants were alive and contacted for the lymphedema semi-annual call. Of those contacted, 83% (N=2431) of the study cohort responded and self-reported their lymphedema status. Among these 2431 respondents, 466 (19.2%) reported that a health care professional had told them they had lymphedema, and 676 (27.8%) self-reported swelling of the arm or hand. In total, 692 (28.5%) women reported yes to either a physician's diagnosis of lymphedema or arm/hand swelling; of these women, 450 (18.5%) reported yes to both a physician's diagnosis and self-report of arm/hand swelling. Demographic, medical characteristics, and health behaviors reported at baseline are provided in Table 2.1. For all respondents, the average age at diagnosis was 51 years. Most women were non-Hispanic White, college graduates, and married. Over half of the women were

classified as overweight or obese. In terms of physical activity, the majority reported participating in at least 3.3 MHW. Approximately 4% of the respondents were current smokers, and over half were never smokers. Most women either had a lumpectomy plus radiation therapy or a mastectomy plus radiation therapy, and the majority received chemotherapy. The average number of lymph nodes removed was fifteen. Most women in the sample did not report having a comorbid medical condition at baseline. When compared to other participants, women with lymphedema were diagnosed at a younger age, more likely to have a higher body mass index, had a larger tumor size, had more lymph nodes removed, more likely to have a mastectomy with radiation therapy, and more likely to have chemotherapy.

Based on results of the univariate tests, variables that were significant were added to binary logistic regression models to determine the association between the baseline variables and lymphedema status. Since the association between lymphedema and osteoporosis was close to statistical significance in the univariate tests, we created a regression model that included it with the other variables that were significant. However, after adjusting for the other variables included in this model, osteoporosis was no longer statistically significant (p=0.214) and not included in the final model. In the final multivariate-adjusted model (Table 2.2), BMI, the number of lymph nodes removed, and breast cancer treatment were significantly associated with lymphedema status. There were 2425 participants included in the final model: 3 participants were missing data on tumor size, 2 were missing data on the number of lymph nodes removed, and 1 participant was missing data on breast cancer treatment.

As shown in Table 2.2, compared to women of normal weight, those who were overweight had 33% higher odds of having lymphedema and those who were obese had twice the odds. Women who underwent a lumpectomy with radiation therapy had

12% higher odds of having lymphedema than those who only had a mastectomy although this result was not significant at the 5% level. In addition, women who had a mastectomy with radiation therapy had over twice the odds to self-report lymphedema compared to those who only had a mastectomy. The more lymph nodes removed increased the odds of developing lymphedema. Compared to women who had 1 to 10 lymph nodes removed, women who had 16 or more lymph nodes excised had 65% higher odds of lymphedema. In summary, having a BMI greater than 25.0 kg/m², breast cancer surgery with radiation therapy, and more than 11 lymph nodes removed were significantly associated with developing breast cancer-related lymphedema.

Figure 2.1 illustrates the significant interaction between BMI and the number of lymph nodes removed [χ^2 (4, N=2425) = 20.20, p<0.01]. Regardless of the number of lymph nodes removed, obese women had higher rates of lymphedema than normal weight and overweight women: odds ratios ranged from 2.31 to 3.60 for obese women across lymph node categories compared to odds ratios of 1.00 to 1.69 for normal weight women.

Further, sensitivity analyses were conducted among women who self-reported a physician diagnosis and arm/hand swelling (N=450) compared to women with no report of lymphedema (N=1739) to further examine the association between baseline risk factors and lymphedema. The results of these analyses were similar to those presented in Tables 2.1 and 2.2 (data not shown).

DISCUSSION

Breast cancer-related lymphedema is an adverse and chronic health condition that affects a significant number of breast cancer survivors. The purpose of this study

was to identify the prevalence of lymphedema in the WHEL cohort of breast cancer survivors and to examine the factors associated with lymphedema among our participants. In our study sample, approximately 29% of the women self-reported lymphedema. Considering the varying definitions used to define lymphedema, our percentage of self-reported lymphedema is comparable to other studies reporting the prevalence of lymphedema among breast cancer survivors [2, 3, 6, 10, 15, 23]. Ahmed and colleagues (2011) stated that 8% of their population reported a lymphedema diagnosis and 37% reported only arm symptoms of lymphedema [6]. Meeske et al., 2009 found that 24% of their population reported lymphedema [15]. Hayes and colleagues (2008) reported that 33% of their study cohort had lymphedema within 6 to 18 months after surgery [23]. Also among a cohort of younger breast cancer survivors, 32% reported persistent arm and/or hand swelling [10].

This cohort analysis identified breast cancer surgery plus radiation therapy, lymph node removal, and body mass index as having a significant association with developing breast cancer-related lymphedema. In terms of breast cancer treatment, having a mastectomy plus receiving radiation therapy showed a two-fold increased odds of developing lymphedema in comparison to having a mastectomy alone. In contrast, other studies have not found breast cancer surgery and/or radiation therapy to be associated with lymphedema [4, 7, 10, 14, 15]. Ahmed and colleagues (2011) did not find breast cancer surgery or radiation therapy to be risk factors for those diagnosed with lymphedema; however, they did report that axillary radiation was associated with self-report of arm symptoms among their study population [6]. Hayes and colleagues (2008) did not find radiation treatment to be associated with lymphedema, yet mastectomy was shown to be a risk factor for lymphedema in their study population [23].

The differences in our results from other studies regarding breast cancer treatment as a risk factor for lymphedema may be attributed to differences in demographics of the study populations or the definition of the breast cancer treatment variable. For example, the age at breast cancer diagnosis varies from study to study; some of the studies have a study population that is younger [4, 10, 15] or older [6, 7] than the WHEL Study population. Further, the percentage of women who received breast cancer surgery or radiation therapy also differs among studies. For example, some studies reported that less than 50% of their population underwent a mastectomy [4, 10, 14, 23] or received radiation therapy [4, 6, 15]. Another key difference is how breast cancer treatment was classified. We chose to combine breast cancer surgery with radiation therapy as our treatment variable; whereas, some of the other studies left these as two separate variables in their analyses. For example, Ahmed and colleagues (2011) classified breast surgery as no surgery or lumpectomy, simple mastectomy, radical mastectomy, or unknown, and they classified radiation therapy into two regions: the axilla and the breast [6]. Our study results confirm findings from other studies that have shown the removal of axillary lymph nodes to be an independent risk factor for lymphedema [4, 6, 7, 10, 13–15]. We found that women with 16 or more lymph nodes removed had 1.65 higher odds of having lymphedema compared to those with 10 or fewer nodes removed. Similar to our findings, Ahmed and colleagues reported that the odds of lymphedema among women with greater than 20 lymph nodes excised was 3.52 times the odds of women with no lymph nodes removed [6]. Meeske et al., 2009 found that those with 10 or more lymph nodes removed had 2.16 higher odds of developing lymphedema compared to those with no lymph nodes removed [15]. Further, studies have shown that even removing only a few lymph nodes can still result in the development of lymphedema [10, 14]. Kwan and

colleagues (2010) found that the risk of lymphedema increased by 4.1% for each lymph node removed [14]. These findings in addition to our study results highlight the importance of removing as few lymph nodes as possible when examining the axillary region for tumor metastases.

While lymph node removal is the most common risk factor cited for breast cancer-related lymphedema, our results show that it is not the only risk factor for lymphedema. Our study found that the higher the BMI, the higher the odds of reporting lymphedema. We found that obese participants had twice the odds to self-report lymphedema as normal weight women. These results are consistent with those of previous studies that have found an association between BMI and lymphedema [6, 8, 10, 11, 13–15]. For example, Ahmed et al., 2011 found that among women with a baseline BMI ≥ 30 kg/m² the odds of having lymphedema were increased by a factor of 3.24 times compared to women with a baseline BMI < 24.9 kg/m² [6]. Among younger breast cancer survivors, Paskett and colleagues (2007) found the odds of persistent swelling were 2.24 times higher for those with a BMI > 30 kg/m² compared to those with a BMI < 25 kg/m² [10]. Ridner et al., 2011 reported that women with a BMI ≥ 30 kg/m² at the time of treatment had a 3.6 times higher odds of developing lymphedema than women with a BMI < 30 kg/m² [11]. In contrast to these findings, Hayes and colleagues found no association between body weight and lymphedema [23]. This difference could be due to the method of measuring lymphedema among the studies. Hayes et al., 2008 used bioimpedance spectroscopy to measure lymphedema status [23]; whereas, our study as well as most of the other studies used self-report of lymphedema.

Additionally, we found that when BMI and the number of excised lymph nodes were considered together, the odds of having lymphedema increased compared to

when these variables were considered independently. Obese participants had higher

odds of developing lymphedema, irrespective of the number of lymph nodes removed,

when compared to normal weight and overweight women. To date, there are no

published studies that have examined the association of BMI/number of lymph nodes

removed with lymphedema status. Our finding of an interaction between BMI and

lymph node removal is novel, and if replicated in other studies, has implications for

counseling women about the risk of lymphedema prior to and after breast cancer

treatment. Lymphedema patient education is of particular importance for all women

who undergo lymph node dissection surgery and have a BMI greater than 30 at the

time of cancer diagnosis. In addition, women who have a BMI greater than 30 after

cancer treatment should also be educated about the risks factors associated with

developing lymphedema.

While the risk factors identified in our study have been reported by others, our

analyses did not identify any other participant characteristics (e.g., age, chemotherapy,

physical activity, or comorbid medical conditions) associated with lymphedema. Other

literature have reported chemotherapy to be associated with lymphedema status [4, 6,

13], yet in our study, chemotherapy was not associated with lymphedema in the

multivariate model. Similar to our findings, others have reported no association

between chemotherapy and lymphedema status [7, 15, 23]. Additionally, some studies

have reported age to be associated with lymphedema [15, 23]; whereas, similar to our

study, others have not found this association [6, 10, 14]. In terms of physical activity,

our study findings are comparable to other studies that did not find a significant

association between level of physical activity and lymphedema [6, 10, 14, 15]. Similar

to the Ahmed et al., 2011 study, we found that comorbid medical conditions at baseline

were not associated with lymphedema [6]. While osteoporosis was borderline

significant in the chi-square tests, its significance disappeared once it was included in the regression model with the other variables.   In contrast to our findings, Meeske et al., 2009 reported that a diagnosis of high blood pressure prior to breast cancer diagnosis was associated with lymphedema [15]. Another study found that breast cancer survivors with lymphedema experience more comorbid medical conditions than those without lymphedema [24].

The inconsistency in findings related to the above characteristics may be due to differences in study designs, sample sizes, or the time frame of assessing lymphedema status after cancer treatment. A key difference between the studies presented above is the type of study design. Some studies were prospective cohort studies [6, 10, 14]; whereas, others were retrospective studies examining claims or registry data [4, 7, 15]. In terms of sample size, our study population of 692 women self-reporting lymphedema is much larger than the other studies; most of which had fewer than 200 women with lymphedema [4, 7, 11, 14, 15, 23]. Some of these studies may not have found significant associations between risk factors and lymphedema due to their small sample size. Further, the time frame between the completion of breast cancer treatment and the assessment of lymphedema varies from study to study. For example, some studies assessed lymphedema status within 3 years of breast cancer surgery [4, 10, 13, 14, 23]; whereas, other studies, including the WHEL Study, assessed lymphedema status at least 4 years postoperatively [6, 7, 15].

The primary limitation for this study is its reliance on self-report for assessing lymphedema status rather than a physical measurement. However, our sensitivity analysis, which compared those with a self-report of a physician's diagnosis and swelling (N=450) to those with no lymphedema (N=1739), produced similar results to the analyses shown in Tables 2.1 and 2.2 comparing women who self-reported

arm/hand swelling and/or a physician diagnosis (N=692) to those with no lymphedema (N=1793). These findings support the use of self-report for breast cancer-related lymphedema status. Also the lymphedema questionnaire used in this study has been validated and shown to accurately identify lymphedema [22]. Additionally, many of the other study variables, such as breast cancer treatment and physical activity, were assessed using self-report measures, which are subject to response bias and may influence the results of the study. Since the baseline information was collected at study entry, which for some participants was up to 4 years after cancer diagnosis, we cannot evaluate the causative relationships between lymphedema and some of the risk factors, such as body mass index, identified in this study. Furthermore, our study baseline BMI variable assessed BMI post-treatment, not pre-treatment or pre-diagnosis. Another study limitation is that participants in the WHEL Study are not representative of all breast cancer survivors; women in the WHEL Study were primarily White, college educated, and highly motivated to participate in a dietary intervention. Hence, the findings from this study may not be generalizable to other breast cancer populations. In contrast to the study limitations, the primary strengths of the study are a large sample size, a 7.3 year average follow-up period, and substantial data collection on health behaviors, treatment variables, and comorbid medical conditions at baseline.

In conclusion, BMI, lymph node removal, and breast cancer treatment were significantly associated with lymphedema among participants in the WHEL Study. These results are consistent with previous findings on the prevalence of lymphedema among breast cancer survivors and may help educate physicians and patients as to the modifiable risk factors associated with lymphedema. While the number of lymph nodes removed and the type of breast cancer treatment may be unavoidable, maintaining or

achieving a healthy weight is a valid target for health behavior interventions aimed at reducing the rates of lymphedema. Future research needs to focus on whether or not modifiable risk factors associated with lymphedema can be effectively targeted in health behavior interventions to prevent the development of breast cancer-related lymphedema.

ACKNOWLEDGEMENTS

Chapter 2, in full, is a reprint of the material as it appears in the Journal of Cancer Survivorship: Dominick SA, Madlensky L, Natarajan L, and Pierce, JP. Risk Factors Associated with Breast Cancer-Related Lymphedema in the WHEL Study. Journal of Cancer Survivorship, 7(1):115-123. DOI: 10.007/s11764-012-0251-9. The final publication is available at www.springerlink.com. Sally Dominick was the primary investigator and author of this paper.

Table 2.1. Baseline participant characteristics by lymphedema status in a cohort of breast cancer survivors.

Characteristic	Overall (*N* = 2431) N (%)	Women with Lymphedema (*N* = 692) N (%)	Women without Lymphedema (*N* = 1739) N (%)	*P* value
Demographics				
Age at Diagnosis, mean [SD (range)], years	51.0 [8.7 (26.0 – 70.0)]	50.4 [8.6 (26.0 – 70.0)]	51.2 [8.7 (27.0 – 70.0)]	0.03
Ethnicity				0.40
White, not Hispanic	2089 (85.9)	585 (84.5)	1504 (86.5)	
Hispanic	126 (5.2)	38 (5.5)	88 (5.1)	
Asian American	80 (3.3)	21 (3.0)	59 (3.4)	
Black/ African American	78 (3.2)	29 (4.2)	49 (2.8)	
Other	58 (2.4)	19 (2.8)	39 (2.2)	
Education				0.39
College Graduate	1349 (55.5)	374 (54.0)	975 (56.1)	
Other	1082 (44.5)	318 (46.0)	764 (43.9)	
Marital Status				0.07
Married	1735 (71.4)	475 (68.6)	1260 (72.5)	
Other	696 (28.6)	217 (31.4)	479 (27.5)	
Body Mass Index				<0.01
< 25 kg/m^2 (normal/underweight)	1086 (44.7)	249 (36.0)	837 (48.1)	
25 – 29.9 kg/m^2 (overweight)	756 (31.1)	216 (31.2)	540 (31.1)	
≥ 30 kg/m^2 (obese)	589 (24.2)	227 (32.8)	362 (20.8)	
Menopausal Status				0.24
Pre-menopausal	252 (10.4)	73 (10.6)	179 (10.3)	
Post-menopausal	1948 (80.3)	541 (78.5)	1407 (81.0)	
Peri-menopausal	227 (9.3)	75 (10.9)	152 (8.7)	
Tumor and Treatment Characteristics				
Grade				0.14
I	423 (17.4)	119 (17.2)	304 (17.5)	
II	963 (39.6)	254 (36.7)	709 (40.8)	
III	840 (34.6)	263 (38.0)	577 (33.1)	
Not applicable or available	205 (8.4)	56 (8.1)	149 (8.6)	

Table 2.1. Continued

Characteristic	Overall (*N* = 2431) N (%)	Women with Lymphedema (*N* = 692) N (%)	Women without Lymphedema (*N* = 1739) N (%)	P value
Tumor Size				<0.01
< 1.5 cm	715 (29.4)	181 (26.2)	534 (30.7)	
1.5 – 1.9 cm	553 (22.8)	142 (20.6)	411 (23.7)	
2.0 – 2.9 cm	649 (26.7)	188 (27.2)	461 (26.5)	
≥ 3.0 cm	511 (21.1)	180 (26.0)	331 (19.1)	
No. Nodes Removed, mean [SD (range)]	15.0 [7.0 (1 – 69)]	16.3 [7.0 (2 – 54)]	14.5 [6.6 (1 – 69)]	<0.01
1 to 10 nodes	614 (25.3)	132 (19.1)	482 (27.8)	
11 to 15 nodes	793 (32.6)	216 (31.2)	577 (33.2)	
≥ 16 nodes	1022 (42.1)	344 (49.7)	678 (39.0)	
Treatment				<0.01
Mastectomy No Radiation	935 (38.5)	239 (34.5)	696 (40.0)	
Lumpectomy plus Radiation	1188 (48.9)	319 (46.1)	869 (50.0)	
Mastectomy plus Radiation	307 (12.6)	134 (19.4)	173 (10.0)	
Chemotherapy	1664 (68.4)	499 (72.1)	1165 (67.0)	0.02
Anti-estrogen Therapy				0.28
Ever Use	1687 (69.5)	468 (67.8)	1219 (70.2)	
No Use	740 (30.5)	222 (32.2)	518 (29.8)	
Health Behaviors				
Smoking status				0.58
Never	1326 (54.9)	380 (55.3)	946(54.7)	
Former	996 (41.2)	285 (41.5)	711 (41.2)	
Current	93 (3.9)	22 (3.2)	71 (4.1)	
Physical Activity, median METs- hour/week (MHW)	10.96	10.00	12.00	0.09
Inactive (MHW < 3.3)	544 (23.1)	172 (25.8)	372 (22.1)	
Mildly-moderately Active (3.3 ≤ MHW < 10.0)	540 (22.9)	159 (23.8)	381 (22.6)	
Active (10.0 ≤ MHW < 20.0)	583 (24.8)	163 (24.4)	420 (24.9)	
Highly Active (MHW ≥ 20.0)	687 (29.2)	173 (26.0)	514 (30.4)	

Table 2.1. Continued

Characteristic	Overall (N = 2431) N (%)	Women with Lymphedema (N = 692) N (%)	Women without Lymphedema (N = 1739) N (%)	P value
Comorbid Medical Conditions				
Arthritis	382(18.8)	113 (19.0)	269 (18.8)	0.98
Cardiovascular Conditions	457 (22.5)	144 (24.2)	313 (21.9)	0.28
Diabetic Conditions	83 (4.1)	28 (4.7)	55 (3.8)	0.45
Digestive Conditions	189 (9.3)	60 (10.1)	129 (9.0)	0.51
Miscellaneous Conditions	166 (8.2)	55 (9.2)	111 (7.8)	0.31
Osteoporosis	119 (5.9)	25 (4.2)	94 (6.6)	0.05

Note: 2x2 tables were tested with Yates' χ^2 test.
Categorical variables with three or more categories were tested with Pearson's χ^2 test.
Continuous variables were tested with independent-samples T-test and Wilcoxon Rank sum test.

Table 2.2. Baseline participant characteristics associated with lymphedema status in a cohort of breast cancer survivors (N=2425).

| | Women with Lymphedema | | | |
Characteristic	N (%)	OR	*P* value	(95% CI)
Demographics				
Age at diagnosis, mean [SD (range)], years	50.4 [8.6 (26.0 – 70.0)]	0.99	0.08	(0.98 – 1.00)
Body Mass Index			<0.01	
< 25 kg/m^2 (normal/underweight)	249 (36.0)	1.00		---
25 – 29.9 kg/m^2 (overweight)	216 (31.2)	1.33		(1.07 – 1.66)
≥ 30 kg/m^2 (obese)	227 (32.8)	2.08		(1.66 – 2.60)
Tumor and Treatment Characteristics				
Tumor Size			0.41	
< 1.5 cm	181 (26.2)	1.00		---
1.5 - 1.9 cm	142 (20.6)	1.02		(0.78 – 1.32)
2.0 – 2.9 cm	188 (27.2)	1.07		(0.83 – 1.38)
≥ 3.0 cm	180 (26.0)	1.25		(0.95 – 1.67)
No. Nodes Removed			<0.01	
1 to 10 nodes	132 (19.1)	1.00		---
11 to 15 nodes	216 (31.2)	1.28		(0.99 – 1.65)
≥ 16 nodes	344 (49.7)	1.65		(1.30 – 2.09)
Treatment			<0.01	
Mastectomy with no Radiation	239 (34.5)	1.00		---
Lumpectomy plus Radiation	319 (46.1)	1.12		(0.91 – 1.37)
Mastectomy plus Radiation	134 (19.4)	2.02		(1.52 – 2.69)
Chemotherapy	499 (72.1)	1.02	0.90	(0.81 – 1.28)

Note: Odd ratios adjusted for all variables in the table. CI indicates confidence interval.
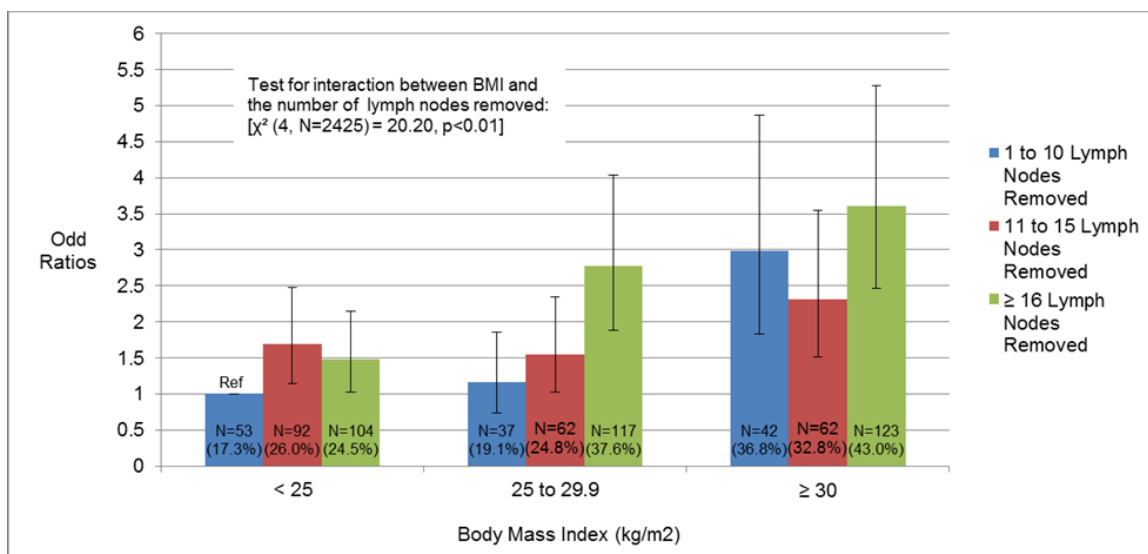
Figure 2.1. Lymphedema rates according to BMI and the number of lymph nodes removed (N=2425).

Note: N (%) is the number and percentage of women with lymphedema in each category. The total number of women with lymphedema equals 692.
Odd ratios (OR) adjusted for the following variables: age at diagnosis, tumor size, treatment, and chemotherapy.
Confidence intervals are indicated by the error bars on the graph.
"Ref" on the first bar indicates that this is the reference category.

REFERENCES

1.   Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER Cancer Statistics Review, 1975-2008. Bethesda, MD: National Cancer Institute; 2011.

2.   Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. Cancer. 1998;83:2776–81.

3.   Erickson VS, Pearson ML, Ganz PA, Adams J, Kahn KL. Arm edema in breast cancer patients. J Natl Cancer Inst. 2001;93:96–111.

4.   Shih Y-CT, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. J Clin Oncol. 2009;27:2007–14.

5.   Smoot B, Wong J, Cooper B, Wanek L, Topp K, Byl N, et al. Upper extremity impairments in women with or without lymphedema following breast cancer treatment. J Cancer Surviv. 2010;4:167–78.

6.   Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast Cancer Res Treat. 2011;130:981–91.

7.   Yen TWF, Fan X, Sparapani R, Laud PW, Walker AP, Nattinger AB. A contemporary, population-based study of lymphedema risk factors in older women with breast cancer. Ann Surg Oncol. 2009;16:979–88.

8.   McLaughlin SA, Wright MJ, Morris KT, Sampson MR, Brockway JP, Hurley KE, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: patient perceptions and precautionary behaviors. J Clin Oncol. 2008;26:5220–6.

9.   Goldberg JI, Wiechmann LI, Riedel ER, Morrow M, Van Zee KJ. Morbidity of sentinel node biopsy in breast cancer: the relationship between the number of excised lymph nodes and lymphedema. Ann Surg Oncol. 2010;17:3278-86.

10.   Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. Cancer Epidemiol Biomarkers Prev. 2007;16:775–82.

11.   Ridner SH, Dietrich MS, Stewart BR, Armer JM. Body mass index and breast cancer treatment-related lymphedema. Support Care Cancer. 2011;19:853-7.

12.   Sakorafas GH, Peros G, Cataliotti L, Vlastos G. Lymphedema following axillary lymph node dissection for breast cancer. Surg Oncol. 2006;15:153–65.

13. Norman SA, Localio AR, Kallan MJ, Weber AL, Torpey HAS, Potashnik SL, et al. Risk factors for lymphedema after breast cancer treatment. Cancer Epidemiol Biomarkers Prev. 2010;19:2734–46.

14. Kwan ML, Darbinian J, Schmitz KH, Citron R, Partee P, Kutner SE, et al. Risk factors for lymphedema in a prospective breast cancer survivorship study: the Pathways study. Arch Surg. 2010;145:1055–63.

15. Meeske KA, Sullivan-Halley J, Smith AW, McTiernan A, Baumgartner KB, Harlan LC, et al. Risk factors for arm lymphedema following breast cancer diagnosis in black women and white women. Breast Cancer Res Treat. 2009;113:383–91.

16. Pierce JP, Faerber S, Wright FA, Rock CL, Newman VA, Flatt SW, et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) study. Control Clin Trials. 2002;23:728–56.

17. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA. 2007;298:289–98.

18. Johnson-Kozlow M, Rock CL, Gilpin EA, Hollenbach KA, Pierce JP. Validation of the WHI brief physical activity questionnaire among women diagnosed with breast cancer. Am J Health Behav. 2007;31:193–202.

19. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32:S498–504.

20. Hong S, Bardwell WA, Natarajan L, Flatt SW, Rock CL, Newman VA, et al. Correlates of physical activity level in breast cancer survivors participating in the Women's Healthy Eating and Living (WHEL) study. Breast Cancer Res Treat. 2007;101:225–32.

21. Bertram LAC, Stefanick ML, Saquib N, Natarajan L, Patterson RE, Bardwell W, et al. Physical activity, additional breast cancer events, and mortality among early-stage breast cancer survivors: findings from the WHEL study. Cancer Causes Control. 2011;22:427–35.

22. Norman SA, Miller LT, Erikson HB, Norman MF, McCorkle R. Development and validation of a telephone questionnaire to characterize lymphedema in women treated for breast cancer. Phys Ther. 2001;81:1192–1205.

23. Hayes SC, Janda M, Cornish B, Battistutta D, Newman B. Lymphedema after breast cancer: incidence, risk factors, and effect on upper body function. J Clin Oncol. 2008;26:3536–42.

24. Ridner SH, Dietrich MS. Self-reported comorbid conditions and medication usage in breast cancer survivors with and without lymphedema. Oncol Nurs Forum. 2008;35:57–63.

CHAPTER 3

The Psychosocial Impact of Lymphedema-related Distress among Breast Cancer

Survivors in the WHEL Study

ABSTRACT

Introduction Lymphedema is a distressing and chronic condition affecting up to 30% of breast cancer survivors. We examined the impact of self-reported lymphedema-related distress on psychosocial functioning among breast cancer survivors in the Women's Health Eating and Living (WHEL) Study. The WHEL Study has a dataset that includes self-report data on lymphedema status, symptoms and distress.

Methods Chi-square tests and binary logistic regression models were used to examine how specific participant characteristics, including lymphedema-related distress, were associated with physical health and mental health as measured by the SF-36 and depressive symptoms assessed by the CES-Dsf.

Results Of the 2,431 participants included in the current study population, 692 (28.5%) self-reported having lymphedema. A total of 335 women reported moderate to extreme distress as a result of their lymphedema and were classified as having lymphedema-related distress. The logistic regression models showed that women with lymphedema-related distress had 50% higher odds of reporting poor physical health (p=0.01) and 73% higher odds of having poor mental health (p<0.01) when compared to women without lymphedema. In contrast, even though lymphedema-related distress was significantly associated (p=0.03) with elevated depressive symptoms in the bivariate analyses, it was not significant in the logistic regression models.

Conclusions Breast cancer survivors with lymphedema-related distress had worse physical and mental health outcomes than women with lymphedema who were not

distressed and women with no lymphedema. Our study findings underscore the

negative impact lymphedema-related distress has on the psychosocial functioning of

breast cancer survivors.

INTRODUCTION

Lymphedema is a burdensome and chronic condition faced by a significant percentage of breast cancer survivors. Of the 2.7 million breast cancer survivors, it is estimated that 6 to 30% of these women will experience lymphedema symptoms [1]. Further, the incidence of arm edema is estimated to be 26% (ranging from 0 – 56%) among breast cancer survivors [2]. Lymphedema usually arises as a result of damage to the lymphatic system near the affected breast region, impeding the flow of lymphatic fluid throughout the affected region and into the arm and/or hand. Depending on the severity of damage to the lymphatic system, the build-up of lymphatic fluid can cause a variety of symptoms. Common symptoms of lymphedema are arm or hand swelling, tenderness, numbness, puffiness, pain, and arm or hand heaviness [3–5]. Additionally, some women will experience serious complications related to lymphedema. Some examples of these complications are impairments in the local immune response, which can result in soft tissue infections with a high fever; cellulitis, which has been reported to occur in up to 63% of patients with breast cancer-related lymphedema; and adverse psychological and physical morbidity [5,6]. Also lymphedema can be a debilitating condition that negatively impacts an individual's psychosocial functioning [7,8].

Previous research studies have shown that women living with breast cancer-related lymphedema experience a diminished quality of life [5,9–13]. In a study of 622 breast cancer survivors, women who self-reported arm or hand swelling had significantly lower mean scores on the mental and physical SF-12 subscales compared to women without swelling [13]. Using data from the Iowa Women's Health Study, Ahmed and colleagues (2008) found that women with self-reported lymphedema (8.1% of the sample) and women with arm symptoms (37.2% of the sample) had lower

health-related quality of life (HRQOL) SF-36 scores compared to women without lymphedema or arm symptoms [9].

While the above studies demonstrate that diminished quality of life is a complication for breast cancer survivors living with lymphedema, a paucity of research studies have examined whether other psychological factors, such as depressive symptoms, are affected by lymphedema status. Oliveri and colleagues (2008) found that there was no difference in depression status as measured by the CES-D between women who reported arm/hand swelling and those who did not [11]. Additionally, Ridner (2005) found no association between CES-D scores between those with lymphedema and those without; differences in CES-D scores were related to body mass index [12].

Although there is clear evidence that women with lymphedema have reduced quality of life, little is known about how distress attributed to lymphedema affects psychosocial functioning (i.e., quality of life and depressive symptoms). The main objective of this study is to examine the psychosocial impact of lymphedema among breast cancer survivors enrolled in the Women's Healthy Eating and Living (WHEL) Study. In particular, we aim to investigate how lymphedema-related distress affects quality of life (i.e., physical and mental health) and depressive symptoms.

METHODS

Study Population

The WHEL Study was a randomized controlled trial that enrolled 3088 female breast cancer survivors to assess the effectiveness of a plant-based diet on breast cancer recurrence and mortality. All participants were within 4 years of an early stage

breast cancer diagnosis categorized using American Joint Committee on Cancer (edition IV) criteria as stage I (≥1cm), stage II, or stage IIIA [14]. Between March 1995 and November 2000, seven study sites (four in California, one each in Arizona, Oregon, and Texas) recruited participants through physicians, tumor registries and community breast cancer events. As previously reported in 2007, the plant-based diet did not significantly alter rates of breast cancer recurrence or mortality for the study participants, who were followed for a median of 7.3 years [15].

Procedures

The majority of WHEL Study participants completed a series of self-administered questionnaires and in-person interviews at 5 study time points [baseline, 1 year, 2 or 3 years (randomly determined), 4 years, and 6 years]. Additionally, WHEL staff contacted participants twice per year to collect information on a variety of health-related topics, such as health status and medical procedures. Details on all study protocols have been reported previously [14]. The institutional review boards at each study site approved the procedures for this study.

Baseline Dataset

All WHEL participants were given a series of baseline assessments that they were asked to complete upon enrollment and prior to randomization. Demographic data were collected at baseline by a telephone screening interview and intake forms. To obtain tumor and treatment characteristics for each participant, medical records including pathology reports were reviewed. Documented variables include tumor grade and size, number of lymph nodes removed, and types of breast cancer treatments (e.g., surgery, chemotherapy, radiation and hormone therapy).

Year 4 Dataset

The current analyses used data (described below) collected at the Year 4 study

time point to coincide with the lymphedema dataset collection time point.

Body Mass Index

During the Year 4 clinic visit, the participant's height and weight were measured

and used to calculate body mass index (BMI). For this study, BMI was categorized as

underweight/normal weight (BMI < 24.9 kg/m^2), overweight (BMI = 25 to 29.9 kg/m^2),

and obese (BMI ≥ 30 kg/m^2).

Health Behaviors

Participants completed a questionnaire on their personal health habits,

including smoking status and a validated 9-item physical activity scale [16].

Frequency, duration and intensity of physical activity were converted into metabolic

units (METs) using a standard compendium in accordance with Ainsworth et al. [17].

As per Hong et al. (2007) and Bertram et al. (2011), the physical activity variable for

the present analyses was based on total MET-hours per week (MHW) values with four

categories: inactive (MHW < 3.3), mildly to moderately active (3.3 ≤ MHW < 10.0),

active (10.0 ≤ MHW < 20.0) and highly active (MHW ≥ 20.0) [18,19].

Comorbid Medical Conditions

Participants were asked to provide self-report information on a variety of

diseases/medical conditions, such as cardiovascular diseases, diabetes, and

gastrointestinal diseases. As per Patterson et al. (2010), comorbid medical conditions

were grouped into general systems patterned after the validated Charleston comorbidity index to avoid overlapping diagnoses and to ensure adequate samples sizes in each group [20]. In total, there were 6 general system categories: arthritis, cardiovascular, diabetic, digestive, osteoporosis, and miscellaneous conditions. For the present analyses, participants were classified as having 0, 1, 2, or 3 or more comorbid medical conditions.

Psychosocial Outcomes

A self-administered 147-item questionnaire was completed by study participants to assess HRQOL and psychosocial functioning. This questionnaire included the SF-36-Item Health Survey (SF-36), and the 8-item Center for Epidemiologic Studies Depression Scale screening form (CES-Dsf). Previous studies have shown these measures to be valid and reliable assessments of quality of life and depressive symptoms among WHEL Study participants [21–23].

The SF-36 has 8 subscales: general health, physical functioning, role limitations caused by physical health problems, bodily pain, vitality, social functioning, role limitations caused by emotional problems, and general mental health. A physical health (PH) summary score was calculated from the general health, physical functioning, role limitations caused by physical health problems, and bodily pain subscales; and a mental health (MH) summary score was computed from the vitality, social functioning, role limitations caused by emotional problems, and general mental health subscales. The range of scores is from 0 to 100, with higher scores indicating better health-related quality of life. The instrument has been widely used in research studies with breast cancer populations and shown to have strong psychometric properties (Cronbach's alpha = 0.75 to 0.91) [24–30]. Based on the previous WHEL analyses showing time to

additional breast cancer events and all-cause mortality is associated with SF-36 PH

scores in the lowest 2 quintiles [20,21], the PH and MH summary scores were divided

in quintiles and categorized as "Poor" (bottom 2 quintiles) and "Moderate/High" (top 3

quintiles) for the present analyses.

The CES-Dsf is a self-report scale used to identify individuals with elevated

depressive symptoms. The total score added from the 8-items can be converted into a

logarithmic scale.   It has been shown to be reliable (Cronbach's alpha = 0.73) and

valid in cancer patients [22]. For this study, total scores ≥ 0.06 in the logarithmic scale

were categorized as elevated depressive symptoms; this cut-off point has been used

previously as an indicator of clinically elevated depressive symptoms [22].

Lymphedema Dataset

Over the time period of March 2003 through August 2006, WHEL staff

contacted participants by telephone to assess lymphedema status among the study

cohort. Each interviewed participant answered questions adapted from Norman and

colleagues' (2001) validated telephone lymphedema questionnaire [31]. To assess the

participant's experience with lymphedema, each woman was asked: 1) "Since your

breast cancer treatment, was there ever a time when your arms or hands were different

sizes from each other?", and 2) "Since your breast cancer treatment, has a health care

professional ever told you that you have lymphedema?". Based on the answers to

these two questions, women were grouped into two categories: 1) the lymphedema

group consisted of women who answered "yes" to one or both of the questions and 2)

the non-lymphedema group consisted of women who responded "no" or "not sure/don't

know" to both questions.

Additional questions were asked to any women who responded in the affirmative to either of the above two questions. These women were asked whether they had currently, previously, or never experienced the following 13 symptoms of lymphedema: swelling; tenderness; numbness; watches, rings, bracelets, clothing becoming tight on one side; puffiness; firm or leathery skin; pain; indentations in skin after leaning against something; difficulty in seeing knuckles or veins; tiredness, thickness, heaviness of hand or arm; difficulty holding or grasping objects; difficulty writing; and infection in the affected arm or hand. In addition, lymphedema-related distress was assessed by the question, "How much did/does your lymphedema distress or bother you?", with 5 response choices. Women who selected "moderately", "quite a bit", and "extremely" were categorized as having lymphedema-related distress, and those were responded with "not at all" or "a little" were considered as not having lymphedema-related distress.

Statistical Methods

Bivariate associations were conducted to assess if participant demographics, tumor and treatment characteristics, health behaviors, comorbid medical conditions, number of current lymphedema symptoms, and lymphedema-related distress were associated with each of the 3 psychosocial outcome measures (i.e., PH, MH, and depressive symptoms) separately. Chi-square tests were used to analyze the categorical variables. Any variables associated with PH, MH, and depressive symptoms at $P<0.05$ were included into the multivariate regression models. Binary logistic regression models were built separately for each outcome measure with variables shown to be statistically significant in the bivariate analyses added to the

models as covariates. Significance for all analyses was set at $P<0.05$. All analyses were conducted using IBM® SPSS® Statistics Version 20.0 (Armonk, NY).

RESULTS

Of the 2917 WHEL participants contacted for the lymphedema telephone assessment, 83% (N=2431) of the study cohort responded and self-reported their lymphedema status. Among these 2431 respondents, 692 (28.5%) women reported yes to either a physician's diagnosis of lymphedema or arm/hand swelling. Of those who answered the lymphedema symptom questions (N=671), 71.7% of women were currently experiencing at least 1 symptom, and 44.2% of women reported experiencing 4 or more current symptoms. The three most common lymphedema symptoms were swelling (57%), puffiness (50%) and having watches, rings, bracelets, or clothing becoming tight on one side (41%) (Figure 3.1). Additionally, of the 685 women who answered the question, "how much did/does your lymphedema distress or bother you?", 335 (48.9%) reported moderate to extreme distress as a result of their lymphedema and were classified as having lymphedema-related distress. When examining lymphedema-related distress and the number of current symptoms, there was a significant association between the number of symptoms and lymphedema distress [χ^2 (3, N=671) = 56.96, $p<0.01$]. Of the 118 women who reported 7 or more symptoms, 87 (73.7%) reported moderate to extreme distress as a result of their lymphedema.

Next, bivariate analyses were conducted to examine how lymphedema-related distress and other participant characteristics measured at baseline or the Year 4 study time points were associated with physical health, mental health and depressive

symptoms. As shown in Table 3.1, lymphedema-related distress was significantly associated with PH, MH and depressive symptoms. Specifically, women who reported lymphedema-related distress were more likely to also self-report poor PH, poor MH and elevated depressive symptoms as compared to those without lymphedema and those with lymphedema yet not distressed. In terms of current symptoms (N=671), 54.2% of women with 7 or more symptoms had poor PH summary scores compared to only 44.2% of those who reported having no current symptoms. Similarly, over 50% of women who reported experiencing 4 or more lymphedema symptoms had poor MH summary scores as compared to 42% of those with 3 or fewer symptoms. In contrast, current lymphedema symptoms were not statistically significantly associated with elevated depressive symptoms. Additionally in the bivariate analyses, poor PH was significantly associated with the following 9 participant characteristics: age at diagnosis, ethnicity, education, marital status, BMI, menopausal status, chemotherapy, comorbid medical conditions, and physical activity. Poor MH was significantly associated with age at diagnosis, education, marital status, BMI, comorbid medical conditions, smoking status, and physical activity. Lastly, age at diagnosis, marital status, BMI, number of lymph nodes removed, comorbid medical conditions, smoking status and physical activity were associated with elevated depressive symptoms at $P<0.05$.

For the binary logistic regression models, the number of current lymphedema symptoms was not included due to its significant collinearity with lymphedema-related distress. The final PH model showed that that women who reported lymphedema-related distress, being unmarried, overweight or obese, having 1 or more comorbid medical conditions, and being physically inactive were more likely to have poor physical health scores. In particular, women with lymphedema had higher odds of

reporting poor PH than women without lymphedema. Additionally, women who reported lymphedema-related distress had 50% higher odds of reporting poor PH compared to women without lymphedema (Table 3.2). After adjusting for all variables in the MH model, women with poor MH scores were more likely to have lymphedema-related distress, have been diagnosed at age 50 and younger, be unmarried, have a BMI ≥ 25 kg/m^2, have at least 1 or more comorbid medical conditions, and be physically inactive. As shown in Table 3.2, women with lymphedema-related distress had 73% higher odds of having poor MH when compared to women with no lymphedema. For the depressive symptoms final regression model, self-report of elevated depressive symptoms was significantly associated with being younger than 50 years at the time of cancer diagnosis, having 10 or fewer lymph nodes removed, having 1 or more comorbid medical conditions, being a current smoker, and being physically inactive. In contrast to the PH and MH models, lymphedema-related distress was not significantly associated with elevated depressive symptoms in the adjusted regression model (Table 3.2).

DISCUSSION

The results of this study showed that lymphedema-related distress was associated with psychosocial functioning among women in the WHEL Study. After examining the relationship between current symptoms and distress specific to lymphedema, we found that the number of current lymphedema symptoms was highly correlated with reporting lymphedema-related distress. Further, our bivariate analyses findings showed that the number of current lymphedema symptoms as well as distress-specific to lymphedema were significantly associated with not only physical health, but

with mental health outcomes as well. The results of our logistic regression models revealed that women with lymphedema-related distress had 50% higher odds of reporting poor physical health and 73% higher odds of having poor mental health when compared to women without lymphedema. In contrast, while lymphedema-related distress was significantly associated with elevated depressive symptoms in the bivariate analyses, it was not significant in the adjusted binary logistic regression models.

Other studies have examined the impact of lymphedema on quality of life as measured by the SF-36 or SF-12 among breast cancer survivors [9–11,13,32–34]. Similar to our study findings, the majority of these studies have shown that women with lymphedema have significantly lower PH summary scores than women without lymphedema [9–11,13,32,33]. These findings are important when considering that poor PH has been shown to be associated with decreased time to additional breast cancer events and all-cause mortality [21]. However, it should be noted that we did not find a significant association between lymphedema and additional breast cancer events or all-cause mortality (data not shown).

Further, we have confirmed findings in multiple studies showing that women with breast cancer-related lymphedema have lower mental health summary scores on the SF-36 and SF-12 [9,11,13,34] . In contrast to our study findings, two studies found no significant differences in SF-36 MH summary scores between those with lymphedema compared to those without breast cancer-related lymphedema [32,33]. These differences in MH findings may be due to participant demographics, sample size, or study objectives, which may influence how participants were selected.

While our study findings for HRQOL measured by the SF-36 in breast cancer survivors with lymphedema confirm the results from other studies, the main difference

between our study and other studies was our focus on examining how self-reported distress attributable to lymphedema impacts PH and MH outcomes. Another difference between our study and others was how we chose to categorize the SF-36 PH and MH summary scores. Our study followed the work of Saquib and colleagues (2011) in categorizing the PH and MH summary scores into quintiles with the bottom two quintiles for each summary score representing either "poor physical health" or "poor mental health" [21]. Scores were categorized into quintiles to allow for ease of interpretation and to rank study participants as to not assume the cut-points for the study population. The other studies discussed above used mean PH and MH scores to describe HRQOL among breast cancer survivors with lymphedema. Regardless of how the PH and MH summary scores were analyzed, our results are similar with these studies in showing that breast cancer survivors with lymphedema have significantly poorer mental and physical health when compared to those without lymphedema.

Due to the dearth of research studies that have examined elevated depressive symptoms measured by the CES-Dsf in women with breast cancer-related lymphedema, ours is the first large, population-based study to report no significant differences in CES-Dsf scores in multivariate models between breast cancer survivors with lymphedema compared to those without lymphedema. Similarly, other studies have found no significant differences in depressive symptoms scores when comparing breast cancer survivors with lymphedema compared to those without lymphedema [11,12]. However, in the bivariate analyses, we found there to be a significant association between elevated depressive symptoms and lymphedema-related distress (P=0.03). After examining the proportion of variance explained for the depressive symptoms models, we found that lymphedema-related distress explained only a small proportion of the variance; whereas, physical activity and body mass index were the

largest contributors to the proportion of variance. These findings help to explain why lymphedema-related distress was only significantly associated with depressive symptoms in the bivariate analyses and not in the multivariate regression models.

The main strength of our study is the use of lymphedema-related distress as a means of determining how lymphedema impacts psychosocial functioning among our study population. Another study strength is its large sample size of women reporting lymphedema (N=692). Most studies examining the psychosocial impact of lymphedema in breast cancer survivors have had fewer than 100 participants reporting lymphedema symptoms [7,8,10–12,32–34]. Other study strengths are the 7.3 year average follow-up period and its comprehensive dataset on tumor and treatment variables, health behaviors, comorbid medical conditions, and psychosocial factors.

In contrast to the study strengths, the primary limitation of this present study is its reliance on self-report for many of the study variables, including lymphedema status. However, the assessment of lymphedema status was obtained through the use of a validated questionnaire that has been shown to accurately identify lymphedema in breast cancer survivors [31]. Further, the study outcome variables (i.e., PH, MH, and depressive symptoms) were collected using validated and reliable instruments. For example, the SF-36 has been used in numerous breast cancer survivorship studies to assess HRQOL [8,9,21,23,32,35]. Bardwell and colleagues (2004) confirmed that response bias did not influence the accuracy of the SF-36 scores in the WHEL Study [23]. Also previous studies have shown the CES-Dsf to be a useful measure to identify elevated depressive symptoms in cancer survivors [8,22]. It should be noted that WHEL Study participants were mostly White, well-educated, and volunteered to be part of an intense dietary intervention; therefore, the study results may not be generalizable to other breast cancer populations. Also due to the cross-sectional nature of the

lymphedema assessment, we cannot comment on the causative relationships between lymphedema and the study outcome variables.

In conclusion, our findings highlight the negative psychosocial impact of lymphedema-related distress among breast cancer survivors. In binary logistic regression models, breast cancer survivors with lymphedema-related distress had worse physical and mental health outcomes than women with lymphedema who were not distressed and women with no lymphedema. These findings are in line with previous studies and confirm that breast cancer survivors with lymphedema report lower health-related quality of life. This study adds to the literature the importance of assessing distress caused specifically by lymphedema when studying breast cancer-related lymphedema. Also future research should develop tailored health behavior interventions to improve psychosocial functioning among breast cancer survivors distressed by their lymphedema.

ACKNOWLEDGEMENTS

Study investigators would like to thank all WHEL Study participants who contributed time and effort to this research.

Chapter 3 is currently being prepared for submission for the publication of the material. Sally A. Dominick, Lisa Madlensky, Loki Natarajan, Hala Madanat, John P. Pierce. The dissertation author was the primary investigator and author of this material.

Table 3.1. Lymphedema characteristics and their association with psychosocial health outcomes in a cohort of breast cancer survivors.

Participant Characteristics	Physical Health		Mental Health		Depressive Symptoms	
	Poor PH N (%)	*P* Value	Poor MH N (%)	*P* Value	Elevated Depressive Symptoms N (%)	*P* Value
Lymphedema Distress		<0.01		<0.01		0.03
No Lymphedema	643 (37.1)		654 (37.7)		210 (12.2)	
Lymphedema and No Distress	155 (44.7)		143 (41.2)		44 (12.8)	
Lymphedema and Yes Distress	169 (50.8)		173 (52.1)		58 (17.6)	
Current Lymphedema Symptoms (N=671)		0.05		0.08		0.73
0 symptoms	84 (44.2)		80 (42.1)		24 (12.8)	
1 to 3 symptoms	76 (41.5)		77 (42.1)		30 (16.6)	
4 to 6 symptoms	93 (53.1)		89 (50.9)		26 (14.9)	
7 or more symptoms	64 (54.2)		63 (53.8)		19 (16.2)	

Table 3.2. Multivariate-adjusted logistic regression models for physical health, mental health and depressive symptoms.

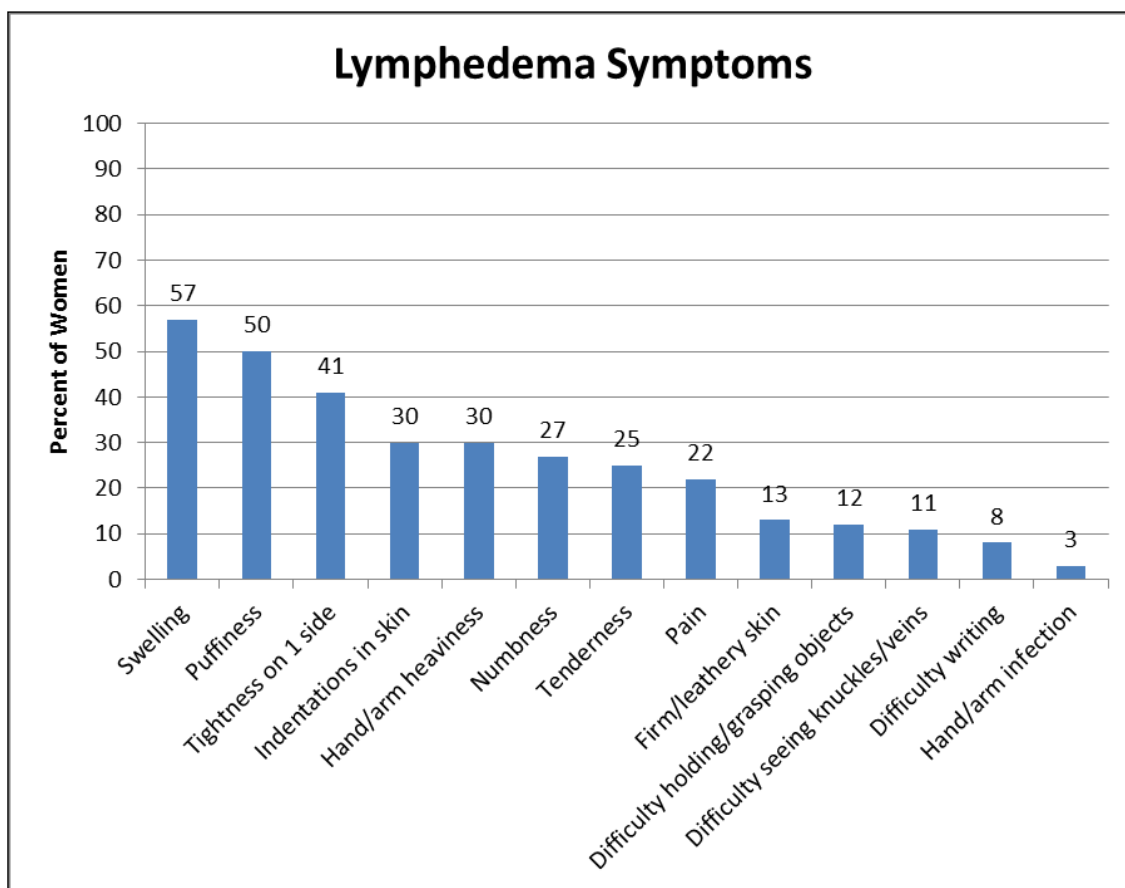|	Poor Physical Health[a] (N = 1834)				Poor Mental Health[b] (N = 1832)				Elevated Depressive Symptoms[c] (N = 1817)			
	Total N (%)	OR	95% CI	P value	Total N (%)	OR	95% CI	P value	Total N (%)	OR	95% CI	P value
Lymphedema Distress				0.01				<0.01				0.13
No Lymphedema	1318 (71.9)	1.00			1317 (71.8)	1.00			1306 (71.9)	1.00		
Lymphedema and No Distress	260 (14.1)	1.25	0.93-1.67		260 (14.2)	1.14	0.86-1.52		258 (14.1)	0.95	0.62-1.46	
Lymphedema and Yes Distress	256 (14.0)	1.54	1.15-2.07		255 (14.0)	1.73	1.31-2.30		253 (14.0)	1.46	0.99-2.15	
Body Mass Index (YR 4)				<0.01				0.04				0.23
< 25 kg/m^2 (normal/ underweight)	742 (40.5)	1.00			742 (40.5)	1.00			733 (40.4)	1.00		
25 – 29.9 kg/m^2 (overweight)	584 (31.8)	1.33	1.04-1.71		583 (31.8)	1.07	0.85-1.36		582 (32.0)	1.27	0.88-1.85	
≥ 30 kg/m^2 (obese)	508 (27.7)	2.41	1.85-3.14		507 (27.7)	1.38	1.06-1.78		502 (27.6)	1.38	0.94-2.02	
Comorbid Medical Conditions (YR 4)				<0.01				<0.01				0.02
0 conditions	690 (37.6)	1.00			690 (37.7)	1.00			688 (37.9)	1.00		
1 condition	620 (33.8)	1.54	1.20-1.96		619 (33.8)	1.18	0.92-1.50		614 (33.8)	1.22	0.84-1.75	
2 conditions	335 (18.3)	2.77	2.05-3.74		334 (18.2)	1.56	1.16-2.08		329 (18.1)	1.66	1.09-2.54	
3 or more conditions	189 (10.3)	3.02	2.09-4.38		189 (10.3)	2.59	1.81-3.72		186 (10.2)	1.98	1.20-3.26	
Physical Activity, METs-hour/week (MHW) (YR 4)				<0.01				<0.01				<0.01
Inactive (MHW < 3.3)	393 (21.4)	1.00			393 (21.5)	1.00			389 (21.4)	1.00		

Figure 3.1. Current symptoms among breast cancer survivors with lymphedema (N=671).

REFERENCES

1.   Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. Cancer. 1998;83(12 Suppl American):2776–81.

2.   Erickson VS, Pearson ML, Ganz PA, Adams J, Kahn KL. Arm edema in breast cancer patients. J Natl Cancer Inst. 2001;93(2):96–111.

3.   Morrell RM, Halyard MY, Schild SE, Ali MS, Gunderson LL, Pockaj BA. Breast cancer-related lymphedema. Mayo Clinic. 2005;80(11):1480–4.

4.   Norman SA, Localio AR, Potashnik SL, Simoes Torpey HA, Kallan MJ, Weber AL, et al. Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. J Clin Oncol. 2009;27(3):390–7.

5.   Sakorafas GH, Peros G, Cataliotti L, Vlastos G. Lymphedema following axillary lymph node dissection for breast cancer. Surg Oncol. 2006;15(3):153–65.

6.   Shih YCT, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. J Clin Oncol. 2009;27(12):2007–14.

7.   Paskett ED, Dean JA, Oliveri JM, Harrop JP. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. J Clin Oncol. 2012;30(30):3726–33.

8.   Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: A systematic review of literature from 2004 to 2011. Psycho-oncology. 2012.

9.   Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. J Clin Oncol. 2008;26(35):5689–96.

10.   Nesvold I-L, Reinertsen KV, Fosså SD, Dahl AA. The relation between arm/shoulder problems and quality of life in breast cancer survivors: a cross-sectional and longitudinal study. J Cancer Surviv. 2010;5(1):62–72.

11.   Oliveri JM, Day JM, Alfano CM, Herndon JE, Katz ML, Bittoni MA, et al. Arm/hand swelling and perceived functioning among breast cancer survivors 12 years post-diagnosis: CALGB 79804. J Cancer Surviv. 2008;2(4):233–42.

12. Ridner SH. Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. Support Care Cancer. 2005;13(11):904–11.

13. Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. Cancer Epidemiol Biomarkers Prev. 2007;16(4):775–82.

14. Pierce JP, Faerber S, Wright FA, Rock CL, Newman V, Flatt SW, et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials. 2002;23(6):728–56.

15. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA. 2007;298(3):289–98.

16. Johnson-Kozlow M, Rock CL, Gilpin EA, Hollenbach KA, Pierce JP. Validation of the WHI brief physical activity questionnaire among women diagnosed with breast cancer. Am J Health Behav. 2007;31(2):193–202.

17. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32:S498–504.

18. Hong S, Bardwell WA, Natarajan L, Flatt SW, Rock CL, Newman VA, et al. Correlates of physical activity level in breast cancer survivors participating in the Women's Healthy Eating and Living (WHEL) Study. Breast Cancer Res Treat. 2007;101(2):225–32.

19. Bertram LAC, Stefanick ML, Saquib N, Natarajan L, Patterson RE, Bardwell W, et al. Physical activity, additional breast cancer events, and mortality among early-stage breast cancer survivors: findings from the WHEL study. Cancer Causes Control. 2011;22:427–35.

20. Patterson RE, Flatt SW, Saquib N, Rock CL, Caan BJ, Parker BA, et al. Medical comorbidities predict mortality in women with a history of early stage breast cancer. Breast Cancer Res Treat. 2010;122(3):859–65.

21. Saquib N, Pierce JP, Saquib J, Flatt SW, Natarajan L, Bardwell WA, et al. Poor physical health predicts time to additional breast cancer events and mortality in breast cancer survivors. Psycho-oncology. 2011; 20(3):252-9.

22. Bardwell WA, Natarajan L, Dimsdale JE, Rock CL, Mortimer JE, Hollenbach K, et al. Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. J Clin Oncol. 2006;24(16):2420–7.

23. Bardwell WA, Major JM, Rock CL, Newman VA, Thomson CA, Chilton JA, et al. Health-related quality of life in women previously treated for early-stage breast cancer. Psycho-oncology. 2004;13(9):595–604.

24. Goodwin PJ, Black JT, Bordeleau LJ, Ganz PA. Health-related quality-of-life measurement in randomized clinical trials in breast cancer--taking stock. J Natl Cancer Inst. 2003;95(4):263–81.

25. Perry S, Kowalski TL, Chang CH. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. Health Qual Life Outcomes. 2007;5:24.

26. Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res. 2008;27:32.

27. McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31(3):247–63.

28. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. Med Care. 1992;30(6):473–83.

29. Ferrans CE. Differences in what quality-of-life instruments measure. J Natl Cancer Inst. 2007;60612(37):22–6.

30. Golden-Kreutz DM, Thornton LM, Wells-Di Gregorio S, Frierson GM, Jim HS, Carpenter KM, et al. Traumatic stress, perceived global stress, and life events: prospectively predicting quality of life in breast cancer patients. Health Psychol. 2005;24(3):288–96.

31. Norman SA, Miller LT, Erikson HB, Norman MF, McCorkle R. Development and validation of a telephone questionnaire to characterize lymphedema in women treated for breast cancer. Phys Ther. 2001;81(6):1192–205.

32. Wilson RW, Hutson LM, Vanstry D. Comparison of 2 quality-of-life questionnaires in women treated for breast cancer: the RAND 36-Item Health Survey and the Functional Living Index-Cancer. Phys Ther. 2005;85(9):851–60.

33.   Dawes DJ, Meterissian S, Goldberg M, Mayo NE. Impact of lymphoedema on arm function and health-related quality of life in women following breast cancer surgery. J Rehabil Med. 2008;40(8):651–8.

34.   Velanovich V, Szymanski W. Quality of life of breast cancer patients with lymphedema. Am J Surg. 1999;177(3):184–8.

35.   Pusic AL, Cemal Y, Albornoz C, Klassen A, Cano S, Sulimanoff I, et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. J Cancer Surviv. 2013; 7(1):83-92.

CHAPTER 4

Patient Compliance with a Health Care Provider Referral for an Occupational

Therapy Lymphedema Consult

ABSTRACT

Introduction Limited information exists on breast cancer patients' compliance to attend outpatient appointments with an occupational therapy (OT) lymphedema specialist. The objectives of this study were 1) to examine patient compliance with a health care provider referral for an OT lymphedema consult and 2) to identify potential barriers to compliance among breast cancer patients.

Methods A retrospective chart review of female breast cancer patients was conducted. Electronic medical records were queried for breast cancer patients, who received a health care provider referral for an OT lymphedema consult between June 1, 2010 and December 31, 2011. Descriptive statistics and Fisher's exact chi-square tests were used to examine how specific participant characteristics were associated with attending an OT appointment.

Results A total of 274 female patients received an OT referral from a health care provider; of these, only 210 patients had a referral related to their breast cancer diagnosis/treatment and were included in the final sample size. Forty-three (20.5%) patients did not attend an OT appointment. The results of the chi-square tests found that non-attenders were more likely to have fewer lymph nodes removed ($P<0.01$) when compared to attenders. The two most common barriers to attendance were health problems and undergoing chemotherapy and/or radiation at the time of the OT referral.

Conclusions This study highlights that while the majority of breast cancer patients were compliant and attended an OT lymphedema consult, some did not attend despite having a provider referral and OT lymphedema services readily available.

INTRODUCTION

Of the estimated 2.7 million breast cancer survivors in the United States, a significant proportion will experience breast cancer-related lymphedema as a late effect of their breast cancer treatment [1–4]. Lymphedema occurs when the lymphatic system is damaged and unable to properly circulate the lymphatic fluid.   This disruption of lymphatic flow results in variety of symptoms, such as arm swelling or tenderness. Depending on the severity of lymphedema symptoms, the management of lymphedema can be quite costly; research from medical claims data found that the 2-year health care costs associated with lymphedema range from $14,877 to $23,167 [5]. A prospective surveillance model (PSM), in which patients receive lymphedema education and arm measurements on a regular basis, has been shown to be a cost-saving and effective method of preventing lymphedema and/or detecting early stages of lymphedema in breast cancer survivors [6–8]. Additionally, the National Lymphedema Network recommends screening and early detection of breast cancer-related lymphedema [6].

Cancer rehabilitation offered as outpatient occupational therapy (OT) services is an integral part of a PSM [7,9]. Occupational therapists (i.e., lymphedema specialists) are trained to provide patients lymphedema prevention education, including risk reduction strategies, as well as lymphedema treatment, if necessary. Research has shown that patient education can prevent the development of lymphedema as well as improve health outcomes among those living with lymphedema [10–13]. Ridner (2006) found that women with lymphedema reported not receiving pretreatment lymphedema education compared to women without lymphedema [13]. Fu and colleagues (2010) found that patient education was an independent predictor of breast

cancer-related lymphedema [11]. These researchers also reported that participants who received lymphedema education reported fewer breast cancer-related lymphedema symptoms than those who did not receive lymphedema education [11]. Further, health care providers (e.g., surgeons, oncologists, and nurses) play a vital role in cancer rehabilitation through referring patients to see an OT lymphedema specialist. Tam and colleagues (2012) found that only 44% of the physicians in their study had ever made a referral for breast cancer-related lymphedema [14].

While provider referrals and OT lymphedema services are important to secondary prevention in cancer survivorship care, patient attendance at cancer rehabilitation services is crucial in order to see improved patient outcomes. To date, no research studies have examined patient attendance at OT lymphedema consult appointments. However, a recent study examined patient attendance at a group educational session for breast cancer survivors referred to a survivorship clinic. Upon receiving the educational session invite, over one third of patients declined to attend the session for the following reasons: time conflicts, distance to the clinic, current medical problems, elderly, non-English speaking, and lack of interest [15]. For cardiac rehabilitation programs, a systematic review found that patient attendance is influenced by a variety of personal and contextual factors, such as personal knowledge of the program, lack of interest in the program, perceived beliefs about risk reduction practices, financial and work constraints, travel distance, and family support and demands [16].

Since little is known about breast cancer patients' compliance with attending an OT lymphedema consult after receiving a referral, the objectives of this study are 1) to determine patient compliance with a health care recommendation to attend an OT

appointment, and 2) to identify potential barriers/reasons for non-attendance, despite receiving a health care provider OT referral.

METHODS

Study Population

The University of California (UC) San Diego Health System has a PSM for breast cancer-related lymphedema; patients who have breast cancer surgery and/or present with lymphedema symptoms during a clinic visit are referred for an OT lymphedema consult as standard protocol. This study was a retrospective chart review of female breast cancer patients, who received a health care provider referral for an OT lymphedema consult, at the UC San Diego Health System, which is the only academic health system in San Diego, California. Patients were included in the study if they had a breast cancer diagnosis, received an OT referral for a lymphedema consult, and if the lymphedema consult referral was related to their breast cancer diagnosis and/or treatment. Patients were excluded if the OT referral was not for a breast cancer-related lymphedema consult.

Procedures

At the UC San Diego Health System, records of all electronic order entries for OT referrals are available in the patients' medical records. Therefore, electronic medical records were queried for breast cancer patients who received a health care provider OT referral for a lymphedema consult between June 1, 2010 and December 31, 2011. From this query, a list of eligible breast cancer patients was created that included the following variables: the name of the health care provider who made the

OT referral, the ordering date of the OT referral, the patient's year of birth, insurance type, height, and weight. Next, medical records from each patient were reviewed to identify and extract OT referral reason, demographics, breast cancer tumor and treatment characteristics, and other study relevant patient characteristics. This study was approved by the local institutional review board. Due to the retrospective time frame of the project and our process for extracting non-identifying data from the medical records, this project was granted a waiver of documentation of informed consent.

Dataset

Demographics

Demographic variables extracted include year of birth to determine current age in years, type of health insurance, height and weight to calculate body mass index (BMI), and relationship status. For this study, type of health insurance was categorized as HMO/PPO, Medicare, Medi-Cal or self-pay. BMI was categorized as underweight/normal weight (BMI < 24.9 kg/m^2), overweight (BMI = 25 to 29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Relationship status was dichotomized into married versus other (i.e., single, divorced or widowed).

Medical Characteristics

Medical variables documented include cancer stage categorized using the American Joint Committee on Cancer (6th edition) criteria [17], number of lymph nodes removed, type of breast cancer surgery (e.g., lumpectomy or mastectomy), year of breast cancer surgery, and administration of chemotherapy and/or radiation therapy. Cancer stage at diagnosis was categorized into stage 0, stage I (IA and IB), stage II

(IIA and IIB), stage III (IIIA, IIIB, and IIIC) and stage IV. For patients who had bilateral cancers, the highest cancer stage at diagnosis was included in the cancer stage variable. The present analysis dichotomized breast cancer surgery into lumpectomy/bilateral lumpectomies and mastectomy/bilateral mastectomies. For patients who had a less invasive surgery followed by a more invasive surgery, the most invasive surgery was used for the surgery variable. For example, if a lumpectomy was followed by a mastectomy, then mastectomy was recorded as the surgery type. Also patients who received mastectomies at two different time points were coded as having bilateral mastectomies and the most recent surgery year was used in the analyses. The number of lymph nodes removed was recorded for each patient; in cases where lymph nodes were removed bilaterally, the average number of lymph nodes removed per patient was included in the analyses.

OT Referral

The primary outcome of this study was attendance at an OT appointment for a lymphedema consult categorized as attenders versus non-attenders. For each patient, the ordering date of the OT referral was extracted; in some cases, there were multiple OT referrals during the study timeframe that were also documented. Additionally, the name of the health care provider and the reason listed on each referral was also extracted. Referral reason was dichotomized into current lymphedema symptoms versus routine post-operative care/lymphedema prevention. Since queried patients had a breast cancer diagnosis, the source of the OT referral was categorized as breast surgical team, breast oncology team, and other physician/nurse. The date of the OT appointment was also recorded to determine the amount of time elapsed between the referral and appointment date. Since patients are recommended to make an OT

appointment within 1 to 2 weeks of the referral date, the amount of time elapsed was

dichotomized into less than or equal to 2 weeks or greater than 2 weeks. For patients

with multiple referrals that went to an OT appointment, the time elapsed was calculated

from the initial referral date to the date of the first OT appointment.

Barriers

For patients who did not go to an OT appointment, potential barriers, such as

health problems, undergoing chemotherapy and/or radiation at the time of the referral,

or primary language (English versus non-English), were extracted from the medical

records.

Statistical Methods

Descriptive statistics were used to characterize the data extracted from the

medical records, including barriers to attending an OT appointment. Bivariate analyses

were conducted to assess if patient demographics, breast cancer tumor and treatment

characteristics, and OT referral source and reason, were associated with attendance at

an OT appointment. Fisher's exact chi-square tests were used to analyze the

categorical variables. Significance for all analyses was set at $P<0.05$. All analyses

were conducted using IBM® SPSS® Statistics version 20.0 (Armonk, NY).

RESULTS

A total of 274 patients received a lymphedema consult OT referral from a health

care provider between June 2010 and December 2011. Sixty-four patients received a

referral for a non-breast cancer-related health problem and were excluded from the

study, making the final study cohort 210 patients. As shown in Table 4.1, the mean

age of study participants was 57.2 years (SD=11.7). The majority of patients were

married (61.7%), had private health insurance (66.5%), and were overweight/obese

(62.9%). In terms of medical characteristics, 69.8% of patients had stage 0, IA, IB, IIA,

or IIB breast cancers. Approximately 96% of patients underwent a lumpectomy or

mastectomy, and 69.8% had chemotherapy and/or radiation. Additionally, patients had

an average of 13.9 lymph nodes removed. In terms of the OT referral source, breast

oncology physicians and nurses referred 49% of patients, and members of the breast

surgical team referred 41% of patients. Approximately 51% of patients were referred to

OT for presenting with current lymphedema symptoms, such as arm swelling or

tightness; the other 49% were referred for lymphedema prevention (i.e., education or

sleeve measurements) or routine post-operative care. Additionally, 127 (61.6%) of the

OT referrals occurred within 2 years of the patient's breast cancer surgery date; of

these referrals, 70.9% were made for lymphedema prevention/routine post-operative

care. In contrast, of the OT referrals that occurred 3 years post-surgery, 86.1% were

made for lymphedema symptoms.

Of those who received a lymphedema consult OT referral, 43 (20.5%) patients

did not attend an OT appointment over the 18 month time period and were classified as

non-attenders. Of the 167 attenders, 83 (49.7%) attended an OT appointment within at

least 2 weeks of the referral ordering date. Twenty-seven patients (12.9%) received

more than one OT referral during the study time period; of these, 88.9% were

compliant with at least one referral to attend an OT appointment. The results of the

chi-square tests found that non-attenders were more likely to have fewer lymph nodes

removed ($P<0.01$) when compared to attenders (Table 4.1). Attenders had an average

of 14 lymph nodes removed; whereas, non-attenders had an average of 11 lymph

nodes removed. Additionally, when examining the number of lymph nodes by referral reason, there was a significant difference in the number of lymph nodes removed for women referred for lymphedema symptoms (M=15.7, SD=9.8) compared to women who were referred for lymphedema prevention/routine post-operative care (M=12.1, SD=9.6), [t(197)=2.64, *P*=0.01].

Figure 4.1 illustrates the potential barriers/reasons for non-compliance documented from the medical records. Approximately 49% of non-attenders had other health problems around the time of the OT referral; some examples of health problems experienced by the non-attenders were seizures, pneumonia, depression, grief, pulmonary embolism, and cancer metastasis. Of the 43 non-attenders, 32.6% were undergoing chemotherapy and/or radiation at the time of the OT referral. Other barriers identified were language (English versus non-English speaking), most likely seen at another clinic, health insurance, and work demands. Additionally, 11.6% of the non-attenders made an OT appointment, yet either cancelled or were a no-show at the appointment.

DISCUSSION

A prospective surveillance model is a crucial strategy in the prevention and treatment of lymphedema among breast cancer survivors. One key component of a PSM is cancer rehabilitation programs, such as occupational therapy lymphedema services. The primary purpose of this study was to examine patient attendance at OT lymphedema appointments after a provider referral within our medical center. Of those referred to an OT lymphedema consult, approximately 21% failed to attend the appointment. The number of lymph nodes removed was the only participant

characteristic shown to have a statistically significant difference between attenders and non-attenders. Numerous research studies have concluded that lymph node removal is a key risk factor for developing breast cancer-related lymphedema [3,18–23]. Since non-attenders had fewer lymph nodes removed, one may posit that a reason for their lack of compliance was that they did not feel they were at risk for lymphedema or in need of an OT lymphedema consult. However, when examining compliance based on the OT referral reason (i.e., current lymphedema symptoms versus routine care/lymphedema prevention), there was no significant difference found between groups.

A secondary objective was to identify potential barriers to patient compliance with attendance at an OT lymphedema consult appointment. A significant proportion of non-attenders (48.8%) were experiencing other health-related problems, such as pneumonia, cancer metastases, or seizures, around the time of the OT referral. Additionally, 32% of non-attenders were currently undergoing either chemotherapy and/or radiation therapy. We also identified language, work, seen at another clinic, and health insurance as other potential reasons for not attending an OT consult. For example, the medical charts of 4 patients indicated they had gone to a clinic other than our medical center to receive lymphedema services. Two patients mentioned at clinic visits that they had not made an OT appointment due to scheduling conflicts with work. Other studies examining non-attendance at medical appointments/programs have also found health problems [15,24], language [15], and work [15,24,25] as barriers to attendance. For example, Wheelock and colleagues (2013) reported that 14 patients declined an invite to an educational session due to a medical condition or their elderly status [15]. In contrast to our study, previous studies also reported forgetfulness [24–26], transportation [25], and lack of interest [15] as barriers to attendance. Our lack of

finding these additional barriers is most likely due to differences in study design; the other studies contacted each non-attender to determine reasons for non-attendance. In contrast, we did not contact non-attenders; instead, we used information documented in the patient's medical chart to determine barriers to attendance.

A key strength of our study is the methodology of a retrospective chart review, which allowed for an examination of patient compliance with a health care provider referral for an outpatient OT lymphedema consult appointment within our medical center. Nevertheless, this study is not without its limitations. First, data collected for this study relied solely on information found in the patients' electronic medical charts, and hence, was subject to incomplete documentation for some of the study variables. For example, common demographic characteristics, such as race and ethnicity, education, and employment status, were not well-documented in the medical charts and were not included in this study. Another limitation is that potential barriers identified cannot be verified with the patient and may not accurately describe the reasons for non-attendance. Also we do not know if health care providers gave their patients any instructions regarding the OT lymphedema consult referral. Additionally, only one medical center was examined in this study and as a result, the findings may not be representative of all medical centers with outpatient OT lymphedema clinics.

Conclusions

While most breast cancer patients were compliant and attended an OT lymphedema consult, some women did not attend, despite having a provider referral and OT lymphedema services readily available. Future research efforts should focus on identifying the personal and contextual barriers to attending outpatient OT lymphedema appointments among breast cancer patients/survivors. Additionally,

health behavior interventions geared towards providers and patients should be created and implemented to increase patient compliance with attending outpatient appointments. For example, multiple provider referrals may encourage patient compliance; 89% of the patients, who received multiple referrals in our study population, were compliant with at least one referral for an OT lymphedema consult. A recent review article found that telephone, mail and text/short message service reminders improved patient attendance at outpatient clinic appointments [27]. Approximately 12% of the non-attenders in our study population made an OT lymphedema consult appointment yet failed to keep it, despite receiving an automated telephone reminder two days prior to their scheduled appointment. Another potential research direction would be to examine the most effective appointment reminder method (e.g., telephone, email and text) for increasing patient attendance among breast cancer survivors. In conclusion, patient attendance at outpatient OT lymphedema appointments is an important aspect of survivorship care. Future research is needed to better understand the individual, interpersonal, institutional, and policy factors that impact patient attendance.

ACKNOWLEDGEMENTS

provided us with the initial list of 274 patients, and Resenia Collins and Patricia Kormanik, who contributed their lymphedema expertise, time and effort to this research project. Study investigators also thank the UC San Diego Health System medical personnel and patients who made this chart review possible.

Chapter 4 is currently being prepared for submission for the publication of the material. Sally A. Dominick, Loki Natarajan, John P. Pierce, Hala Madanat, Lisa Madlensky. The dissertation author was the primary investigator and author of this material.

Table 4.1. Participant characteristics by occupational therapy (OT) appointment attendance in a cohort of breast cancer survivors.

Characteristic	Overall (*N* = 210) N (%)	Women who Attended OT Appt (*N* = 167) N (%)	Women who Did Not Attended OT Appt (*N* = 43) N (%)	*P* value
Demographics				
Age,	57.2	57.1	57.5	0.61
Mean [SD (range)], years	[11.7 (25-92)]	[11.3 (25-92)]	[13.3 (33-91)]	
25 to 44	29 (13.8)	21 (12.6)	8 (18.6)	
45 to 64	126 (60.0)	102 (61.1)	24 (55.8)	
≥ 65	55 (26.2)	44 (26.3)	11 (25.6)	
Relationship Status				0.22
Married	129 (61.7)	106 (63.9)	23 (53.5)	
Other	80 (38.3)	60 (36.1)	20 (46.5)	
Health Insurance Type				0.60
HMO/PPO	131 (66.5)	107 (66.9)	24 (64.9)	
Medicare	45 (22.8)	36 (22.5)	9 (24.3)	
Medi-Cal	19 (9.7)	16 (10.0)	3 (8.1)	
Self-Pay	2 (1.0)	1 (0.6)	1 (2.7)	
OT Referral Source				0.24
Breast Surgical Team	86 (41.0)	68 (40.7)	18 (41.9)	
Breast Oncology Team	103 (49.0)	85 (50.9)	18 (41.9)	
Other Physician/Nurse	21 (10.0)	14 (8.4)	7 (16.2)	
OT Referral Reason				0.74
Current Lymphedema Symptoms	108 (51.4)	87 (52.1)	21 (48.8)	
Routine Post-op/Lymphedema Prevention	102 (48.6)	80 (47.9)	22 (51.2)	
Body Mass Index				0.43
< 25 kg/m^2 (normal/underweight)	78 (37.1)	65 (38.9)	13 (30.2)	
25 – 29.9 kg/m^2 (overweight)	69 (32.9)	55 (32.9)	14 (32.6)	
≥ 30 kg/m^2 (obese)	63 (30.0)	47 (28.1)	16 (37.2)	
Medical Characteristics				
Stage (AJCC 6th Edition)				0.18
0	10 (5.0)	6 (3.7)	4 (9.6)	
I (IA, IB)	54 (26.7)	43 (26.9)	11 (26.2)	
II (IIA, IIB)	77 (38.1)	64 (40.0)	13 (31.0)	
III (IIIA, IIIB, IIIC)	55 (27.2)	44 (27.5)	11 (26.2)	
IV	6 (3.0)	3 (1.9)	3 (7.1)	

Table 4.1. Continued

Characteristic	Overall (N = 210) N (%)	Women who Attended OT Appt (N = 167) N (%)	Women who Did Not Attended OT Appt (N = 43) N (%)	P value
No. Nodes Removed, Mean [SD (range)]	13.9 [9.8 (0-44)]	14.5 [9.7 (0-44)]	11.2 [9.9 (0-32)]	<0.01
0 nodes	5 (2.5)	1 (0.6)	4 (10.5)	
1 to 10 nodes	76 (38.2)	59 (36.7)	17 (44.7)	
11 to 20 nodes	69 (34.7)	61 (37.9)	8 (21.1)	
≥ 21 nodes	49 (24.6)	40 (24.8)	9 (23.7)	
Breast Cancer Surgery				0.86
Lumpectomy/Bilateral Lumpectomies	86 (42.6)	68 (42.2)	18 (43.9)	
Mastectomy/Bilateral Mastectomies	116 (57.4)	93 (57.8)	23 (56.1)	
Time since Breast Cancer Surgery, years				0.23
≤ 1	68 (33.0)	56 (33.7)	12 (30.0)	
2	59 (28.6)	51 (30.7)	8 (20.0)	
≥ 3	79 (38.4)	59 (35.6)	20 (50.0)	
Chemotherapy	143 (69.8)	117 (70.5)	26 (66.7)	0.70
Radiation	143 (69.8)	116 (69.9)	27 (69.1)	1.00

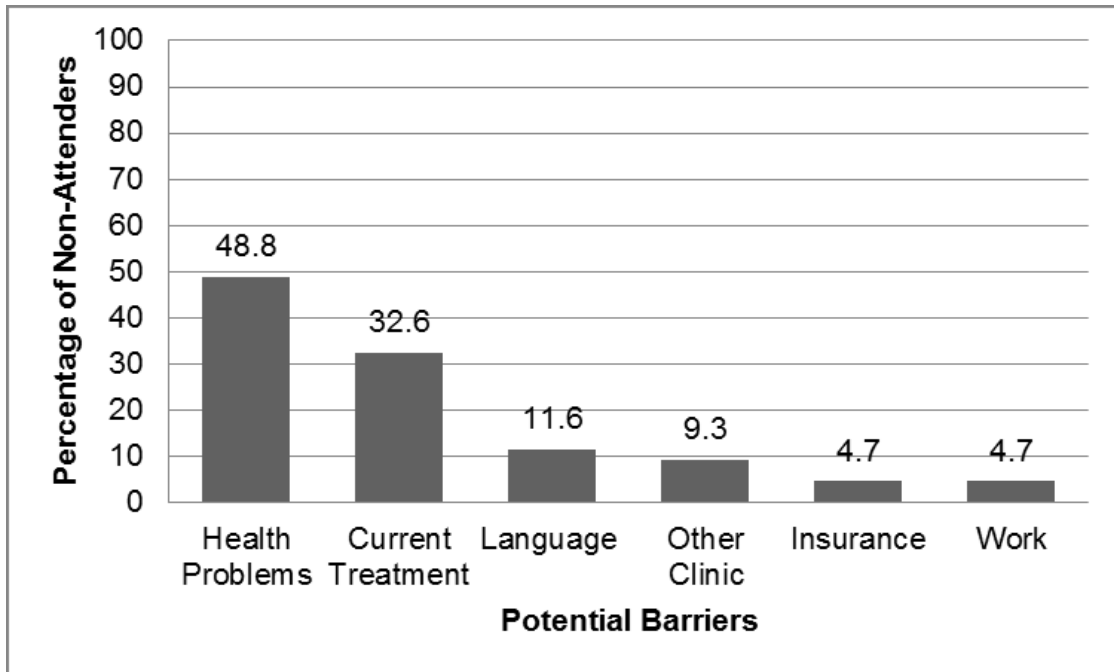Note: Categorical variables were tested with Fisher's Exact χ^2 test.

Figure 4.1. Potential barriers for not attending an occupational therapy appointment after a health care provider referral (N=43).

REFERENCES

1.   Howlader, N, Noone, AM, Krapcho, M, Neyman, N, Aminou, R, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations) 2012. Bethesda, MD: National Cancer Institute. Bethesda, MD: National Cancer Institute.

2.   Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. Cancer. 1998;83(12 Suppl American):2776–81.

3.   Erickson VS, Pearson ML, Ganz PA, Adams J, Kahn KL. Arm edema in breast cancer patients. J Natl Cancer Inst. 2001;93(2):96–111.

4.   Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GKD, Scott-Conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. Ann Surg Oncol. 2009;16(7):1959–72.

5.   Shih YCT, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: A 2-year follow-up study. J Clin Oncol. 2009; 27(12):2007-14.

6.   National Lymphedema Network (NLN). Screening and measurement for early detection of breast cancer related lymphedema. San Francisco; 2011.

7.   Stout NL, Binkley JM, Schmitz KH, Andrews K, Hayes SC, Campbell KL, et al. A prospective surveillance model for rehabilitation for women with breast cancer. Cancer. 2012;118(8 Suppl):2191–200.

8.   Stout NL, Pfalzer LA, Springer B, Levy E, McGarvey CL, Danoff JV, et al. Breast cancer-related lymphedema: comparing direct costs of a prospective surveillance model and a traditional model of care. Phys Ther. 2012;92(1):152–63.

9.   Silver JK, Gilchrist LS. Cancer rehabilitation with a focus on evidence-based outpatient physical and occupational therapy interventions. Am J Phys Med Rehabil. 2011;90(5 Suppl):S5–S15.

10.   Cheifetz O, Haley L. Management of secondary lymphedema related to breast cancer. Can Fam Physician. 2010;56(12):1277–84.

11.   Fu MR, Chen CM, Haber J, Guth AA, Axelrod D. The effect of providing information about lymphedema on the cognitive and symptom outcomes of breast cancer survivors. Ann Surg Oncol; 2010;17(7):1847–53.

12.   Sherman KA, Koelmeyer L. The role of information sources and objective risk status on lymphedema risk-minimization behaviors in women recently diagnosed with breast cancer. Oncol Nursing Forum. 2011;38(1):E27–36.

13. Ridner SH. Pretreatment lymphedema education and identified educational resources in breast cancer patients. Patient Educ Couns. 2006; 61(1):72-9.

14. Tam EK, Shen L, Munneke JR, Ackerson LM, Partee PN, Somkin CP, et al. Clinician awareness and knowledge of breast cancer-related lymphedema in a large, integrated health care delivery setting. Breast Cancer Res Treat. 2012;131(3):1029–38.

15. Wheelock A, Mihalis E, Hamolsky D, Ernest ML, Lopez NS, Hwang J, et al. Survivorship clinic group educational sessions: adoption, acceptance, and attendance. J Cancer Educ. 2013;28(1):79–83.

16. Clark AM, King-Shier KM, Thompson DR, Spaling MA, Duncan AS, Stone JA, et al. A qualitative systematic review of influences on attendance at cardiac rehabilitation programs after referral. Am Heart J. 2012;164(6):835–45.e2.

17. (AJCC) American Joint Committee on Cancer. Staging Resources [Internet]. [cited 2013 Apr 4]. Available from: http://www.cancerstaging.org/staging/index.html

18. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast Cancer Res Treat. 2011;130:981–91.

19. Yen TWF, Fan X, Sparapani R, Laud PW, Walker AP, Nattinger AB. A contemporary, population-based study of lymphedema risk factors in older women with breast cancer. Ann Surg Oncol. 2009;16(4):979–88.

20. Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. Cancer Epidemiol Biomarkers Prev. 2007;16(4):775–82.

21. Norman SA, Localio AR, Kallan MJ, Weber AL, Torpey HAS, Potashnik SL, et al. Risk factors for lymphedema after breast cancer treatment. Cancer Epidemiol Biomarkers Prev. 2010;19(11):2734–46.

22. Meeske KA, Sullivan-Halley J, Smith AW, McTiernan A, Baumgartner KB, Harlan LC, et al. Risk factors for arm lymphedema following breast cancer diagnosis in Black women and White women. Breast Cancer Res Treat. 2009;113(2):383–91.

23. Dominick SA, Madlensky L, Natarajan L, Pierce JP. Risk factors associated with breast cancer-related lymphedema in the WHEL Study. J Cancer Surviv. 2013;7(1):115–23.

24. Cusini M, Auxilia F, Trevisan V, Visconti U, Castaldi S. A telephone survey on the reasons for non-attendance in a dermatological clinic. G Ital Dermatol Venereol. 2008;143(6):353–7.

25.   Wilkinson J, Daly M. Reasons for non-attendance: audit findings from a nurse-
       led clinic. J Prim Health Care. 2012;4(1):39–44.

26.   Roberts K, Callanan I, Tubridy N. Failure to attend out-patient clinics: is it in our
       DNA? Int J Health Care Qual Assur. 2011;24(5):406–12.

27.   Stubbs ND, Geraci SA, Stephenson PL, Jones DB, Sanders S. Methods to
       reduce outpatient non-attendance. Am J Med Sci. 2012;344(3):211–9.

CHAPTER 5

Discussion

DISCUSSION

Lymphedema is a chronic condition that warrants continued attention in the field of breast cancer survivorship. While advancements in breast cancer treatments have helped to reduce the risk of lymphedema, it is still a problem for many breast cancer survivors. The objectives of this dissertation were to: 1) identify the risk factors associated with breast cancer-related lymphedema, 2) assess the association between lymphedema-related distress and psychosocial functioning (i.e., quality of life and depressive symptoms), and 3) investigate patient compliance with attending an OT lymphedema consult after receiving a provider referral.

Summary of Study Findings and Suggestions for Future Research

Study #1: Risk Factors Associated with Breast Cancer-Related Lymphedema in the WHEL Study

Consistent with previous studies, this study identified breast cancer surgery plus radiation therapy, lymph node removal, and body mass index as being independently associated with a statistically significant higher risk of developing breast cancer-related lymphedema. Having a mastectomy plus receiving radiation therapy showed a two-fold increased odds of developing lymphedema in comparison to having a mastectomy alone. Our study found that the more lymph nodes removed increased the odds of self-reporting lymphedema. Additionally, breast cancer survivors who were overweight or obese had significantly higher odds of having lymphedema compared to those of normal weight. While the type of breast cancer treatment (e.g., lymph node removal, surgery, and radiation therapy) is typically selected to maximize the chance of cure while minimizing side effects, including lymphedema, maintaining or achieving a

healthy weight is a valid target for health behavior interventions aimed at reducing the rates of lymphedema. From our study population, we found that 33% of overweight/obese women reported lymphedema compared to 23% of normal weight women. With this in mind, we calculated that a 10% shift of participants from the overweight/obese group to the normal weight group would result in a 9.6% reduction in the rates of lymphedema occurrence. Since levels of physical activity and dietary intake are two primary ways to reduce or maintain body weight, future research should be undertaken to target these modifiable lifestyle behaviors as a means of preventing the development of breast cancer-related lymphedema.

Study #2: The Psychosocial Impact of Lymphedema-related Distress among Breast Cancer Survivors in the WHEL Study

To our knowledge this was the first study to assess lymphedema-related distress and its association with psychosocial functioning among a large cohort of breast cancer survivors. Since 49% of women with lymphedema in our study sample were moderately to severely distressed by their lymphedema, we were able to examine the association between lymphedema-related distress and psychosocial functioning. Specifically our data provides novel evidence that women who reported moderate to severe distress as a result of their lymphedema had worse physical and mental health scores when compared to those without lymphedema. These findings are important because previous research has shown an association between poor physical health and additional breast cancer events and all-cause mortality [1]. In contrast, this study did not find lymphedema-related distress to be significantly associated with elevated depressive symptoms in the final multivariate model.

Although previous studies have shown reduced quality of life among breast cancer survivors living with lymphedema, our study is the first to characterize distress caused specifically by lymphedema and show that it negatively affects HRQOL in breast cancer survivors. Our final multivariate models for physical and mental health illustrate a gradient that shows women reporting lymphedema-related distress had poorer quality of life outcomes compared to women reporting lymphedema without distress and women without lymphedema. Our study also found that the current number of lymphedema symptoms was highly correlated with having moderate to severe lymphedema-related distress. Future research should focus on investigating whether management of lymphedema symptoms reduces lymphedema-related distress in breast cancer survivors. Additionally, this study identified physical activity, body mass index, and comorbid medical conditions as modifiable factors associated with psychosocial functioning among breast cancer survivors living with lymphedema. Future intervention research should consider targeting these modifiable factors as a means of improving psychosocial functioning among breast cancer survivors with lymphedema.

Study #3: Patient Compliance with a Health Care Provider Referral for an Occupational Therapy Lymphedema Consult

To date, this is the first retrospective chart review study to examine patient compliance with an OT lymphedema consult appointment among breast cancer patients who received a referral from a health care provider. This study provides evidence that breast cancer patients who did not attend an OT appointment were more likely to have fewer lymph nodes removed when compared to attenders. This represents an important finding that needs to be investigated further to determine the

reasons why patients who have fewer lymph nodes removed are less likely to attend an OT lymphedema consult. Additionally, this study found that some potential reasons for non-attendance were current health problems, undergoing breast cancer treatment, language barrier, lack of insurance coverage, and work-related scheduling conflicts. However, these reasons were collected from the patients' medical records and may not be inclusive of all barriers to attendance. Future research is warranted in order to fully determine the reasons for non-compliance.

Recommended Interventions

The findings from this dissertation highlight some important modifiable health behaviors and lifestyle factors related to breast cancer-related lymphedema. In particular, some potential areas to target with intervention research identified by this dissertation project are weight loss/management, lymphedema-related distress, and barriers to patient attendance at lymphedema prevention/treatment appointments. The following recommended interventions based upon theoretical frameworks are informed by this dissertation as well as current literature in the field of breast cancer survivorship.

Study #1 Recommended Interventions

Based on the findings that being overweight or obese is a significant risk factor for developing lymphedema, weight loss and/or management is a valid target for health behavior research either through increasing physical activity levels and/or encouraging healthy dietary patterns. Some breast cancer survivors may be hesitant to engage in physical activity that requires the use of their affected shoulder/arm for fear that it will result in the development of lymphedema or exacerbation of lymphedema symptoms.

However, in the past decade, research has shown there is no adverse effect of exercise on breast cancer-related lymphedema [2]. Hence, breast cancer patients/survivors should be made aware of these findings and encouraged to exercise on a regular basis. Also since studies have and are being implemented to address the issues of maintaining a healthy weight among breast cancer survivors, these studies should consider including lymphedema as a study outcome.

Based on our study findings that breast cancer treatment and lymph node removal are risk factors for lymphedema, any breast cancer patient who has lymph nodes removed and/or undergoes breast cancer surgery is at risk for developing lymphedema. Drawing from constructs in the Transactional Model of Stress and Coping and the Health Belief Model (HBM), research focusing on understanding and addressing the perceived susceptibility and perceived severity of developing lymphedema among breast cancer patients will provide valuable information that can be incorporated into lymphedema prevention education programs.

Study #2 Recommended Interventions

A key and novel finding from this dissertation project is that breast cancer survivors with lymphedema experience a significant amount of distress resulting in decreased psychosocial functioning. Future research should examine the pathways in the Transactional Model of Stress and Coping to better understand the mediating processes and moderators in how lymphedema-related distress impacts psychosocial functioning. One may posit that health behavior interventions integrating stress reduction activities targeting lymphedema-related distress primary and secondary appraisals and coping skills (e.g., cognitive-behavioral coping strategies, positive appraisals, and identity reconstruction as a cancer survivor with lymphedema) may

reduce the distress associated with lymphedema and improve psychosocial functioning.   For example, cognitive-behavioral coping strategies focus on reducing maladaptive thoughts and actions, while promoting cognitions and behaviors that improve functional coping [3]; cognitive-behavioral coping interventions have been shown to positively influence psychosocial functioning among cancer survivors [4]. Also since this dissertation project showed that women reporting more lymphedema symptoms had higher levels of lymphedema-related distress, interventions investigating the effects of lymphedema symptom management on lymphedema-related distress are warranted. Additionally, since physical activity and BMI were associated with psychosocial functioning, weight management interventions are also applicable to improving psychosocial outcomes among breast cancer survivors living with lymphedema.

Study #3 Recommended Interventions

Findings from this dissertation showed that even with a provider referral some breast cancer patients do not attend OT lymphedema consult appointments. In particular, we found that women with fewer lymph nodes removed were less likely to attend an OT lymphedema consult. In accordance with the above intervention recommendations for Study #1, one may posit that non-attenders have differing perceptions of lymphedema susceptibility and severity compared to attenders. Intervention research should determine if constructs from the HBM and the Transactional Model of Stress and Coping explain the motivation behind patient attendance at an OT lymphedema consult. For example, an intervention study should examine if perceived susceptibility to developing lymphedema, perceived severity of lymphedema, perceived control and self-efficacy to attending an OT appointment, and

perceived barriers concerning the behavior, and cues to action (i.e., provider referral) are related to attending an OT lymphedema consult appointment among breast cancer survivors [5–7]. Additionally, future research should be conducted to more fully understand and identify barriers to OT appointment attendance among breast cancer patients/survivors.

Conclusions

Breast cancer-related lymphedema is a distressing and chronic condition affecting a significant proportion of breast cancer survivors. This dissertation project conducted a detailed investigation of breast cancer-related lymphedema, resulting in three distinct manuscripts. Taken together, the findings from this dissertation identified: 1) who gets breast cancer-related lymphedema, 2) that lymphedema-related distress impacts quality of life, and 3) who attends an OT lymphedema consult appointment and potential barriers to attendance. Since the majority of breast cancer patients will transition from patient to survivor, oncology care teams, including physicians, nurses, occupational therapists, and public health professionals, should promote healthy lifestyle changes to prevent the development of lymphedema as well as to manage the physical and psychosocial impact of lymphedema.

REFERENCES

1.   Saquib N, Pierce JP, Saquib J, Flatt SW, Natarajan L, Bardwell WA, et al. Poor physical health predicts time to additional breast cancer events and mortality in breast cancer survivors. Psycho-oncology. 2011; 20(3):252-9.

2.   Kwan ML, Cohn JC, Armer JM, Stewart BR, Cormier JN. Exercise in patients with lymphedema: a systematic review of the contemporary literature. J Cancer Surviv. 2011;320–36.

3.   Corey G. Theory and practice of counseling and psychotherapy. 7th ed. Scarbourough, ON: Brooks/Cole; 2005.

4.   Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. Int J Psychiatry Med. 2006;36(1):13–34.

5.   Janz NK, Becker MH. The Health Belief Model: a decade later. Health Educ Q. 1984;11(1):1–47.

6.   Janz, NK, Champion, VL, Stretcher V. The Health Belief Model. In: Glanz, K, Rimer, BK, Lewis F, editor. Health Behavior and Health Education: Theory, Research and Practice. 3rd ed. San Francisco: Jossey-Bass; 2002. p. 45 – 66.

7.   Wenzel L, Glanz K, Lerman C. Stress, coping and health behaviors. In: Glanz K, Rimer B, Lewis F, editors. Health Behavior and Health Education. Theory, Research and Practice. 3rd ed. San Francisco: Jossey-Bass; 2002. p. 210–39.

APPENDICES

Appendix 1: Protection of Human Subjects

Human subjects research protocols were submitted and approved by an institutional review board in San Diego (UCSD) for this dissertation study. Key sections of the protocol are included below.

Risk to Human Subjects

For Chapters 2 and 3 (i.e., the WHEL Study), the research was secondary data analyses of existing data, and as a result, the potential risks to subjects was minimal to non-existent. The participants had already completed the study assessments and signed informed consent documents at each of the clinical sites indicating their consent for use of their non-identifying questionnaire data in research. A dataset stripped of all identifying information was prepared and used by Ms. Dominick. For the larger WHEL Study, data were abstracted from hospital medical records, and participants completed self-administered questionnaires or in-person interviews.

Chapter 4 (i.e., the chart review) had minimal potential risks. One such risk was the loss of confidentiality. To ensure the confidentiality, none of the 18 elements specified in the HIPAA list of identifying data were collected.

Adequacy of Protection against Risks

For Chapters 2 and 3, participants were recruited at 7 study sites (University of California San Diego and Davis, Stanford University, Kaiser Permanente Oakland and Portland, University of Arizona Tucson, and the MD Anderson Cancer Center) through physicians, tumor registries and community breast cancer events between March 1995 and November 2000. Prior to signing the consent form and being randomized into the

study, all study participants were given the option to decline participation. The WHEL

Study was compliant with HIPAA rules for informed consent. The WHEL Study

obtained a Federal Certificate of Confidentiality that limits the right to subpoena study

data to ensure protection of participant information. For this dissertation project,

participants' identifying information was not included in the dataset.

For Chapter 4, Ms. Dominick reviewed UC San Diego Health System electronic

medical records through the EPIC system and extracted data to a spreadsheet that

formed the study database. No identifying information was extracted to the study

database. In addition, none of the 18 HIPAA identifying elements of the medical record

were recorded. All research information collected was saved as password protected

electronic files residing on a secure server within the Moores UCSD Cancer Center.

We were granted a waiver of documentation of informed consent for this project.

Potential Benefits

For Chapters 2 and 3, participants benefited from this dissertation research

because they contributed to the scientific knowledge of the physical and psychosocial

factors associated with breast cancer-related lymphedema. In addition, the findings

from this research will have the potential to be included in cancer survivor educational

programs and health behavior interventions.

For Chapter 4, there was no direct benefit to any individual patient whose

medical record was reviewed. The potential benefit was the gain in scientific

knowledge regarding patient compliance with health care provider referrals to attend an

outpatient OT lymphedema consult appointment.

In light of the benefits and the minimal risk involved, the risk to benefit ratio is

highly favorable for this dissertation project.

Appendix 2: Lymphedema Questionnaire

WHEL Study Lymphedema Questionnaire

These questions will be asked over the telephone during a WHEL Study participant's semi-annual call.

Lymphedema is the swelling of the arm or hand due to fluid buildup following surgery. Many WHEL participants have experienced lymphedema after their breast cancer treatment. We would like to take about 5 extra minutes on today's call to ask you about your experiences with lymphedema.

1. Since your breast cancer treatment, was there ever a time when your arms or hands were different sizes from each other? ☐ Yes ☐ No ☐ Not Sure/Don't Know

2. Since your breast cancer treatment, has a health care professional ever told you that you have lymphedema? ☐ Yes ☐ No ☐ Not Sure/Don't Know

IF NO to both 1 and 2, stop. "That ends our questions for you about lymphedema today. Thank you very much for taking this time to answer these questions."

IF YES to either 1 or 2,
3. Which of the following symptoms have you experienced due to your lymphedema?

	Currently	**Previously**	**Never**
Swelling	☐	☐	☐
Tenderness	☐	☐	☐
Numbness	☐	☐	☐
Watches, rings, bracelets, clothing becoming tight on one side	☐	☐	☐
Puffiness	☐	☐	☐
Firm or leathery skin	☐	☐	☐
Pain	☐	☐	☐
Indentations in skin after leaning against something	☐	☐	☐
Difficulty in seeing knuckles or veins	☐	☐	☐
Tiredness, thickness, heaviness of hand or arm	☐	☐	☐
Difficulty holding or grasping objects	☐	☐	☐
Difficulty writing	☐	☐	☐
Infection in the affected hand or arm	☐	☐	☐

4. How much time passed from the completion of your breast cancer treatment to the start of your lymphedema symptoms? ___days ___weeks ___months ___years

5. I'm going to list some treatments for lymphedema. For each one, please let me know whether or not you ever used this to treat your lymphedema.
   Physical therapy (includes massage).............. ☐ Yes. ☐ No

Have you ever been fitted with a pressure sleeve? ....☐ Yes ☐ No
Medication ....☐ Yes.☐ No (YES:
Specify_____)

5a. Did you try anything else for your lymphedema? (open text field _____)

6. Would you say that the difference in the size of your arms or hands was/is:
☐ Very slight (you are the only one who would notice)
☐ Noticeable to people who know you but not to strangers
☐ Very noticeable?

7. How much did/does your lymphedema distress or bother you? Would you say,
☐ Not at all ☐ A little ☐ Moderately ☐ Quite a bit ☐ Extremely

"That ends our questions for you about lymphedema today. Thank you very much for taking this time to answer these questions."