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Lymphedema in female breast cancer cases diagnosed in Iowa

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LYMPHEDEMA IN FEMALE BREAST CANCER CASES DIAGNOSED IN IOWA

by

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An Abstract

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of the requirements for the Doctor of
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ABSTRACT

Lymphedema of the arm is a complication that occurs in about 10-20% of women treated for breast cancer. Breast cancer treatment can damage or disrupt normal lymphatic pathways, causing fluid to accumulate in the arm. This condition is called lymphedema. Swelling of the arm can be painful and disfiguring, negatively impacting the quality of life of afflicted individuals. Lymphedema is a progressive disorder that requires prompt diagnosis and treatment to prevent the occurrence of more serious complications, such as infection or severe disability of the arm. Past research have attempted to identify risk factors that influenced the development of lymphedema, however conflicting results were observed between studies.

Therefore, a comprehensive literature review was conducted to identify studies that examined the effect of prognostic and/or personal factors on lymphedema. In the meta-analyses, results from each independent study were abstracted and pooled with other studies using the random-effects model. In an effort to examine additional factors that were not widely studied, a retrospective cohort study was conducted on women diagnosed with breast cancer in Iowa during 2004.

A questionnaire was developed to collect information on arm activities, co-morbidity, and lymphedema-related symptoms. Eligible women were identified from the State Health Registry of Iowa and data were collected through computer-assisted telephone interviews. At the end of the interview, each woman was asked to measure the circumference of her right and left arm one hand width above and below the elbow crease.

The meta-analysis found that mastectomy (as opposed to a lumpectomy), axillary dissection (as opposed to sentinel node biopsy), radiation therapy, presence of positive nodes, obesity (body mass index >30), low education (less than high school), presence of any co-morbidity, injury and infection increased the risk of developing lymphedema. The

cohort study found that the presence of axillary dissection and radiation, cancer stage, positive nodes, large tumor size, high body mass index, and younger women increased the risk of lymphedema.

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Graduate College
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CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

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To Apollos, Mary, and Sarah Tsai

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CHAPTER1: INTRODUCTION

Overview

Breast cancer is the most common cancer among women in the United States.[1] In 2010, an estimated 207,090 women will be diagnosed with breast cancer in the United States,[2] accounting for 28% of all newly diagnosed female cancers with 90% of these women surviving five years.[2] Current advances have allowed for earlier diagnosis and the administration of better and more effective treatments to prolong life.[3, 4] Complications following breast cancer treatment include darkened skin, muscle aches, and lymphedema.[5]

As survival improves, quality of life becomes even more crucial. Longer lifespan and improved survival have contributed to the increase in arm lymphedema among breast cancer survivors.[1, 6, 7] Thus, arm lymphedema has become an increasingly important problem. Arm lymphedema is the retention of lymph fluid in the upper extremities. Swelling of the arm, wrist, and hand can be painful, disabling, disfiguring, and elevates infection risks, thus severely affecting quality of life.[8-10] Unless otherwise specified, lymphedema of the arm secondary to breast cancer will be referred to as lymphedema.

Review of Lymphedema

Definition and Physiology

Lymphedema occurs when the lymphatic system is impaired.[11] When the system is functioning normally, fluids and proteins are forced out of the capillaries into the interstitial space and are removed by macrophages or the venous system. Remaining fluids not taken up by the capillaries are drained by the lymphatic system.[12-14] The exchange of fluid is balanced by hydrostatic and oncotic pressure, which dictates the direction of fluid flow between capillaries and interstitial space.[1, 12, 15]

Smooth muscle contractions, neighboring arteries, valves, respiratory movements, and skeletal muscle contractions all contribute to the propulsion of lymph fluid through lymph vessels.[9, 14] When one of these systems malfunctions, accumulation of fluid can occur. Lymphatic system disruption by surgical removal of lymph nodes, damage to lymph vessels from radio- or chemotherapy, increased capillary permeability, and inability to propel lymph can lead to lymphedema.[16, 17] Thus, the impairment of the lymphatic system may lead to lymphedema, and ultimately, fibrosis and elevated risk of infection.[16, 18]

Primary lymphedema is mostly congenital, and is characteristic of individuals born lacking lymph vessels and nodes. Secondary lymphedema is acquired and caused by damage to the lymphatic system. Hence, the latter and more common form,[19] is experienced by breast cancer survivors. Acute lymphedema is thought to be rare, develops shortly post diagnosis[20] and resolves within months.[21] Chronic lymphedema develops several months post diagnosis and does not resolve.

Time to Onset

The time from diagnosis of breast cancer to onset of physician-diagnosed lymphedema varies. The average onset time to lymphedema is approximately one year.[22, 23] Acute lymphedema develops within 2 months after treatment, while chronic lymphedema usually occurs 20 months post treatment.[24] About 50% of breast cancer survivors with lymphedema are diagnosed within 3 years of their breast cancer.[25-29]

Lymphedema Measurement

There are numerous ways in which lymphedema can be diagnosed. Lymphedema can be identified through objective or subjective measures. Objective measurements include arm circumference, water displacement, and MFBIA (multiple frequency bioelectrical impedance analysis). Most studies used the following definitions to be

indicative of lymphedema: 1) arm circumference, >2 cm difference between either arms or same arm pre-and post-surgery, and 2) water displacement, >200 ml difference.[30] However, variation to these "standard" definitions exists across research studies and health providers. Subjective measurements consist of identifying pertinent arm symptoms, such as heaviness of arm. Once again, depending on the assessor, lymphedema can be defined based on one symptom, or a set of symptoms. The combination of how lymphedema was measured and defined affects who will be classified as having lymphedema.

Lymphedema Incidence

The incidence rate of lymphedema varies widely (3-60%) among studies because of differing follow-up times and definitions of lymphedema. Prospective studies, with large sample sizes, provide the best estimates of incidence. Based on such studies, the incidence of arm lymphedema occurs in about 10%-20% of women treated for breast cancer.[20, 25, 27, 31-38]

Potential Risk Factors for Lymphedema

Risk factors for lymphedema are not well understood.[39] We know very little as to why lymphedema occurs in some but not in others who underwent the same treatment.[8, 40] The onset, progression, and amount of tissue swelling due to lymphedema vary widely indicating unidentified factors.[9, 18, 40] Chronic lymphedema is multi-factorial.[41, 42]

Physical Activity of the Arm

After receiving treatments, breast cancer survivors are routinely instructed to follow precautions that include wearing gears or garments to protect the ipsilateral arm from puncture or trauma and avoid heavy lifting and strenuous arm exercise, such as weight lifting. These instructions are thought to help prevent and/or manage

lymphedema. However, in the case of vigorous arm exercise, little research justifies that claim, and it continues to be a highly controversial topic. This is a potential area for intervention. For decades, oncology experts have cautioned breast cancer survivors against vigorous upper arm exercise because such activities can increase lymph production through tissue tears and inflammation.[43-45] In fact, breast cancer women who were given arm care advice or have a fear of developing lymphedema are more likely to avoid any strenuous arm activity.[46] Conversely, it has been found that lymphatic flow during steady exercise increases 2 to 3 times compared to resting flow.[18] In addition, isometric exercises cause muscles to contract without lengthening (resistance), thereby stimulating a pumping action that propels lymph through the vessels.[47] Compounding the matter, it was found that the majority of breast cancer women have an insufficient amount of exercise.[48] Furthermore, individual reports by breast cancer survivors conflict regarding the direction of association between lymphedema and arm activity.

Few studies on physical activity have been conducted.[49-52] Studies observing breast cancer survivors participating in vigorous upper body exercise (dragon boat training) did not find significant changes in arm volume.[53-55] Moreover, some studies even showed a protective effect.[49-51] One study found a significant reduction in exercise post-surgery but before lymphedema onset (excluding lower body exercise) among lymphedema cases but not controls.[49] Another study randomized breast cancer survivors into physical therapy treatment or control groups. The incidence of lymphedema in the treatment group (11%) was lower than that of the control group (30%).[50] Only 3 studies specifically looked at arm/hand activities and lymphedema. Current information about lymphedema given out by health care professionals needs to be updated.[46] To the best of our knowledge, no studies examined both the intensity and position of upper extremity activity and their effect on arm lymphedema.[50-52]

Personal Risk Factors

Several studies examined co-morbidity as a risk factor for lymphedema. Physiologic systems are closely linked and the failure of any one of these systems can disrupt the delicate fluid balance between vessels and extracellular space. For example, heart failure causes blood pressure to drop, which increases filtration of fluid from the vessels due to increased pressure on capillary walls. Immune disorders lead to inflammatory events that cause blood vessels to leak fluid into the extracellular space. Other disorders, such as thyroid disease and kidney failure, also play a role in this regulation. While individually, the co-morbid conditions mentioned can lead to edema in limbs, each co-morbid effect on lymphedema development needs investigation.[56]

High body mass Index (BMI) is a potential risk factor for lymphedema that also hinders lymphedema treatment.[57] Multiple studies have shown that a BMI of 30 or greater may be a contributor to lymphedema.[58-60]

Older age, higher BMI, weight gain after surgery, presence of co-morbidity, infections, and exercise are identified as potential lymphedema risk factors.[28, 49, 61-63] Even so, there are still many inconclusive study results due to small sample sizes and lack of a control group. Diverse methods used to determine the presence of arm lymphedema (water displacement, arm circumference) and subjects' selection (hospital-based, population-based) contributed to the lack of generalization and replication of studies.[40] Investigation of modifiable risk factors such as arm exercise and obesity may play a key role in preventing lymphedema.

Prognostic Risk Factors

For disease-related factors, several studies have identified the number of lymph nodes removed, tumor size, and stage to be predictive of lymphedema.[32, 33, 64] Extent of axillary dissection, surgical procedures, radiotherapy to the axillary region and

chemotherapy were found to be treatment-related risk factors for lymphedema.[32, 38, 62, 65] However, with the exception of axillary dissection and radiotherapy, conflicting results have been reported with the remaining risk factors.[41, 42] Thus, further clarification is needed. Adding to the complication, many of these risk factors are interrelated. For example, patients with more advanced stage of cancer typically have more radical surgery and a greater number of lymph nodes removed.[66]

The literature indicated that subjects exposed to either extensive node dissection or axillary radiotherapy have the highest risk of developing lymphedema during their lifetimes; thus women who were treated with both surgery and radiotherapy are at highest risk. Other risk factors have also been examined. The type of surgery performed is indicated as a modifiable risk factor. It was thought that less invasive techniques would reduce the incidence of lymphedema. However, even after improvements in surgical techniques, a significant incidence of lymphedema still exists.[67] In particular, the advent of sentinel biopsy (SLN) over the past 7-10 years has generated palpable excitement and inspired research. Within the last 5 or 6 years, increasing numbers of surgeons are using this technique. By 2004, it is estimated through SEER*Stat (25% of U.S. population) that about 29% of breast cancer surgeries involved SLN without axillary dissection. This percentage jumped to 37% in 2006. Axillary node dissection is reserved for those patients in whom SLN is positive. Although early research showed that SLN decreased lymphedema rates in breast cancer survivors, it is possible that the risks for SLN were underestimated while the risks of axillary dissection were overestimated.[68] Recent research looking at SLN had a short follow-up time of a year or two, limiting the ability to detect its long-term consequences.

Significance of Research

A recent NCI Cancer Bulletin reported that many cancer survivors are unaware that they are afflicted with a potentially serious treatment complication called

lymphedema.[69, 70] There are numerous ways to detect lymphedema in a clinical setting, with the majority involving a measurement device comparing one arm to the other. However, unless a woman is actively monitored for lymphedema, as in the case of enrolling in a prospective research study, a casual examination done at regular checkups may not detect the presence of moderate lymphedema due to the lack of noticeable difference.[6] Hence, it is suspected that some lymphedema cases are not physician-diagnosed. This indicates an underestimation of lymphedema cases that result in many unmanaged cases.

Lymphedema is a progressive condition in which early detection is crucial. If left untreated, lymphedema can become debilitating or a source for sepsis. Identifying subclinical cases may halt progression and improve quality of life. Although a >2 cm difference between arm circumferences is a useful objective method for identifying cases, subjective arm symptoms also allow for the identification of less evident cases.

There is a need for a tool that can identify potential lymphedema based on both objective and subjective symptoms. This tool can be disseminated to breast cancer survivors to raise awareness of lymphedema. Survivors found to have probable lymphedema can then seek a clinician for proper evaluation, management, or treatment.

Lymphedema lowers the quality of life in individuals afflicted through physical, functional, emotional, social, and time constraints.[6, 71] Quality of life of breast cancer survivors with arm problems (e.g., swelling) are four times more likely to be affected than those without.[30, 37, 72, 73] Lymphedema has forced some women to give up their hobbies or employment and others have had to incorporate lymphedema treatments into their busy schedules. Therefore, lymphedema has significant implications for breast cancer survivors.[74]

It is important to identify modifiable factors, such as upper extremity exercise and obesity, which can attenuate the development of lymphedema. In addition, it is unclear

why one person develops lymphedema while another does not,[69] thus considerable disagreement persists regarding the significance of risk factors.[27]

Since muscle contractions from physical activity help move lymph fluid through lymphatic channels,[12] certain upper arm activities may prevent lymphedema. To evaluate the controversial guidelines regarding physical activity in place for breast cancer survivors, there is a need to study the effect of arm usage in two ways: intensity and position (above or below the heart). Doing so will allow for a better assessment of lymphedema risk. Identifying specific arm activities that are preventive of lymphedema will increase quality of life.

Evidence shows that subjects with co-morbidities are more likely to develop lymphedema. The mechanisms are unclear and warrant attention. With reported rates of lymphedema ranging from 3-60%,[62] it is of interest to investigate how rates vary with different follow-up intervals and definitions of lymphedema.

Comparison of 2002 and 2004 Breast Cancer Cases

Both the 2002 and 2004 Iowa cases were used to study breast cancer and lymphedema. 2002 cases were randomly selected for the pilot study and the 2004 cases were recruited for the main portion of the study. Distribution of demographics (race and marital status) and disease-related factors (number of positive nodes) were obtained using SEER*Stat[75] and remained similar between 2002 and 2004 cases. However differences in distribution were observed for surgical treatments. In 2004, 33% of cases, as opposed 44% in 2002, received modified radical mastectomy. More cases received less invasive surgical procedures such as lumpectomy in 2004. Similarly, there was an increase from 12% (2002) to 22% (2004) for SLN and a corresponding decrease for axillary dissection. In addition, there was a 12% increase (from 10% in 2002 to 22% in 2004) in cases that had 1-2 lymph node(s) removed as opposed to 3 or more nodes removed. For further comparisons in Iowa, the 2007 breast cancer case distribution is as follows; modified

radical mastectomy (36%), SLN (38%), and 1-2 lymph node(s) removal (29%). Surgical treatment for breast cancer has become less invasive in more recent years. This is most noticeably observed by the increased percentage of SNL performed, from 12% in 2002 to 38% in 2007.

Breast Cancer Descriptive Data in Iowa

Based on 2000 census data, Iowa has a predominately white population (93.9%) in which 97.5% of those 5 years or older speak English well, 86.1% of those over 25 years or older have at least a high school education, and 57.8% of those 15 years or older are currently married [76, 77]

Inclusion/Exclusion Criteria for 2004 Iowa Breast Cancer Cases

We examined the frequencies of 2004 breast cancer cases in Iowa using SEER*Stat.[75] Based on prior literature and SEER data, several exclusion criteria are listed to decrease bias and confounding. Only first primary, invasive breast cancer cases were included in this study.

1) Nine men diagnosed with breast cancer in 2004 were excluded from this study.
2) Only live subjects were included. Based on the 2003 cohort, the 5-year observed survival rate was 82% (As of spring of 2010, the 5-year observed survival was not available for 2004)
3) Women 80 or older at the time of breast cancer diagnosis were excluded due to poor 5-year survival. Their 5-year observed survival rate is 55% compared to 87% for women under 80 years old. Excluding this group did not greatly affect the generalizability of study results.
4) Women who were diagnosed with invasive cancer that had spread to distal sites and nodes (Stage IV) were excluded from this study. The 5-year observed survival rate for

women with stage IV is 20%, compared to stage I-III (more localized) cancer's rate of 82%. Survival is an important component for the development of lymphedema.

5) We also excluded subjects with multiple primary cancers because they may have been treated for another cancer, which may affect the lymphatic system in ways that can bias the results of this study.

Demographics of 2004 Iowa Breast Cancer Cases

Approximately 98% of our study population is white, around 62% married, and near 100% speak English. According to the Iowa Cancer Registry, there were no women under the age of 20 diagnosed with breast cancer in 2004.

Prognostic Factors among 2004 Iowa Breast Cancer Cases

Tumor size and tumor stage: The majority of Iowa subjects (64%) had a breast tumor that was less than 20 mm in diameter. Thirty-two percent had a tumor between 20-50 mm. Twenty-eight percent of women had positive nodes.

Treatment: Around 51% of cases underwent partial mastectomy (lumpectomy) and about 33% underwent modified radical mastectomy. Around 92% of the women had lymph nodes removed, of which, 32% had sentinel node biopsy only and 60% had their regional nodes removed. A SLN involves detection and removal of the first lymph node in the chain draining the affected area of the breast.[78] Approximately 67% had 3 or more nodes removed during surgery. More than 51% were treated with beam radiation.

Objectives

As survival from breast cancer increases, lymphedema gains importance as a potential adverse outcome. The purpose of this study is to collect and analyze lymphedema-related factors among breast cancer women diagnosed in Iowa during 2004. The long-term goal of this study is to improve lymphedema diagnosis and to identify

factors that prevent, delay or alleviate chronic lymphedema in patients with breast cancer. The specific aims for this project are as follows:

1) Conduct a meta-analysis to determine the association between breast cancer treatment-related factors and the development of lymphedema;
2) Perform a meta-analysis to observe the relationship between risk factors, particularly modifiable factors, and lymphedema among breast cancer survivors; and
3) Conduct a retrospective survey among a cohort of women diagnosed with breast cancer in Iowa during 2004. The goals of this study are to:
    a. Estimate the cumulative incidence of lymphedema;
    b. Identify factors that are related to lymphedema development after breast cancer diagnosis and treatment; and
    c. Assess the relationship between type and intensity of physical activity and the development of lymphedema.

CHAPTER 2: THE RISK OF DEVELOPING ARM LYMPHEDEMA AMONG BREAST CANCER SURVIVORS: A META-ANALYSIS OF TREATMENT FACTORS

Summary of Findings

Background: As more women survive breast cancer, long-term complications that affect quality of life, such as lymphedema of the arm, gain greater importance. Numerous studies have attempted to identify treatment and prognostic factors for arm lymphedema, yet the magnitude of these associations remains inconsistent. *Methods:* A PubMed search was conducted through January 2008 to locate articles on lymphedema and treatment factors after breast cancer diagnosis. Random-effect models were used to estimate the pooled risk ratio. *Results:* The authors identified 98 independent studies that reported at least one risk factor of interest. The risk ratio (RR) of arm lymphedema was increased after mastectomy when compared to lumpectomy RR=1.42 (95% confidence interval [CI] 1.15 -1.76), axillary dissection compared to no axillary dissection RR=3.47 (95% CI, 2.34-5.15), axillary dissection compared to sentinel node biopsy RR=3.07 (95% CI, 2.20 -4.29), radiation therapy RR=1.92 (95% CI, 1.61-2.28), and positive axillary nodes RR=1.54 (95% CI, 1.32-1.80). These associations held when studies using self-reported lymphedema were excluded. *Conclusions:* Mastectomy, extent of axillary dissection, radiation therapy and the presence of positive nodes increased the risk of developing arm lymphedema after breast cancer. These factors likely reflected lymph node removal, which most surgeons consider to be the largest risk factor for lymphedema. Future studies should consider examining sentinel node biopsy vs. no dissection with a long follow-up time post surgery to see if there is a benefit of decreased lymphedema compared to no dissection.

Introduction

Breast cancer is the most prevalent cancer among females in the United States.[79] In 2008, an estimated 182,460 women will be diagnosed with breast cancer, accounting for 26% of all newly diagnosed female cancers with 89% of these women surviving five years.[79] Lymphedema of the arm (here referred to as lymphedema) is a complication that affects about 20% of breast cancer survivors.[80, 81] There is a direct correlation between the longevity of breast cancer survivors and subsequent lymphedema development.[28] Due to an increase in survivorship in breast cancer patients, many who suffer from lymphedema were not offered sentinel node biopsy. Therefore, there are a larger number of women than in the past, who might benefit from this data. As the breast cancer survival rate increases, lymphedema will potentially impart more women.

While there are numerous published studies examining the association between breast cancer treatment factors and lymphedema, the strengths of such associations are not consistent across studies. Mastectomy, radiation, and axillary node dissection often disrupt or damage the lymphatic system,[82] and are believed by many to influence the development of lymphedema. The purpose of this study is to conduct a detailed meta-analysis to examine the strength and consistency of observed associations between treatment factors and lymphedema secondary to breast cancer diagnosis.

Methods

Literature Search

A comprehensive search was performed in PubMed using MeSH headings and keywords to identify articles published between 1950 and January 2008. The MeSH headings and keywords used in this search included breast cancer, lymphedema, mastectomy, sentinel node biopsy, radiation therapy, chemotherapy, positive nodes, and

risk factors. Relevant and review articles were identified and their references were checked for additional studies.

Data Abstractions

Data were abstracted for treatment factors of interest, along with study design, study location, and method of lymphedema measurement. Study designs included prospective cohort studies, retrospective cohort studies, randomized controlled trials and case-control studies. Studies were conducted worldwide. Lymphedema measurement refers to the technique used to determine the presence or absence of lymphedema and included: arm circumference (centimeters), water displacement (volume), optoelectronic volometer, charts, multiple frequency bioelectrical impedance analysis (MFBIA), self-report, or unclear/not stated. Each study was double-checked for data entry errors. Breast cancer treatment factors included type of surgery, extent of lymph node dissection, radiation therapy, chemotherapy, and the presence of positive nodes. The risk ratio that adjusted for the highest number of confounders was recorded and pooled.

Inclusion and Exclusion Criteria

Articles that only included women with lymphedema, and thus had no control group were excluded (n=7). Additionally, articles that did not either report risk ratio estimates (RR) and 95% confident intervals (CIs) or provide sufficient information to calculate the RR and its variance were excluded from the meta-analysis (n=28). Articles that have identical or overlapping study populations were grouped as one study to avoid duplication of results (n=1).

Statistical Analysis

Random-effects models were used to estimate the pooled RR for these dichotomous factors.[83, 84] Variation both within and between studies (i.e., heterogeneity)

is a concern. Hence, the random-effect model was chosen rather than the fixed-effect model. This model assumes that a random group of studies was selected from the total pool of studies and thus leads to wider CIs. This was done to prevent any studies (especially ones with large heterogeneity) from dominating the standard errors. Statistical tests for homogeneity were carried out to determine if the effect found was consistent across studies. To examine and reduce heterogeneity, we stratified analyses by lymphedema measurement. We initially stratified studies by those that reported 1) circumference differences, 2) water displacement or multiple frequency bioelectrical impedance analysis (MFBIA), or optoelectronic volometer, 3) clinical diagnosis (medical records, examined by physician or other clinical personnel), and 4) self-report, excluding studies that did not state how lymphedema was defined. Heterogeneity was rarely reduced ($P>0.20$) in these sub-analyses with no pattern seen (data not shown). Therefore, we stratified by self-reported and non-self-reported measurement of lymphedema because of a concern that self-report would be associated with more misclassification. We also stratified analyses by study design, location, and sample size. As another attempt to eliminate heterogeneity, we also ran analyses restricting to studies published in 1980 or later.

The natural log of the RR and its variance were needed for each study to calculate the pooled RR. The variances were calculated from either reported CIs or based on the number of exposure and non-exposed cases and controls. Studies[35, 85-90] that reported no data but stated no association between variables of interest and lymphedema were assigned RR estimates of 1.0 in an attempt to avoid publication bias. The variances for such studies were estimated by using the number of cases and controls and the average exposure percentage gathered from other studies. Pooled RRs were reported with 95% CIs. All statistical tests were 2-sided and a p-value <0.05 was considered statistically significant.

The presence of publication bias was evaluated qualitatively using a funnel plot (data not shown). Funnel plots were constructed for each of the five risk factors of interest (mastectomy, axillary dissection, radiation therapy, chemotherapy, and presence of positive nodes), plotting the RRs against their standard errors. No clear evidence of publication bias was seen.

Results

We identified 98 unique study populations that assessed the relationship between treatment factors and the development of lymphedema. The majority of the studies were cohort studies. Approximately 40% of the studies were conducted in either the United States or Canada. Most studies measured lymphedema based on differences in arm circumference (n=47), water displacement (n=13) or clinical diagnosis (n=11). The measurement method and definitions for lymphedema among these studies are summarized in Table 2.1. Duration of follow-up varied. In some studies, all participants were followed for an identified period of time. In others, follow-up time varied from individual to individual. All these variations among studies contributed to the heterogeneity observed in this meta-analysis. Table 2.1 also lists the study designs and countries of origin for the studies reviewed. Table 2.2 describes the location of study, sample size, risk factors reported, definition and measurement of lymphedema, and the length of follow-up for each study. Twenty-five studies reported mastectomy, 49 radiation therapy, 22 sentinel node biopsy, 18 chemotherapy, and 32 on the presence of positive nodes.

Table 2.3 reports the pooled RRs for lymphedema and each breast cancer treatment factor. Since self-reported lymphedema was of concern, we also provide analyses stratified by self-reported and non-self-reported measurement of lymphedema (excluding 8 studies that did not state how they defined lymphedema). Non-self-reported studies accounted for 62-93% of the overall studies for the data shown in Table 2.3.

Overall, the studies tended to be heterogeneous (p-value < 0.20). Mastectomy increased the risk of lymphedema RR=1.42 (95% CI, 1.15-1.76) compared to lumpectomy, as did radical mastectomy compared to less invasive forms of mastectomy RR=3.28 (95% CI, 2.35-4.59). The RR increased for lymphedema when axillary dissection was performed, whether compared to sentinel node biopsy (SNB) or to no axillary dissection. Figure 2.1 plots the individual study RR estimates and CI for axillary dissection compared to SNB, along with the pooled estimate.

Overall, subjects who had received any radiation therapy were at a significantly increased risk of developing lymphedema RR=1.92 (95% CI, 1.61-2.28) (Table 2.3). Among subjects who received radiation, those who had the axilla irradiated had an increased risk for developing lymphedema compared to those who did not. As expected, there was no association between chemotherapy and lymphedema. The risk of lymphedema was elevated among breast cancer survivors who had positive nodes versus those who did not RR=1.54 (95% CI, 1.32-1.80).

Stratifying data by study design, location, and sample size did not account for the heterogeneity seen, nor did excluding studies published prior to 1980 (data not shown). However, the association for positive nodes was strongest among studies that used non-self-report (e.g., arm circumference or water displacement) to determine lymphedema. Among the 98 independent study populations, only 10 reported adjusted RRs. Of these 10, 8 adjusted for other treatments and 8 adjusted for age.

Discussion

Our comprehensive review of risk factors for lymphedema among breast cancer survivors showed that women who underwent treatments including mastectomy compared to lumpectomy, axillary dissection, and radiation therapy were at an increased risk of developing lymphedema. Axillary dissection has more than a 3-fold increased risk compared to no dissection. When axillary dissection was compared to SNB the

increased risk was similar. This may suggest that SNB doesn't increase lymphedema risk as axillary dissection does, however, we were not able to directly look at this since no studies reported SNB compared to no dissection. It is important to note that women who were found to have positive nodes during SNB generally went on to have axillary dissection.

Most studies identified axillary dissection as a risk factor for lymphedema. Similarly, many surgeons believe that lymphedema risk is strongly attributed to axillary dissection. Thus far, SNB has been offered as an option that might decrease side effects including lymphedema. Unfortunately, our pooled analyses could only examine this possibility indirectly. SNB's long-term impact on lymphedema requires further investigation, especially compared to no dissection. Since SNB is a relatively new procedure, future studies will be able to follow breast cancer survivors for more than two years after treatment.[91]

Surgical procedures to remove a breast tumor also vary, ranging from the most invasive (radical mastectomy) to the least invasive (lumpectomy). It is unclear why mastectomy, compared to lumpectomy, showed an increased risk of lymphedema. This difference may reflect severity or may reflect lack of adjustment for other treatments. Alternatively, mastectomy may have been chosen over lumpectomy in patients with larger tumors. Neither total mastectomy nor lumpectomy generally disturbs the axillary region unless coupled with axillary dissection. Radical and modified radical mastectomy, are currently reserved for more advanced cancer cases. The association between type of surgery and lymphedema suggests that the type of surgery may play a role in the development of lymphedema. While a number of studies[25, 36, 92-94] reported mastectomy to increase lymphedema risk, other studies observed that the difference in lymphedema incidence rates between mastectomy and lumpectomy diminished after 2 years.[27, 36, 62, 95, 96] Since many studies were conducted with short follow-up times of up to 2-3 years post-surgery, the increased risk of lymphedema seen may have been due to short follow-up

times. When we stratified studies by length of follow-up, the association between mastectomy and lymphedema was strongest for studies with 3 years of follow-up or less with little or no association among studies with 4 or more years of follow-up. It is possible that subjects who underwent mastectomy have earlier onset of lymphedema, while subjects who underwent lumpectomy develop lymphedema later, thus diminishing the difference between the prevalence of lymphedema cases between mastectomy and lumpectomy survivors.

Radiation therapy can promote the development of lymphedema by blocking lymph vessels or by compressing lymph vessels through radiation fibrosis.[95] An association with lymphedema was detected for both radiation therapy to the axilla and radiation therapy to an unspecified location. However, a stronger association with lymphedema was seen among those who received radiation therapy to the axilla. The association observed looking at any radiation therapy versus no radiation therapy is questionable because a portion of subjects who received radiation may have been irradiated in the axillary area.[25, 65, 97-99] Hence, the effect perceived may have been attributed to radiation to the axilla and needs to be interpreted with caution.

One study suggested that breast cancer survivors who were treated with both radiation therapy and axillary dissection are at the highest risk of developing lymphedema.[100] We were not able to look at this due to the lack of studies reporting on subjects who received both radiation therapy and axillary dissection. Radiation therapy is generally given to patients who have greater than 3 positive nodes. Positive nodes, which are strongly linked to radiation therapy and axillary dissection, were also related to the development of lymphedema.

Overall, we saw no association with chemotherapy, but pooling US and Canada studies have suggested an association. In the past, practice in the US was to only administer chemotherapy to breast cancer patients who had positive nodes. Therefore, chemotherapy in early studies may be a marker for positive nodes. In 2000, a NIH

consensus statement reported that all localized breast cancer patients, regardless of nodal, hormonal, or menopausal status should be treated with either chemotherapy or some other systemic therapy.[101] The increased risk observed from chemotherapy in the US prior to the year 2000 may have been attributed to the presence of positive nodes.

A limitation is that the studies defined lymphedema in a variety of ways, potentially adding to the heterogeneity of risk ratios seen among studies. Lymphedema can be measured subjectively (self-report) or objectively (e.g. Circumference and water displacement) and have different classification standards. While the classification of lymphedema differs, recent studies have generally adapted the following definitions to be indicative of lymphedema: 1) circumference >2 cm either between arms or same arm pre- and post-surgery and 2) water displacement >200 ml.[30] The combination of how lymphedema was measured and defined affects who will be classified as having lymphedema. These differences can in turn affect the detection of significant associations between lymphedema and risk factors under investigation. We also looked at the pooled RR for each risk factor by decade the article was published. In general, we did not see any drastic trends or change in pooled RR from decade to decade. However, we did notice a slight reduction in the magnitude of pooled RR from articles published in the year 2000-2007 compared to 1944-1998. The changes in surgical and other treatment practices including chemotherapy throughout the past few decades may have reduced the observed association.[30] It is possible that pooling different studies can help balance out the subtle lymphedema risk differences caused by diverse lymphedema measurements or definitions.

One limitation of any meta-analysis is the potential for publication bias. The funnel plots we evaluated showed no evidence of publication bias. However, we do not know how many of these 98 studies conducted analyses of treatment factors that they did not report. Heterogeneity between studies is a problem, as shown in Table 2.3. Comparisons were made across different study designs and lymphedema measurements,

but heterogeneity persisted. Other possible contributors to heterogeneity include lack of adjustment for potential confounding factors, length of follow-up (one month to over 15 years), decade in which the study was conducted, as well as, lymphedema measurement and definition as discussed above. This meta-analysis contains both prospective and retrospective studies. Most studies typically extracted treatment risk factors from medical records. Hence, the potential for recall bias was greatly reduced. The majority of studies did not adjust for potential confounding factors. In particular, positive nodes need to be taken in account. The presence of positive nodes can determine whether axillary dissection and radiation therapy are needed. Moreover, surgery and radiation assert their own independent risk to lymphedema. Non-treatment related factors such as body mass index, infection and injuries were not controlled for in the original data. These factors may also play a role in the development of lymphedema. Failure to control for such confounders can lead to an overestimation or underestimation of an effect, if such factors are also related to the treatments examined here. It is a limitation of this study that the majority of the original data were not adjusted for potential confounders; however to bias results, such factors would also need to be related to the treatment examined. Future studies should address confounding, particularly confounding effects of other treatments.

It should be noted that each breast cancer patient has an individualized treatment plan based on her personal preferences and disease characteristics. In general, the more invasive the tumor, the more invasive the treatment received. When studying potential treatment risk factors, it is important to adjust for disease characteristics and other risk factors that are suspected to confer a risk to lymphedema development. Most studies did not report an adjusted RR and the significant associations observed in this meta-analysis may have been confounded by other risk factors.

Conclusions

An increased risk of lymphedema following breast cancer treatment was related to mastectomy (rather than lumpectomy), axillary dissection, radiation therapy, and lymph node status. These findings support the common belief that only treatments which disrupt the follow of lymph through the axilla will lead to the development of lymphedema. Nevertheless, it is important to note that treatments received are dependent on tumor characteristics. Any individual treatment can be administered sequentially or concurrently with other treatment(s). The inability to adjust for other treatments can affect findings and such adjustment was rarely reported in the studies reviewed here. Sentinel node biopsy with short follow-up time post surgery was found to be beneficial compared to axillary dissection. Since this is a relatively new procedure, future research needs to evaluate the long-term effect of SNB.

Table 2.1. Summary Characteristics of Studies Included in a Meta-analysis of Prognostic Risk Factors for Lymphedema

	Number of studies	Range of follow-up
Lymphedema Measurement [a]		
Circumference >1.5 cm difference	2	1 month-29 years
Circumference >2 cm difference	20	3 months-10.5 years
Circumference >2.5 cm difference	4	5 months-109 months
Circumference >5% change	2	Up to 56 months
Circumference >10% change	2	~ 55 months
Circumference to calculate volume	5	6 weeks-13 years
Other Circumference [b]	12	3 months-30 years
Water Displacement	13	12 months-14 years
MFBIA, optoelectronic volometer	2	6 months-2 years
Self-report	17	3 months-6 years+
Clinically Diagnosed [c]	11	3 months-10 years
Unclear/Not Stated	8	14 months-15 years
Study Designs		
Prospective Cohorts	40	6 weeks-25 years
Retrospective Cohorts	43	1 month-30 years
Randomized Controlled Trials	10	1 year-3.3 years
Case-control Studies	5	Not applicable
Location of Study		
United States	31	1 month-30 years
Canada	6	3 months-15 years
Europe [d]	49	63 months-14 years
Asia [d]	3	3 months-10 years
Australia	7	6 weeks-3 years
Middle East [d]	2	6 months-10 years

Source: The original publication is available at http://dx.doi.org/10.1245/s10434-009-0452-2

cm =centimeters; MFBIA= multiple frequency bioelectrical impedance analysis

[a] Comparison either between arms or same arm pre- and post-surgery

[b] Other circumference measures included <3cm mild/slight lymphedema, <4cm mild, >1cm, >3cm, or unclear cut-points

[c] Clinical diagnosis: assessment by clinicians, and medical records

[d] European countries: Austria, Brussels, Denmark, Finland, France, Germany, Greece, Italy, Ireland, Poland, Sweden, Switzerland, The Netherlands, Turkey, United Kingdom, Yugoslavia; Asian countries: India, Japan; Middle Eastern country: Israel

Table 2.2. General Characteristics of Studies Included in a Meta-analysis of Prognostic Risk Factors for Lymphedema

Author	Year	Location of study	Sample size	Risk factor(s)[a]	Lymphedema measurement (definition)	Length of follow-up or year of diagnosis
Circumference (n=47)						
Haines[102]	2007	Australia, Brisbane	193	Mast	Circumference to calculate volume (10% increase pre- versus post-surgery)	6 weeks post-surgery
Langer [103]	2007	Switzerland, 13 centers	651	ADSNB	Circumference (>2cm pre- versus post-surgery or subjective symptoms)	Mean time ~30 months
Graham[104]	2006	Australia, Sydney	91	Rad to Axilla, Chemo	Circumference to calculate volume (>200ml between arms)	Varies patients from 1993-2000
Lee[105]	2006	Australia	61		Circumference (>2cm difference between arms)	NS
Mathew[106]	2006	UK, Gwynedd	506	ADSNB, PN	Circumference (>2cm between arms)	At least 2 years
Schulze [107]	2006	Germany	135	ADSNB, Rad	Circumference (>10%)	~55 months
Soran[52]	2006	US, PA	156	Mast, Rad, PN	Circumference (>2cm swelling in arm)	1990-2000
Wilke[31]	2006	US, 126 institutions	~2000	Rad	Circumference (>2cm pre- versus post-surgery)	6 months
Clark[25]	2005	UK, West Sussex	251	Mast, Rad, Rad to Axilla, PN	Circumference to calculate volume (>20% between arms and diagnosed by physician)	3 years post-surgery
Purushotham [108]	2005	UK, Cambridge	298	ADSNB	Circumference (self-report)	1 year

Table 2.2. Continued

Ronka [109]	2005	Finland, Helsinki	83	ADSNB	Circumference to calculate volume (5-10% increase, pre- vs. post-surgery)	12 months post- surgery
Armer[110]	2004	US, Midwest	100	ADSNB, ADY	Circumference (>2cm between arms)	6/1999-8/1999
Deo[82]	2004	India	299	Rad, Rad to Axilla, Chemo	Circumference (>3cm between arms is moderate lymphedema)	At least 1 year
Ozaslan[100]	2004	Turkey	240	Rad, Chemo, PN,	Circumference (>2cm between arms)	18-43 months
Van der Veen[99]	2004	Brussels	245	Rad, PN	Circumference (>2.5cm between arms)	NS
Golshan[111]	2003	US, IL	125	ADSNB	Circumference (>2cm between arms)	Not Stated
Powell[38] Coen	2003	US, MA	714	ADY, RadA, Chemo, PN	Circumference (>2cm between arms)	10 years
Querci Della[87]	2003	UK	189	Mast, Rad	Circumference (>5% difference between arms)	NS
Albrecht[112]	2002	Germany	502	ADSNB, Rad	Circumference	3 years minimum
Haid[113]	2002	Austria, Feldkirch	197	ADSNB	Circumference (>2cm between arms)	14-60 months
Meric[35]	2002	US, TX	294	ADY, Rad to Axilla, Chemo, PN	Circumference (anywhere <3cm between arm=grade1 lymphedema)	~8 years
Herd-smith[32]	2001	Italy, Florence	1278	Mast, Rad, Chemo, PN	Circumference (>5% difference between arms)	Median follow-up 56 months

Table 2.2. Continued

Hojris[114]	2000	Denmark	84	Rad, Chemo	Circumference to calculate volume (>200ml between arms)	6-13 years
Johansen[86]	2000	Denmark	266	RadA, PN	Circumference (>2cm between arms or receiving therapy for arm edema)	3.5-10.5 years
Schunemann[93, 115]	1998	Germany	5868	Mast, MastR, Rad, PN	Circumference (>2cm between arms)	1972-1995 breast cancer patients
Ferrandez[116]	1996	France	683	Mast	Circumference	Mean follow-up 14 months
Kiel[117]	1996	US, IL	183	PN	Circumference (>1.5cm increase from last exam)	Every 6 months after radiation
Paci[51]	1996	Italy, Florence	238	Mast	Circumference (<4cm is light lymphedema between arms)	5 years
Tasmuth[88]	1996	Finland, Helsinki	93	Mast, PN	Circumference (>2cm between arms)	1 year post-surgery
Keramopoulos[118]	1993	Greece, Athens	104	Mast, Rad, PN	Circumference (>2cm between arms)	At least 3 months post-surgery
Gerber[119]	1992	US, NIH	131	Mast	Circumference (>2cm difference pre and post op arm)	NS
Werner[29]	1991	US, NY	282	ADSNB, Chemo, PN	Circumference (>2.5cm between arms)	7-109 months
Ryttov[120]	1988	Denmark	57	Rad	Circumference (>2.5cm difference between arms)	Surgery: 10/1982-12/31/1983
Borger [121]	1987	The Netherlands	58	PN	Circumference (>2cm between arms)	Median 33 months

Table 2.2. Continued

Delouche[122]	1987	France, Paris	410	ADY	Circumference (>2cm between arms as more than mild lymphedema)	At least 5 years
Pezner[61]	1986	US, CA	74	ADSNB, Rad to Axilla, Chemo	Circumference (>2.5cm between arms)	5-41 months after radiation
Pierquin[123]	1986	Yugoslavia	3030	ADY, Rad	Circumference (>2cm between arms)	Varies, multiple follow-ups
Kuno[124]	1984	Japan	1115	MastR	Circumference (>2cm between arms)	3 months-10 years
Brismar[95]	1983	Sweden, Stockholm	134	MastR, Rad, PN	Circumference (>2cm between arms)	12-18 months
Watson[125]	1963	Canada	590	Rad, PN	Circumference (unclear)	Varies /unclear: patient at clinic from 1960-1961
West[126]	1959	US, NY	104	Rad, PN	Circumference (>1cm =slight lymphedema between arms)	3 months-30 years
Treves[127]	1957	US, NY	768	Rad, PN	Circumference (up to 3 cm is slight lymphedema)	Varies /unclear :Seen 1937-1943
Villasor[128]	1955	US, MD	79	Rad	Circumference (>1cm between arms)	Not stated
Daland[85]	1950	US, Boston	90	PN	Circumference	2.5 months -25 years post-surgery
Lobb[129]	1949	US, WA	51	Rad, PN	Circumference (1.6+cm between arms)	1 month -29 years
MacDonald[130]	1948	US, CA	55	PN	Circumference (>10% increase from pre-surgical arm at any segments)	1944 +

Table 2.2. Continued

Holman[131]	1944	US, NY	100	Rad, PN	Circumference (<3cm is lowest category or swelling)	6 months -11 years
Water displacement, multiple frequency bioelectrical impedance analysis (MFBIA), or optoelectronic volometer (n=15)						
Hayes[132]	2005	Australia, Brisbane	176	Rad, Chemo	MFBIA (3 Standard Deviation above normal between arms)	6 months after diagnosis
Sener[20]	2004	US, IL	420	ADSNB	Water Displacement (anywhere <20% difference between arms=mild)	Median time=24 months
Nagel[97]	2003	The Netherlands	106	Rad	Water Displacement (>200ml between arms)	1995-1996 years of diagnosis
Beaulac[6]	2002	US, MA	151	Mast, Rad, Chemo	Water Displacement (>200ml between arms)	Treated between 1986-2000
Box[50]	2002	Australia, Brisbane	57	Rad	Water Displacement (>200ml difference between arms)	24 months post-surgery
Kwan[73]	2002	Canada, Vancouver	112	ADY, Rad to Axilla	Water Displacement (>200ml between arms)	Treated 1993-1997
Duff[89]	2001	Ireland	100	Mast	Optoelectronic volometer (>200ml difference between arms)	6 months to 2 years
Johansson[133]	2001	Sweden	61	Rad, Rad to Axilla	Water displacement (>10% between arms)	2 years
Edwards[27]	2000	Australia	201	Mast, ADSNB	Water Displacement (>10% between arms)	Within, 3 years, diagnosed 1994-1996
Tengrup[134]	2000	Sweden	110	Rad	Water Displacement (>10% in relation to pre-operative volume)	Since 1992
Thompson[135]	1995	Australia, Edinburgh	121	ADSNB ,Rad	Water Displacement (>200ml between arms)	At least 12 months after radiation

Table 2.2. Continued

Hladiuk[136]	1992	Canada, Alberta	57	Rad, PN	Water Displacement (>10% between arms)	12 months post-surgery
Segerstrom[137]	1992	Sweden	136	Rad, Rad to Axilla	Water Displacement (>150ml between arms)	2 years
Swedborg[138]	1981	Sweden	175	Rad	Water Displacement (>10% between arms)	3/1971-10/1976
Nikkanen[139]	1978	Finland	76	MastR	Water Displacement (>150cc between arms)	4.5-14 years
Self-report (n=17)						
Bani[41]	2007	Germany	742	Mast, Rad, Chemo, PN	Self-report	Average follow-up 4.5 years since disease
Paskett[42]	2007	US, 4 centers	622	Mast, ADSNB, ADY, Rad, Chemo	Self-report	3 years
Mansel [34]	2006	UK	1031	ADSNB	Self-report	11/1999-7/2003
Ridner [92]	2006	US, southeastern	149	Mast, Rad, Chemo	Self report	NS
Barranger[140]	2005	France	115	ADSNB	Self-report	Mean time ~20 months
Karki[141]	2005	Finland, Satakunta	110	Mast	Self-report	12 months post-surgery
Blanchard[142]	2003	US, MN	776	ADSNB	Self-report	At least 1 year
Geller[62]	2003	US, Vermont	145	Mast, ADY, Rad, Chemo, PN,	Self-report	6-21 months
Schijven[98]	2003	The Netherlands	393	ADSNB, Rad, Rad to Axilla	Self-report	Within 3 years

Table 2.2. Continued

Yap [143]	2003	Canada	370	ADY, Rad	Self-report	Average 3.3 years
Swenson[144]	2002	US, MN	211	Mast, ADSNB	Self-report	1 year
Schrenk[145]	2000	Austria	70	ADSNB	Self-report	4-28 months post-surgery
Mortimer[36]	1996	UK	1151	Mast, Rad	Self-report	Questionnaire sent 6/1991
Maunsell[146]	1993	Canada	223	Mast, ADY	Self-report	3 months post-surgery
Sarin [147]	1993	India, Bombay	289	ADY	Self-report	Median ~37 months
Aitken[148]	1989	UK, Edinburgh	94	ADSNB, Rad, PN	Self-report	Median 5-6 years
Kissin[149]	1986	UK	200	ADSNB, ADY, Rad	Self-report	At least 1 year
Clinically diagnosed (n=11)						
Hinrichs[23]	2004	US, NY	105	Rad, Chemo	Clinically diagnosed (treating physician)	Treated:1/1/1995-4/20/2001
Johansson [49]	2002	Sweden	142	Mast, Rad, Rad to Axilla, Chemo	Clinically diagnosed (medical record)	Edema notes 1/1997-6/1998 *mailed Questionnaire 2/1999
Suneson[22]	1996	Sweden	362	PN	Clinically diagnosed (medical record)	Diagnosed: 1983 AND 1988
Cabanes[150]	1992	France, Institut Curie	658	ADY	Clinically diagnosed (physician)	Entered into trial 7/1983-7/1987
Hoe[151]	1992	UK	118	Mast, PN	Clinically diagnosed (medical record)	NS
Senofsky[152]	1991	US, FL	278	Rad, Rad to Axilla	Clinically diagnosed (medical record)	Surgery: 1975-1990
Dewar[153]	1987	France	592	Rad	Clinically diagnosed	Mean follow-up 78 months

Table 2.2. Continued

Larson[154]	1986	US, MA	475	ADSNB, ADY, Rad to Axilla, Chemo, PN	Clinically diagnosed (radiologist)	6 years
Mozes[155]	1982	Israel	226	MastR, Rad	Clinically diagnosed (examination)	Surgery: 1960-1977
Feigenberg[90]	1977	Israel	160	MastR, Rad	Clinically diagnosed (medical record)	6 months-10 years
Fitts[156]	1954	US, PA	130	Rad, PN	Clinically diagnosed	3-5 months interval till 1957
Unclear (n=8)						
Kopanski[157]	2003	Poland	97	Rad, PN	Unclear	NS
Giuliano[158]	2000	US, CA	125	ADSNB	Unclear	Unclear, multiple follow-up exams
Ragaz[159]	1997	Canada, Vancouver	318	Rad	Unclear	15 years
Pierquin[160]	1991	France, Creteil	245	ADY	Unclear	Treated 1961-1974
Benson[161]	1986	UK, Yorkshire	960	ADSNB	Unclear	2-7 years
Veronesi[94]	1981	Italy	701	Mast	Unclear	6/1973-1976
Say[162]	1974	US, MO	1531	MastR, Rad	Unclear	Treated: 1940-1965
Nicholson[163]	1948	US, GA	283	MastR	Unclear	At least 5 years

Source: The original publication is available at http://dx.doi.org/10.1245/s10434-009-0452-2

[a] Mast=Mastectomy vs. Lumpectomy or Partial Mastectomy, MastR= Radical Mastectomy versus Mastectomy, ADSNB=Axillary dissection vs. Sentinel Node Biopsy, ADY=Axillary dissection yes vs. no, Rad= Radiation therapy yes vs. no, Rad to Axilla= Radiation to axilla yes vs. no, Chemo=chemotherapy yes vs. no, PN=positive nodes yes vs. no

Table 2.3. Pooled Risk Ratios among 98 Studies of Secondary Lymphedema of the Arm and Reported Prognostic Factors[a]

	All studies[b]				Non self-report[c]				Self-report			
	Number of studies	Homo-geneity p-value	RR[d]	95% CI	Number of studies	Homo-geneity p-value	RR[d]	95% CI	Number of studies	Homo-geneity p-value	RR[d]	95% CI
Surgical Procedures												
Lumpectomy Mastectomy	25	<0.0001	ref 1.42	- 1.15-1.76	16	<0.0001	ref 1.42	- 1.08-1.87	8	0.0127	ref 1.34	- 0.93-1.93
Other Mastectomy Radical Mastectomy	8	0.0208	ref 3.28	- 2.35-4.59	6	0.2194	ref 2.66	- 2.01-3.52	0			
Sentinel Node Biopsy (SNB) Axillary Dissection	22	<0.0001	ref 3.07	- 2.20-4.29	14	0.0002	ref 2.99	- 1.89-4.74	7	0.0024	ref 3.54	- 2.06-6.08
No Axillary Dissection Axillary Dissection	13	0.0600	ref 3.47	- 2.34-5.15	8	0.0467	ref 3.19	- 1.99-5.10	4	0.2200	ref 3.50	- 1.28-9.56
No Positive Nodes Positive Nodes	32	0.0008	ref 1.54	- 1.32-1.80	28	0.0054	ref 1.59	- 1.35-1.86	3	0.0805	ref 1.41	- 0.79-2.54
Non-Surgical Procedures												
No Radiation Therapy Radiation Therapy	49	<0.0001	ref 1.92	- 1.61-2.28	37	<0.0001	ref 1.91	- 1.54-2.37	9	0.2232	ref 2.13	- 1.68-2.69
No Axilla Radiation Therapy Axilla Radiation Therapy	14	0.0283	ref 2.97	- 2.06-4.28	13	0.0198	ref 3.06	- 2.02-4.63	1	n.a.	ref 2.44	- 1.31-4.52

Table 2.3 Continued

No Chemotherapy	18	0.3923	ref	-	14	0.5486	ref	-	4	0.1027	ref	-
Chemotherapy			1.11	0.95-1.31			1.10	0.90-1.35			1.29	0.86-1.94

Source: The original publication is available at http://dx.doi.org/10.1245/s10434-009-0452-2

ref=reference group

[a] Based on a random-effects model

[b] Includes 8 studies where lymphedema measurement was unknown/not stated

[c] Restricted to lymphedema measured via circumference differences, water displacement, multiple frequency bioelectrical impedance analysis, optoelectronic volometer, clinical diagnosis (medical records, assessment by clinicians)

[d] The RR that adjusted for the most number of confounders was used

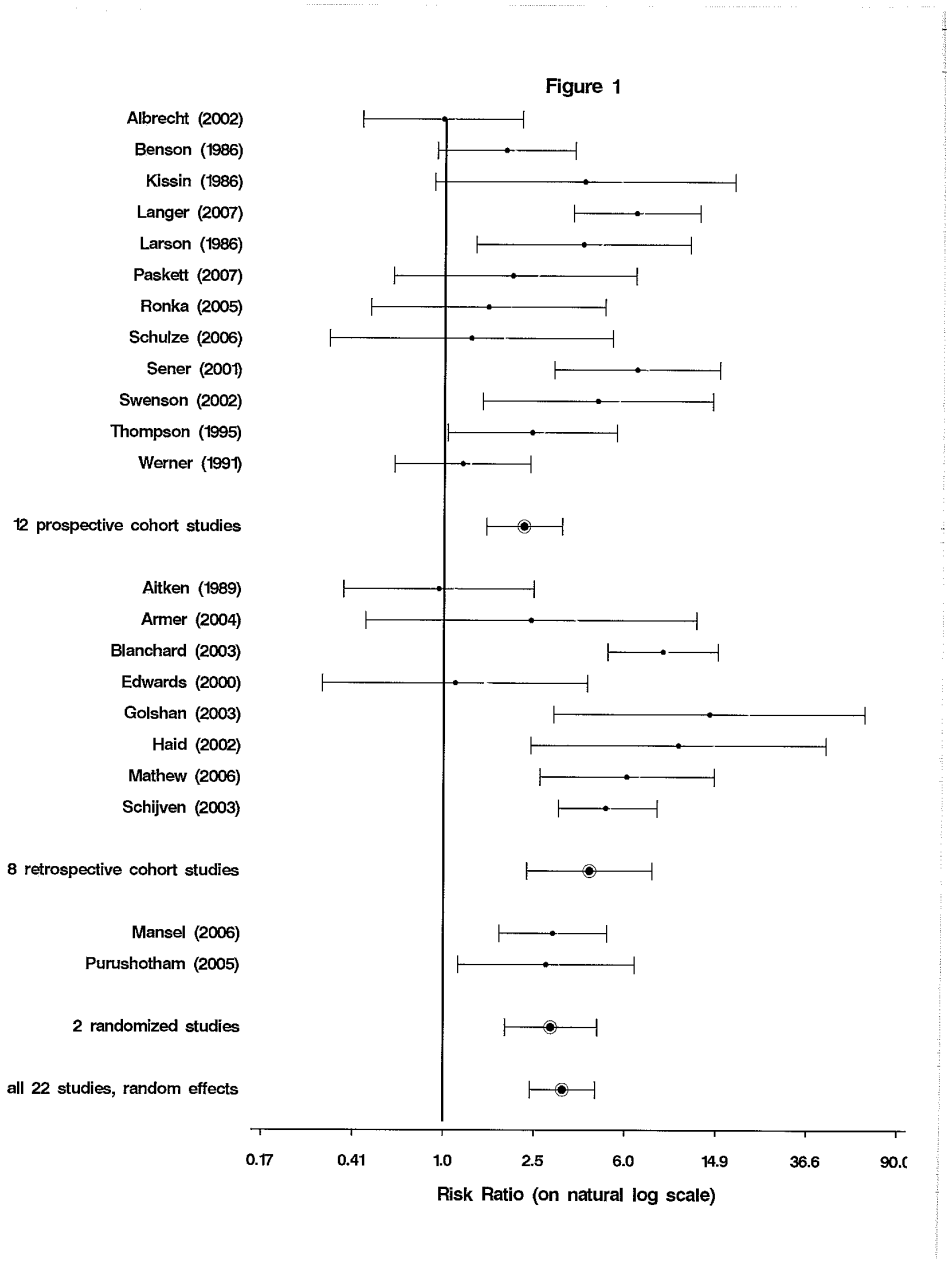


Figure 2.1. Risk ratio (RR) and 95% confidence intervals for lymphedema of the arm (following breast cancer) when axillary dissection was compared to sentinel node biopsy for the 22 studies sorted by first author and stratified by study design, along with the overall pooled estimate based on a random-effects model.

Source: The original publication is available at http://dx.doi.org/10.1245/s10434-009-0452-2

CHAPTER 3: A META-ANALYSIS OF PERSONAL RISK FACTORS FOR THE DEVELOPMENT OF LYMPHEDEMA AMONG BREAST CANCER SURVIVORS

Summary of Findings

Background: Lymphedema is a serious complication resulting from breast cancer treatments. Recent research has suggested that individual susceptibility to the development of lymphedema may be modified by factors such as body mass index (BMI) and physical activity. *Methods:* A PubMed search was conducted through January 2010 to locate articles on factors related to arm lymphedema among breast cancer women. The random effects model was used to estimate pooled risk ratios (RRs) and 95% confidence intervals (95% CI) for both dichotomous and dose-response variables. *Results:* Fifty-two independent studies were identified and analyzed where at least one factor of interest was reported. When the factors were dichotomized, elevated risks of arm lymphedema were consistently seen for obesity (RR=2.46, 95% CI: 1.37, 4.42), lower education (RR=1.35, 95% CI: 1.12, 1.63), presence of co-morbidity (RR=1.88, 95% CI: 1.41, 2.50), and injury to arm (RR=1.87, 95% CI: 1.04, 3.34). Similar increases in risk were seen for obesity and education when analyzed using dose-response analysis. *Conclusions:* No significant association was seen with physical activity. Obesity, lower education, co-morbidity, and injury to arm are associated with the development of lymphedema secondary to breast cancer. Modifiable risk factors such as BMI may delay or prevent the onset of arm lymphedema.

Introduction

Breast cancer is the most prevalent cancer affecting women in the United States.[2] In 2010, an estimated 207,090 women will be diagnosed with breast cancer, accounting for 28% of all newly diagnosed female cancers (excluding non-melanotic skin cancers)

with 90% of these women surviving five years.[2] Lymphedema of the arm (here referred to as lymphedema) is a treatment complication that affects about 20% of breast cancer survivors. [80, 81] As survivorship increases, quality of life issues, including lymphedema become more prominent.[28]

Some treatments are consistently linked to lymphedema including radiation therapy and axillary dissection.[164] However, among women with similar treatments, it is unclear why some develop lymphedema and others do not. It is possible that modifiable factors, such as body mass index (BMI) and physical activity, may play a crucial role in the prevention of lymphedema.

The purpose of this study was to conduct a detailed meta-analysis to examine the strength and consistency of observed associations between lymphedema secondary to breast cancer diagnosis and personal risk factors including BMI, physical activity, dominant side, socio-demographic factors, and related diseases that have been reported in the literature.

Methods

Literature Search

A widespread search was performed in PubMed using MeSH headings and keywords to seek out articles published between 1950 and January 2010. The MeSH headings and keywords used in this search included breast cancer, lymphedema, BMI, physical activity, age, education, marital status, co-morbidity, infection, injury to arm, and dominant hand. Relevant and review articles were identified and their references examined for additional studies. Original articles that reported at least one factor of interest were considered for inclusion in this meta-analysis.

Data Abstractions

Data were abstracted for factors of interest, along with study design, study location, and method of lymphedema measurement. Study designs included prospective and retrospective cohort studies, randomized controlled trials and case-control studies. Studies were conducted in global locations. Lymphedema measurement refers to the technique used to determine the presence or absence of lymphedema and included: arm circumference (centimeters), water displacement (volume), multiple frequency bioelectrical impedance analysis (MFBIA), clinical diagnosis (including medical records), and self-report. The data abstracted included case and control distribution by each risk factor along with reported risk ratios (RR) and confidence intervals (CI). Each study was double-checked for data entry errors. Factors associated with lymphedema included age, education, marital status, co-morbidity, injury to arm, infection, BMI, physical activity, and dominant hand. Modifiable factors were BMI and physical activity. The risk ratio that adjusted for the most confounders was recorded and pooled. This was done making the assumption that the original studies properly adjusted for confounders within their study. Meta-analysis methods for pooling reported risk ratios make this assumption.

If available, the risk ratios and the 95% confidence intervals were abstracted from studies. Otherwise, the crude risk ratios and 95% confidence intervals were calculated from available data. The 95% confidence intervals were used to calculate the variances. The pooled risk ratio was calculated from the natural log of the risk ratios and their variances. A risk ratio of 1.0 was assigned to studies[28, 76, 111, 128] that reported in the text no association between a factor of interest and lymphedema; the variance was estimated based on the number of subjects. For continuous or multi-level variables, the dose-response method was used to look for a linear effect.[165]

Exclusion Criteria

Articles with only lymphedema cases were excluded from the meta-analysis (n=8). Additionally, articles that did not report a risk ratio and 95% confidence interval or provide adequate information to determine the risk ratio and its variance were excluded (n=8). Articles with identical or overlapping study populations were grouped together to avoid duplication or over-weighting of their results (n=2).[92, 166]

Statistical Analysis

Random-effects models and fixed-effects models were used to estimate the pooled risk ratio. The random-effects model was emphasized in this paper because heterogeneity is a concern. This model assumes that a random selection of studies was drawn from a comprehensive pool of studies. Hence this model is more conservative and accounts for variations between studies.[83, 84]

Heterogeneity

Statistical tests for homogeneity were carried out to determine if the effect found was consistent across studies. The Cochran Q was used to assess the presence of heterogeneity in dichotomous analyses. For linear dose response effect, heterogeneity was estimated using the "I squared" (variation of Q) statistic.[167] In an effort to account for heterogeneity, each factor was stratified by study design, location and sample size when 3 or more studies were available to pool. Determination of lymphedema was also stratified by self-reported and non-self-reported (circumference, water displacement, MFBIA, and clinical diagnosis) cases.

Dose-response

In dose-response analysis, the categories were fitted to a log-linear model while correcting for correlations within studies. The mean for each category was estimated using the mid-point of the range. National Health and Nutrition Examination Survey descriptive data were used to set the lower and upper limits for BMI midpoint calculation. It was thought that 95% of the population would have a BMI between 15 and 50, thus the mid-point for the lowest category was base calculated between the upper bound and 15; whereas the midpoint for the highest category was calculated between the reported lower bound and 50. Due to lack of a reported means for each category and a lack of reported upper and lower bounds, these estimates provided the best estimate of the mean.

Dichotomous Response

For dichotomous BMI analyses, a BMI of ≥30 (obese) was compared to a BMI of <30.[168] Studies that used body surface area, weight in pounds, or only looked at BMI≥25 were not included in the dichotomous BMI analyses.[169, 170] Level of physical activity referred to both whole and targeted body parts. Targeted body parts included arm, hand, and pectoral muscle. Physical activity achieved through traditional exercise or therapy was included in the physical activity analyses.

For dichotomous age analyses, comparison was made between an age≥60 and age < 60. We chose 60 years of age because most studies reported data that allowed this comparison to be done. Studies that only made comparisons for age≥50 or age≥55 were excluded from the dichotomous age analyses.[117] Survivors with a high school education or less were compared to those with at least a high school education, and married or living together was compared to all other marital status.

Studies reported co-morbid conditions in various ways. Some studies only looked at specific co-morbid conditions such as hypertension and/or diabetes, others only looked at the presence of any co-morbidity (e.g. hypertension, diabetes, osteoporosis, arthritis), and the remainder looked at both specific conditions and the presence of any co-morbidity. Risk ratios were pooled for the presence of any co-morbidity (as provided by individual studies), hypertension, and diabetes. Infection refers to wound infection, including post-surgical infections. Studies that did not specifically state wound infection or post-surgical infections were excluded from analyses because we were unable to determine the source of such infections. Injury to the arm was defined as trauma or puncture to the arm and dominant hand refers to treatment applied to the subject's dominant side.

The presence of publication bias was evaluated qualitatively using a funnel plot.

Results

We included 52 independent study populations that evaluated the impact of at least one factor on lymphedema.[6, 23, 25, 28, 29, 31, 32, 38, 41, 42, 49-52, 58-60, 62, 65, 72, 82, 92, 99, 100, 102, 104, 105, 111, 114, 116, 118, 125, 128-130, 132, 137, 139, 143, 156, 157, 171-185] Cohort studies dominated this meta-analysis (n=44), and over 55% of the studies were carried out in North America. Only 8 studies (15%) relied solely on self-reported data to determine the presence of lymphedema. Circumference measurement, defined as a difference of > 2 cm between arms (or pre- vs. post surgery in one arm), was the method of choice for classifying lymphedema (Table 3.1). Follow-up varied from study to study. Some studies followed their subjects individually (different observation windows), while others were followed in a group (same observation window). Table 3.2 provides a detailed description of each study: year results published, study design, location of study, sample size, risk factors reported, definition and measurement of lymphedema, and the length of follow-up. Table 3.3 depicts studies not included in data analysis due to exclusion criteria.

Funnel plots were constructed for each risk factor of interest, plotting the risk ratios against their standard errors. No clear evidence of publication bias was seen (data not shown).

Dichotomous Response

Table 3.4 shows the pooled risk of lymphedema following breast cancer diagnosis, looking at modifiable factors (BMI and physical activity), socio-demographic factors (age, education, and marital status), disease/injuries, and dominant side surgery. Obesity (BMI>30) was found to be positively associated with lymphedema (RR=2.46, 95% CI: 1.37, 4.42). An association with lymphedema was also seen for low education (RR =1.35, 95% CI: 1.12, 1.63), the presence of any co-morbid condition (e.g. hypertension, diabetes, cardiovascular disease, osteoporosis, arthritis, RR=1.88, 95% CI: 1.41, 2.50), and injury to the arm (RR=1.87, 95% CI: 1.04, 3.34). Wound infection was marginally associated with arm lymphedema (RR= 2.6, 95% CI: 0.95, 4.68). No association with lymphedema was found with physical activity, age >60, marital status, hypertension, diabetes, and dominant hand.

When studies were stratified by study design, prospective studies found age>60 to be associated with arm lymphedema (RR=1.31, 95% CI: 1.04, 1.65).For hypertension, sub-analysis for non-self-reported measurements (RR=1.42, 95% CI: 1.04, 1.92) and large sample size (RR=1.99, 95% CI: 1.45, 2.73) showed a positive association with lymphedema. Furthermore, no association was observed when only arm specific activities were pooled for physical activity (not shown). Stratification by study design, location, and determination of lymphedema reduced some heterogeneity; however no distinct pattern of reduction was observed (data not shown).

Linear Dose-response

Dose-response analyses were examined when 3 or more studies reported dose data including BMI, age, or years of education. BMI showed a linear association (increase of 5 BMI units) with lymphedema (RR=1.40, 95% CI: 1.23, 1.59) (Table 3.5). When stratified by arm measurement, non-self-reported measurements remained significantly elevated. For a 4-year decrease in education, the risk ratio for lymphedema increased by 1.28 (95% CI: 1.08, 1.51). The pooled estimate for an increase in 10 years in age was not associated with lymphedema. However, an increased association between age and lymphedema was seen when only studies with more than 200 subjects were pooled (RR=1.25, 95% CI: 1.03, 1.52). Studies were found to be heterogeneous for both BMI and age.

Discussion

This meta-analysis found obesity, low education, injury, and co-morbidity to be associated with the development of lymphedema of the arm after breast cancer diagnosis. Heterogeneity, attributed to diverse study methods, was a concern.

Modifiable Factors

Our dose response analysis showed risk to increase with each increasing unit of BMI, suggesting a linear correlation between BMI and risk of developing arm lymphedema The pooled analyses for obesity (BMI >30) also showed a large increase in risk of lymphedema. Obesity can lead to delays in healing, promote infections and lymphatic obstruction.[15, 52, 57] It can also be an indicator for an unhealthy lifestyle. Obesity affects treatment for breast cancer, since it can be more difficult to operate on an obese individual.[186] Moreover, higher dosages of radiation/chemotherapy may be needed for obese individuals due to higher body surface area.[35] Obesity also increases the risk of

developing other co-morbidities.[187, 188] Co-morbidities can independently compound the association with lymphedema.[65, 82] Only 2 studies [58], [100] that looked at BMI adjusted for co-morbidity. Because obesity is intricately linked to many other factors, it is difficult to tell if obesity directly contributes to the development of lymphedema or if the observed effect is confounded by other factors. Non-self-reported (objective) lymphedema measurement is less subject to bias, and shows an appreciable risk for developing lymphedema with increasing BMI in this study.

Physical activity levels were not associated with lymphedema. The lack of an association observed between physical activity and lymphedema may be explained by the varying methods of physical activity measurement. Although most studies looked at overall physical activity level, a number of studies looked at physical activities targeted to specific body parts (arm, hand, pectoral muscle). Little to no change with the pooled risk ratio was seen when only activities pertaining to the arms/hand were pooled (data not shown). An inverse association with physical activity was expected because muscle contractions are necessary for propulsion of lymph fluid through the lymphatic system.[47] One study suggested that exercises done post-operatively may help develop collateral pathways to further prevent lymphedema.[59] Adding to this diversity in physical activity measurement, some of the physical activities reported from studies are part of breast cancer rehabilitation or therapy. Physical activity from therapy, rehabilitation, or strength training exercises after breast cancer surgery showed a protective association with lymphedema (RR=0.61, 95% CI: 0.39, 0.95). Further research looking specifically at the impact of arm activity on lymphedema may clarify this association.

Socio-demographic Factors

While an overall association with age was not seen, prospective cohort studies (n=4) found older age to be significantly associated with lymphedema. Older women may have a lower capability to form collateral pathways for lymph flow.[177] While

spousal support or increase amount of housework may be linked to being married and are hypothesized to have an effect on lymphedema,[42, 175] marital status was not associated with lymphedema in this meta-analysis.

Women with 12 or less years of education (high school graduate) were found to have an increased risk of developing lymphedema. It is possible that women with a higher education level are more aware of the consequences of developing lymphedema and took additional precaution to prevent its development. Additionally, subjects with lower education may have fewer resources available to them. This may have contributed to this difference in risk.

Co-morbid Conditions

The presence of co-morbidity, studies reporting the risk ratio for any co-morbidity, was found to increase the risk of lymphedema. Co-morbidities, such as congestive heart failure, emphysema, and chronic bronchitis can affect fluid balance in the body, hence aggravating or promoting arm lymphedema in breast cancer survivors. Although the overall risk ratios for hypertension and diabetes were not associated with lymphedema, an association was observed with studies stratified into non-self-report measurements and large sample sizes. Hypertension can promote lymphedema by forcing additional fluid out of capillaries. That, along with an impaired lymphatic system can lead to an accumulation of lymph fluid in the arm.[62] Anti-hypertensive treatments may have confounded the overall pooled risk ratio between hypertension and lymphedema. Geller et al.[62] found that taking anti-hypertensive medication is protective of lymphedema.[62] Hypertension that is controlled by medication may have masked the risk observe between hypertension and lymphedema.

This meta-analysis observed a borderline association between lymphedema and wound/post-operation infections. Caution must be taken when interpreting these results because it is not clear if the infection poses a risk for developing lymphedema or if

having lymphedema increases the chance of infection.[137] Sub-analysis for infection found that studies conducted outside of US and Canada showed an increased risk for developing lymphedema from wound or post-operation infection. The low risk of postoperative infection in hospitals in the US and Canada may have made it difficult to detect any such association.

Injury was found to increase the risk of lymphedema. Van der Veen et al.[99] stated that burns or punctures from medical procedures can damage the lymphatic system, thus increasing the lymph load. Both infection and injury can cause inflammation that can increase accumulation of lymph fluid in the arm. However, recall bias is a concern for both infection and injury as women with lymphedema may be more likely to recall infections or injuries to their arm than women without lymphedema.[28, 178]

Dominant Hand

Treatment applied to the dominant side of subject was not associated with lymphedema. Hayes et al.[132] theorized that treatment to the dominant side may actually be protective of lymphedema. The more frequent use of the dominant arm may have prevented lymphedema from developing. However, this effect was not seen in this meta-analysis. It is possible that breast cancer survivors, increasingly aware of the consequences of lymphedema, are extra cautious with the use of their arm after treatments.

Strengths

Meta-analyses overcome several limitations of individual studies. About half of the studies presented in Table 3.2 had less than 200 subjects and may have lacked the power to detect clinically relevant differences. Pooling multiple studies increases the power to detect associations. It also provides a way to investigate conflicting results from independent studies. Review articles may be qualitative and subjective whereas

meta-analyses are a quantitative way to pool study results, thus are more objective and may avoid personal bias. Therefore, it efficiently updates researchers by integrating and condensing material.

Limitations

Meta-analyses cannot overcome the limitations of original studies such as poor study design, selection bias, measurement errors, inadequate data collections, or lack of appropriate modeling of confounding. Publication bias is always a potential issue with meta-analyses. It is likely that publication bias was minimized in this study because most studies identified analyzed multiple factors of interest. This allowed factors that showed no association to be published along side of other factors that may or may not exhibit an association with lymphedema. However, some studies may only report factors with the strongest associations. Funnel plots did not show a clear indication of publication bias.

Conclusions

Many studies identified did not adjust for what we might consider relevant confounders and some only presented crude data. Since breast cancer treatments are linked to disease and personal status, potential confounders such as type of breast cancer surgery, axillary dissection, radiation, and BMI should be considered. While several studies measured these factors and may have examined them as potential confounders in the data we pooled, it is unlikely that all studies did so, thus properly adjusting for potential confounders. Futures studies need to account for potential confounders when estimating risk ratio for lymphedema. In conclusion, this meta-analysis found that high BMI, lower educational level, presence of any co-morbidity, injury and wound infection were associated with the development of lymphedema. These data may suggest that decreasing BMI and avoiding infection or injury to the arm may decrease arm lymphedema risk.

Table 3.1. Summary of 52 Studies in a Meta-Analysis of Risk Factors for Lymphedema

	Number of studies	Range of follow-up
Lymphedema measurement [a]		
Circumference >2 cm difference	13	3 month – 13 years
Circumference >2.5 cm difference	3	5 months – 109 months
Circumference >3 cm difference	2	no follow-up time stated
Circumference to calculate volume	3	6 weeks – 13 years
Other Circumference [b]	6	1 month – 29 years
Water displacement	6	20 months – 14 years
MFBIA, optoelectronic volometer	1	6 months
Self-report	8	6 months- 8 years
Others (examined/noted/medical record)	7	NS (no range)
Unclear	1	NS (no range)
Combination [c]	2	3 years – 20 years
Study designs		
Prospective cohorts	18	6 weeks – 13 years
Retrospective cohorts	26	1 month - 29 years
Randomized controlled trials	2	NS (no range)
Case-control studies	6	NS (no range)
Location of study		
United States	26	1 month – 29 years
Canada	3	20 months – 3.3 years
Europe [d]	15	3 months – 14 years
Asia [d]	3	1 year - 2 years
Australia	5	6 weeks – 2 years

MFBIA= multiple frequency bioelectrical impedance analysis; cm =centimeters

[a] Comparison either between arms or same arm pre- and post-surgery

[b] Other circumference measures included <4 light lymphedema, >5%, >1.6cm or >1cm

[c] Self-report and objective methods (clinical diagnosis, circumference >0.5 inch) used

[d] European countries: Brussels, Denmark, Finland, France, Germany, Greece, Italy, Poland, Sweden, The Netherlands, Turkey, United Kingdom; Asian countries: Hong Kong, India, Korea

Table 3.2. Analytical Study of Risk Factors and Secondary Lymphedema

Author	Year	Location of study	Sample Size	Risk Factor(s) reported	Lymphedema measurement/ definition	Length of Follow-up or year of diagnosis	Study Design
Armer[171]	2005	US, Midwest	100	age(<60, 60+)	Circumference/ >2cm between arms	Over 3 months	Retrospective
Bani[41]	2007	Germany	742	< high school, years of education, marital status	Self-report	Average follow up 4.5 years since breast cancer diagnosis	Retrospective
Beaulac[6]	2002	US, MA	151	injury	Water Displacement/ >200ml between arms	Treated between 1986-2000	Retrospective
Berlin[172]	1999	Sweden, Vaxjo	226	age(<60, 60+), age(cat)	Water Displacement/ >100ml between arms (unilateral surgery), pre- vs. post-surgery (bilateral surgery)	Within 5 years	Prospective
Box[50]	2002	Australia, Brisbane	57	BMI(cont), ex(arm), age(cont), infect, dominant hand	Water Displacement/ >200ml between arms	24 months post-surgery	Prospective
Clark[25]	2005	UK, West Sussex	251	age(<60, 60+), injury, dominant hand	Circumference to calculate volume/ >20% between arms or Clinical diagnosis (health care professional)	3 years post-surgery	Prospective
Clough-Gorr[173]	2009	US	400	BMI(<30, 30+), ex(body) , age(cat), years of education, marital status, co-morbid(any)	Self-report	Up to 87 months post-surgery	Prospective

Table 3.2. Continued

Deo[82]	2004	India	299	Co-morbid(any)	Circumference/ >3cm between arms is moderate lymphedema	At least 1 year	Retrospective
Ferrandez[116]	1996	France	683	BMI(<30, 30+), infection, dominant hand	Circumference	Mean follow up 14 months	Retrospective
Fitts[156]	1954	US, PA	130	BMI(<30, 30+), infection	Clinical diagnosis (examination)	3-5 months interval until 1957	Prospective
Geller[62]	2003	US, VT	145	BMI(<30, 30+), BMI(cat), < high school, years of education, marital status, co-morbid(hypertension)	Self-report	6-21 months	Prospective
Golshan[111]	2003	US, IL	125	dom	Circumference/ >2cm between arms	NS	Retrospective
Graham[104]	2006	Australia, Sydney	91	BMI(cont), age(cont), dominant hand	Circumference to calculate volume/ >200ml between arm	From 1993-2000	Retrospective
Haines[102]	2007	Australia, Brisbane	193	age(cont), infection, dominant hand	Circumference to calculate volume/ 10% increase pre-vs. post-surgery	6 weeks post-surgery	Prospective
Hayes[174]	2008b	US	2579	age(<58, 58+)	Clinical diagnosis (radiation oncologist)	Treated: 1950-2005	Retrospective
Hayes[132, 175]	2005, 2008	Australia, Brisbane	176	ex(body), age(cont), < high school, years of education, marital status, injury, dominant hand	MFBIA/ 3 Standard Deviation above normal between arms	6 months after diagnosis	Prospective
Helyer[176]	2009	Canada, Toronto	137	BMI(cont)	Water Displacement/ >200ml	Median follow up 20 months	Prospective
Herd-smith[32]	2001	Italy, Florence	1278	age(cat)	Circumference/ >5% between arms	Median follow up 56 months	Prospective

Table 3.2. Continued

Hinrichs[23]	2004	US, NY	105	BMI(<30, 30+), infection	Clinical diagnosis (noted by treating physician)	Treated:1/1/1995-4/20/2001	Retrospective
Hojris[114]	2000	Denmark	84	BMI(<30, 30+), age(cont)	Circumference to calculate volume/ >200ml between arms	6-13 years	Prospective
Johansson[49]	2002	Sweden	142	BMI(<30, 30+), < high school, marital status, infect, dominant hand	Clinical diagnosis (medical record)	Edema noted 1/1997-6/1998 *mailed questionnaire 2/1999	Case-Control
Keramopoulos[118]	1993	Greece, Athens	104	age(<60, 60+), age(cat)	Circumference/ >2cm between arm	At least 3 months post-surgery	Retrospective
Kopanski[157]	2003	Poland	97	BMI(<30, 30+), BMI(cat)	Unclear	NS	Case-Control
Lee[105]	2006	Australia	61	ex(body)	Circumference/ >2cm between arms	NS	Randomized Controlled Trials
Lobb[129]	1949	US, WA	51	infection	Circumference/ >1.6 cm between arm	1 month-29 years	Retrospective
MacDonald[130]	1948	US, CA	55	BMI(cat)	Clinical diagnosis (medical record)	1944 +	Retrospective
Mak[177]	2008	Hong Kong	202	BMI(cont), ex(arm), age(cont), < high school, marital status, co-morbid(hypertension), co-morbid(diabetes), co-morbid(any), injury, dominant hand	Circumference/ >3cm between arms	Recruited: 5/2004-12/2005	Case-Control
Mclaughlin[178]	2008	US, NY	936	injury, dominant hand	Circumference/ >2cm between arms	3-8 years post-surgery	Prospective

Table 3.2. Continued

Meeske[58]	2008	US. CA	494	BMI(<30, 30+), BMI(cat), ex(body), age(cat), co-morbid(hypertension), co-morbid(diabetes)	Self-report	Average 4 years after diagnosis	Prospective
Nikkanen[139]	1978	Finland	76	BMI(<29, 29+),	Water Displacement/ >150cc between arms	4.5-14 years	Retrospective
Oliveri[179]	2008	US	245	age(<60, 60+), age(cat), < high school, years of education, marital status	Circumference/ >2cm between arms	12 years	Retrospective
Ozaslan[100]	2004	Turkey	240	BMI(cat), age(<60, 60+), age(cat), co-morbid(hypertension), co-morbid(diabetes)	Circumference/ >2cm between arms	18-43 months	Retrospective
Paci[51]	1996	Italy, Florence	238	ex(arm)	Circumference/ <4cm is light lymphedema between arms	5 years	Retrospective
Park[59]	2008	Korea	450	ex(body), age(cat), < high school, years of education, marital status	Circumference/ >2cm between arms	12-24 months	Retrospective
Paskett[42]	2007	US, 4 centers	622	BMI(<30, 30+), ex(body), agec, < high school, marital status	Self-report	3 years	Prospective
Petrek[28]	2001	US, NY	211	BMI(<30, 30+), ex(arm), < high school, injury	Circumference/ >0.5 inch between arms or Self-report (arm swelling or heaviness)	20 years	Retrospective
Pezner[180]	1986	US, CA	74	age(<60, 60+)	Circumference/ >2.5cm between arms	5-41 months after radiation	Retrospective

Table 3.2. Continued

Powell[38]	2003	US, MA	714	age(<60, 60+)	Circumference/ >2cm between arms	10 years	Prospective
Ridner[60, 72, 92, 181]	2005, 2006, 2008	US, Southeastern	149	BMI(<30, 30+), < high school, years of education, marital status, co-morbid(hypertension), co-morbid(diabetes), co-morbid(any)	Self report/questionnaire	NS	Case-Control
Roses[182]	1999	US, NY	200	BMI(<30, 30+)	Circumference/ >2cm between arms	12.3-159.3 months	Prospective
Segerstrom[137]	1992	Sweden	136	dominant hand	Water Displacement/ >150ml between arms	2 years	Retrospective
Shih[183]	2009	US	854	age(cont)	Clinical diagnosis (health claims)	NS	Retrospective
Soran[52]	2006	US, PA	156	ex(hand), co-morbid(hypertension), co-morbid(diabetes), infect	Circumference/ >2cm swelling in arm	1990-2000	Case-Control
Swenson[184]	2009	US, MN	188	ex(arm), co-morbid(hypertension), co-morbid(diabetes), injury, dominant hand	Clinical diagnosis	Enroll: 1/2004-8/2007	Case-Control
van der Veen[99]	2004	Brussels	245	injury, dominant hand	Circumference/ >2.5cm between arms	NS	Retrospective
Ververs [65]	2001	The Netherlands	400	co-morbid(any)	Circumference/ >2cm between arms	NS	Retrospective
Villasor[128]	1955	US, MD	79	BMI(<30, 30+), co-morbid(diabetes), injury	Circumference/ >1cm between arms	NS	Retrospective
Watson[125]	1963	Canada	590	BMI(<30, 30+), ex(body)	Circumference	Varies /unclear: patients at clinic from 1960-1961	Retrospective

Table 3.2. Continued

Werner[29]	1991	US, NY	282	BMI(<29.2, 29.2+)	Circumference/ >2.5cm between arms	7-109 months	Prospective
Wilke[31]	2006	US, 126 institutions	~2000	BMI(<30, 30+), BMI(cat), age(<60, 60+), age(cat)	Circumference/ >2cm pre-vs. post-surgery	6 months	Prospective
Yap [143]	2003	Canada	370	BMI(cont), age(cat)	Self-report	Average 3.3 years	Randomized Controlled Trials
Yen [185]	2009	US	1338	age(cat)	Self-report	2-4 years after surgery	Retrospective

Abbreviations: age(cont)=age continuous, age(cat)=age category, BMI(cont)=body mass index continuous, BMI(cat)=body mass index category, dom=dominant hand, ex(arm)=arm physical activity, ex(body)=whole body physical activity, NS= not stated

Table 3.3. Analytical Study of Risk Factors and Secondary Lymphedema: Not included in Analysis

Author	Year	Location of study	Sample Size	Risk Factor(s) reported	Lymphedema measurement/definition	Length of Follow-up or year of diagnosis	Study Design
Ahmed [169]	2008	US	1287	BMI (25)	Self-report	Average 8 years	Retrospective
Kiel [117]	1996	US, IL	183	Age (55)	Circumference/ >1.5cm pre-vs. post-surgery	Every 6 months after radiation	Prospective
Sagen [170]	2009	Norway	204	BMI (25)	Water Displacement/ >200ml	2 years	Randomized Controlled Trials

Abbreviations: BMI (25)=body mass index >25 vs.≤25, Age (55) = age >55 vs. ≤55

Table 3.4. Pooled Risk Ratio for Secondary Lymphedema of the Arm after Breast Cancer and Personal Risk Factors (Dichotomous Categories)

		Fixed Effects Model		Homogeneity	Random Effects Model	
	n	RR	95% CI	P Value	RR	95% CI
Modifiable factors						
BMI >30 (obese +)	18	1.95	1.70, 2.24	<0.001	2.46	1.37, 4.42
Physical activity (arm + other)	13	0.92	0.77, 1.10	0.017	0.88	0.66, 1.17
Socio-demographic						
Age 60+ [a]	10	1.05	0.91, 1.20	0.056	1.14	0.90, 1.44
Less than high school	10	1.35	1.12, 1.63	0.503	1.35	1.12, 1.63
Married or living together	10	0.91	0.76, 1.09	0.044	0.87	0.67, 1.14
Diseases/injury afflictions						
Hypertension	7	1.54	1.21, 1.97	0.028	1.40	0.94, 2.07
Diabetes	7	1.09	0.76, 1.58	0.464	1.09	0.76, 1.58
Presence of any co-morbidity	5	1.88	1.41, 2.50	0.602	1.88	1.41, 2.50
Wound infection and post-op only	8	2.26	1.50, 3.40	0.003	2.11	0.95, 4.68
Injury (arm trauma, puncture)	9	1.92	1.44, 2.57	<0.001	1.87	1.04, 3.34
Other						
Dominant side surgery	13	0.97	0.82, 1.14	0.003	1.03	0.77, 1.36

[a] Included one study looking at >58 years old

Table 3.5. Pooled Risk Ratio for Arm Lymphedema (Dose-response Analysis)

		RR[b]	95% CI	Homogeneity P Value
BMI Overall (increased by 5 units)	11	1.40	1.23, 1.59	0.005
Self-report measurement	3	1.16	0.96, 1.40	0.149
Non-Self-report measurement				0.101
	6	1.41	1.22, 1.64	
Age Overall (increased by 10 years)	19	1.02	0.93, 1.12	0.002
Self-report measurement	6	0.79	0.69, 0.91	0.023
Non-Self-report measurement	11	1.12	1.02, 1.23	0.661
Education Overall (decreased by 4 years)	7	1.28	1.08, 1.51	0.461
<200 sample size	3	1.59	0.88, 2.87	0.111
200+ sample size	4	1.25	1.03, 1.52	0.774

[a]All other stratification showed similar results as the overall estimate

[b]Random-effects model

CHAPTER 4: DEVELOPMENT OF QUESTIONNAIRE USED IN THE IOWA BREAST CANCER AND ARM LYMPHEDEMA STUDY

Overview

An important component of any study collecting self-reported information is the development of the questionnaire. A poorly designed survey asking ambiguous questions can lead to inaccurate and/or heterogeneous responses. In addition a poorly structured questionnaire can cause subjects to become frustrated during the interviewing process. Thus, when possible and appropriate, questions may come from other standardized surveys. It is essential that any newly developed questionnaire be tested and modified to avoid these shortcomings. Furthermore, when researchers develop new items or scales, they need subject input on interpreting some words and/or phrases. Such input can be obtained from focus groups or cognitive interviewing, depending on what sorts of items are being developed.

Changes Made Based on Cognitive Interviewing

The subjects that participated in the cognitive interviewing provided us with additional examples for arm lymphedema treatments (e.g., elevate arm) and physical activity examples (e.g., hanging-up clothes). These examples were subsequently incorporated into the questionnaire for the full study. We also reworded the phrase "recovered from treatment" to "resuming routine household activities" as the women were struggling with what recovered from treatments meant. Through cognitive interviewing, we also learned that most subjects with lymphedema did not have trouble recalling the month and year they were diagnosed with the condition. Within these subjects 5 out of 12 reported having lymphedema based on self-reported physician-diagnosed lymphedema.

Cognitive Interviewing Methods

A general model for cognitive interviewing was developed by Tourangeau.[189] This model is categorized into four main parts: 1) Comprehension of the question, 2) Retrieval of information, 3) Decision processes and 4) Response processes. Comprehension of the question aims to understand if the subject can understand the question by how it is worded. Retrieval of information consists of determining the kind of mental process the subject used to arrive at her final answer. Decision processes shows how much mental effort was devoted to answering a question accurately. It also looks to see if the subject was holding back the truth to avoid shame. Response processes tests to see if the response produced by the subject can be categorized into one of the predetermined responses. Within this there are two main cognitive interviewing methods: 1) think-aloud and 2) verbal probing. For the think-aloud method, the respondent verbalizes her thought process in regards to the question asked. Verbal probing uses both scripted and spontaneous probes to understand the subject's thought process. We used verbal probing for cognitive interviewing but subjects were encouraged to verbalize their thought process.

The Cognitive Interview

We used cognitive interviewing to develop an appropriate questionnaire. We recruited 12 breast cancer patients (diagnosed prior to 2003) that were coming into the Holden Cancer Comprehensive Center at the University of Iowa Hospital and Clinics for routine breast cancer follow-up. They were informed that their participation was needed to improve the clarity of the questionnaire and they were compensated with a $10 gift card. About half of the women had physician-diagnosed lymphedema. The principal investigator and an interviewer conducted the cognitive interviewing which took about 15-30 minutes for each woman. The women were asked to assess how selected questions

were comprehended and interpreted. The selected items that were tested during cognitive interviewing included recall of dates (e.g. when they were diagnosed with arm lymphedema and when did they feel recovered after breast cancer treatments), a list of arm symptoms, and a list of arm activities for different intensity and positioning. Questions were modified after feedback from 6 subjects before recruiting additional subjects for cognitive interviewing. They were also asked to follow the printed instruction for measuring their arm circumference one hand width above and below the elbow crease to evaluate the quality of the instructions.

Questionnaire Development of the Full Survey

In order to study arm lymphedema among breast cancer survivors, the questionnaire used in this study was developed using several methods. Portions of the questionnaire were developed by using previously established questionnaires. Chronic conditions asked in the questionnaire were based on the National Health and Nutrition Examination Survey (NHANES) and in the Behavioral Risk Factor Surveillance System (BRFSS). The arm activity section of the questionnaire was based on the International Physical Activity Questionnaire (IPAQ)[190] and the lifetime total physical activity questionnaire.[191] The remaining sections were developed by the investigators as described below.

Pilot Testing of the Questionnaire

Women diagnosed with breast cancer in 2002 were randomly selected from the Iowa Cancer Registry to participate in the pilot study. The same inclusion and exclusion criteria used to select eligible subjects in our full study were used in the pilot study. Passive physician consent and subject letters were sent out to 52 women. Both the process itself and the interview were executed to test for problems. Pilot subjects were

able to answer the lymphedema treatment list (e.g., elevate arm) modified based on the cognitive interviewing. Few difficulties were experienced.

The most significant change we made from piloting the questionnaire was in the arm activity section. The arm activity questions were reformatted from fill in the blanks to multiple choices. The responses gathered from this the pilot were used to categorized the frequency of arm activity into the multiple choices format. Also, the order of the arm activity questions was changed to facilitate the interviewing process as a number of piloted subjects got frustrated during this section.

Quality Control

To ensure quality of data collection, the interviewers confirmed each subject's name and birth date before proceeding with the interview. For quality assurance purposes, a digital voice recording of the interview was made with the participants' permission. The principal investigator closely monitored the first 50 interviews by either listening in on the interview or going over the digital voice recordings to identify any problems. As needed, the principal investigator went back over available voice recordings to pinpoint the potential source of error(s). Discrepancies were discussed with the interviewers to strengthen their training. One interviewer who could not follow the protocol was removed from the research team.

Developing the Definition of Lymphedema

The main focus of this study was to look for factors that contributed or modified the onset of chronic or persistent lymphedema. We defined chronic lymphedema as lymphedema that was persistent at the time of our interview, which was 5-6 years after breast cancer diagnosis. Clinical cases of lymphedema were identified through self-reporting a diagnosis by a physician. A woman was considered to have lymphedema in our study if she was physician-diagnosed with lymphedema that has not resolved at the

time of the interview. Lymphedema cases that were resolved (no longer persistent) were not considered as lymphedema cases unless they were identified as subclinical cases. Subclinical cases were identified through an objective arm measurement (difference of >2cm between arm circumference) or subjective arm symptoms. For arm circumference, subjects were asked to measure the circumference of both their right and left arm one hand width above and below the elbow crease. The arm symptoms asked in this questionnaire were compiled from various published studies.[73, 192, 193] An expert panel was assembled to identify arm symptoms that someone with lymphedema would most likely experience. The five arm symptoms identified were termed major arm symptoms. They were 1) shirt sleeve felt tight or irritated arm, 2) arm felt swollen, 3) arm felt heavy, 4) arm felt tense, and 5) arm felt hard. The other arm symptoms were termed minor arm symptoms. All the arm symptoms asked in the questionnaire can be seen in Appendix B (question numbers: L5, L6 / NL2, NL4). Subjects were considered to have lymphedema if they experienced at least two major and at least four total arm symptoms within the last three months prior to interview. Two arm symptoms "arm felt warm" and "arm experienced abnormal sensations" were not included in the subjective lymphedema definition based on clinical input and low kappa coefficients as described below.

The final definition used for this study incorporated both clinical and subclinical cases of arm lymphedema because it was deemed important to capture subclinical cases. When comparisons between objective (physician diagnoses, arm circumference) and subjective (arm symptoms only) definitions of lymphedema were made, the relative risks found were similar (Table 4.1). This indicated that it would be appropriate to combine both objective and subjective definitions of lymphedema into one comprehensive definition.

Arm Symptoms Comparisons

To further assess the value of using arm symptoms to detect subclinical cases of arm lymphedema, comparisons between different assessments of arm lymphedema were made (Table 4.2). We found the percentages of subjects with any given arm symptoms were comparable between women with physician-diagnosed lymphedema (not resolved - subjects with persistent lymphedema at time of interview) and women identified to have lymphedema based on arm symptoms. This provided some evidence that the subjective definition of lymphedema (arm symptoms) may reflect similar lymphedema cases as physician-diagnosed lymphedema. When using physician-diagnosed lymphedema as the gold standard, we also found arm symptoms to be more comparable then arm measurement (Table 4.3). We also found that lymphedema may present itself either through either objective or subjective indications (Table A.1). However, arm circumference is still an effective means of identifying arm lymphedema in breast cancer survivors. Subjects with >2cm difference between arms were 5 to 6 times more likely to experience major arm symptoms than subjects who were not considered to have arm lymphedema (Table 4.2).

When we compared participants with physician-diagnosed resolved and unresolved lymphedema, we found that subjects with unresolved lymphedema reported more major and total arm symptoms than subjects with resolved lymphedema (Table A.2). This is consistent with what we would expect to see if self-reported data were accurate. However, some subjects who reported resolved lymphedema continued to have arm symptoms that indicate lymphedema. This suggested that some degree of misclassification could occur if subjective assessment was not used to determine arm lymphedema. These findings gave support for considering both objective and subjective assessments as important for determining the presence of arm lymphedema.

Reliability of Study Questionnaire

To test the reliability of the study questionnaire, we re-interviewed 19 subjects who were identified to have arm lymphedema based on our study definition (doctor diagnosed lymphedema, >2cm between arms or have arm symptoms indicative of lymphedema) and 20 subjects who were not found to have arm lymphedema based on our study definition approximately 6 weeks after their initial interview. The Kappa coefficient was calculated for all dichotomous variables. A weighted kappa coefficient was estimated for education. Kappa coefficients were used to test the reliability of the questionnaire. Most questions have a kappa coefficient between 0.4-0.8, indicating fair to good agreement (Table 4.4). The lowest kappa coefficients were observed for specific arm activities with a kappa coefficient of about 0.3 for swimming after breast cancer diagnosis. The kappa coefficients for chronic conditions are generally pretty high (kappa >0.6) with the exception of coronary heart disease and kidney failure (kappa=0.48). Both of these conditions have a low prevalence among participants. More variations in kappa coefficients were observed for arm symptoms ranging from 0.38 to 0.93. Arm felt hard had the lowest kappa coefficient, while shirt sleeve felt tight had the highest. Arm felt hard may have the lowest kappa coefficient because it was a difficult symptom for subjects to assess. Shirt sleeve felt tight may have the highest coefficient because it was often the first indication of arm lymphedema and may be the most consistent arm symptom. This variability may be explained through arm symptoms that may have come and go due to lymphedema treatments and other external factors. Since subjects were asked to report arm symptoms experienced within the last three months, some symptoms that may be evident one month may be less evident the next month and vice versa.

Overall, the questionnaire was found to be reliable. Arm activities tended to have lower reliability due to recall. Time sensitive questions, such as arm symptoms within the

past three months, also increase the variability of these questions. Low kappa coefficient led to the exclusion of two arm symptoms (arm felt warm and abnormal sensation in arm) from the subjective lymphedema definition. These symptoms were not considered to be major arm symptoms. Even though some physical activities have lower kappa coefficients, they were not excluded from analysis because they were factors of interest. The low reliability may have prevented an association to be detected if it existed.

Summary

Both the cognitive interviewing and the pilot study provided valuable information that improved both the flow and quality the questionnaire. In particular, our original format for arm activity was a point of frustration for many subjects and the interviewers. The change in format greatly reduced that frustration, which in turn improved the quality of collected data and the ease of the interview. In addition, a reliability study was conducted to test the consistency of responses. Arm symptoms with low reliability were excluded from the study.

Table 4.1. Comparison of Objective and Subjective Indication of Lymphedema among Women Diagnosed with Breast Cancer in Iowa, 2004 [a]

		Objective indication of lymphedema [b]			Subjective indication of lymphedema only [c]		
	Controls	Cases	RR	CI	Cases	RR	CI
Surgery							
Lumpectomy	243	38	Ref		16	Ref	-
Mastectomy	56	11	1.26	0.61-2.61	2	0.54	0.12-2.43
Radical Modified Mastectomy	119	31	1.67	0.99-2.81	4	0.51	0.17-1.56
Radiation							
No	159	26	Ref	--	**7**	Ref	-
Yes	258	54	1.28	0.77-2.13	15	1.32	0.53-3.31
Nodes examined							
1-2	114	11	Ref	-	6	Ref	-
3-6	108	19	1.82	0.83-4.01	2	0.35	0.07-1.78
7-10	57	13	2.36	0.99-5.61	5	1.67	0.49-5.69
>10	124	36	3.01*	1.46-6.19	9	1.38	0.48-3.99
Positive nodes							
0	300	45	Ref	-	9	Ref	-
1-2	69	18	1.74	0.95-3.19	11	5.31*	2.12-13.32
>2	38	17	2.98*	1.55-5.73	2	1.75	0.37-8.42
Chemotherapy							
No	208	33	Ref	-	7	Ref	-
Yes	209	45	1.36	0.83-2.21	15	2.13	0.85-5.34
Hormone therapy							
No	183	38	Ref	-	9	Ref	-
Yes	227	40	0.85	0.52-1.38	13	1.16	0.49-2.79
Stage							
I	235	35	Ref	-	7	Ref	-
II	139	25	1.21	0.69-2.10	13	3.14*	1.22-8.06
III	30	19	4.25*	2.16-8.36	1	1.12	0.13-9.41
Axillary dissection							
No	154	18	Ref	-	4	Ref	-
Yes	254	62	2.09*	1.19-3.66	18	2.73	0.91-8.21
Body Mass Index							
<18.5	4	0	-	-	0		-
18.5-24.9	138	15	Ref	-	7	Ref	-
25-29.9	140	23	1.51	0.76-3.02	5	0.70	0.22-2.27
30-34.9	83	18	2.0	0.95-4.17	2	0.48	0.10-2.34
35-39.9	35	10	2.63*	1.09-6.35	3	1.69	0.42-6.87
40+	17	13	7.04*	2.87-17.26	5	5.80*	1.66-20.31

Table 4.1. Continued

Age							
25-49	49	11	Ref	-	9	Ref	
50-54	57	7	0.55	0.20-1.52	7	0.67	0.23-1.93
55-59	60	12	0.89	0.36-2.19	1	0.09	0.01-0.74
60-64	61	12	0.88	0.36-2.16	1	0.09	0.01-0.73
65-69	51	14	1.22	0.51-2.95	2	0.21	0.44-1.04
70-74	56	12	0.96	0.39-2.36	2	0.19	0.40-0.94
75+	86	12	0.62	0.26-1.50	0	-	-
Co-morbidity[d]							
No	155	22	Ref	-	12	Ref	-
Yes	265	58	1.54	0.91-2.62	10	0.49	0.21-1.15
Arm activity below shoulders[e]							
High	100	24	Ref	-	4	Ref	-
Medium	146	26	1.19	0.65-2.16	8	2.19	0.65-7.43
Low	160	28	1.87*	1.03-3.40	10	4.0*	1.22-13.10
Arm activity above shoulders[e]							
High	195	12	Ref	-	3	Ref	-
Medium	159	21	0.54	0.25-1.17	8	0.82	0.21-3.22
Low	49	44	0.92	0.45-1.88	11	0.92	0.25-3.43

*Significant relative risk (RR) as measured by the odds ratio

[a] The number of total subjects (N=522) does not always sum to this total because of missing data

[b] Physician diagnosis of lymphedema that has not resolved (persistent lymphedema) or >2cm difference between arms

[c] Experienced at least two major and at least five total arm symptoms within the three months prior to interview

[d] Co-morbidity indicates the presence of one or more of the following conditions: high blood pressure, high cholesterol, heart attack, coronary heart disease, stroke, congestive heart failure, emphysema, chronic bronchitis, asthma, thyroid problems, liver conditions, weak or failing kidneys, osteoporosis, diabetes, and arthritis

[e] Arm exercise below the shoulder one year after breast cancer treatment recovery

Table 4.2. Comparison of Symptoms among Objective and Subjective Determination of Arm Lymphedema among Breast Cancer Cases in Iowa, 2004

Mutually Exclusive Definitions of Lymphedema:	Physician Diagnosed Lymphedema (NOT Resolved) [a] N (%)	> 2cm difference in arm measurements (non-MD dx) [b] N (%)	Only had symptoms [c] N (%)	Not diagnosed with lymphedema
N=	44	36	22	450
Major symptoms				
Shirt sleeve felt tight	24 (54.55)	8 (22.22)	13 (61.90)	14 (3.33)
Arm felt swollen	27 (62.79)	6 (16.67)	12 (54.55)	16 (3.81)
Arm felt heavy	18 (40.91)	6 (17.14)	19 (86.36)	12 (2.87)
Arm felt hard	8 (18.60)	3 (8.33)	4 (19.05)	3 (0.72)
Minor Symptoms				
Arm felt numb	17 (38.64)	5 (13.89)	17 (77.27)	48 (11.43)
Arm felt stiff	9 (20.45)	5 (13.89)	9 (40.91)	11 (2.63)
Arm felt painful	16 (36.36)	4 (11.11)	15 (71.43)	33 (7.88)
Arm felt tense	5 (11.63)	1 (2.86)	10 (45.45)	10 (2.38)
Rash on arm	8 (18.18)	4 (11.11)	4 (18.18)	14 (3.33)
Cannot see knuckles	6 (13.64)	0 (0)	1 (4.55)	1 (0.24)
Cannot see veins	5 (11.36)	0 (0)	2 (9.52)	2 (0.48)
Rings felt tight	12 (38.71)	9 (29.03)	9 (52.94)	56 (14.81)

[a] Includes subjects who also had arm measurement differences > 2 cm and ≥ 4 symptoms

[b] Includes subjects who also had ≥4 symptoms

[c] At least 2 major symptoms and a total of at least 4 symptoms as self-reported by subjects

Table 4.3. Comparing Definition of Lymphedema using Sensitivity, Specificity and Positive Predictive Value

Gold-standard: physician-diagnosed arm lymphedema					
	Gold-standard				
>2cm between arms (arm circumference)	No	Yes	Total		
No	330	21	351	Sensitivity:	38.2
Yes	36	13	49	Specificity:	90.2
Total	366	34	400	Positive predictive value:	26.5
	Gold-standard				
Arm symptoms	No	Yes	Total		
No	452	25	477	Sensitivity:	43.2
Yes	26	19	45	Specificity:	94.6
Total	478	44	522	Positive predictive value:	42.2
Gold-standard: >2cm between arms (arm circumference)					
	Gold-standard				
Arm symptoms	No	Yes	Total		
No	332	36	368	Sensitivity:	26.5
Yes	19	13	32	Specificity:	94.6
Total	351	49	400	Positive predictive value:	40.6

Table 4.4. Reliability of Selected Questionnaire Items among 39 Iowa Breast Cancer Survivors who Participated in the Reliability Portion of the Study, 2004 [a]

	Kappa		Kappa
General		**Chronic conditions**	
Breast cancer laterality	0.90	High blood pressure	0.88
Dominant hand	0.94	High cholesterol	0.95
Education	0.95	Heart attack	1.0
Marital status	1.0	Coronary heart disease	0.48
Treatment		Stroke	1.0
Radiation	1.0	Congestive heart failure	1.0
Radiation to the axilla	0.44	Emphysema	1.0
Specific arm activities		Chronic bronchitis	0.87
Swimming	0.30	Asthma	0.92
Playing tennis	0.95	Thyroid condition	0.94
Weightlifting	0.32	Liver	0.65
Gardening	0.69	Kidney	0.48
Lymphedema		Osteoporosis	0.68
Physician-diagnosed lymphedema	0.89	Diabetes	0.91
Arm symptoms		Arthritis	0.64
Shirt sleeve felt tight	0.93		
Arm felt swollen	0.66		
Arm felt heavy	0.79		
Arm felt hard	0.38		
Arm felt tense	0.84		

CHAPTER 5: LYMPHEDEMA AMONG IOWAN WOMEN DIAGNOSED WITH BREAST CANCER IN 2004

Summary of Findings

Background: Breast cancer-related arm lymphedema is a serious complication that can adversely affect quality of life. Various factors, including breast cancer treatment and risk factors play an important role in the development, prevention of lymphedema. *Methods:* Women diagnosed with breast cancer in Iowa during 2004 were identified by the Iowa Cancer Registry and recruited, of these 522 women completed a 15-20 minute computer assisted telephone interview. The interview included questions about chronic conditions, arm activities, demographics, and lymphedema status. Arm lymphedema was determined through self-reported physician diagnosis, a difference in arm circumference (>2 cm), or having multiple major arm symptoms. Treatment- and disease-related characteristics were obtained from the Iowa Cancer Registry and subject interview information. Relative risks (RR) and 95% confidence intervals (CI) were estimated through logistic regression. *Results:* Arm lymphedema was identified in 19.5% of participants. Participants treated by both axillary dissection and radiation therapy were more likely to have arm lymphedema than women treated with axillary dissection alone (RR=2.41, 95% CI of 1.11-5.22). Women with more advanced cancer stage, positive nodes, and larger tumors were found to be at higher risk of developing lymphedema, even after adjusting for treatment factors such as axillary dissection. High BMI was also an important risk factor (RR=5.71, 95% CI: 2.53, 12.87). Arm activity level was not found to be associated with arm lymphedema. *Conclusions:* This study identified treatment, disease and demographic factors that contributed to the onset of arm lymphedema. Arm activity was not found to be associated with arm lymphedema.

Introduction

In the United States, breast cancer is the most common female cancer.[2] American Cancer Society estimates that 207,090 women will be diagnosed with breast cancer in 2010. Ninety percent of which will survive at least five years after diagnosis.[194] Lymphedema of the arm (here forward referred to as lymphedema) is a complication from breast cancer treatment that impacts breast cancer survivors. Lymphedema causes the accumulation of fluid (swelling) in the arm and 15-20% of breast cancer survivors are expected to develop this condition in their lifetime.[37] Lymphedema is a progressive disease. If not treated and controlled, severe pain and disability can result.

Despite numerous amount of published research, many questions regarding lymphedema risk factors remain unanswered. Research evaluating treatment or personal risk factors has yielded conflicting results. Guidelines have warned breast cancer survivors to stay away from vigorous or repetitive exercise, but these are now being challenged.[53, 195] Some recent evidence disputes vigorous arm activities as harmful.[46]

The current study looks at the effect treatment, and personal risk factors have on the development of lymphedema among females diagnosed with breast cancer in Iowa during 2004 and followed through 2010 for symptoms of lymphedema.

Methods

Breast cancer cases were identified through the ICR. The ICR is a population-based registry that is part of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program. A total of 2164 breast cancer cases were diagnosed in the state of Iowa during 2004.

Recruitment

A letter was sent to the physician of each subject, seeking passive physician consent to contact the subject regarding this research study. If no physician information was available, this step was bypassed. The physician had three weeks to notify Iowa Cancer Registry (ICR) if there were any contraindications as to why the woman should not be approached for this study.

Once passive physician consent was received, an invitation letter was sent to each woman inviting her to participate in this study. Elements of consent, as required by the Internal Review Board at the University of Iowa, were included in the letter. To maximize contact, subjects with no valid phone number were sent a modified letter requesting them to contact the study coordinator if they were interested in participating in this study. Two weeks after mailing the letters, a trained interviewer contacted the subject by phone to request their participation in the study (Appendix C).

Tracing

In an attempt to maximized response rates, subjects with incorrect addresses or disconnected or wrong phone numbers were traced for new addresses and/or numbers. Voter's registration list, Accurint, and internet white and yellow pages were used for tracing.

Call Attempts

In order to increase the response rates, subjects received up to 10 call attempts at different days of the week and different times of the day. The majority of call attempts were made from 5 to 9 pm. No more than 2 calls were made per day, unless the woman requested a call-back.

Study population

A total of 2164 breast cancer cases were identified by the ICR as diagnosed in the state of Iowa during 2004. Subjects eligible for this study included females diagnosed with unilateral invasive breast cancer in 2004, Iowa resident at diagnosis date, had no prior or subsequent cancer diagnosis (breast or otherwise) with the exception of in-situ cervical cancer, and were less than 80 years old at the time of diagnosis. We excluded breast cancer cases who were males (N=9), had previous or subsequent cancer diagnosis (N=323), or had more than one primary tumor (N=174). An additional 76 cases with stage IV breast cancer and 236 cases age 80 or older at breast cancer diagnosis were also excluded. Subjects known to be deceased (N=145) were also not included in this study.

Among the 2164 cases diagnosed with breast cancer in 2004, 1201 met our inclusion criteria. Fifteen subjects were determined to be ineligible due to mental impairment or illnesses and physicians provided contraindication to contacting another 16 subjects. Thus, we attempted to contact 1170 subjects. We were unable to make contact with 150 subjects due to untraceable addresses (N=43) or phone numbers (N=107). Therefore, phone contact was made with 1020 women. Of those contacted, 281 (27.2%) women refused to participant in this study. Twenty-five additional subjects were deemed ineligible at the time of the interview. Reasons for ineligibility included mental impairment, non-English speaker, and breast cancer in both breasts. Interviewers were unsuccessful in reaching 192 (18.6%) subjects after 10 call attempts. In total 522 (50.6%) women we contacted agreed to participate in this study (Figure 5.1).

Prognostic factors

Demographic, disease- and treatment-related factors were abstracted by the ICR staff through medical records. Demographic data requested from the ICR included date of birth and marital status. Disease-related data included date of breast cancer diagnosis,

laterality of cancer, tumor size, cancer stage (based on AJCC 6th edition), number of lymph nodes examined and number of positive lymph nodes found. Treatment-related data included date and type of first-course therapy (surgery, chemotherapy, radiation and hormone therapy), surgery type, scope of lymph node dissection and number of lymph nodes removed. The interview was designed to collect information not available through the ICR records.

To check the generalizability of study results, disease characteristics and treatment data were compared between participants and non-participants (Table A.3.). No significant differences between participants and non-participants were found for disease characteristics and breast cancer treatments, indicating that the study results may be generalized to breast cancer cases diagnosed in Iowa during 2004.

Interview

We used cognitive interviewing to develop part of the questionnaire. Twelve breast cancer patients, half with physician-diagnosed lymphedema, gave us feedback on how selected questions and arm circumference instructions were comprehended and interpreted. These selected items included recall of physician diagnosis dates for lymphedema, arm symptoms and examples of arm activities. Based on comments, we added elevating the arm as treatment for lymphedema and further tailored the physical activity examples. We also reworded a few phrases for clarity. Further pilot testing suggested reformatting the frequency of arm activity from fill in the blank to multiple choice questions and some re-ordering to facilitate the interviewing process.

Computer-assisted telephone interviewing (CATI) was used and programmed in Blaise software. The CATI program allowed for data checks during the interview to minimize data entry errors. The average time of interview was 17 minutes. Demographic information that was collected included marital status, highest level of education, hand dominance, along with self-reported height and weight to calculate body

mass index (BMI). An additional treatment factor not available from the ICR (radiation therapy to the axilla) was also collected. The Kappa coefficient between self-reported radiation treatment and ICR radiation data was 0.90. The radiation data from ICR was used for the analysis. A portion of the interview focused on arm activities including specific arm activities (swimming, playing tennis, weightlifting, and gardening) and overall arm activity levels. Overall arm activities were broken down into four combinations based on the positioning of the arm during activity (above or below the shoulders) and the intensity of the activity (vigorous or moderate). Each subject was asked to estimate the number of hours/week they performed each of these four combinations of arm activity during three different time frames. The time frames of interest were: 1) the past year, 2) one year prior to breast cancer diagnosis, and 3) one year after the subject was able to resume routine household activities. For each of the three time frames, the frequency and the intensity of arm activities were combined into low, medium and high arm activity levels. The arm activity level for above or below each shoulder was calculated separately.

Information regarding arm lymphedema was also collected through the CATI in three different areas. First, subjects were asked if they were ever diagnosed by a physician with arm lymphedema. Second, they were asked if they experienced 13 specific arm/hand symptoms within the last three months. Third, they were asked to measure the arm circumference of both arms at two different locations, one hand width above and below the elbow crease. Data regarding lymphedema treatments were also collected. Subjects were asked if they used specific methods at least once a week to treat or prevent arm lymphedema. Subjects were also asked if they had an arm infection, had been diagnosed with various chronic conditions, had taken airplane trips the year after breast cancer diagnosis, or had attended physical therapy.

Lymphedema Categorization

Lymphedema was characterized in 3 different ways; 1) physician-diagnosed, not resolved, or 2) objective assessment in which the circumference of the affected arm was more than 2cm larger than the other arm, or 3) by having multiple self-reported arm symptoms (a subjective assessment). For the objective assessment, a subject was asked to measure her arm circumference of both arms one hand width above and below the elbow crease. A >2cm difference between arms either above or below the elbow crease indicated arm lymphedema. For the subjective assessment, a subject must be presented with at least two of five major arm symptoms (shirt sleeve felt tight, arm felt swollen, heavy, tense or hard) and at least four total arm symptoms to be labeled as having lymphedema. Total arm symptoms were determined by the sum of both major and minor arm symptoms. Minor arm symptoms included arm felt numb, stiff, or painful, rash/itchiness of arm, other arm symptoms, cannot see knuckles, or veins in hand, and ring(s) felt tight. In this report a woman was considered to have lymphedema if she has positive indication of lymphedema based on any of the three assessment criteria, which are further described in Table 5.1.

Reliability

For the reliability portion of this study, 19 subjects with lymphedema and 20 subjects without lymphedema agreed to be re-interviewed approximately 6 weeks after the initial interview. Most of these questions reported kappa coefficient between 0.4-0.8, which indicated fair to good agreement.

Statistical Analysis

Univariate risk ratios (RR) and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression. Potential confounders were identified

prior to analysis based on biologic plausibility. Estimates were adjusted for confounders that conferred a 10% or greater change from the crude RR. For factors of interest in which less than 20 subjects indicated they had the condition, confounders that presented a >20% change from the crude RR were adjusted for in the final estimate.

Results

Cumulative Incidence of Arm Lymphedema

Arm lymphedema subsequent to breast cancer treatment was identified in 102 (19.5%) participants. The time to lymphedema onset was only defined among subjects who were physician-diagnosed or reported a time for the onset of arm symptoms. It was defined as the time between initial breast cancer treatment and onset of arm symptoms (Figure 5.2). The majority of lymphedema cases were diagnosed within two years after the initial breast cancer treatment. The cumulative incidence of arm lymphedema at two years was 11.5%. Most acute cases of physician-diagnosed lymphedema (lymphedema cases that were resolved and no longer persistent) appeared shortly (within a year) after initial breast cancer treatment. The majority of physician-diagnosed lymphedema cases were persistent cases.

Participants' Characteristics

The average age of participants at the time of interview was 63 years and the mean BMI at the time of interview was 28.8 kg/m^2. Around 30% of participants were college graduates and over 65% were married. Neither education level nor marital status was associated with lymphedema (Table 5.2). Over one-third (36%) of participants were obese (BMI $\geq$ 30 kg/m^2), and 32% were considered to be of normal weight (BMI of <25 kg/m^2). Subjects who were 75+ years old at the time of interview were less likely to develop arm lymphedema then younger subjects under 50 years old (RR=0.35, 95% CI:

0.15, 0.81). Participants with a BMI of 40 or greater were 5-6 times more likely to develop lymphedema (RR=5.71, 95% CI: 2.53, 12.87) than those with a BMI between 18.5 and 24.9 kg/m^2 (Table 5.2). An increasing RR trend was observed as BMI classification increased.

Breast cancer disease and treatment

Only seven women did not receive either surgical or radiation treatments (Table A.4). In regards to surgical treatments, 57% and 34% of women were treated with lumpectomy and sentinel nodes biopsy, respectively, with an average of 8 nodes removed. Radiation therapy was received by 63% of women, and among those who received radiation, 30% claimed that radiation was directed in the axilla area. Over half of the participants reported having chemotherapy and/or hormone therapy as part of their breast cancer treatment

Axillary dissection and radiation were found to interact (p=0.01). The combination of both axillary dissection and radiation therapy showed a risk more strongly associated with lymphedema then either axillary dissection or radiation alone. Radiation, in the presence of axillary dissection, was associated with lymphedema (RR=2.61, 95% CI: 1.27, 5.39) (Table 5.3).

For cancer characteristics, 87% of participants (including unstaged cases) were classified as having stage I or II breast cancer. Only 30.5% (excluding missing data) were detected with positive nodes and the mean tumor size was 19mm. Lymphedema of the arm was associated with stage III cancer (RR=2.52, 95% CI: 1.25, 5.10), the presence of positive nodes (RR=2.09, 95% CI: 1.07, 4.09), and tumors >30mm (RR=2.62, 95% CI: 1.11, 6.17) (Table 5.4). Type of surgery, radiation to the axilla, chemotherapy, hormone therapy, and number of lymph nodes removed were not found to be associated with the development of arm lymphedema after adjusting for confounding (Table 5.4).

Chronic Conditions

Around 64% of participants reported having been diagnosed with at least one chronic condition, but most of these were not linked with the development of lymphedema. The most common ailments among participants (excluding don't know or missing) were high blood pressure (28.5%), high cholesterol (25.8%), and arthritis (28.3%). Lymphedema was linked to chronic bronchitis (RR=3.30, 95% CI: 1.23, 8.85), however less than 20 subjects reported having the condition. Participants who were diagnosed with immune disorders, osteoarthritis or rheumatoid arthritis (RR=1.56, 95% CI: 0.93, 2.62) and/or kidney failure (RR=4.70, 95% CI: 0.91, 24.29) had a borderline increased risk for developing arm lymphedema (Table 5.5).

Arm Activity

No associations were found between arm lymphedema and specific arm activities including swimming, playing tennis, weightlifting or gardening (Table 5.6). For arm activity level, the time frame of greatest interest was the year after resuming routine household activities (recovered from treatment). This time period is most likely to represent the arm activity level before or around the time of arm lymphedema onset. The mean time to resuming household activities after first treatment was six months, with 26% returning less than one month after receiving treatment(s). When looking at arm activities above the shoulders, no association between arm activity level and lymphedema was found. For arm activities below the shoulders, lower levels of activity were found to be a risk for the development of lymphedema. The highest risk was observed for the lowest level of arm activity (RR=2.40, 95% CI: 1.38, 4.20) (Table 5.6). This risk was no longer observed when the RR was estimated using only participants that did not report a change in arm activity before and after breast cancer diagnosis (RR=1.56, 95% CI: 0.60, 4.03).

Other Personal Factors

Surgery on dominant side, and air travel, were not found to be associated with lymphedema in this study (Table 5.6). There were only 16 (3.1%) subjects who reported having an arm infection. However, all reports of arm infection(s), with the exception of one participant, occurred after the onset of lymphedema or lymphedema-related arm symptoms.

Lymphedema Perceptions

Subjects with lymphedema were asked what they thought caused their arm lymphedema; 58.3% attributed breast cancer treatment, in particularly lymph node removal, as the main cause of their lymphedema. Other subjects (N=1 for each of the following) thought something they did may have contributed to their lymphedema, such as carrying heavy objects, weightlifting too early, or too much arm activities. We found that 75% of the subjects who thought they may have lymphedema were determined by our study definition to have lymphedema. Whereas 9.1% of subjects who were not physician-diagnosed and did not think they may have lymphedema were identified by our study definition to have lymphedema.

Discussion

We found arm lymphedema to be prevalent in 19.5% of participants among women diagnosed with breast cancer in Iowa in 2004. Among women with known (physician-diagnosed) or estimated lymphedema diagnosis dates (based on when arm symptoms occurred), most developed lymphedema within the first two years after surgery. However, a limitation is that all measures of lymphedema were based on self-report. This study found that obesity and a low level of arm activity below the shoulders were associated with the development of arm lymphedema. However, this finding may

have been attributed to decreased level of arm activity due to lymphedema. One study[59] suggested that exercise may be beneficial in preventing or delaying the onset of arm lymphedema. The results found in this study may be further generalized to include all female White non-Hispanic population living in the United States.

Inclusion of Subjects Who Had No Surgery or Lymph Nodes Removed

Out of the 522 participants, 12 subjects did not receive surgery or have any of their lymph nodes removed (Table A.4). Although none of them went on to develop lymphedema, they were still included in this study for several reasons. First, all of these subjects were diagnosed with stage I or unstaged breast cancer. Although they did not receive surgical intervention, most of them (83%) received other types of breast cancer treatment, such as radiation (42%), chemotherapy (25%) or hormones therapy (42%). Third, inclusion of these subjects would allow study results to be generalized to survivors who did not receive surgical intervention. Lastly, one of the main concerns for including these subjects in the analysis was that study results would be diluted. This was not found to be the case because the univariate RRs with or without these subjects were very similar.

Axillary Dissection and Radiation Therapy

An increase in arm lymphedema risk was observed when both axillary dissection and radiation therapy were performed. A number of studies[23, 32, 73, 93, 118, 149] have suggested that the addition of radiation therapy to axillary dissection increased the risk of arm lymphedema. Radiation after axillary dissection may have induced fibrosis that could compress or block lymphatic vessels. Participants in this study who had radiation and not axillary dissection were generally diagnosed with early stage breast cancer (stage I or II), received lumpectomy, had no positive nodes, and had 6 or less nodes removed.

These participants were early cancer cases who had less invasive treatments. Hence, it is likely that this group of subjects was treated less aggressively. Conversely, women who receive both axillary dissection and radiation therapy tended to be stage III (21% vs.0%), have positive nodes (48% vs. 3%), and have larger tumors (22.7 vs.14.6).

Number of Lymph Nodes Removed

Participants with greater than10 lymph nodes removed were found to have an increased risk of developing lymphedema in the presence of radiation therapy. However the effect observed went away when the RR was adjusted for axillary dissection. Our results were similar to Heyler et al.[176] in that we also observed a trend of increasing risk as increasing number of nodes were removed. Overall, published reports have supported[23, 25, 28, 196] and refuted [6, 64, 185] this finding. Since axillary dissection was identified as a confounder, the association with the development of arm lymphedema may have been attributed to the intactness of the lymphatic network in the axilla rather than how many nodes were removed.[196] Axillary dissection, a procedure that disrupts the lymphatic network, remained associated with lymphedema even after adjusting for the number of lymph nodes removed.

Disease Stage

Advanced cancer stage and positive nodes generally necessitate more invasive breast cancer treatments. Due to low 5-year survival, stage IV breast cancer cases were not included in the analysis. There were 17 participants with unstaged breast cancer that were included in this study. Due to the low number of participants that were unstaged, they were not included in the staging analysis, but were included in other analyses. While breast cancer treatments are thought to be the major contributors to lymphedema, the association between arm lymphedema and advance stages of cancer, positive nodes, or large tumors persisted even after adjusting for axillary dissection. It is possible that more

advanced disease or larger tumors have the ability on their own to cause disruptions or damages that interfere with the lymphatic network.

Chronic Conditions

The presence of most chronic conditions did not influence the subsequent development of lymphedema. While it was speculated that conditions such as high blood pressure and diabetes may exacerbate a damaged lymphatic system due to increased hydrostatic pressure, we did not find such an association in this study. The lack of association may be due to medications taken to control high blood pressure[62], therefore negating the effect of increased hydrostatic pressure. Both chronic bronchitis and kidney conditions were linked to the development of lymphedema. We are unsure why there is a link between chronic bronchitis and lymphedema. It is possible that severe coughing associated with chronic bronchitis may disrupt healing from surgery thus negatively affecting lymphatic vessels, leading to lymphedema. This association observed may also be due to chance. However it is possible that a malfunctioning kidney can overwhelm the fluid exchange system, since its main function is to maintain fluid balance. While this may lead to the development of edema, not necessarily lymphedema, addition sources of fluid imbalances may further complicate an already delicate lymphatic system. There were not enough subjects with these conditions in our study to draw a conclusion at this point. Arthritis and autoimmune disorder were also found to be associated with lymphedema. The effect, however, was not significant. It is important to note that osteoarthritis was the most common condition reported by subjects and is not autoimmune related. However, arthritis or other autoimmune disease is characterized by inflammation to the joints, blood or lymph vessels and is a potential source that may contribute to lymphedema.

Demographics

While most of the previously published studies did not find an association between age and lymphedema, our finding is similar to Geller et al.[62] in that we found younger women to be associated with developing arm lymphedema. It was suggested that one reason for this finding has to do with younger women having more aggressive cancer which required more invasive treatments.[42] In this study, we found that women under the age 50 at the time of interview were much more likely to have positive nodes (41% versus 19%), or be diagnosed with breast cancer staged II or III rather than stage I. Since their disease was more advanced, they were also slightly more likely to receive axillary dissection. Also, younger women are more active outside of the home and are more likely to notice the effects of lymphedema.[171] Another theory for explaining this association was that older women tend to have extensive co-morbidity and would pay less attention to arm symptoms. Hence, arm symptoms related to lymphedema may have been under-reported.[171, 197]

BMI also played a significant role in the development of lymphedema. The association with increased BMI was still evident when only physician-diagnosed cases of lymphedema were used to indicate lymphedema. This suggests that the association seen with BMI and lymphedema was not an artifact of measurement error by obese subjects. Obesity, because of larger tissue volume and higher fat contents, may have increased the difficulty of performing an axillary dissection or required different breast cancer treatment techniques,[35 64] therefore contributing to the association seen for participants with higher BMI. Another contributing factor for lymphedema may be due to the increased amount of adipose tissue acting as a reservoir for lymphatic fluids.[35] Also, the presence of chronic condition(s) may further impair a lethargic lymphatic system by disrupting fluid balance.

Post-operative Arm Activity

Specific activities were not found to be associated with lymphedema. Among women who weight lifted, 30% of them had their arms elevated above their heart most of the time. However, an increased amount of time spent weightlifting above the heart was not found to be associated with lymphedema. The results from this study were similar to other studies in that none of the specific activities or overall arm activity level showed increased arm activity to be a risk for arm lymphedema.[198] When looking at overall arm activity level a year after resuming household activities, low level of arm activities above the shoulders was not shown to contribute to arm lymphedema. Contrary, low level of arm activities below the shoulders was found to be associated with arm lymphedema. However, this may be a reflection of decreased level of arm activity due to the presence of lymphedema. As a higher percentage of women with lymphedema reported a decrease in arm activity level after breast cancer treatment than women not diagnosed with lymphedema (Table 5.7). It is possible that an effect was not observed with arm activities done above the shoulder because the vast majority of arm activities were done below the shoulders.

It took an average of 9 months for subjects with lymphedema to resume routine household activities (the time frame of interest). By that time, at least 8% (Total 20%) of lymphedema cases had already developed. Hence, participants may be developing or had already developed lymphedema by the time they resumed routine household activities. To further examine this, the RR was calculated using only subjects that had no change in arm activity level from a year before breast cancer diagnosis to a year after resuming household activities. We found that the lowest level of arm activity (RR=1.56, 95% CI: 0.60, 4.03) was not associated with arm lymphedema. This finding supports that post-operative arm exercise is not harmful and may play a beneficial role in preventing lymphedema. However more research is needed to test this theory. Increased levels of

arm activity after breast cancer treatment may encourage the development of collateral lymphatic pathways, thus preventing the onset of arm lymphedema.[59, 199]

Other Factors

Although air travel has been speculated by both clinicians and breast cancer survivors to be a potential risk factor for arm lymphedema, such an association was not observed in our study or the study by Kilbreath et al.[200] An association was seen between infection and lymphedema with a RR of8.51. The association between infection and lymphedema was also present rather we were looking at physician-diagnosed resolved or physician-diagnosed not resolved lymphedema. However, all but one participant had an arm infection after being diagnosed with arm lymphedema. It is probable that having arm lymphedema puts breast cancer survivors at risk for getting an arm infection due to decreased lymphatic circulation.

Strengths

This study was conducted using a population-based cohort of breast cancer survivors 5 to 6 years after breast cancer diagnosis**,** thereby avoiding erroneous inclusion of acute lymphedema cases. Participants reporting physician-diagnosed lymphedema were additionally asked if their condition has since resolved to decrease misclassification. Furthermore, objective and subjective assessments were applied to capture subclinical cases. Thirty-two percent of subjects reporting resolved lymphedema were later identified to have lymphedema through subclinical means. In addition, obtaining lymphedema status 5 or more years after breast cancer diagnosis allowed us to observe the long term risk from treatments, as many studies have short follow up times of 1-2 years after diagnosis or treatments.

Limitations

The biggest challenge was that the physician diagnosis of lymphedema was self-reported and was not further confirmed through medical charts. Additionally, our two other measures of lymphedema were also self-reported. Although there were no established questionnaire available to measure upper arm activity, our questionnaire was modeled after other established physical activity questionnaires and underwent cognitive interviewing and piloting during questionnaire development. Due to caller identification and increased usage of cell phones, we were unable to reach as many subjects as we anticipated. A letter was sent to potential subjects we could not reach to request their phone numbers in an attempt to address this technological problem.

Conclusions

Among this cohort of breast cancer survivors, we found lymphedema to be prevalent in 19.5%, with most developing lymphedema within the first 2 years after surgery. The presence of both axillary dissection and radiation therapy doubled the risk of developing arm lymphedema. Younger age and high BMI also were associated with arm lymphedema development. Low level of arm activity was not found to be associated with arm lymphedema. This study indirectly suggests that maintaining a normal BMI may reduce the risk of developing lymphedema. However, further assessments of these findings through prospective intervention studies are needed.

Table 5.1. Distribution of Lymphedema Assessments among Study Participants Diagnosed with Breast Cancer in Iowa, 2004.

	Participants N=522	%
Physician diagnosed lymphedema		
Unresolved	44	8.4
Resolved	28	5.4
Not diagnosed	450	86.2
Arm measurement		
>2cm difference between arms	49	9.4
≤ 2 cm difference between arms	351	67.2
Missing	122	23.4
Arm symptoms[a]		
Subjective indication of arm lymphedema	45	8.6
No subjective indication of arm lymphedema	477	91.4
Study Definition of arm lymphedema[b]		
Arm lymphedema	102	19.5
No arm lymphedema	420	80.5

[a] Subjective indication is present if subject has at least 2 major symptoms and at least 4 total symptoms

[b] Physician-diagnosed (not resolved), >2cm difference between arms, and subjective indication of arm lymphedema

Table 5.2. Relative Risk of Demographic Factors and Lymphedema among Subjects Diagnosed with Breast Cancer in Iowa, 2004

	Lymphedema		Crude		Adjusted	
	Yes	No	RR	CI	RR	CI
Age						
25-49	20 (19.6)	49 (11.7)	Ref		Ref [a]	
50-54	14 (13.7)	57 (13.6)	0.62	0.28-1.35	0.59	0.26-1.35
55-59	13 (12.8)	60 (14.3)	0.55	0.25-1.23	0.52	0.22-1.19
60-64	13 (12.8)	61 (14.5)	0.54	0.24-1.20	0.45	0.20-1.05
65-69	16 (15.7)	51 (12.1)	0.77	0.36-1.65	0.63	0.28-1.45
70-74	14 (13.7)	56 (13.3)	0.62	0.28-1.37	0.58	0.26-1.33
75+	12 (11.8)	86 (20.5)	0.34	0.15-0.76	0.35	0.15-0.81
Trend OR [b]			0.53	0.28-1.00	p-value	0.051
Education						
≤ High school	45 (44.6)	192 (46)	Ref		Ref [c]	
Some college	25 (24.8)	98 (23.5)	1.09	0.63-1.88	0.91	0.51-1.62
≥ College	31 (30.7)	127 (30.5)	1.04	0.63-1.73	0.95	0.55-1.64
Trend OR [b]			1.05	0.63-1.74	p-value	0.8561
Married						
No	33 (33)	124 (29.5)	Ref		Ref [d]	
Yes	67 (67)	296 (70.5)	0.85	0.53-1.36	0.76	0.47-1.23
Body mass index (kg/m^2) [f]						
<18.5	0	4 (1)	N/A		N/A	
18.5-24.9	22 (21.8)	138 (33.1)	Ref		Ref [e]	
25-29.9	28 (27.7)	140 (33.6)	1.26	0.68-2.30	1.25	0.68-2.32
30-34.9	20 (19.8)	83 (19.9)	1.51	0.78-2.94	1.56	0.79-3.06
35-39.9	13 (12.9)	35 (8.4)	2.33	1.07-5.08	2.45	1.01-5.43
40+	18 (17.8)	17 (4.1)	6.64	2.98-14.80	5.71	2.53-12.87
Trend OR [b]			5.08	2.51-10.28	p-value	<0.0001
Obesity	51 (50.5)	135 (32.4)	2.13	1.37-3.31	2.25 [d]	1.44-3.53
Overweight	79 (78.2)	275 (66)	1.85	1.11-3.10	1.93 [d]	1.15-3.24

Note: Total number of subjects may not add up to 522 due to missing data

[a] Adjusted for BMI, axillary dissection, and number of lymph nodes removed

[b] Trend OR from the lowest to highest categories

[c] Adjusted for BMI, age

[d] Adjusted for age

[e] Adjusted for axillary dissection, age

[f] Mantel-Haenszel chi-square test for trend <0.001

Table 5.3. Interaction Effect on Arm Lymphedema between Axillary Dissection and Radiation

	Lymphedema		Crude		Adjusted	
	Yes	No	RR	CI	RR	CI
Axillary dissection						
No Radiation			Ref	-	Ref [a]	-
Radiation	56 (70.0)	139 (43.9)	1.91	1.12-3.28	2.61	1.27-5.39
No axillary dissection						
No Radiation			Ref	-	Ref [a]	-
Radiation	13 (59.1)	114 (75.0)	0.48	0.19-1.22	0.47	0.10-2.29

[a] Adjusted for age and surgery type

Table 5.4. Relative Risk of Lymphedema by Breast Cancer Treatment and Disease Factors among Subjects Diagnosed with Breast Cancer in Iowa, 2004

	Lymphedema		Crude		Adjusted	
	Yes	No	RR	CI	RR	CI
Surgery						
Lumpectomy	54 (52.9)	243 (58.1)	Ref		Ref [a]	
Mastectomy	13 (12.8)	56 (13.4)	1.05	0.53-2.05	1.17	0.56-2.46
Modified radical mastectomy	35 (34.3)	119 (28.5)	1.32	0.82-2.14	1.08	0.62-1.88
Trend OR [b].			1.15	0.91-1.46	p-value	0.2459
Radiation to the axilla[c]						
No	60 (65.2)	272 (61.8)	Ref		Ref [a]	
Yes	32 (34.8)	107 (28.2)	1.36	0.84-2.20	1.25	0.76-2.04
Chemotherapy						
No	40 (40)	208 (49.9)	Ref		Ref [e]	
Yes	60 (60)	209 (50.1)	1.49	0.96-2.33	1.09	0.67-1.78
Hormones therapy						
No	47 (47)	183 (44.6)	Ref		Ref [a]	
Yes	53 (53)	227 (55.4)	0.91	0.59-1.41	0.90	0.58-1.40
# of lymph node removed [f]						
0-2	17 (16.8)	126 (30.4)	Ref		Ref [e]	
3-6	21 (20.8)	108 (26.0)	1.44	0.72-2.87	1.04	0.48-2.26
7-10	18 (17.8)	57 (13.73)	2.34	1.13-4.87	1.29	0.50-3.33
>10	45 (44.6)	124 (29.9)	2.69	1.46-4.95	1.45	0.61-3.47
Trend OR [b]			2.69	1.53-4.70	p-value	0.0005
Stage [f]						
Stage I	42 (42)	235 (58.2)	Ref		Ref [e]	
Stage II	38 (38)	139 (34.4)	1.53	0.94-2.49	1.11	0.66-1.89
Stage III	20 (20)	30 (7.4)	3.73	1.94-7.18	2.52	1.25-5.10
Trend OR [b]			3.35	1.79-6.26	p-value	0.0002
Positive nodes [f]						
0	54 (52.9)	300 (73.7)	Ref		Ref [e]	
1-2	29 (28.4)	69 (17.0)	2.34	1.39-3.93	1.81	1.03-3.19
>2	19 (18.6)	38 (9.3)	2.78	1.49-5.18	2.09	1.07-4.09
Trend OR [b]			3.14	1.76-5.60	p-value	0.0001

Table 5.4. Continued

Primary tumor size [f]						
0-9	15 (15.8)	106 (26.6)	Ref		Ref [g]	
10-14	17 (17.9)	88 (22.1)	1.37	0.65-2.89	1.17	0.54-2.54
15-29	39 (41.1)	158 (39.6)	1.74	0.92-3.32	1.38	0.68-2.82
30+	24 (25.3)	47 (11.8)	3.61	1.74-7.49	2.62	1.11-6.17
Trend OR [b]			3.32	1.64-6.70	p-value	0.0008

Note: Total number of subjects may not add up to 522 due to missing data

[a] Adjusted for age, radiation to axilla and axillary dissection

[b] Trend OR from the lowest to highest categories

[c] Among subjects who received radiation therapy

[d] Adjusted for age

[e] Adjusted for age and axillary dissection

[f] Mantel-Haenszel chi-square test for trend <0.001

[g] Adjusted for age, axillary dissection, chemotherapy, and number of lymph nodes removed

Table 5.5. Chronic Conditions and the Risk of Lymphedema among Iowa Breast Cancer Survivors Diagnosed in 2004 and followed through 2010

	Lymphedema		Crude		Adjusted [b]	
Chronic conditions [a]	Cases (Y/N)	Controls (Y/N)	RR	CI	RR	CI
High blood pressure	29/72	116/292	1.01	0.63-1.64	0.92	0.53-1.59
High cholesterol	25/75	107/304	0.95	0.57-1.57	1.06	0.61-1.82
Heart attack	2/100	7/412	1.18	0.24-5.75	1.84	0.36-9.49
Coronary heart disease	2/99	8/410	1.04	0.22-4.95	1.69	0.35-8.30
Stroke	1/101	10/408	0.40	0.05-3.19	0.51	0.06-4.16
Congestive heart failure	1/100	3/416	1.39	0.14-13.47	1.78	0.18-17.49
Emphysema	1/101	3/416	1.37	0.14-13.34	2.49	0.25-25.02
Chronic bronchitis	8/92	10/409	3.56	1.37-9.26	3.30	1.23-8.85
Asthma	12/90	30/387	1.72	0.85-3.49	1.63	0.78-3.39
Thyroid condition	18/84	57/361	1.36	0.76-2.43	1.56	0.84-2.90
Liver	1/99	11/404	0.37	0.05-2.91	0.41	0.05-3.32
Kidney failure	4/97	3/416	5.72	1.26-25.95	4.70	0.91-24.29
Osteoporosis	8/93	31/384	1.07	0.47-2.39	1.38	0.57-3.29
Diabetes	9/92	30/386	1.26	0.58-3.07	0.96	0.42-2.20
Arthritis	35/66	109/299	1.46	0.91-2.32	1.56	0.93-2.62

[a] These conditions were diagnosed prior to breast cancer diagnosis or prior to a diagnosis of lymphedema

[b] Adjusted for age and BMI

Table 5.6. Relative Risk of Arm Activities and Lymphedema among Subjects Diagnosed with Breast Cancer in Iowa, 2004

	Lymphedema		Crude		Adjusted	
Arm activities	Yes	No	RR	CI	RR	CI
General:						
Swimming	18 (17.8)	74 (17.7)	1.01	0.57-1.78	0.89 [a]	0.49-1.62
Playing tennis	1 (1)	8 (1.9)	0.51	0.06-4.12	0.57[a]	0.07-4.70
Weightlifting	27 (26.5)	107 (25.5)	1.05	0.64-1.72	1.11[a]	0.66-1.85
Gardening	67 (65.7)	254 (60.5)	1.25	0.80-1.97	1.30 [a]	0.81-2.07
Above the shoulders: 1 year <u>before</u> breast cancer						
High	31 (30.7)	68 (16.7)	Ref		Ref [b]	
Medium	31 (30.7)	168 (41.2)	0.41	0.23-0.72	0.43	0.24-0.77
Low	39 (38.6)	172 (42.5)	0.50	0.29-0.86	0.57	0.32-1.01
Below the shoulders: 1 year <u>before</u> breast cancer						
High	54 (54)	194 (47.7)	Ref		Ref [b]	
Medium	31 (31)	144 (35.4)	0.77	0.47-1.26	0.79	0.48-1.30
Low	15 (15)	69 (17.0)	0.78	0.41-1.47	0.91	0.47-1.75
Above the shoulders: 1 year <u>after</u> resuming routine activities						
High	15 (15.2)	49 (12.2)	Ref		Ref [b]	
Medium	29 (29.3)	159 (39.5)	0.60	0.30-1.20	0.65	0.32-1.31
Low	55 (55.6)	195 (48.4)	0.92	0.48-1.77	1.08	0.56-2.12
Below the shoulders: 1 year <u>after</u> resuming routine activities						
High	28 (28)	160 (39.4)	Ref		Ref [b]	
Medium	34 (34)	146 (36)	1.33	0.77-2.30	1.34	0.77-2.33
Low	38 (38)	100 (24.6)	2.17	1.26-3.76	2.40	1.38-4.20
Above shoulders: Past year						
High	156(15.7)	49 (11.9)	Ref		Ref [b]	
Medium	30 (29.4)	165 (40.2)	0.56	0.28-1.11	0.62	0.31-1.23
Low	56 (54.9)	197 (47.9)	0.87	0.46-1.65	1.06	0.54-2.04
Below shoulders: Past year						
High	33 (33.3)	166 (32.7)	Ref		Ref [b]	
Medium	33 (33.3)	148 (36.2)	1.12	0.66-1.91	1.14	0.67-1.94
Low	33 (33.3)	95 (23.3)	1.75	1.01-3.01	2.04	1.16-3.56

Table 5.6. Continued

Dominant hand	55 (56.7)	193 (46.8)	1.49	0.95-2.32	1.47 [b]	0.94-2.30
Arm Infection	11 (11)	6 (1.4)	8.51	3.07-23.61	8.04 [b]	2.89-22.4
Airplane Trip (any)	42 (41.2)	172 (41.7)	0.98	0.63-1.52	0.93 [b]	0.59-1.44

[a] Adjusted for BMI, age

[b] Adjusted for age

Table 5.7. Changes in Arm Activity among Breast Cancer Survivors in Iowa Diagnosed in 2004 from One Year before Breast Cancer Diagnosis to One Year after Resuming Routine Household Activities

Arm Lymphedema Diagnosed:	1 year or less		1.5- 5 years		>5 years		No Lymphedema	
	N	%	N	%	N	%	N	%
Upper vigorous								
Decreased [a]	18	40.9	5	27.8	4	13.8	54	13.1
No change	24	54.6	12	66.7	22	75.9	335	81.5
Increased	2	4.6	1	5.6	3	10.3	22	5.4
Upper moderate								
Decreased [a]	13	27.7	5	26.3	5	17.2	39	9.6
No change	33	70.2	14	73.7	24	82.8	355	87.4
Increased	1	2.1	0	0	0	0	12	3.0
Lower vigorous								
Decreased [a]	24	51.1	10	52.6	5	17.9	52	12.8
No change	23	48.9	9	47.4	22	78.6	347	85.7
Increased	0	0	0	0	1	3.6	6	1.5
Lower moderate								
Decreased [a]	13	27.7	3	15.8	3	10.7	43	10.4
No change	34	72.3	16	84.2	24	85.7	363	88.1
Increased	0	0	0	0	1	3.6	6	1.5

[a] Decreased = A decrease in arm activity level after resuming household activities as compared to the arm activity level before breast cancer diagnosis

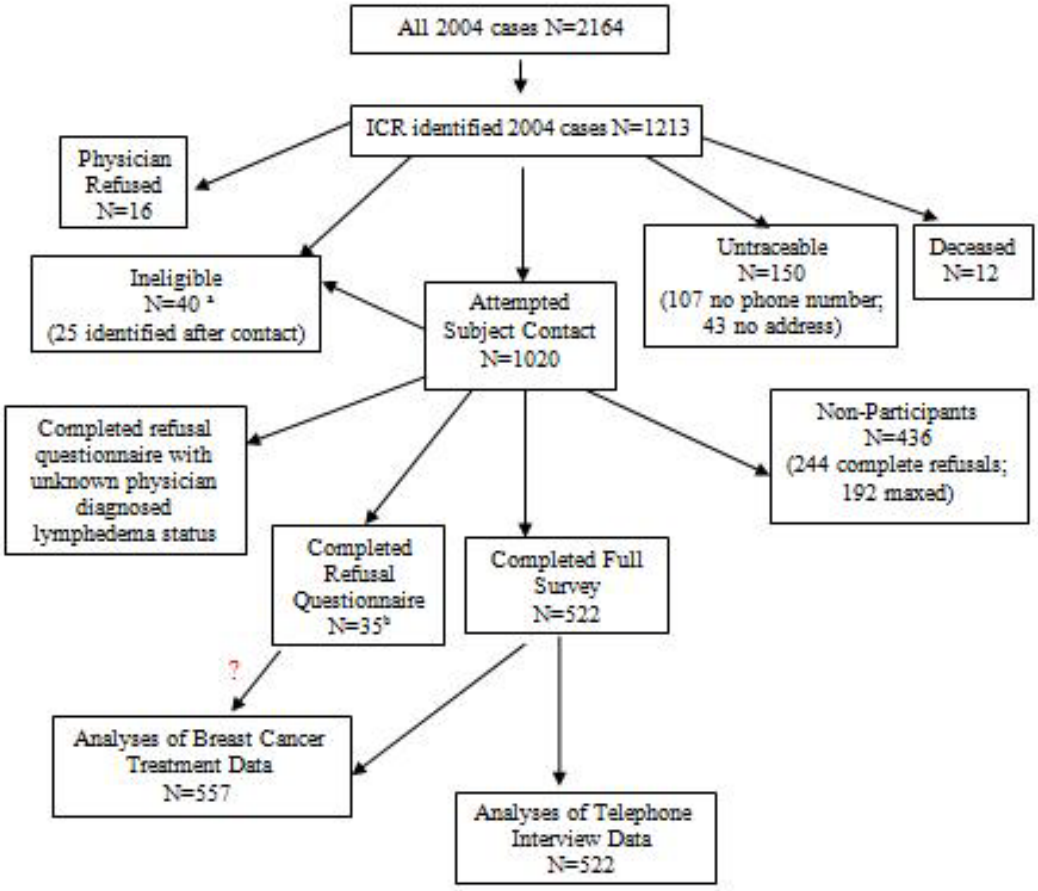


Figure 5.1. Recruitment Flow Chart of Breast Cancer Survivors Diagnosed with Breast Cancer in Iowa, 2004

[a] Reason for ineligibility include breast cancer in both breast, mentally handicapped, does not speak English, illness, hard of hearing, not diagnosed in 2004 and no arms

[b] Refusal questionnaire included physician diagnosis of lymphedema, but does not differentiate between resolved and unresolved. It did not include arm measurements and only included a few symptoms. Thus, adding these 35 subjects to analyses of treatment data will represent under diagnosis of lymphedema

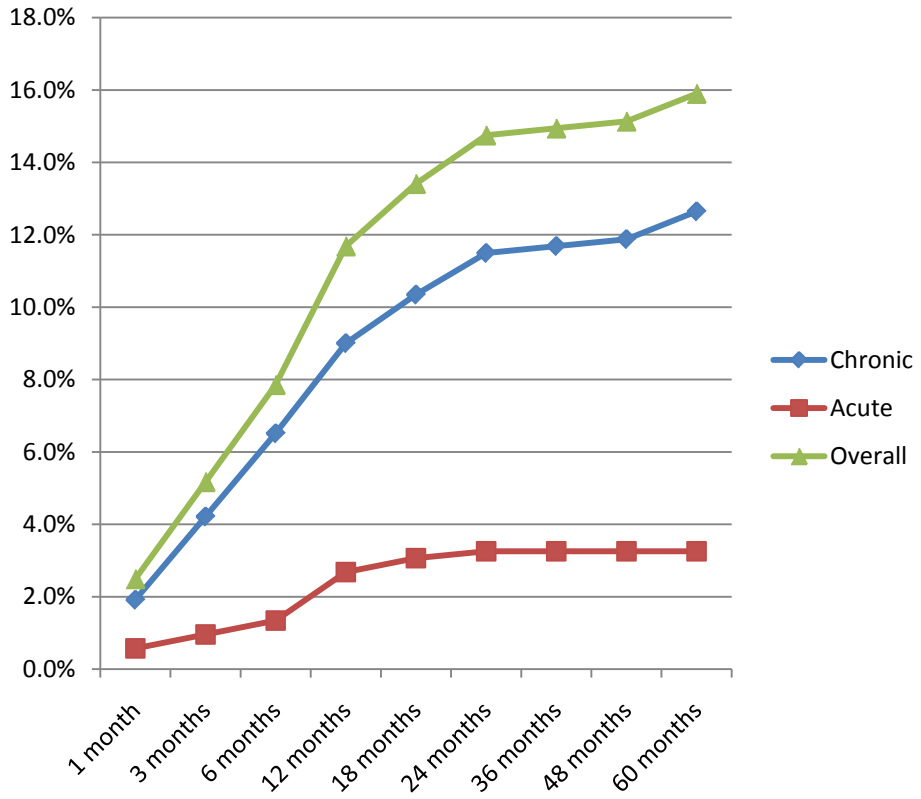


Figure 5.2. Cumulative Incidence of Arm Lymphedema diagnosed by a physician or by having 4 + symptoms among Breast Cancer Survivors in Iowa, 2004

CHAPTER 6: CONCLUSION

Previous studies of lymphedema have reported prevalence rates ranging from 0%[201] to 60%[116] with the majority of estimates around 10-20%. In our 2004 Iowa cohort of breast cancer survivors, we found that arm lymphedema affected around 20% of participating survivors. If left untreated, it can lead to serious inconveniences and consequences.

My results from the meta-analyses found lymphedema to be associated with treatments including mastectomy (over lumpectomy), extensive axillary dissection, radiation, and the presence of positive lymph nodes. The 2004 cohort of breast cancer survivors in Iowa similarly found that arm lymphedema was association with axillary dissection, radiation and presence of positive nodes. Both the meta-analysis and this study support that breast cancer treatment and higher cancer stages imposed a risk on lymphedema. However in the cohort study, an increased risk in lymphedema was only observed when both axillary dissection and radiation was used to treat breast cancer. Additionally, pooled evidence seen in the meta-analyses of associations with lymphedema and obesity, education, presence of co-morbidity, and injury to the arm revealed important risk factors for arm lymphedema after breast cancer. Among our 2004 cohort of breast cancer survivors in Iowa, we found similar associations with obesity. We did not observe an association with education and co-morbidity, and arm injuries was not examined in this study. Although we did not find an association with the presence of any co-morbid condition, it is probable that having arthritis or other autoimmune disorder may play a role in lymphedema due to immune attacks to the lymph vessels.

Meta-analysis of Treatment Factors

While numerous published studies have examined the association between breast cancer treatment factors and lymphedema, findings were not consistent across studies. The purpose of the meta-analysis in chapter 2 was to examine the strength and consistency of treatment-related factors by pooling findings from individual studies. Mastectomy, radiation, and axillary dissection often disrupt or damage the lymphatic system, and were believed by many to influence the development of lymphedema. Our pooled results confirmed these findings. The pooled analysis also found the presence of positive nodes, but not chemotherapy, to be associated with arm lymphedema.

Meta-analysis of Personal Factors

Aside from treatment factors, other factors, including modifiable factors were also found to contribute to the development of arm lymphedema. The purpose of the meta-analysis in chapter 3 was to look at the association between various personal factors and arm lymphedema. One particular focus was to look at modifiable risk factors such as body mass index and physical activities. Pooled analysis found that obesity (BMI >30), low education, injury and having at least one co-morbid condition increased the risk of developing arm lymphedema. Wound infection was also found to elevate the risk, but its effect was not significant. Age > 60 and hypertension was also identified as potential risk factor when stratification by study design, sample size, and self-report was done. Marital status, dominant hand, and diabetes were not found to be linked to arm lymphedema.

Breast Cancer Complication Study

The breast cancer complication study, alternatively title “Lymphedema among Iowan Women diagnosed with Breast Cancer in 2004” was a retrospective cohort study that looked at effect treatment, disease, personal and modifiable factors had on

lymphedema. For treatment factors, the combination of both axillary dissection and radiation was found to double the risk of arm lymphedema, thus was controlled for in other analyses. Diseases related factors such as advanced stage, presence of positive nodes, and large tumor size were found to be associated with lymphedema. Younger age and high BMI were also linked with lymphedema onset. Low level of arm activities below the shoulders was found to increase the likelihood of developing arm lymphedema. Surgery, chemotherapy, hormone therapy, number of lymph nodes removed, marital status, education, dominant hand were not found to be association with lymphedema.

The presence of any co-morbidity was not found to be linked with arm lymphedema. It is possible that kidney conditions, chronic bronchitis or arthritis may play a role in the development of lymphedema. However we were unable to draw a conclusion based on the sparse number of subjects with these conditions.

Meta-analysis versus Breast Cancer Complication Study

One of the biggest issues with pooled results from the meta-analysis papers was lack of adjustments for confounders. This may have contributed to the differences in findings between the meta-analysis results and the breast cancer complication study. Both the meta-analysis and the breast cancer complication study found axillary dissection and radiation to play a role in lymphedema development. However the breast cancer complication study only found a risk when both axillary dissection and radiation therapy were used to treat breast cancer. Many previous studies who contributed to the pooled results for the meta-analysis did not consider the modifying effect axillary dissection and radiation have on each other.

Diseases-related factors such as advanced stage, presence of positive nodes, and large tumor size were found to be associated with lymphedema in our cohort, similar to the results of the meta-analyses. Neither the meta-analyses nor study of Iowa women with breast cancer found an association with chemotherapy. Additionally, both our study

and the meta-analysis identified high BMI as a risk factor for lymphedema. Marital status and dominant hand were not found to be associated in either the meta-analysis or the breast cancer complication study.

While surgery type was found to have an effect on lymphedema in the meta-analysis, it was not identified as a risk factor in the breast cancer complication study. The distribution of axillary dissection among breast cancer surgery may explain the lack of association observed in this study. While 97% of subjects who had radical modified mastectomy had axillary dissection, it was observed that 54% of subjects with lumpectomy also had axillary dissection. Since axillary dissection had been consistently identified as the main culprit for impairing/damaging the lymphatic system, the high prevalence of axillary dissection in the reference group (lumpectomy) contributed to the current finding of no association.

Contrary to the meta-analyses, we saw an association between younger women and development of lymphedema. Furthermore, when pooled studies were stratified by study designs, prospective studies showed older women to have an increased risk for lymphedema. This contrasting result may be explained by the use of arm symptoms to identify lymphedema. Many published studies relied solely on objective measurements to determine lymphedema and may have failed to capture more subtle cases that did not meet the predetermined objective criteria. Younger breast cancer survivors are more likely to be active working women[62] and thus may be more aware of their arm symptoms than older women. Studies not incorporating arm symptoms to detect the presence of lymphedema may not observe this effect.

Physical activity was not associated with arm lymphedema in the meta-analysis. However, studies pooled in the meta-analysis measured physical activity in a variety of ways potentially causing heterogeneity. Thus, not all pooled studies may have been comparable. Furthermore, our study of Iowa women diagnosed with breast cancer in 2004 focused on arm movement separately above and below the shoulder and was

designed to measure arm activity level using frequency, intensity and positioning of arms.. The breast cancer complication study found low level of arm activities below the shoulders to be a risk for arm lymphedema. It is possible that the lack of details in assessing arm activities may have hindered prior studies from detecting a difference.

Both low education and co-morbidity were found to be associated with arm lymphedema in the meta-analysis, but were not found to be risk factors in our study of Iowa women. The rural population in Iowa may be less defined by education level than urban populations. The pooled association between any morbidity and lymphedema was based on different chronic conditions in different studies, thus it pooled heterogeneous conditions. Furthermore, there is lack of biologic plausibility for associations between lymphedema and the specific co-morbidities, such as chronic bronchitis, seen in our study. Overall, it is difficult to draw conclusions regarding co-morbidities based either on our study or the meta-analysis.

Future Directions

Lymphedema of the arm is a breast cancer complication that continues to affect the quality of life for breast cancer survivors through physical and psychological limitations. The research shows that while treatments for breast cancer increase the risk of lymphedema, modifiable factors such as body mass index and arm activity may be able to alleviate the risk posed by the cancer treatments.

While we found that decreasing arm activities below the shoulder were associated with the development of arm lymphedema, the association may be partially attributed to decreased arm activity due to lymphedema. An intervention designed to specifically study arm activities before lymphedema development is needed to further examine if increased arm activity below the shoulder may delay or prevent the development of arm lymphedema following breast cancer surgery. . A prospective study would greatly limit

recall bias as well as record more details regarding arm activity. It would also allow the onset of arm lymphedema to be monitored.

APPENDIX A: SUPPLEMENTARY TABLES

Table A.1. Comparison of objective (>2cm difference arms) and subjective (arm symptoms) among physician and non-physician-diagnosed lymphedema in breast cancer cases diagnosed in Iowa, 2004 [a]

	Physician-Diagnosed Lymphedema (Resolved) N (%)	Physician-Diagnosed Lymphedema (NOT Resolved) N (%)	Non- Physician-Diagnosed Lymphedema N (%)
N=	28	44	450
<=2cm between arms	18 (64.3)	21 (47.7)	312 (69.3)
Arm symptoms [b] – No	15 (83.33)	15 (71.43)	302 (96.79)
Arm symptoms [b] –Yes	3 (16.67)	6 (28.57)	10 (3.21)
>2cm between arms	3 (10.7)	13 (29.5)	33 (7.3)
Arm symptoms [b] – No	2 (66.67)	4 (30.77)	30 (90.91)
Arm symptoms [b] –Yes	1 (33.33)	9 (69.23)	3 (9.09)
Missing arm measurements	7 (25.0)	10 (22.7)	105 (23.3)
Arm symptoms [b] – No	4 (57.14)	6 (60.00)	99 (94.29)
Arm symptoms [b] –Yes	3 (42.86)	4 (40.00)	6 (5.71)

[a] Only participants (N=522) were included in this table

[b] Arm symptoms are present if a subject presents with at least 4 arm symptoms, 2 of which are considered major symptoms. Major symptoms included: shirt sleeve felt tight, arm felt swollen, heavy, tense or hard. Minor symptoms included: arm felt numb, stiff, painful, rash on arm/itchy, other symptoms, and hand symptoms such as rings felt tight, and cannot see veins or knuckles.

Table A.2. Major and Total Arm Symptoms Counts among Iowa Subjects with Physician Diagnosed Lymphedema at Various Time Intervals, 2004 [a]

Date from initial breast cancer treatment to date of physician diagnosis [b]	<6 months	6 months to <1year	1 year to <3 years	3 years +
N=	29	16	16	7
Months to interview				
Mean	68.94	68.53	69.94	70.03
Median	69.37	68.3	69.78	69.20
Mode	64.4	N/A	N/A	N/A
Range	61.8 -75.47	59.8-73.97	64.6-74.8	67.5-73.6
Major symptoms[c]				
Mean	1.31	1.5	2.13	2.0
Median	1.0	1.0	2.0	2.0
Mode	0.0	0.0	0.0	0.0
Range	0 – 5	0 – 5	0 – 5	0 – 5
Total symptoms				
Mean	3.0	3.13	3.63	3.57
Median	3.0	1.5	3.0	3.0
Mode	1.0	1.0	1.0	0.0
Range	0 – 12	0 – 10	0 – 10	0 – 10
Restricted to subjects with physician-diagnosed arm lymphedema that has not resolved				
N=	19	8	10	5
Months to interview				
Mean	67.90	67.06	70.23	69.49
Median	68.17	67.03	70.50	67.80
Mode	-	N/A	N/A	N/A
Range	61.8-75.0	59.8 – 72.0	65.0 -74.7	67.5 -72.4
Major symptoms [c]				
Mean	1.47	2.13	2.6	1.8
Median	1.0	2.5	2.5	2.0
Mode	1.0	0.0	2.0	3.0
Range	0 – 5	0 – 5	0 – 5	0 – 3
Total symptoms				
Mean	3.37	4.5	4.4	3.0
Median	3.0	4.0	3.5	3.0
Mode	4.0	0.0	3.0	0.0
Range	0 -12	0 – 10	0 – 10	0 – 6

Table A.2. Continued

Among subjects with physician-diagnosed arm lymphedema (resolved)				
N=	10	8	6	2
Months to interview				
Mean	70.91	70.0	69.47	71.38
Median	71.58	70.27	68.88	71.38
Mode	N/A	N/A	N/A	N/A
Range	64.4-75.5	65.6-73.97	64.6-74.8	69.2-73.6
Major Symptoms [c]				
Mean	1.0	0.88	1.33	2.5
Median	0.0	1.0	1.0	2.5
Mode	0.0	1.0	0.0	N/A
Range	0 – 4	0 – 2	0 – 3	0 – 5
Total Symptoms				
Mean	2.3	1.75	2.33	5.0
Median	1.0	1.0	2.0	5.0
Mode	1.0	1.0	1.0	N/A
Range	0 – 7	1 – 4	0 – 5	0 – 10

[a] Only participants (N=522) were included in this table

[b] 3 subjects who claimed to develop lymphedema before any treatment was administered were removed from this analysis

[c] Major symptoms include: shirt sleeve felt tight, arm felt swollen, heavy, tense or hard

Table A.3. Comparison of Participants, Partial Participants, and Non-Participants among Women Diagnosed with Breast Cancer in Iowa, 2004

	Participants N (%)	Refusal Survey[a] N (%)	Non-participants N (%)
Total N=	522	37	436
Surgery			
Lumpectomy	297 (57.12)	17 (45.95)	244 (56.22)
Mastectomy	69 (13.27)	7 (18.92)	64 (14.75)
Modified Radical Mastectomy	154 (29.62)	13 (35.14)	126 (29.03)
Radiation			
No	192 (36.99)	18 (48.65)	164 (37.88)
Yes	327 (63.01)	19 (51.35)	269 (62.12)
Stage			
Stage 1	277 (54.96)	23 (65.71)	236 (55.40)
Stage 2	177 (35.12)	10 (28.57)	150 (35.21)
Stage 3	50 (9.92)	2 (5.71)	40 (9.39)
Chemotherapy			
No	248 (47.97)	28 (75.68)	230 (53.12)
Yes	269 (52.03)	9 (24.32)	203 (46.88)
Hormone therapy			
No	230 (45.10)	22 (61.11)	221 (51.52)
Yes	280 (54.90)	14 (38.89)	208 (48.48)
Positive lymph nodes			
0	354 (69.55)	26 (81.25)	311 (72.83)
1-2	98 (19.25)	4 (12.50)	71 (16.63)
>2	57 (11.20)	2 (6.25)	45 (10.54)
Mean	1.06	0.50	0.79
Median	0.0	0.0	0.0
Mode	0.0	0.0	0.0
Range	0-39	0-6	0-23
# lymph nodes examined			
1-2	131 (25.99)	10 (33.33)	129 (30.50)
3-6	129 (25.60)	9 (30.00)	104 (24.59)
7-10	75 (14.88)	5 (16.67)	63 (14.89)
>10	169 (33.53)	6 (20.00)	127 (30.02)
Mean	7.96	5.65	7.53
Median	6.0	3.5	5.0
Mode	1.0	1.0	1.0
Range	0-44	0-19	0-37

Table A.3. Continued

Tumor size (mm)				
	0-9	121 (24.49)	12 (35.29)	99 (24.03)
	10-14	105 (21.26)	5 (14.71)	95 (23.06)
	15-29	197 (39.88)	14 (41.18)	153 (37.14)
	30+	71 (14.37)	3 (8.82)	65 (15.78)
	Mean	19.05	15.79	18.84
	Median	15.0	14.0	15.0
	Mode	15.0	15.0	15.0
	Range	1-145	2-50	1-120
Scope of lymph node				
	Biopsy only	12 (2.30)	4 (10.81)	8 (1.83)
	Sentinel Node Biopsy	176 (33.72)	11 (29.73)	180 (41.28)
	Regional nodes removed	334 (63.98)	22 (59.46)	248 (56.88)
Axillary dissection				
	No	176 (34.51)	11 (33.33)	180 (42.06)
	Yes	334 (65.49)	22 (66.67)	248 (57.94)
Age				
	25-49	69 (13.22)	2 (5.41)	51 (11.70)
	50-54	71 (13.60)	1 (2.70)	52 (11.93)
	55-59	73 (13.98)	1 (2.70)	63 (14.45)
	60-64	74 (14.18)	6 (16.22)	58 (13.30)
	65-69	67 (12.84)	7 (18.92)	52 (11.93)
	70-74	70 (13.41)	7 (18.92)	53 (12.16)
	75+	98 (18.77)	13 (35.14)	107 (24.54)
	Mean	63.04	70.32	64.23
	Median	62.0	71.0	64.0
	Mode	61.0	69.0	58.0
	Range	35-85	45-84	29-85

[a] Short questionnaire asking about lymphedema status and arm symptoms if subject refused to participate

Table A.4.Comparison of Participation and Surgical Status among Breast Cancer Cases in Iowa, 2004

	Total subjects N (%)	Non-participants N (%)	Participants N (%)	Refusal Survey[a] N (%)	Untraceable[b] N (%)	Dead N (%)	Ineligible[c] N (%)	Physician Refusal N (%)
Total eligible subjects identified by Iowa Cancer Registry								
Total N=	1213[d]	436	522	37	150	12	40	16
no surgery or nodes removed	41 (3.38)	8 (1.83)	12 (2.30)	4 (10.81)	9 (6.04)	2 (16.67)	4 (10.0)	2 (16.50)
Among subjects who did not have surgery or nodes removed								
Developed lymphedema	N/A	N/A	0	0	N/A	N/A	N/A	N/A
Radiation								
No	22	5	7	1	5	1	2	1
Yes	19 (46.34)	3 (37.50)	5 (41.67)	3 (75.0)	4 (44.44)	1 (50.0)	2 (50.0)	1 (50.0)

[a] Short questionnaire asking about lymphedema status and arm symptoms if subject refused to participate

[b] Subjects that were not contacted due to incorrect address or phone number

[c] Ineligible subjects include: mentally impaired, breast cancer in both breasts, non-English speaking, too ill to participate, and hard of hearing

[d] Number of subjects initially identified by Iowa Cancer Registry

APPENDIX B: QUESTIONNAIRE

S1. Hello. May I speak with _____?

1. YES [GO TO S2 AFTER SUBJECT COMES ON]

2. NOT AVAILABLE, CORRECT NUMBER [GO TO SCHEDULINGNAME]

3. SUBJECT NO LONGER IN THIS HOUSEHOLD
   [IF SUBJECT NO LONGER IN THIS HOUSEHOLD]
   [IF AVAILABLE, ASK FOR NEW CONTACT INFORMATION:
   SCRIPT- PLEASE ASK FOR CONTACT INFORMATION FOR THE SUBJECT IF AVAILABLE AND RECORD IN CALL SHEET]
   [RECORD IN CALL SHEET][SAVE AND END INTERVIEW]

4. DECEASED
   [IF DECEASED]
   I'm very sorry to hear that. We will note this in our records. [RECORD IN CALL SHEET] [GO TO END CALL2]

5. WRONG NUMBER
   [IF WRONG NUMBER]
   Did I dial (_ _ _) _ _ _ - _ _ _ _?
   IF YES: I must have the wrong number. I'm sorry.
   IF NO: I dialed the wrong number. I'm sorry.
   [RECORD IN CALL SHEET][GO TO END CALL2]

6. LEAVE MESSAGE ON MACHINE
   I'm calling from the State Health Registry of Iowa at the University of Iowa regarding a research study we are conducting. We will attempt to reach [Subject's name] at another time, or she can call Julie at (319) 335-8089. Thank you.

S2. My name is _____. I'm calling from the State Health Registry of Iowa. I'm calling to follow up on a letter we mailed out regarding our breast cancer study. Did you receive this letter?

1. Yes [GO TO S5]
2. No
3. REFUSED TO PARTICIPATE [GO TO RFQ1]

S3. Would you prefer that I resend the letter or tell you about this study over the phone?

1. RESEND LETTER [GO TO S3.1.PERSON]

S3.1.PERSON. First, let me make certain that I've reached the correct individual. Have I reached __LINK FULL NAME__ who reported a date of birth of __LINK BIRTHDATE__?

1. YES [GO TO S3.1.ADDRESS]
2. NO [APOLOGIZE AND RECORD IN CALL SHEET] [GO TO END CALL2]

S3.1.ADDRESS. Is your address __LINK TO ADDRESS__?

1. YES: Thank you, we will resend this letter to you right away. Again, thank you for your time.

2. NO: [RECORD NEW ADDRESS] Thank you, we will resend this letter to you right away. Again, thank you for your time.

2. TALK ABOUT STUDY OVER PHONE [GO TO S3A]

3. REFUSED TO PARTICIPATE [GO TO RFQ1]

S3A. This is a research study conducted by investigators at the State Health Registry of Iowa and the College of Public Health. The purpose of the study is to learn about the consequences of breast cancer treatment. This research will involve a 15 to 20-minute telephone interview asking you questions regarding your experience as a survivor of breast cancer.
There are no foreseeable risks to participating in this research study and you will not benefit personally. However we hope what we learn can benefit others in the future. This information will be linked to your existing data in the State Health Registry of Iowa. All of your information will be kept strictly confidential; however federal regulatory agencies and the University of Iowa Institutional Review Board may inspect and copy records pertaining to this research. You will not be identified from any report or article we published pertaining to this study. You will not be paid for being in this study. Your participation is completely voluntary. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify. Do you have any questions regarding the rights of human subjects?

1. Yes
2. No [GO TO S5]
3. REFUSE TO PARTICIPATE [GO TO RFQ1]

S4. To learn more about rights of research subjects or research-related injury, you can write to the Human Subjects Office at 300 College of Medicine Administration Building, The University of Iowa, Iowa City, Iowa, 52242, call number (319) 335-6564, or e-mail to irb@uiowa.edu. [GO TO SCHEDULING]

S5. You were identified by the State Health Registry of Iowa because you were diagnosed with breast cancer in _LINK TO YEAR OF DX_. We are concerned with the impact of breast cancer on patients. All your answers will remain confidential and will be used for research purposes only. You will not be individually identified in any of the study reports. This interview will take about 15 to 20 minutes and you can interrupt me at any time.

Would now be a good time to answer some questions?

1. Yes [GO TO S6]
2. No [GO TO SCHEDULING]

S6. To ensure the quality of this research, we plan to audio tape this interview. All recordings will be erased at the conclusion of this study. If you do not wish to be taped, please let us know. Is it alright for me to record this interview?

1. Yes [START RECORDING]
2. No [NO RECORDING]

S7. To make sure we have the right person, is your birthday (___LINK TO ICR DATE OF BIRTH__)?

1. Yes [GO TO BSIDE]
2. No [GO TO EXIT INTERVIEW]
3. DK/REF [GO TO VERIFYING]

****

REFUSAL QUESTIONNAIRE

We are interested in how many women with breast cancer have trouble with their arm or get lymphedema.

RFQ1. Would you be willing to answer a few questions regarding your arm? It will only take a couple of minutes.

1) Yes [go to RFQ2]
2) No [SAVE AND EXIT]

Some women experience swelling or retention of fluid in their arm after breast cancer treatments. This condition is called lymphedema and is caused by the accumulation of lymph fluid in the arm.

RFQ2. At any time after your breast cancer diagnosis, did a doctor ever tell you that you have lymphedema or swelling of the arm?

1) Yes
2) No [Go to RFQ4]
3) DK [Go to RFQ4]
4) REF [SAVE AND EXIT]

RFQ3. What month and year were you diagnosed with lymphedema?
IF SUBJECT HESITATES OR TAKES TOO LONG, ENCOURAGE SUBJECT TO GIVE AN ESTIMATE

ENTER MONTH_____ ___DK ___REF
ENTER YEAR _____ ___DK __ REF

During the past 3 months, have you experienced any of the following symptoms in your _LINK TO ICR LATERALITY ___ arm?

RFQ4	Has your shirt sleeve felt tight or has it irritated your arm?	Yes	No	DK/REF
RFQ5	Has your arm felt swollen	Yes	No	DK/REF
RFQ6	Has your arm felt painful?	Yes	No	DK/REF
RFQ7	Have your rings felt tight?	Yes	No	DK/REF/ NO RINGS

RFQ8 [SELECT CONTINUE TO INTERVIEW IF SUBJECT EXPRESSES INTEREST IN PARTICIPATING, OTHERWISE EXIT INTERVIEW]

1) EXIT INTERVIEW [ENDING SCRIPT]
2) CONTINUE TO INTERVIEW [GO TO BSIDE]

CATI PROGRAMMER: ADD ALLOWANCE FOR A WOMAN TO AGREE TO ANSWER THE REMAINDER OF THE QUESTIONNAIRE IF THEY VOLUNTEER TO THE INTERVIEWER (I.E., THE INTERVIEWER WILL NOT ASK THEM) BUT THEN THEY NEED TO BE MARKED AS KNOWING THE STUDY HYPOTHESIS.

****
EXIT AND END CALL SCRIPTS

SCHEDULING. [GO TO CALL DOCUMENTATION TABLE]
What times would be most convenient for me to call you back?
Thank you, we look forward to speaking with you.

SCHEDULINGNAME [GO TO CALL SHEET]
What times would be most convenient for me to call [SUBJECT's NAME] back?
Thank you, we look forward to speaking with [SUBJECT's NAME] you.

END CALL. We greatly appreciate your participation and your consideration of this study. Thank you.

END CALL2. Thank you for your time, have a good day.

VERIFYING. Thank you for your participation. However, without verifying this answer I cannot continue with this interview. Thank you for your time and have a good day.

EXIT INTERVIEW. I'm sorry to bother you. We will document this in our records. Thank you and have a good day.

NOT ELIGIBLE EXIT INTERVIEW. We greatly appreciate your participation and your consideration of this study. However, you are currently not eligible for this study. We appreciate your time

ENDING SCRIPT. Thank you for answering this questionnaire, we value your participation and contribution to this research project.

****

BSIDE. In which breast was your breast cancer diagnosed?

1. Right
2. Left
3. Both [GO TO NOT ELIGIBLE, EXIT INTERVIEW]
4. DK/REF [GO TO VERIFYING]

Q1. Did you receive radiation therapy as a treatment for breast cancer?

1. Yes
2. No [GO TO Q2]
3. DK/REF [GO TO Q2]

Q1. What were the specific areas in which you received radiation therapy?

A	Was it in the Breast/Chest?	Yes	No	DK
B	Was it in the Axillary Area/Arm pit?	Yes	No	DK
C	Was it in any Other areas? [GO TO Q1D]	Yes	No	DK
D	Please specify [OPEN ENDED QUESTION]	Yes	No	DK

Q2. What month and year did you resume routine household activities, with little or no hindrance, after receiving breast cancer treatment(s)?

_____MONTH _____YEAR

Q3. Since your breast cancer diagnosis, have you experienced an infection in your __LINK BSIDE_ arm? Such infection may be accompanied by a fever or may have required antibiotics.

1. Yes
2. No [GO TO Q4]
3. Yes to other arm [GO TO Q4]
4. DK/REF [GO TO Q4]

Q3A. Since your breast cancer diagnosis, how many times have you had an infection in your _ LINK BSIDE ___ arm?

_____ TIMES

Q4. We are interested in chronic conditions that you have.

Did a doctor, nurse or other health professional <u>ever</u> tell you that you had abnormally high blood pressure (hypertension)?

1. Yes
2. Told borderline high or pre-hypertensive [GO TO Q5]
3. No [GO TO Q5]
4. DK/REF [GO TO Q5]

Q4A. Was this before or after your breast cancer diagnosis?

1. Before
2. After
3. DK/REF

Q4B. Was this only when you were pregnant?

1. Yes
2. No
3. DK/REF

Did a doctor, nurse or other health professional ever tell you that you had any of the following health conditions?

Q5	High cholesterol?	Yes	No[Q6]	DK/REF
Q5A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q6.	Heart attack, also called a myocardial infarction?	Yes	No[Q7]	DK/REF
Q6A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q7.	Coronary heart disease or Angina?	Yes	No[Q8]	DK/REF
Q7A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q8.	Stroke or brain attack?	Yes	No[Q9]	DK/REF
Q8A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q9.	Congestive heart failure?	Yes	No[Q10]	DK/REF
Q9A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q10.	Emphysema?	Yes	No[Q11]	DK/REF
Q10A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q11.	Chronic bronchitis?	Yes	No[Q12]	DK/REF
Q11A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q12.	Asthma?	Yes	No[Q13]	DK/REF
Q12A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q13.	Thyroid problems?	Yes	No[Q14]	DK/REF
Q13A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q14.	Any kind of liver conditions?	Yes	No[Q15]	DK/REF

Q14A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q15.	Weak or failing kidneys? Do not include kidney stones, bladder infections, or incontinence.	Yes	No[Q16]	DK/REF
Q15A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q16.	Osteoporosis?	Yes	No[Q17]	DK/REF
Q16A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q17.	Pre-diabetes, diabetes or "sugar diabetes"?	Yes	No[Q18]	DK/REF
Q17A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF
Q18.	Some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia (Include osteoarthritis)?	Yes	No[Q19]	DK/REF
Q18A.	Was this before or after your breast cancer diagnosis?	Before	After	DK/REF

Q19. <u>After your breast cancer</u> treatment(s) were you treated by a physical therapist?

1. Yes
2. No [GO TO Q20]
3. DK/REF [GO TO Q20]

Q19A. For how many weeks did you attend physical therapy because of your breast cancer treatment?

_____WEEKS [OPTIONS 1-52, DK]

Q20. Now I'm going to ask about your participation in some specific activities after your breast cancer diagnosis, treatment(s), and recovery.

Did you swim?

1. Yes
2. No [GO TO Q21]
3. DK/REF [GO TO Q21]

Q20A. How many days per week, including weekends, did you swim?

_____DAYS/WEEK [OPTIONS 0-7, DK] [IF 0 GO TO Q21]

Q20B. How many minutes per day did you swim?

_____MINUTES/DAY [OPTIONS 0-1440, DK]

Q21. Did you play tennis?

1. Yes
2. No [GO TO Q22]
3. DK/REF [GO TO Q22]

Q21A. How many days per week, including weekends, did you play tennis?

_____DAYS/WEEK [OPTIONS 0-7, DK] [IF 0 GO TO Q22]

Q21B. How many minutes per day did you play tennis?

_____MINUTES/DAY [OPTIONS 0-1440, DK]

Q22. Did you do weight training for your arms?

1. Yes
2. No [GO TO Q23]
3. DK/REF [GO TO Q23]

Q22A. How many days per week, including weekends, did you do weight training for your arms?

_____DAYS/WEEK [OPTIONS 0-7, DK] [IF 0 GO TO Q23]

Q22B. How many minutes per day did you do weight training for your arms?

_____MINUTES/DAY [OPTIONS 0-1440, DK]

Q22C. How often were your arms elevated above your heart when you were lifting weights? Would you say… [READ OPTIONS]

1. Never
2. Rarely
3. Sometimes
4. Most of the time
5. All of the time
6. DK/REF

Q23. Did you garden?

1. Yes
2. No [GO TO Q24]
3. DK/REF [GO TO Q24]

Q23A. How many days per week, including weekends, did you garden?

_____DAYS/WEEK [OPTIONS 0-7, DK] [IF 0 GO TO Q24]

Q23B. How many minutes per day did you garden?

_____MINUTES/DAY [OPTIONS 0-1440, DK]

Q24. Are there any physical activities that you used to do that you stopped doing after your breast cancer diagnosis?

1. Yes
2. No [GO TO Q25]
3. DK/REF [GO TO Q25]

Q24A. What are these activities? [OPEN ENDED ANSWER]

Q24B. Why did you stop doing them? [OPEN ENDED ANSWER]

Q25. How many round-trip airplane trips did you take in the 12 months after you recovered from breast cancer treatment(s)?

_____TRIPS [OPTIONS 0-97, DK]

Q26. How many one-way airplane trips did you take in the 12 months after you recovered from breast cancer treatment(s)?

_____TRIPS [OPTIONS 0-97, DK]

****

PUV1. Now I am going to ask about activities you did around the house or at work. Please look at the arm activity sheet sent to you with the letter. I will be asking you questions from this sheet. If you do not have this sheet, you can still answer these questions.

I am going to ask you about 4 different types of arm activities. These activities include both vigorous and moderate arm activities, above and below your shoulders. I'm going to start with **vigorous** arm activities that usually require your arms to be **lifted above your shoulders,** such as playing tennis, lifting heavy objects, or weight lifting.

Did you do **vigorous** arm activities that **required** your arms to be lifted above your shoulders in **the past year**?

1) Yes
2) No [Go to PUV2]
3) DK/REF [Go to PUV2]

PUV1CAT. On average, how many **hour(s) per week,** did you do **vigorous** arm activities that **required** your arms to be lifted above your shoulders in **the past year**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PUV2. Did you do **vigorous** arm activities that **required** your arms to be lifted above your shoulders, **one year prior to your breast cancer diagnosis**?

1) Yes
2) No [Go to PUV3]
3) DK/REF [Go to PUV3]

PUV2CAT. On average, how many **hour(s) per week**, did you do **vigorous** arm activities that **required** your arms to be lifted above your shoulders, **one year prior to your breast cancer diagnosis**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PUV3. Did you do **vigorous** arm activities that **required** your arms to be lifted above your shoulders, **one year after you were able to resume routine household activities**?

1) Yes
2) No [Go to PUM1]
3) DK/REF [Go to PUM1]

PUV3CAT. On average, how many **hour(s) per week,** did you do **vigorous** arm activities that **required** your arms to be lifted above your shoulders, **one year after you were able to resume routine household activities**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PUM1. Now think about **moderate** arm activities that usually require your arms to be **lifted above your shoulders,** such as dusting high places, hanging up clothes, or playing golf.

Did you do **moderate** arm activities that **required** your arms to be lifted above your shoulders in **the past year**?

6) Yes
7) No [Go to PUM2]
8) DK/REF [Go to PUM2]

PUM1CAT. On average, how many **hour(s) per week,** did you do **moderate** arm activities that **required** your arms to be lifted above your shoulders in **the past year**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PUM2. Did you do **moderate** arm activities that **required** your arms to be lifted above your shoulders, **one year prior to your breast cancer diagnosis**?

1) Yes
2) No [Go to PUM3]
3) DK/REF [Go to PUM3]

PUM2CAT. On average, how many **hour(s) per week**, did you do **moderate** arm activities that **required** your arms to be lifted above your shoulders, **one year prior to your breast cancer diagnosis**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PUM3. Did you do **moderate** arm activities that **required** your arms to be lifted above your shoulders, **one year after you were able to resume routine household activities**?

1) Yes
2) No [Go to PLV1]
3) DK/REF [Go to PLV1]

PUM3CAT. On average, how many **hour(s) per week**, did you do **moderate** arm activities that **required** your arms to be lifted above your shoulders, **one year after you resumed routine household activities**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PLV1. The next few questions refer to activities you did around the house or at work that did **not** require your arms to be lifted above your shoulders. First think about **vigorous** arm activities such as scrubbing the floor, rowing, raking leaves or shoveling snow that **did not** require your arms to be elevated above your shoulders.

Did you do **vigorous** arm activities that did **not** require your arms to be lifted above your shoulders in **the past year**?

1) Yes
2) No [Go to PLV2]
3) DK/REF [Go to PLV2]

PLV1CAT. On average, how many **hour(s) per week,** did you do **vigorous** arm activities that did **not** require your arms to be lifted above your shoulders in **the past year**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PLV2. Did you do **vigorous** arm activities that did **not** require your arms to be lifted above your shoulders, **one year prior to your breast cancer diagnosis**?

1) Yes
2) No [Go to PLV3]
3) DK/REF [Go to PLV3]

PLV2CAT. On average, how many **hour(s) per week**, did you do **vigorous** arm activities that did **not** require your arms to be lifted above your shoulders, **one year prior to your breast cancer diagnosis**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PLV3. Did you do **vigorous** arm activities that did **not** require your arms to be lifted above your shoulders, **one year after you were able to resume routine household activities?**

1) Yes
2) No [Go to PLM1]
3) DK/REF [Go to PLM1]

PLV3CAT. On average, how many **hour(s) per week,** did you do **vigorous** arm activities that did **not** require your arms to be lifted above your shoulders, **one year after you resumed routine household activities**? Would you say… [READ OPTIONS]

1) Less than 1 hour
2) 1 to 2 hours
3) More than 2 hours but less than 5 hours
4) 5 or more hours
5) DK/REF

PLM1. Now think about **moderate** arm activities such as washing dishes, vacuuming, gardening, playing the piano, or bowling that did **not** require your arms to be elevated above your shoulders.

Did you do **moderate** arm activities that **did not** require your arms to be lifted above your shoulders in **the past year**?

1) Yes
2) No [Go to PLM2]
3) DK/REF [Go to PLM2]

PLM1CAT. Please listen carefully as the following categories have changed. On average, how many **hour(s) per week,** did you do **moderate** arm activities that did **not** require your arms to be lifted above your shoulders in **the past year**? Would you say… [READ OPTIONS]

1) Less than 3 hours
2) Between 3 and 10 hours
3) More than 10 hours but less than 20 hours
4) 20 or more hours
5) DK/REF

PLM2. Did you do **moderate** arm activities that did **not** require your arms to be lifted above your shoulders, **one year prior to your breast cancer diagnosis**?

1) Yes
2) No [Go to PLM3]
3) DK/REF [Go to PLM3]

PLM2CAT. On average, how many **hour(s) per week**, did you do **moderate** arm activities that did **not** require your arms to be lifted above your shoulders, **one year prior to your breast cancer diagnosis**? Would you say… [READ OPTIONS]

1) Less than 3 hours
2) Between 3 and 10 hours
3) More than 10 hours but less than 20 hours
4) 20 or more hours
5) DK/REF

PLM3. Did you do **moderate** arm activities that did **not** require your arms to be lifted above your shoulders, **one year after you were able to resume routine household activities**?

1) Yes
2) No [Go to L1]
3) DK/REF [Go to L1]

PLM3CAT. On average, how many **hour(s) per week**, did you do **moderate** arm activities that did **not** require your arms to be lifted above your shoulders, **one year after you resumed routine household activities**? Would you say… [READ OPTIONS]

1) Less than 3 hours
2) Between 3 and 10 hours
3) More than 10 hours but less than 20 hours
4) 20 or more hours
5) DK/REF

****

Some women experience swelling or retention of fluid in their arm after breast cancer treatments. This condition is called lymphedema and is caused by the accumulation of lymph fluid in the arm.

L1. At any time after your breast cancer diagnosis, did a <u>doctor</u> ever tell you that you have lymphedema or swelling of the arm?

1. Yes
2. No [GO TO NL1]
3. DK [GO TO NL1]
4. REF [GO TO VERIFYING SCRIPT and END/SAVE INTERVIEW]

L2. What month <u>and</u> year were you diagnosed with lymphedema? [IF SUBJECT HESITATES OR TAKES TOO LONG, ENCOURAGE SUBJECT TO GIVE AN ESTIMATE]

ENTER MONTH_____
ENTER YEAR _____

L3. In which arm was lymphedema diagnosed?

1. Right
2. Left
3. Both [GO TO NOT ELIGIBLE and SAVE /END INTERVIEW]
4. DK/REF [GO TO VERIFYING and END/SAVE INTERVIEW]

L4. During the past 3 months, have you noticed a difference in size between your right and left <u>upper or lower arms</u>?

1. Yes
2. No [GO TO L5]
3. DK/REF [GO TO L5]

L4A. What month and year did you first notice this difference in size?

ENTER MONTH_____
ENTER YEAR _____

L4B. During the past 3 months, would you say that, on average, the difference in the size of your upper or lower arms was:

1. Very slight; you are the only person who would notice this
2. Noticeable to people who know you well, but not to strangers
3. Very noticeable
4. DK/REF

L5. During the past 3 months, have you experienced any of the following symptoms in your _L3___ arm?

A	Has your shirt sleeve felt tight or has it irritated your arm?	Yes	No	DK/REF
B	Has your arm felt swollen?	Yes	No	DK/REF
C	Has your arm felt heavy?	Yes	No	DK/REF
D	Has your arm felt numb?	Yes	No	DK/REF
E	Has your arm felt stiff?	Yes	No	DK/REF
F	Has your arm felt warm?	Yes	No	DK/REF
G	Has your arm felt painful?	Yes	No	DK/REF
H	Has your arm felt tense?	Yes	No	DK/REF
I	Has your arm felt hard?	Yes	No	DK/REF
J	Have you had a rash on your arm or has your arm felt itchy or red?	Yes	No	DK/REF
K	Have you experienced abnormal sensations in your arm such as tingling?	Yes	No	DK/REF
L	Have you experienced any other symptoms in your arm? (IF YES GO TO L5.L2, ELSE GO TO L6)	Yes	No	DK/REF
L2	What are these symptoms? [OPEN ENDED]			

L6. During the past 3 months, have you experienced any of the following symptoms in your __L3__ hand?

A	You couldn't see the knuckles on your hand?	Yes	No	DK/REF
B	You couldn't see the veins in the hand?	Yes	No	DK/REF
C	Have your rings felt tight?	Yes	No	DK/REF /NO RINGS

L7. Have you experienced hardening of the tissues, skin changes, or non-pitting edema on your __L3_ arm?

1. Yes
2. No
3. DK/REF

L8. About how many weeks before your lymphedema diagnosis did you start having arm symptoms?

_____WEEKS [OPTIONS 0.0-312.0, DK]

L9. Do you treat the lymphedema in your _L3__ arm with any of the following at least once a week?

A	Wear a compression sleeve?	Yes	No	DK/REF
B	Use a sleeve pump?	Yes	No	DK/REF
C	Attend physical therapy sessions?	Yes	No	DK/REF
D	Massage your arm or have it massaged?	Yes	No	DK/REF
E	Exercise your hand and arm?	Yes	No	DK/REF
F	Take supplements (e.g. vitamin)?	Yes	No	DK/REF
G	Take medications?	Yes	No	DK/REF
H	Elevate arm?	Yes	No	DK/REF
I	Use other methods? (IF YES GO TO L9.I2, ELSE L10)	Yes	No	DK/REF
I2	What are these methods? [OPEN ENDED]			

- [If both A and (C or E) are checked also answer Q32]

L10. Has your lymphedema (retention of fluid) completely resolved?

1. Yes
2. No
3. DK /REF

[IF ANSWERED YES TO Q5 THEN ANSWER L11, OTHERWISE SKIP TO (NEXT QUESTION) LL4-LL18 IF APPLICABLE]

L11. You previously told me you had an infection in your __L3 _ arm. Did it occur before, after or both before and after your diagnosis of lymphedema?

1. Before
2. After
3. Before and After
4. DK/REF

You previously told me a doctor, nurse or other health professional <u>have diagnosed you with the following health condition(s)</u> after your breast cancer diagnosis.

LL4.	Was your high blood pressure diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF

LL5.	Was your high cholesterol diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL6.	Was your heart attack, also called a myocardial infarction, diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL7.	Was your coronary heart disease or Angina diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL8.	Was your stroke or brain attack diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL9.	Was your congestive heart failure diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL10.	Was your emphysema diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL11.	Was your chronic bronchitis diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL12.	Was your asthma diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL13	Was your thyroid problem(s) diagnosed before or after you were diagnosed with arm lymphedema?	Before	After	DK/REF
LL14.	Was your liver condition(s) diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL15.	Was your weak or failing kidney(s) diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL16.	Was your osteoporosis diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL17.	Was your pre-diabetes, or diabetes diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF
LL18.	Was your arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia diagnosed before or after you were diagnosed with lymphedema?	Before	After	DK/REF

L12. Did you lift heavy objects the month prior to developing lymphedema?

1. Yes
2. No
3, DK/REF

L13. What do you think caused your lymphedema after you were treated for breast cancer?

_____ ___DK/REF [OPEN ENDED QUESTION]

[GO TO Q27 OR Q28]

[QUESTIONS FOR THOSE NOT DIAGNOSED WITH LYMPHEDEMA]

NL1. While a doctor has not diagnosed you with lymphedema of the arm, we are interested in learning about arm conditions and symptoms that may be associated with breast cancer diagnosis.

During the past 3 months, have you noticed a difference in size between your right and left upper or lower arms?

1. Yes
2. No [GO TO NL2]
3. DK/REF [GO TO NL2]

NL1A. What month and year did you first notice this difference in size?

ENTER MONTH_____
ENTER YEAR _____

NL1B. During the past 3 months, would you say that, on average, the difference in the size of your upper or lower arms was:

1. Very slight; you are the only person who would notice this
2. Noticeable to people who know you well, but not to strangers
3. Very noticeable
4. DK/REF

NL2. During the past 3 months, have you experienced any of the following symptoms in your __BSIDE__ arm?

A	Has your shirt sleeve felt tight or has it irritated your arm?	Yes	No	DK/REF
B	Has your arm felt swollen?	Yes	No	DK/REF
C	Has your arm felt heavy?	Yes	No	DK/REF
D	Has your arm felt numb?	Yes	No	DK/REF
E	Has your arm felt stiff?	Yes	No	DK/REF
F	Has your arm felt warm?	Yes	No	DK/REF
G	Has your arm felt painful?	Yes	No	DK/REF
H	Has your arm felt tense?	Yes	No	DK/REF
I	Has your arm felt hard?	Yes	No	DK/REF
J	Have you had a rash on your arm or has your arm felt itchy or red?	Yes	No	DK/REF
K	Have you experienced abnormal sensations in your arm such as tingling?	Yes	No	DK/REF
L	Have you experienced any other symptoms in your arm? (IF YES GO TO NL2.L2, ELSE GO TO NL3 OR NL4)	Yes	No	DK/REF
L2	What are these symptoms? [OPEN ENDED]			

[ANSWER NL3 ONLY IF ANSWERED POSITIVELY TO ANY ITEM IN NL2]

NL3. What month and year did you first start noticing the majority of the symptom(s) you just indicated was present in your __BSIDE__ arm?

ENTER MONTH_____
ENTER YEAR _____

NL4. During the last 3 months, have you experienced any of the following symptoms in your __BSIDE__ hand?

A	You couldn't see the knuckles on your hand?	Yes	No	DK/REF
B	You couldn't see the veins in the hand?	Yes	No	DK/REF
C	Have your rings felt tight?	Yes	No	DK/REF/ NO RINGS

[ANSWER NL5 ONLY IF ANSWERED YES TO Q5 AND ANSWERED POSITIVELY TO ANY ITEM IN NL2 OTHERWISE SKIP TO NL6]
NL5. You previously told me you had an infection in your __BSIDE _ arm, did it occur before, after or both before and after you start noticing arm symptoms?

1. Before
2. After
3. Before and After
4. DK/REF

[ONLY ANSWER NL6 IF NL1=yes, OR IF ANSWERED YES TO ANY ITEM IN NL2]
NL6. Have you experienced hardening of the tissues, skin changes, or non-pitting edema on your _ BSIDE__ arm?

1. Yes
2. No
3. DK/REF

NL7. Do you think it is likely that you may have lymphedema of the arm? [IF HESITATION OCCURS, REDEFINE LYMPHEDEMA]

1. Yes
2. No
3. DK/REF

You may have received information or been told about methods to prevent lymphedema of the arm after breast cancer diagnosis.

NL8. Do you do any of the following at least once a week?

A	Wear a compression sleeve?	Yes	No	DK/REF
B	Use a sleeve pump?	Yes	No	DK/REF
C	Attend physical therapy sessions?	Yes	No	DK/REF
D	Massage your arm or have it massaged?	Yes	No	DK/REF
E	Exercise your hand and arm?	Yes	No	DK/REF
F	Take supplements (e.g. vitamins, herbs)?	Yes	No	DK/REF
G	Take medications?	Yes	No	DK/REF
H	Elevate arm?	Yes	No	DK/REF
I	Use other methods? [IF YES GO TO NL8.I2]	Yes	No	DK/REF
I2	What are these methods? [OPEN ENDED]			

****

[ANSWER Q27 IF BOTH A AND (C OR E) WERE CHECKED IN L9 OR NL8]

Q27. Do you wear a compression sleeve when you're exercising?

1. Yes
2. No
3. DK/REF

Q28. We have a few more general questions for you.

Are you right or left handed?

1. Right
2. Left
3. Ambidextrous (Both or Neither)
4. DK/REF

Q29. What is your height in feet and inches?

ENTER # OF FEET _____ [OPTIONS 4-7, DK]
ENTER # OF INCHES _____ [OPTIONS 1-12, DK]

Q30. What is your weight in pounds?

_____(# of pounds) [OPTIONS 50-600, DK]

Q31. At the time of breast cancer diagnosis, what was your weight in pounds?

_____(# of pounds) [OPTIONS 50-600, DK]

Q32. What is the highest grade or year of school you have completed?

1. 8th grade or less
2. Some high school
3. High school graduate or GED certificate
4. Some college
5. College/university graduate
6. Post-college work
7. DK/REF

Q33. What is your current marital status?

1. Single (never married)
2. Married
3. Separated
4. Divorced
5. Widowed
6. DK/REF

For this portion of the interview, we need you to use the tape measure that is included with your letter. You may have recorded your answers down on the sheet.

[IF SUBJECT DOES NOT HAVE TAPE MEASURE, ASK THEM TO GO GET IT IF THEY KNOW WHERE IT IS. IF SUBJECT DOES NOT HAVE TAPE MEASURE AT ALL, EXIT INTERVIEW]

MR1.
What is the circumference of your right arm in centimeters, one hand width above your right elbow crease? [OPTIONS 15.0-61.0cm]

MR2.
What is the circumference of your right arm [in centimeters], one hand width below your right elbow crease? [OPTIONS 15.0-61.0cm]

ML1.
What is the circumference of your left arm [in centimeters], one hand width above your left elbow crease? [OPTIONS 15.0-61.0cm]

ML2.
What is the circumference of your left arm [in centimeters], one hand width below your left elbow crease? [OPTIONS 15.0-61.0cm]

AFTER ML2, GO TO ENDING SCRIPT "Thank you for answering this questionnaire, we value your participation and contribution to this research project"

INTERVIEWERS ONLY
RECUR. DID THE SUBJECT INDICATE THAT SHE HAD A RECURRENCE OF BREAST CANCER AFTER HER INITIAL DIAGNOSIS IN 2004?

1) YES
2) NO

CANCER. DID THE SUBJECT MENTION THAT SHE HAD ANY OTHER CANCER (NON-BREAST) DIAGNOSIS EITHER BEFORE OR AFTER HER 2004 BREAST CANCER DIAGNOSIS?

1) YES
2) NO

APPENDIX C: RECRUITMENT AND CONSENT MATERIALS

Letter to Physicians

Dear Dr. [Doctor Last Name],

We are conducting a National Cancer Institute funded study of women who were diagnosed with breast cancer. **Complications of Breast Cancer Treatment Study** is a population-based investigation of breast cancer occurring in women under the age of 80 at the time of cancer diagnosis. *The goal of the Complications of Breast Cancer Treatment Study is to learn about the consequences of breast cancer treatment.*

This study is being conducted by the State Health Registry of Iowa. One of your patients, **«FIRSTNAME» «LASTNAME»,** has been identified as a person who was diagnosed with breast cancer in 2004 and, if willing, may be able to participate in this study.

The study will collect information through a telephone interview that will take about 20-30 minutes to complete. This is an observational study, *not* a clinical trial. There will be no "treatment" or other intervention performed. Participation will not interfere with your care of this patient, or influence treatment decisions that you and your patient make. Information obtained from your patient will be kept confidential and secure, and we will not release or report information that could be used by anyone outside of the study to identify your patient or your practice. Our study protocol has been approved by the Institutional Review Board at the University of Iowa (UI IRB #200712733).

We will contact eligible patients about the study unless we hear from you within three weeks. **If you have a specific reason why we should not contact your patient, please contact Michele West by phone at 319-335-7497 or by fax at 319-335-8610.**

Many patients with cancer welcome the chance to participate in a study that might help others. However, we will make it clear to your patient that she is under no obligation to participate in the Complications of Breast Cancer Treatment Study, that participation will not affect her care or treatment in any way, and that she may withdraw consent to participate in the study at any time. If your patient declines to participate we will respect the decision and will not attempt to contact her again. Please do not hesitate to contact us if you have any questions about this study. Thank you for your support of this important research.

Sincerely yours,

Charles F. Lynch, MD, PhD
Medical Director
(319) 384-5006

Michele West
Study Coordinator
(319) 335-7497

Letter to Potential Participants

Dear [Patient Name],

We are writing to invite you to participate in a research study called the **Complications of Breast Cancer Treatment Study**. The purpose of this study is to learn about consequences of breast cancer treatments in an effort to improve the quality of life for breast cancer survivors.

We are inviting you to be in this study because you were diagnosed with breast cancer in 2004. We obtained your name and address from the State Health Registry of Iowa, which is Iowa's statewide cancer surveillance program located at the University of Iowa. Approximately 1000 women will take part in this study at the University of Iowa. The study is being funded by the National Cancer Institute.

If you agree to participate, we would like you to complete a 15 to 20-minute telephone interview. An interviewer will make a few attempts to contact you in about 2 weeks to ask if you wish to participate in this research study. If so, you may participate in the interview at that time or schedule a time convenient to you. You will be asked about your experience as a survivor of breast cancer. You are free to skip any question you would prefer not to answer. Interviews will be audio-taped so that the supervisor can ensure that your answers were correctly recorded. The recordings will be destroyed after they have been checked. You have the right to refuse to be recorded and this will not affect your ability to participate in the study. This information will be linked to your existing data in the State Health Registry of Iowa, including surgery and treatments you received for your breast cancer.

Included with this letter are a tape measurement, instruction sheet for measuring your arm circumference, and an arm activity sheet. If possible please fill out your arm circumference measurements and arm activity sheet prior to the interview. Please keep the contents of this letter and the tape nearby for the interview.

We will also re-contact about 10% of participants 3-6 weeks after they initially complete the interview. These randomly chosen participants will be asked to complete the same interview a second time. The purpose is to assess how consistently subjects report information that is difficult to recall.

We will keep the information you provide confidential, however federal regulatory agencies and the University of Iowa Institutional Review Board (a committee that reviews and approves research studies) may inspect and copy records pertaining to this research. Personal identifying information is stored in password protected computerized files that are accessible only by authorized research staff. Documents containing personal identifiers are stored in lockable file cabinets. If we write a report about this study, we will do so in such a way that you cannot be identified. These data are collected under the Public Health Service Act (42U.S.C. 241, 284 and 285-285a-5) and will only be used by research scientists or may be released, at your request, to a congressional office in response to a congressional inquiry.

There are no known risks from being in this study, and you will not benefit personally. However, we hope that others may benefit in the future from what we learn as a result of this study. You will not have any costs for being in the Complications of Breast Cancer

Treatment Study. You will not be paid for being in this research study. Taking part in this research study is completely voluntary. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

If you have any questions about the research study itself, or if you experience a research-related injury, please contact Julie Coughlin at the address above or by phone at (319) 335-8089. If you have questions about the rights of research subjects, please contact the Human Subjects Office, 300 College of Medicine Administration Building, The University of Iowa, Iowa City, IA 52242, (319) 335-6564, or e-mail irb@uiowa.edu. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

Thank you very much for your consideration.

Charles F. Lynch, MD, PhD
Medical Director

Phone Number Request Letter to Potential Participants

Dear [Patient Name],

Previously, we sent you a letter inviting you to participate in a research study about consequences of breast cancer treatments in an attempt to help explore ways to improve the quality of life for breast cancer survivors. We are inviting all women diagnosed with breast cancer in 2004 to participate. We obtained your name from the State Health Registry of Iowa, which is Iowa's statewide cancer surveillance program located at the University of Iowa.

We are sending you this letter because we were unable to contact you by phone. If you are interested in this research study and wish to participate, please call **Julie Coughlin at (319) 335-8089** to schedule an interview at a time convenient to you. Please let her know you are calling about the "**Complications of Breast Cancer Treatment Study**". If you did not receive the prior letter about this study, please let her know and we will resend the information.

Again, the interview will take about 15 to 20 minutes. You will be asked about your experience as a survivor of breast cancer. You are free to skip any question you would prefer not to answer.

Thank you very much for your consideration.

Charles F. Lynch, MD, PhD
Medical Director

Arm Activity Worksheet Sent to Potential Participants

When the interviewer calls you, you will be asked about the following 4 types of arm activities you have done before and after your breast cancer diagnosis. Below are a few examples of activities we are interested in.

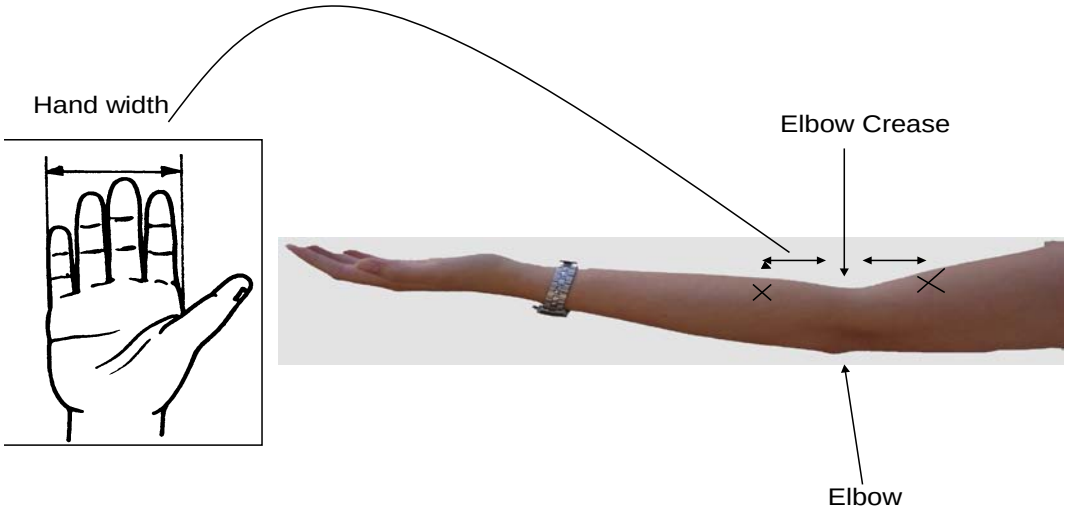
		In the past year	one year prior to breast cancer diagnosis	one year after you were able to resume routine household activities
		Did you do the following types of activities? **(Circle Yes or No)****		
a) Arms above shoulders 	**<u>Vigorous* arm activity above shoulders</u>** **examples:** playing tennis, lifting heavy objects, weight lifting, stocking shelves	Yes / No	Yes / No	Yes / No
	<u>Moderate arm activity above shoulders</u> **examples:** dusting high places, hanging up clothes, putting dishes/items above head, writing on chalk board/board, physical therapy, playing violin	Yes / No	Yes / No	Yes / No
b) Arms below shoulders 	**<u>Vigorous* arm activity below shoulders</u>** **examples:** scrubbing floor, rowing, raking leaves, shoveling snow, gardening activities that require great effort, moving heavy objects like furniture	Yes / No	Yes / No	Yes / No
	<u>Moderate arm activity below shoulders</u> **examples**: washing dishes, vacuuming, gardening, laundry, cooking, playing piano, bowling, computer work	Yes / No	Yes / No	Yes / No

*Vigorous is defined as activities that cause your heart to beat faster or cause you to breathe harder

**Also think about how many hours/week you spent doing these activities

Arm Circumference Instruction Sheet Sent to Potential Participants

Please use the tape measure that is included with your initial letter to measure the circumference of your arms. If needed, feel free to ask someone to assist you.



To do this, straighten out your right arm, palm up, in front of you. Then measure the circumference of your right arm one hand width (see picture) **above** the inside elbow crease of your arm and write down this measurement in centimeters. Then also measure the circumference one hand width **below** your elbow crease.

Right arm

a) _____ cm around, one hand width **above** crease

b) _____ cm around, one hand width **below** crease

Now, take the same measurements on you left arm.

Left arm

c) _____ cm around, one hand width **above** crease

d) _____ cm around, one hand width **below** crease

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