Published in final edited form as:
Breast Cancer Res Treat. 2011 December ; 130(3): 981–991. doi:10.1007/s10549-011-1667-z.

Risk Factors for Lymphedema In Breast Cancer Survivors, the Iowa Women's Health Study

Rehana L. Ahmed, M.D, Ph.D.[1], **Kathryn H. Schmitz, Ph.D., M.P.H.**[2], **Anna E. Prizment, Ph.D., M.S., M.P.H.**[3], and **Aaron R. Folsom, M.D., M.P.H.**[3]

[1]The University of Minnesota Department of Dermatology, Mayo Mail Code 98, 420 Delaware St SE, Minneapolis, MN 55455

[2]University of Pennsylvania, Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, 921 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104

[3]The University of Minnesota, Division of Epidemiology and Community Health, 1300 S Second Street, Suite 300, Minneapolis, MN 55454

Abstract

Background—Risk factors for lymphedema and related arm symptoms in breast cancer (BC) survivors have not been examined using a large prospective population-based cohort.

Methods—The Iowa Women's Health Study (IWHS) collected self-reported data for diagnosed lymphedema in 2004, and data for cancer diagnosis, treatment, behavioral and health characteristics between 1986–2003. We studied 1,287 women, ages 55–69 at baseline, who developed unilateral BC: n=104 (8%) with diagnosed lymphedema, n=475 (37%) with arm symptoms but without diagnosed lymphedema, and n=708 without lymphedema. Age- and multivariate-adjusted logistic regression models examined risk factors for lymphedema and related arm symptoms (OR [95% confidence interval]).

Results—The mean time between BC and the 2004 survey was 8.1±5.0 (mean±SD) years. After multivariate adjustment (not including time since BC diagnosis), the following cancer characteristics were positively associated with lymphedema: tumor stage (regional vs. in situ: 3.92[1.61–9.54]), number of excised nodes (highest vs. lowest quintile: 3.52[1.32–9.34], P_{trend}=0.003), tumor-positive nodes (yes vs. no 2.12 [1.19, 3.79]) and adjuvant chemotherapy (yes vs. no: 3.05[1.75–5.30]). Several health characteristics were positively associated with lymphedema: baseline body mass index (highest vs. lowest tertile: 3.24[1.70–6.21]), waist and hip circumference, and general health (fair/poor vs. excellent: 3.44[1.30–9.06]). Positive associations with arm symptoms were: number of excised nodes (highest vs. lowest quintile: 2.38[1.41–4.03], P_{trend}=0.007), axillary radiation (yes vs. no: 1.72 [1.15–2.57]) and baseline general health (fair/poor vs. excellent: 4.27 [2.60–7.00]).

Conclusions—In the IWHS, obesity, poorer general health, and markers of more advanced cancer were risk factors for lymphedema and related arm symptoms in BC survivors.

Corresponding Author: Rehana L Ahmed, MD, PhD, University of Minnesota Department of Dermatology, Mayo Mail Code 98, 420 Delaware Street SE, Minneapolis, MN 55455-0392.

INTRODUCTION

Lymphedema, a late-effect of several cancers and their treatment, poses health risks, alters medical care costs [1], and impacts quality of life for cancer survivors [2]. Although up to 70% of women who develop lymphedema do so within 1–2 years post-treatment [3, 4], lymphedema may develop at any time from initial treatment to twenty years or more later [3]. Definitions of upper-extremity lymphedema vary depending on the thresholds chosen for limb swelling, clinical signs and symptoms [5, 6]. Variability in measurement thresholds and methodology, as well as length of follow-up time explains the broad range of estimates for the prevalence of lymphedema in breast cancer (BC) survivors (0–56%) [7]. Up to 50% of BC survivors report symptoms consistent with lymphedema, with or without a clinical diagnosis [3]. While lymphedema may be managed, there are no definitive cures.

Lymphedema arises from physical disruption or compression of axillary lymphatic channels from tumor invasion, surgery, or radiation therapy; a synergistic effect of axillary dissection and radiation therapy on lymphedema risk has been reported [5–6, 8–9]. BC treatment targeted at the axilla [5–6, 9] is hypothesized to induce damage interrupting lymph transport such that lymph volume exceeds transport capabilities [6], eventually leading to abnormal accumulation of tissue protein, edema, and chronic inflammation within the arm [10]. One-third of BC patients receive axillary lymph node dissection at initial treatment [11]. Further, a large percentage of women who initially receive sentinel lymph node biopsy go on to have further axillary dissection [12]. Thus, a large percentage of BC survivors are at risk of developing lymphedema related to axillary node dissection. Other factors may play a role in lymphedema development, given that sentinel node biopsy alone is associated with up to 7% risk [13]. The variation in time to onset of lymphedema after cancer therapy implies there may be a window during which modifiable risk factors alter the course to lymphedema. It is unknown whether or not risk factors differentially affect lymphedema severity.

Several case-series and cohorts of BC survivors have been assembled to examine risk factors for lymphedema, with mixed conclusions [e.g. 3, 13–15, 20–36]. Patients in many of these studies have been assembled from a single or multiple BC treatment centers, with patient and treatment characteristics gathered either at the time of BC diagnosis or retrospectively. We aimed to examine associations of BC characteristics and treatment, and patient pre-diagnostic health characteristics with lymphedema or arm symptoms. We used data from a large population-based prospective cohort study, the Iowa Women's Health Study (IWHS), to examine these associations in BC survivors with a history of diagnosed lymphedema, or related arm symptoms without diagnosed lymphedema, versus those with neither arm symptoms nor lymphedema.

MATERIALS AND METHODS

Population

Methods for the IWHS have been described [16]. Briefly, primary aims of the IWHS in 1984 were to determine if the distribution of body fat (waist/hip) and other lifestyle factors predict the incidence and prognosis of chronic diseases [16]. The baseline age-range included post-menopausal women, an age-group at increased risk for chronic disease [16].

In January 1986, a dietary and lifestyle questionnaire was mailed to 99,826 randomly-selected women aged 55–69 years with valid Iowa driver's licenses in 1985. The 41,836 women who completed questionnaires (42%) constituted the cohort. Five follow-up questionnaires updated vital status, residence, and exposure information; response rates were 91% in 1987, 90% in 1989, 83% in 1992, 79% in 1997, and 70% in 2004. The vital status of non-responders was determined through the National Death Index. The IWHS was approved by the University of Minnesota's Institutional Review Board.

Incident BC cases diagnosed within Iowa were ascertained between 1986 through December 2003 by linkage to the State Health Registry of Iowa, which participates in the National Cancer Institute's Surveillance, Epidemiology and End-Results (SEER) program. Migration from Iowa was <1% annually, allowing nearly complete follow-up of cancer incidence [17]. BC comprised International Classification of Diseases of Oncology, Third Edition, codes C50.0–C50.9. After excluding 1,383 women with BC at baseline, 40,453 women were followed. From 1986–2003, 2,816 developed incident BC: 2,657 unilateral and 159 bilateral cases. Of the 2,657 women with unilateral BC, 718 had died by 2004, leaving 1,939 unilateral cases. Of these, 1,287 women with unilateral BC(48%) completed the 2004 follow-up questionnaire and comprise the sample used for analysis; of the remainder, 565 did not respond and 87 failed to complete the lymphedema questions [2].

Measurements

Breast Cancer and Treatment—Diagnosis date, histology, stage, estrogen and progesterone receptor status, tumor size, surgery type (first surgery following diagnosis), number of lymph nodes excised and presence of metastasis were obtained from SEER. SEER data include first-course treatment only. For women with >1 tumor in the same breast (n=16), we assigned the largest tumor size, most advanced stage, and most radical surgery completed; for these participants, the total number of lymph nodes examined and the number positive were determined. On the IWHS 2004 follow-up survey, patients selected whether they had ever received any of the following adjuvant BC treatments: radiation to the breast or axilla, chemotherapy, or tamoxifen. If an option was left blank, the participant was coded as having "no/unknown" history of that treatment. These data were not validated.

Health and Lifestyle—The baseline questionnaire in 1986 collected self-reported demographic (race, occupation, education, marital status), general health, and behavioral characteristics (smoking, alcohol, exercise) [16]. At baseline and follow-ups, women self-reported medical history, including interim cancer, diabetes, hypertension, and heart disease diagnoses. "Comorbidity index" was the sum of self-reported illnesses --- diabetes, heart disease, and hypertension --- and was modeled categorically (0, 1, 2–3).

Participants self-reported height at baseline and weight at baseline and follow-ups. Body mass index (BMI) was calculated as weight (kilograms) divided by baseline height (meters) squared; categories were defined as underweight <18.5, normal 18.5–24.9, overweight 25.0–29.9, and obese ≥30.0 kg/m^2. Waist (1 inch above the umbilicus) and hip (maximal protrusion) circumferences were measured at baseline by a friend or spouse; waist/hip (WHR) was calculated [18].

Lymphedema—The 2004 follow-up questionnaire included a self-report measure of lymphedema diagnosis, arm symptoms, and treatment, validated in another sample, and with a specificity of 0.90 and sensitivity of 0.86–0.92 for diagnosing lymphedema compared to clinical assessment [19]. This questionnaire was administered to women with BC in the overall cohort. Questions included whether or not over the prior three months the participant noticed her upper extremity ipsilateral to the cancer was larger, or she experienced symptoms such as altered function, puffiness, swelling, and/or pain, compared to the contralateral side [19].

Analysis and Statistical Methods

Based on the lymphedema survey responses, three groups of BC survivors (n=1287) were defined for analysis: 1) having *lymphedema*, if participants reported ever receiving a diagnosis of lymphedema (n=104); 2) having *arm symptoms without diagnosed lymphedema*, if participants answered "yes" to any of the questions about arm symptoms and did not have diagnosed lymphedema (n=475); and 3) *without lymphedema or arm symptoms*, if participants answered "no" to all questions (n=708).

SAS software (v8.02, SAS Institute Inc., Cary, NC) was used. P-values were 2-sided. For analysis of BC surgery, a history of "no surgery" was combined with "lumpectomy", as only 1 participant in the lymphedema group and 4 participants in each of the other groups had a history of "no surgery". When >10% of data were unknown for a given variable, a separate "unknown" category was created for analysis. Age- and multivariate-adjusted logistic regression models were used to examine risk factors for lymphedema or for arm symptoms without lymphedema (OR [95% confidence interval]). Potential risk factors were selected a priori for evaluation based on the literature and our hypotheses. Individual risk factors, adjusted for relevant covariates, were examined in separate logistic regression models for risk of lymphedema compared to no lymphedema/arm symptoms (one set of models) and risk of arm symptoms compared to no lymphedema/arm symptoms (another set of models). Tests for linear trend across categories of exposure were obtained by modeling categories as ordinal variables. Potential confounders were evaluated separately for each model, and retained if they were associated with lymphedema/arm symptoms and/or changed age-adjusted parameter estimates by ≥10%. Final models are noted in the tables. Variables evaluated as potential covariates, but not added to final models because they did not meet criteria, included: time since BC diagnosis, education, marital status, alcohol consumption, baseline physical activity, tumor estrogen/progesterone receptor status, surgical history, number of excised lymph nodes, or tamoxifen use.

In exploratory analyses, we evaluated effect modification by modeling a set of cross-product terms for categorical risk factors. Given published observations of synergistic associations between axillary dissection and adjuvant cancer therapy on lymphedema development [20–22], we examined effect modification between nodal dissection or tumor-positive lymph nodes with radiation therapy or chemotherapy. Sensitivity analyses were performed to include participants with missing data for tumor lymph node status first in the group with negative nodes and separately in the group with positive nodes.

RESULTS

Participants

The mean time between BC diagnosis and the 2004 follow-up lymphedema survey was 8.1±5.0 (mean±SD) years. Participants were 99.8% White. Comparisons between non-respondents (n=1,283) and respondents (n=1,287) to the 2004 follow-up survey have been published [2]. Briefly, compared to respondents, non-respondents were more likely to be >62 years of age at baseline (59.5% vs. 45.1%), to have a baseline BMI >30 (28.7% vs. 24.1%), regional (22.9% vs. 13.7%) or distant (5.7% vs. 0.2%) disease at BC diagnosis, and positive lymph nodes at diagnosis (25.8% vs. 15.5%) [2]. Six non-responders were underweight (BMI<18.5kg/m^2), similar to responders (discussed below).

Table 1 presents data for baseline and 2004 demographic, health and lifestyle characteristics. Participants with diagnosed lymphedema or arm symptoms without diagnosed lymphedema were more likely to have comorbidity than women without lymphedema or arm symptoms. Compared with other participants, women with diagnosed lymphedema had higher BMI at baseline and in 2004, poorer baseline general health, a positive history of tobacco and ethanol use. Seven participants were underweight (BMI<18.5kg/m^2) and were included in the group of BMI<24.9 kg/m^2; excluding their data did not alter results. BC and treatment characteristics are in Table 2. Compared with other participants, women with diagnosed lymphedema were more likely to have had more advanced BC at diagnosis (distant metastases, larger tumor size, more lymph nodes excised, and tumor-positive nodes), and to have undergone adjuvant therapy (radiation and chemotherapy). There was no variation by tumor estrogen/progesterone receptor status (data not shown).

Odds ratios comparing cancer and treatment characteristics of respondents with self-reported lymphedema or arm symptoms to those without lymphedema or arm symptoms are presented in Table 2. In age- and multivariate-adjusted models, the following cancer characteristics were positively associated with lymphedema (OR[95% CI]): tumor stage (regional vs. in situ: 3.92[1.61–9.54]), number of excised nodes (highest vs. lowest quintile: 3.52[1.32–9.34], $P_{linear\ trend}$=0.003), tumor-positive lymph nodes (yes vs. no: 2.12[1.19–3.79]), and adjuvant chemotherapy (yes vs. no: 3.05[1.75–5.30]). A borderline association was identified for tamoxifen. Associations did not reach statistical significance for: tumor size, extent of surgery, a history of radiation to the breast or axilla, or tumor hormone receptor status. Cancer characteristics associated with arm symptoms (without diagnosed lymphedema) were identified for: number of excised nodes (highest vs. lowest quintile: 2.38[1.41–4.03], $P_{linear\ trend}$=0.007), tumor-positive nodes (yes vs. no: 1.44[1.08–2.19]), and axillary radiation (yes vs. no: 1.72[1.15–2.57]).

After age and multivariate adjustment, the following behavioral and health characteristics were positively associated with lymphedema (Table 3): baseline BMI (highest vs. lowest tertile: 3.24[1.70–6.21]), waist circumference (highest vs. lowest tertile: 1.99[1.10–3.60]), hip circumference (highest vs. lowest tertile: 2.43[1.30–2.55]), and baseline general health (fair/poor vs. excellent: 3.44[1.30–9.06]). Lymphedema was not associated with hypertension, heart disease, diabetes, history of alcohol use, baseline physical activity, or occupation. After multivariate adjustment, baseline general health (fair/poor vs. excellent:

4.27[2.60–7.00]) was associated with arm symptoms. Positive unadjusted associations for comorbidity index, BMI, and waist circumference were attenuated with multivariable adjustment. Physical activity, occupation, or smoking were not associated with arm symptoms.

After multivariate adjustment, tumor-positive lymph nodes modified the association of radiation to the axilla or breast with lymphedema (Table 4), and the association of radiation to the breast with arm symptoms, such that those with tumor-positive nodes who also had radiation had a higher than expected risk of lymphedema (7.1[1.77–28.58]) or arm symptoms (5.16[1.85–14.39]). Sensitivity analyses did not alter interpretation of the associations observed. There was no effect modification between tumor-positive nodes and chemotherapy or between the number of lymph nodes removed (≤4 vs. >4) and radiation or chemotherapy with either lymphedema or arm symptoms (data not shown).

DISCUSSION

In this prospective population-based cohort we observed that in addition to markers of more advanced BC (advanced stage and lymph node metastasis) and its treatment (more lymph nodes removed and chemotherapy), there are potentially modifiable behavioral characteristics associated with greater risk of lymphedema and related arm symptoms. In particular, obesity and poorer general health were associated with greater risk of lymphedema and related arm symptoms.

The IWHS represents one of the first prospective population-based cohort to examine risk factors for lymphedema in BC survivors and for those with arm symptoms without diagnosed lymphedema. Women with arm symptoms without a diagnosis of lymphedema may have subclinical lymphedema or they may have one of a multitude of possible other arm morbidities common after breast cancer (such as limited range of motion or muscular injury). We previously reported that a low percentage of women in this group had knowledge of lymphedema [2], which may have lead to a misclassification error whereby some of these women might meet diagnostic criteria for lymphedema. Several case series, cohorts, randomized trials, and case-control studies of BC survivors have examined risk factors for lymphedema. The majority of these studied patients recruited from cancer treatment centers. By contrast, one recent study identified 1,338 participants from Medicare data [13], and another identified 997 participants from the Kaiser Permanente Northern California medical care program [14]. Methodology across studies has varied in terms of study design, size, patient characteristics, measurements that focused on treatment-related factors or included patient health and behavioral characteristics, and timing of follow-up. A meta-analysis that examined BC and treatment-related characteristics as risk factors for lymphedema reported that of the 98 studies, only ten had used multivariable-adjusted analyses [23]. Differences in methodology may contribute to the mixed outcomes across studies.

While findings have varied, more advanced cancer and treatment-related outcomes have consistently been associated with lymphedema and arm morbidity. In the meta-analysis noted above [23], the authors identified positive associations (RR [95% CI]) of arm

lymphedema with axillary lymph node dissection (axillary dissection vs. no dissection: 3.47 [2.34–5.15] and axillary dissection vs. sentinel lymph node biopsy: 3.07 [2.20–4.29]), findings similar to IWHS. The authors also reported associations between lymphedema and positive lymph nodes, more extensive surgery, radiation therapy to any site or to the axilla, and no association with tumor stage or chemotherapy [23]. Three recent studies add to these data. In a study by Paskett et al (2007) of 622 premenopausal BC survivors, having a greater number of lymph nodes removed was associated with developing and persistent swelling (self-reported of the hand or arm) and chemotherapy was associated with developing swelling; by contrast, tumor-positive lymph nodes, type of surgery (including reconstructive), and radiation therapy were not associated with swelling [15]. In Norman et al (2010), axillary dissection and chemotherapy were associated with lymphedema in 631 BC survivors, and axillary dissection modified the effect of chemotherapy on lymphedema; by contrast, neither sentinel node biopsy nor radiation therapy to any site were associated with lymphedema [22]. In Kwan et al (2010), the authors reported a 4.1% increased risk of transient or persistent lymphedema with each lymph node removed; additionally, they reported an association between chemotherapy and persistent lymphedema, a non-significant association between radiation therapy and lymphedema, and no association between adjuvant hormonal therapy and lymphedema [14]. In the IWHS, chemotherapy was positively associated with lymphedema, and axillary radiation therapy was positively associated with arm symptoms, but not diagnosed lymphedema. Axillary radiation therapy was positively associated with arm symptoms without diagnosed lymphedema; additionally, radiation therapy modified the effect of tumor-positive lymph nodes to increase lymphedema and arm symptom occurrences. In two other reports, axillary dissection modified the effect of radiation therapy on lymphedema [20–21], which was not observed in IWHS. In addition to the studies noted above, three additional studies are relevant (two of these were included in the meta-analysis). There was a positive association between anthracyclin-based chemotherapy and lymphedema in 300 women [24]. There was an association between chemotherapy and lymphedema in 494 women in unadjusted but not multivariable-adjusted analysis, and no association with tamoxifen [4]. By contrast, in 990 BC survivors followed for five years, there was no association with either chemotherapy or tamoxifen and “arm problems” [25].

Several health and behavioral characteristics were associated with lymphedema or arm symptoms in IWHS. In larger series of BC survivors, obesity has been associated with increased risk of lymphedema, including obesity at cancer diagnosis and weight gain following treatment in many [3–4, 14–15, 22, 25–26] but not all studies [27–28]. Obesity may alter risk of lymphedema via increased stress to the lymphatics, enhanced inflammation, increased trauma, or prolonged healing from surgery (via longer surgical procedures, longer healing times, and seroma formation). We hypothesized that diseases affecting the circulation (coronary artery disease, hypertension, or diabetes mellitus) may increase lymphedema or arm symptoms. However, after adjustment for obesity, there were no associations with these comorbidities, individually or collectively. By contrast, other studies reported positive associations between comorbidity (coronary artery disease or diabetes mellitus) and “arm problems” [25] and between comorbidity (diabetes mellitus, hypertension, chronic renal failure, congestive heart failure, myxedema) and lymphedema

[24], with multivariate-adjustment. An association between hypertension and lymphedema was reported [4], as well as a negative association between anti-hypertensive medication use and lymphedema after age- but not multivariable-adjustment [27]. Other studies have not observed associations between lymphedema and hypertension or diabetes mellitus [21, 29]. Self-reported general health was associated with lymphedema and to a greater degree with arm symptoms in IWHS. In IWHS, better general health has been associated with lower mortality and comorbidity.

Age at IWHS baseline or at cancer diagnosis was not associated with lymphedema or arm symptoms, although age in IWHS has a limited range. Overall, findings regarding an association between age and lymphedema have been mixed, as authors have reported an association between lymphedema and greater age [30–31], younger age [4, 27, 32], or no association [20–21, 33–34]. In a cohort of 494 women, younger women (< 50 years of age) had a higher risk of developing lymphedema than older women (OR per year of age = 0.96 [95% CI: 0.93–0.99]); younger compared to older women were more likely to have received chemotherapy (50% vs. 25%), which was also associated with lymphedema [4].

The medical community has debated the safety of physical activity for BC survivors in terms of lymphedema risk. Similar to other authors [3–4, 14–15], we did not identify associations of physical activity or occupation with lymphedema or arm symptoms after multivariable-adjustment. Geller et al (2003) reported work outside the home increased lymphedema, though not after adjustment for axillary dissection [27]. Engel et al (2003) reported an increased risk of arm symptoms with non-office work occupations [25]. Quick bursts of or strenuous activity may increase injury, particularly in an unconditioned limb. Indeed, infection or injury to the limb post-operatively or after cancer treatment have been associated with lymphedema [3, 26, 30, 35–36]. A recent review of clinical trial data concluded that carefully controlled physical activity does not alter risk of lymphedema occurrence or worsening of lymphedema symptoms and may be a means to modify obesity and improve overall health and quality of life in BC survivors [37].

Strengths of our study include the large population-based cohort with the ability to study several potential risk factors. IWHS self-reported anthropometric and SEER measurements were validated and taken prior to BC, treatment and lymphedema or arm symptom assessment. Comprehensive data on cancer diagnosis and primary treatment are available through SEER. Limitations require discussion. Data on adjuvant therapies (chemotherapy, radiation therapy and tamoxifen) were self-reported and were not validated. Other limitations include that the cohort comprises a predominantly white population, lymphedema and arm symptoms data were self-reported, and there were missing data for tumor size and lymph node status. We did not have data on the date of lymphedema diagnosis, history of arm infection, injury, the use of lymphedema therapies, reconstructive surgery, or BC recurrence, factors which may impact lymphedema. Given when these participants were diagnosed with BC, our sample includes fewer with sentinel lymph node biopsy than would be likely in a cohort recruited today. Both response and survivors biases are possible given the number of non-responders and women who died between the diagnosis of BC and the 2004 survey.

In summary, obesity, worse general health, and markers of more advanced cancer were associated with lymphedema and related arm symptoms in BC survivors. Obesity and general health are potentially modifiable. Given the time-lag between BC, its treatment, and onset of lymphedema for some survivors, there may be a window of opportunity in which to intervene to modify risk. Improvements in lymphedema symptoms have been reported from weight loss through diet [38] and exercise [39–40]. Further clinical trials will determine if interventions targeted toward modifiable risk factors, particularly obesity, will prevent lymphedema in BC survivors.

Acknowledgments

The authors are indebted to the Iowa Women's Health Study staff and participants for their contributions, as well as to Sandra Norman and co-authors for use of their lymphedema survey.

Funding: NCI RO1CA39742 (IWHS)

References

1. Shih Y-CT, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TH, Perkins GH, Elting LS. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. J Clin Oncol. 2009; 27:2007–2014. [PubMed: 19289624]
2. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors, the Iowa Women's Health Study (2008). J Clin Oncol. 26:5689–5696. [PubMed: 19001331]
3. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer. 2001; 92(6):1368–1377. [PubMed: 11745212]
4. Meeske KA, Sullivan-Halley J, Smith AW, McTiernan A, Baumgartner KB, Harlan LC, Bernstein L. Risk factors for arm lymphedema following breast cancer diagnosis in Black women and White women. Breast Cancer Res Trtmnt. 2009; 113:383–391.
5. Szuba A, Shin WS, Strauss HW, Rockson S. The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. J Nucl Med. 2003; 44(1):43–57. [PubMed: 12515876]
6. Mortimer PS. The pathophysiology of lymphedema. Cancer. 1998; 83(12 Suppl American):2798–2802. [PubMed: 9874400]
7. Erickson VS, Pearson ML, Ganz PA, Adams J, Kahn KL. Arm edema in breast cancer patients. J Natl Cancer Inst. 2001; 93:96–111. [PubMed: 11208879]
8. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. Cancer. 1998; 83(12 Suppl American):2776–2781. [PubMed: 9874397]
9. Mortimer PS, Bates DO, Brassington HD, Stanton AWB, Strachan DP, Levick JR. The prevalence of arm oedema following treatment for breast cancer. QJ Med. 1996; 89:377–380.
10. Grabois M. Breast cancer. Postmastectomy lymphedema. State of the art review. Phys Med Rehabil Rev. 1994; 8:267–277.
11. Rescigno J, Zampell JC, Axelrod D. Patterns of axillary surgical care for breast cancer in the era of sentinel node biopsy. Ann Surg Oncol. 2009; 16:687–696. [PubMed: 19101768]
12. Yi M, Giordano SH, Meric-Bernstam F, Mittendorf EA, Kuerer HM, Hwang RF, Bedrosian I, Rourke L, Hunt KK. Trends in and outcomes from sentinel lymph node biopsy (SNLB) alone vs. SLNB with axillary lymph node dissection for node-positive breast cancer patients: experience from the SEER database. Ann Surg Oncol. 2010; 17:S343–S351.
13. Yen TWF, Fan X, Sparapani R, Laud PW, Walker AP, Nattinger AB. A contemporary population-based study of lymphedema risk factors in older women with breast cancer. Ann Surg Oncol. 2009; 16:979–988. [PubMed: 19194754]
14. Kwan ML, Darbinian J, Schmitz KH, Citron R, Partee P, Kutner SE, Kushi LH. Risk factors for lymphedema in a prospective breast cancer survivorship study, the Pathways Study. Archives of Surgery. 2010; 145:1055–1063. [PubMed: 21079093]

15. Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. Cancer Epidemiology Biomarkers and Prevention. 2008; 16:775–82.
16. Folsom AR, Kaye SA, Sellers TA, Hong CP, Cerhan JR, Potter JD, Prineus RJ. Body fat distribution and 5-year risk of death in older women. JAMA. 1994; 269:483–487. published erratum in JAMA 269:1254, 2004. [PubMed: 8419667]
17. Bisgard KM, Folsom AR, Hong C, Sellers TA. Mortality and cancer rates in nonrespondents to a prospective study of older women: 5-year follow-up. Am J Epidemiol. 1994; 139:990–1000. [PubMed: 8178787]
18. Kushi LH, Kaye SA, Folsom AR, Soler JT, Prineas RJ. Accuracy and reliability of self-measurement of body girths. Am J Epidemiol. 1988; 128:740–748. [PubMed: 3421240]
19. Norman SA, Miller LT, Erikson HB, Norman MF, McCorkle R. Development and validation of a telephone questionnaire to characterize lymphedema in women treated for breast cancer. Phys Ther. 2001; 81(6):1192–1205. [PubMed: 11380275]
20. Kissen MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphedema following the treatment of breast cancer. Br Jnl Surg. 1986; 73:580–4.
21. Ozaslan C, Kuru B. Lymphedema after treatment of breast cancer. The Am J Surg. 2004; 187:69–72.
22. Norman SA, Localio AR, Kallan MJ, Weber AL, Torpey HA, Potashnik SL, Miller LT, Fox KR, DeMichele A, Solin LJ. Risk factors for lymphedema after breast cancer treatment. Cancer Epi Biomarkers Prevention. 2010; 19(11):2734–46.
23. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GKD, Scott-Connor C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. Annals Surgical Oncology. 2009; 16:1959–1972.
24. Deo SVS, Ray S, Rath GK, Shukia NK, Kar M, Asthana S, Raina V. Prevalence and risk factors for development of lymphedema following breast cancer treatment. Indian Jnl of Cancer. 2004; 41(1):8–12.
25. Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Hölzel D. Axillary surgery severely affects quality of life: results of a 5-year prospective study in breast cancer patients. Breast Canc Rsrch Trtmnt. 2003; 79:47–57.
26. McLaughlin SA, Wright MJ, Morris KT, Giron GL, Sampson MR, Brockway JP, Hurley KE, Riedel ER, Van Zee KI. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. Jnl Clin Oncology. 2008; 26:5213–5219.
27. Geller BM, Vacek PM, O'Brien P, Secker-Walker RH. Factors associated with arm swelling after breast cancer surgery. Jnl of Women's Health. 2003; 12(9):921–930.
28. Larson D, Weinstein M, Goldbert I, Silver B, Recht A, Cady B, Silen W, Harris JR. Edema of the arm as a function of the extent of axillary surgery in patients with stage I–II carcinoma of the breast treated with primary radiotherapy. Int J Radiat Oncol Biol Phys. 1986; 12:1575–82. [PubMed: 3759582]
29. Soran A, D'Angelo G, Begovic M, Ardic F, Harlak A, Samuel Wieand H, Vogel VG, Johnson RR. Breast cancer-related lymphedema – what are the significant predictors and how they affect the severity of lymphedema? Breast J. 2006; 12(6):536–43. [PubMed: 17238983]
30. Pezner RD, Patterson MP, Hill LR, Lipsett JA, Desai KR, Vora N, Wong JY, Luk KH. Arm lymphedema in patients treated conservatively for breast cancer: relationship to patient age and axillary node dissection technique. Int J Radiat Oncol Biol Phys. 1986; 198:2079–83. [PubMed: 3793544]
31. Kiel KD, Rademacker AW. Early-stage breast cancer: arm edema after wide excision and breast irradiation. Radiology. 1996; 198:279–283. [PubMed: 8539394]
32. Armer J, Fu MR. Age differences in post-breast cancer lymphedema signs and symptoms. Cancer Nurs. 2005; 29:200–207. [PubMed: 15915063]
33. Clark B, Sitzia J, Harlow W. Incidence and risk of arm oedema following treatment for breast cancer: a three-year follow-up study. Q J Med. 2005; 98:343–348.

34. Kuehn T, Klauss W, Darsow M, Regele S, Flock F, Maiterth C, Dahlbender R, Wendt I, Kreienberg R. Long-term morbidity following axillary dissection in breast cancer patients – clinical assessment, significance for life quality and the impact of demographic, oncologic and therapeutic factors. Breast Cancer Res Treat. 2000; 64:275–86. [PubMed: 11200778]

35. Segerstrom K, Fjerle P, Graffman S, Nystrom A. Factors that influence the incidence of brachial oedema after treatment of breast cancer. Scand J Plast Reconstr Surg Hand Surg. 1992; 26:223–7. [PubMed: 1411352]

36. Sener SF, Winchester DJ, Martz CH, Feldman JL, Cavanaugh JA, Winchester DP, Weigel B, Bonnefoi K, Kirby K, Morehead C. Lymphedema after sentinel Lymphadenectomy for breast carcinoma. Cancer. 2001; 92:748–52. [PubMed: 11550143]

37. Schmitz KH, Courneya KS, Mathews C, Demark-Wahnefried W, Galvão DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, Schwartz AL. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Medicine Sci in Sports Exercise. 2010; 42:1409–1426.

38. Shaw C, Mortimer P, Judd PA. A randomized controlled trial of weight reduction as a treatment for breast cancer-related lymphedema. Cancer. 2007; 10(8):1868–74. [PubMed: 17823909]

39. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, Bryan CJ, Williams-Smith CT, Greene QP. Weight-lifting in women with breast cancer-related lymphedema. N Engl J Med. 2009; 361:664–73. [PubMed: 19675330]

40. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Lewis-Grant L, Smith R, Bryan CJ, Williams-Smith CT, Chittams J. Weight-lifting for women at risk for breast cancer-related lymphedema. JAMA. 2010; 304(24):2699–2705. [PubMed: 21148134]

Table 1

Prevalence or Mean ± SE of selected baseline and 2004 characteristics in participants who developed unilateral breast cancer from 1986–2004 and responded to the 2004 follow-up questionnaire, Iowa Women's Health Study

Characteristic	Without lymphedema or arm symptoms (n = 708)	Diagnosed lymphedema (n = 104)	Arm symptoms without lymphedema (n = 475)
Age at baseline (y)	61.0 ± 0.2	60.5 ± 0.4	61.1 ± 0.2
Age at breast cancer diagnosis (y)	71.0 ± 0.2	70.8 ± 0.5	71.05 ± 0.3
Time since breast cancer diagnosis (y)	8.1 ± 0.2	7.8 ± 0.5	8.2 ± 0.2
BMI baseline, ≥ 25kg/m^2 (%)	60.3	78.9	65.9
BMI 2004, ≥ 25kg/m^2 (%)	59.1	80.4	64.5
≥ High school education (%)	87.4	91.3	82.3
Currently married, baseline (%)	79.4	79.6	80.7
Occupation, baseline (%)			
Homemaker/never worked	16.0	19.2	20.7
Professional/clerical work	45.0	51.0	39.0
Farm/craftwork	39.0	29.8	40.3
Smoking at baseline (%)			
Never	69.6	57.3	69.6
Past	19.5	30.1	19.6
Current	10.9	12.6	10.8
Pack-years at baseline	7.2 ± 0.6	9.6 ± 1.5	7.7 ± 0.8
Ethanol consumption at baseline, g/day	3.4 ± 0.3	4.8 ± 1.0	3.5 ± 0.4
Any regular physical activity, baseline (%)	42.4	42.2	41.1
Estrogen replacement at baseline (%)			
Current/former	41.3	39.4	47.1
Never	58.7	60.6	52.4
Comorbidity Index, (% positive)	55.1	60.6	59.6
History of hypertension	49.0	50.0	53.3
History of diabetes	8.2	6.7	11.8
History of heart disease	13.6	19.2	19.4

Table 2

Odds ratios for developing lymphedema or arm symptoms by tumor at diagnosis and treatment-related characteristics, Iowa Women's Health Study

Breast cancer characteristics at diagnosis	No lymphedema or symptoms (n = 708)		Lymphedema (n = 104)		Arm Symptoms (n = 475)		Lymphedema[a]		Arm Symptoms[b]	
							Age-Adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)[c]	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)[c]
	No.	%	No.	%	No.	%				
Cancer Stage[d]										
In situ	114	16.1	7	6.7	75	15.8	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Local	477	67.4	69	66.3	301	63.4	2.35 (1.05, 5.36)	2.13 (0.94, 4.83)	0.96 (0.69–1.33)	0.91 (0.65, 1.28)
Region/distant	111	15.7	27	26.0	95	20.0	4.00 (1.67, 9.56)	3.92 (1.61, 9.54)	1.30 (0.87–1.94)	1.21 (0.80, 1.84)
Unknown	6	0.8	1	1.0	4	0.8	---	---	---	---
Tumor size[d]										
0–10mm	226	31.9	24	23.1	130	27.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
10–20mm	242	34.2	43	41.3	188	39.6	1.71 (1.00, 2.91)	1.71 (0.99–2.96)	1.35 (1.00–1.80)	1.32 (0.98, 1.78)
>20mm	163	23.0	29	27.9	100	21.0	1.68 (0.94, 2.99)	1.66 (0.92–3.02)	1.06 (0.77–1.48)	1.04 (0.74, 1.47)
Unknown	77	10.9	8	7.7	57	12.0	1.00 (0.43–2.32)	---	1.29 (0.86–1.93)	1.36 (0.90, 2.07)
Surgery[d]										
No surgery or lumpectomy	264	37.3	37	35.6	154	32.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Simple mastectomy	34	4.8	3	2.9	17	3.6	0.65 (0.19–2.24)	0.74 (0.21, 2.60)	0.87 (0.47–1.60)	0.92 (0.48, 1.73)
Radical mastectomy	410	57.9	64	61.5	304	64.0	1.13 (0.73–1.76)	1.13 (0.72, 1.77)	1.28 (1.00–1.65)	1.24 (0.95, 1.59)
Unknown	0		0		0		---	---	---	---
# Nodes examined[d,e]										
0	110	16.5	8	8.5	52	11.6	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
1–4	53	8.0	2	2.1	27	6.0	0.50 (0.10, 2.45)	0.52 (0.10, 2.62)	1.09 (0.62–1.93)	1.23 (0.68, 2.24)
5–10	151	22.6	23	24.5	119	26.5	2.00 (0.86, 4.66)	1.90 (0.79, 4.57)	1.68 (1.12–2.53)	1.69 (1.10, 2.59)
11–20	289	44.4	48	51.1	188	41.9	2.24 (1.02, 4.89)	2.23 (1.00, 4.97)	1.38 (0.95–2.02)	1.42 (0.96, 2.11)
>20	50	7.5	13	13.8	54	12.0	3.56 (1.39, 9.14)	3.52 (1.32, 9.34)	2.30 (1.38–3.82)	2.38 (1.41, 4.03)
Unknown	13	2.0	0		9	2.0		Ptrend = 0.003		Ptrend = 0.007
Nodes positive[d,e]										

Breast cancer characteristics at diagnosis	No lymphedema or symptoms (n = 708)		Lymphedema (n = 104)		Arm Symptoms (n = 475)		Lymphedema[a]		Arm Symptoms[b]	
							Age-Adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)[c]	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)[c]
	No.	%	No.	%	No.	%				
No	471	70.7	65	69.2	317	70.6	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	78	11.7	20	21.3	76	16.9	1.88 (1.08, 3.29)	2.12 (1.19, 3.79)	1.45 (1.02–2.04)	1.44 (1.08, 2.19)
Unknown	117	17.6	9	9.6	56	12.5	0.89 (0.5101.53)	0.98 (0.56–1.72)	0.76 (0.56–1.03)	0.76 (0.55–1.04)
Radiation treatment[f]										
No/unknown	655	92.0	90	86.5	419	88.2	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes Axilla	57	8.0	14	13.5	56	11.8	1.76 (0.94, 3.29)	1.77 (0.92, 3.40)	1.57 (1.06, 2.32)	1.72 (1.15, 2.57)
No/unknown	477	67.0	61	58.7	319	67.2	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes Breast	235	33.0	43	41.3	156	32.8	1.40 (0.92, 2.14)	1.46 (0.94, 2.27)	1.00 (0.78–1.29)	1.10 (0.85, 1.42)
Chemotherapy[f]										
No/unknown	643	90.3	81	77.9	422	88.8	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	69	9.7	23	22.1	53	11.2	2.58 (1.53, 4.38)	3.05 (1.75, 5.30)	1.17 (0.80–1.72)	1.26 (0.85, 1.87)
Tamoxifen use[f]										
No/unknown	402	56.5	46	44.2	272	57.3	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	310	43.5	58	55.8	203	42.7	1.60 (1.06, 2.42)	1.57 (1.02, 2.41)	0.96 (0.76–1.22)	0.97 (0.76, 1.24)

[a] Comparing participants with lymphedema to participants without lymphedema or symptoms.

[b] Comparing participants with arm symptoms without diagnosed lymphedema to participants without lymphedema or symptoms.

[c] Adjusted for baseline age, BMI (tertiles), smoking history (categorical and pack-years, continuous), occupational history (categorical), and general health (categorical).

[d] From SEER

[e] Variable exists from 1988–2003, but not 1986–87; therefore women diagnosed with unilateral breast cancer from 1988 onward are included in analyses (no lymphedema/symptoms: n=670, lymphedema: n=94, and arm symptoms: n=449).

[f] Self-report from the 2004 follow-up questionnaire.

Table 3

Odds ratios for developing lymphedema or arm symptoms by baseline body composition and health characteristics, Iowa Women's Health Study

Baseline Characteristic[d]	No lymphedema or symptoms (n = 704)		Lymphedema (n = 104)		Arm Symptoms (n = 475)		Lymphedema[a]		Arm symptoms[b]	
							Age-Adjusted OR (95% CI)	Multivariate-adjusted OR[c] (95% CI)	Age-Adjusted OR (95% CI)	Multivariate-adjusted OR[c] (95% CI)
	No.	%	No.	%	No.	%				
BMI (kg/m^2)										
≤24.9	281	39.7	22	21.2	162	34.1	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
25–29.9	280	39.5	47	45.2	184	38.7	2.16 (1.27, 3.69)	2.00 (1.10, 3.64)	1.14 (0.87–1.49)	1.06 (0.79, 1.42)
≥30	147	20.8	35	33.6	129	27.2	3.04 (1.72, 5.37)	3.24 (1.70, 6.21)	1.52 (1.12–2.06)	1.31 (0.93, 1.83)
Waist (inches)										
≤31.88	257	36.4	27	26.0	144	30.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
32.00–36.25	247	34.9	33	31.7	143	30.1	1.30 (0.76, 2.24)	1.05 (0.56, 1.95)	1.03 (0.77–1.38)	1.00 (0.73, 1.37)
≥36.37	203	28.7	42	40.4	186	39.3	2.02 (1.20, 3.40)	1.99 (1.10, 3.60)	1.63 (1.23–2.17)	1.33 (0.97, 1.82)
Hip (inches)										
≤39.25	252	35.6	23	22.6	145	30.7	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
39.37–42.63	231	32.7	36	35.3	160	33.8	1.72 (0.99, 3.00)	1.94 (1.02, 3.66)	1.20 (0.90–1.60)	1.13 (0.83, 1.54)
≥42.75	224	31.7	43	42.2	168	35.5	2.10 (1.23, 3.60)	2.43 (1.30, 4.55)	1.30 (0.98–1.73)	1.14 (0.84, 1.57)
General health										
Excellent	230	32.8	21	20.2	93	19.8	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Good	432	61.6	73	70.2	304	64.5	1.85 (1.11, 3.09)	2.07 (1.12, 3.80)	1.73 (1.31–2.31)	1.63 (1.21, 2.19)
Fair/Poor	39	5.6	10	9.6	74	15.7	2.80 (1.23, 6.41)	3.44 (1.30, 9.06)	4.69 (2.97–7.40)	4.27 (2.60, 7.00)
Comobidity index										
0	318	44.9	41	39.4	192	40.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
1	290	41.0	48	46.2	183	38.5	1.31 (0.84–2.05)	1.01 (0.59, 1.71)	1.04 (0.80–1.35)	0.86 (0.65, 1.13)
2+	100	14.1	15	14.4	100	21.1	1.18 (0.62–2.22)	0.87 (0.42, 1.79)	1.65 (1.19–2.30)	1.14 (0.82, 1.65)
Physical activity										
Low	303	43.5	51	50.5	238	50.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Medium	220	31.5	28	27.7	120	25.4	0.77 (0.47–1.27)	0.94 (0.53, 1.67)	0.69 (0.52–0.91)	0.79 (0.59, 1.07)
High	174	25.0	22	21.8	114	24.2	0.78 (0.45–1.33)	1.28 (0.69, 2.35)	0.83 (0.62–1.11)	1.01 (0.74, 1.38)

Baseline Characteristic[d]	No lymphedema or symptoms (n = 704)		Lymphedema (n = 104)		Arm Symptoms (n = 475)		Lymphedema[a]		Arm symptoms[b]	
							Age-Adjusted OR (95% CI)	Multivariate-adjusted OR[c] (95% CI)	Age-Adjusted OR (95% CI)	Multivariate-adjusted OR[c] (95% CI)
	No.	%	No.	%	No.	%				
Occupation										
Homemaker	333	47.5	58	56.3	268	57.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Craft/farm	205	29.2	24	23.3	112	24.0	1.58 (0.86–2.89)	1.28 (0.65, 2.53)	1.26 (0.91–1.75)	1.04 (0.73, 1.47)
Professional	163	23.3	21	20.4	87	18.6	1.48 (0.92–2.39)	1.49 (0.88, 2.55)	0.84 (0.65–1.09)	0.88 (0.67, 1.16)
Smoking										
Never	275	39.1	31	29.8	191	40.3	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Former	112	15.9	20	19.2	98	20.7	1.85 (1.15–2.97)	1.57 (0.81, 3.08)	1.0 (0.68–1.47)	0.97 (0.65, 1.43)
Current	317	45.0	53	51.0	185	39.0	1.32 (0.68–2.54)	1.37 (0.48, 3.88)	1.0 (0.74–1.35)	0.86 (0.49, 1.53)

[a] Comparing participants with lymphedema to participants without lymphedema or symptoms.

[b] Comparing participants with arm symptoms without diagnosed lymphedema to participants without lymphedema or symptoms.

[c] Anthropometric characteristics (BMI, waist, hip), physical activity, comorbidity index adjusted for baseline age, positive lymph nodes (yes/no), tumor size (categories), tumor stage (categories), chemotherapy (yes/no), radiation (any site, yes/no), smoking history (categories and pack-years, continuous), occupational history (categories), and general health at baseline (categorical). Baseline general health, smoking, occupational history adjusted for baseline age, BMI (categories), tumor size (categories), positive lymph nodes (yes/no), chemotherapy (yes/no), radiation therapy (any, yes/no), and each other.

[d] 1986 baseline IWHS survey.

Table 4

Odds ratios for developing lymphedema or arm symptoms according to presence of tumor positive lymph nodes at diagnosis by any history of radiation treatment (no/unknown vs. yes)

Variable	Lymphedema[a,c]		Arm symptoms[b,c]	
	Negative nodes	Positive nodes	Negative nodes	Positive nodes
Radiation axilla				
No/unknown	1.0 (referent) n=62 L[d] n=435 NL[f]	1.0 (referent) n=11 L n=67 NL	1.0 (referent) n=286 AS[e] n=435 NL	1.0 (referent) n=55 AS n=67 NL
Yes	0.55 (0.15, 1.96) n=3 L n=36 NL	7.1 (1.77, 28.58) n=9 L n=11 NL	1.53 (0.89, 2.60) n=31 AS n=36 NL	5.16 (1.85, 14.39) n=21AS n=11 NL
	$P_{interaction}$ = 0.01		$P_{interaction}$ = 0.21	
Radiation breast				
No/unknown	1.0 (referent) n=46 L n=320 NL	1.0 (referent) n=8 L n=59 NL	1.0 (referent) n=222 AS n=320 NL	1.0 (referent) n=45 AS n=59 NL
Yes	0.85 (0.45, 1.56) n=19 L n=151 NL	4.90 (1.43, 16.81) n=12 L n=19 NL	1.01 (0.73, 1.41) n=95 AS n=151 NL	4.29 (1.81, 10.16) n=31 AS n=19 NL
	$P_{interaction}$ = 0.04		$P_{interaction}$ = 0.02	

[a] Comparing participants with lymphedema to participants without lymphedema or symptoms.

[b] Comparing participants with arm symptoms without diagnosed lymphedema to participants without lymphedema or symptoms.

[c] Adjusted for baseline age, BMI (categories), history of smoking (categories and pack-years, continuous), occupational history (categories), general health at baseline (categories), tumor stage (categories), tumor size (categories), and history of chemotherapy (yes/no).

[d] L = BrCa survivors with lymphedema.

[e] AS = BrCa survivors with arm symptoms without a history of lymphedema.

[f] NL = BrCa survivors without lymphedema or arm symptoms.