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ORIGINAL REPORT

Lymphedema and Quality of Life in Breast Cancer Survivors: The Iowa Women's Health Study

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
The impact of lymphedema or related arm symptoms on health-related quality of life (HRQOL) in breast cancer (BrCa) survivors has not been examined using a large population-based cohort.

Patients and Methods
The Iowa Women's Health Study (IWHS) collected self-report data for lymphedema, arm symptoms, and HRQOL (Medical Outcomes Study Short Form-36) in 2004 and data for cancer diagnosis, treatment, and behavioral and health characteristics between 1986 and 2003. We studied 1,287 women, age 55 to 69 years at baseline, who developed unilateral BrCa. We used cross-sectional analyses to describe the prevalence of lymphedema and arm symptoms and multivariate-adjusted generalized linear models to compare HRQOL (physical functioning, bodily pain, general health, physical and emotional role limitations, vitality, social functioning, and mental health) between the following three survivor groups: women with lymphedema (n = 104), women with arm symptoms without diagnosed lymphedema (n = 475), and women without lymphedema or arm symptoms (n = 708).

Results
The mean (± SE) time between BrCa diagnosis and lymphedema survey was 8.1 ± 0.2 years. Of BrCa survivors, 8.1% self-reported diagnosed lymphedema, and 37.2% self-reported arm symptoms. Knowledge of lymphedema was low among survivors without diagnosed lymphedema (n = 1,183). After multivariate adjustment, women with diagnosed lymphedema or arm symptoms without diagnosed lymphedema had lower physical and mental HRQOL compared with women without lymphedema or arm symptoms. Effect sizes were mild to moderate. There was a dose-response relation between number of arm symptoms and lower HRQOL.

Conclusion
In the IWHS, HRQOL was lower for BrCa survivors with diagnosed lymphedema and for those with arm symptoms without diagnosed lymphedema. Clinical trials are needed to determine what interventions can improve lymphedema and impact HRQOL for BrCa survivors.

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INTRODUCTION

Breast cancer (BrCa) survivors face unique health challenges, such as lymphedema, that may impact their health-related quality of life (HRQOL). The prevalence of lymphedema varies from 0% to 56%;[1] up to 50% of survivors report symptoms consistent with lymphedema, with or without a clinical diagnosis.[2] In BrCa survivors, lymphedema is chronic, progressive swelling that involves the arm, shoulder, neck, or torso from physical disruption or compression of lymphatic channels from tumor invasion, surgery, or radiotherapy.[3,4] Lymphedema is often clinically defined as swelling of at least 200 mL by volume or 2 cm by circumference measurement of the affected limb compared with the nonaffected limb.[5] Lymphedema may develop at any time from initial treatment to 20 years later.[2]

Change in HRQOL is a recognized major health outcome of cancer treatment. HRQOL incorporates the following three overlapping domains of functioning as they relate to health status: physical, psychological, and social.[6] Individuals' overall life satisfaction, perceptions of their health status, and ability to take part in valued activities are components of HRQOL.[6] Lymphedema or arm symptoms may impact HRQOL in several ways. Physical and physiologic morbidities secondary to lymphedema include infection, skin changes, altered sensation, pain, and decreased range of motion, strength, and function.[4,7-13] Fine motor function may be disturbed with subclinical lymphedema.[5] A larger arm

size may require women to alter activities of daily living, clothing, sleep, employment, and sport.[8] As reviewed by Erickson et al,[1] psychological morbidities associated with lymphedema include anxiety, depression, sexual dysfunction, disturbance of body image, and social avoidance. Psychological distress correlates with increasing number of lymphedema symptoms.[14]

The impact of lymphedema or related arm symptoms on HRQOL in BrCa survivors has not been examined using a large population-based sample. Authors have examined HRQOL in BrCa survivors with lymphedema compared with those without lymphedema,[1,9,13,15-19] although few[9,18] have examined the impact of subclinical disease or arm symptoms related to lymphedema on HRQOL. We used data from the Iowa Women's Health Study (IWHS) to describe the prevalence of lymphedema and arm symptoms and to compare HRQOL in the following three groups of BrCa survivors: women with diagnosed lymphedema, women with arm symptoms related to lymphedema but without diagnosed lymphedema, and women with no history of lymphedema or arm symptoms.

PATIENTS AND METHODS

Population

Methods for the IWHS have been described.[20] Briefly, in January 1986, a dietary and lifestyle questionnaire was mailed to 99,826 randomly selected women aged 55 to 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 nonresponders to follow-up surveys was determined through the National Death Index. The IWHS was approved by the University of Minnesota's Institutional Review Board.

Incident BrCas 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 less than 1% annually, allowing for nearly complete follow-up of cancer incidence.[21] BrCa comprised International Classification of Diseases of Oncology, Third Edition, codes C50.0 to C50.9. After excluding 1,383 women with BrCa at baseline, 40,453 women were observed, and from 1986 to 2003, 2,816 women developed incident BrCa (unilateral, n = 2,657; bilateral, n = 159). One thousand two hundred eighty-seven women with unilateral BrCa completed the 2004 follow-up questionnaire and compose the sample used in these analyses; of the remainder, 1,283 women did not respond, and 87 did not complete the entire survey. Among nonrespondents, 56% had died.

Measurements

BrCa and treatment. Diagnosis date, histology, stage, estrogen and progesterone receptor status, tumor size, surgery type, number of lymph nodes examined, and presence of metastasis were obtained from SEER. For women with more than one tumor in the same breast (n = 16), we assigned the largest tumor size, most advanced stage, and most radical surgery completed; the total number of lymph nodes examined and the number of positive nodes were calculated.

Health and lifestyle. The baseline questionnaire in 1986 collected demographic data, including race, occupation, education, and marital status.[20] At baseline and follow-ups, women reported medical history, including interim cancer, diabetes, hypertension, and heart disease diagnoses.

Participants reported their present height 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 normal (< 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), and obese (≥ 30.0 kg/m^2).[22]

Lymphedema. The 2004 follow-up questionnaire included a validated self-report measure of lymphedema diagnosis, arm symptoms, and treatment that was developed by Norman et al.[23] This survey had a specificity of 0.90 and sensitivity of 0.86 to 0.92 for diagnosing lymphedema compared with clinical assessment.[23] Questions included whether or not, over the last 3 months, the participant noticed that her upper extremity ipsilateral to the cancer was larger or the participant experienced symptoms such as altered function, puffiness, swelling, and/or pain compared with the contralateral side.[23] IWHS participants were classified as follows: having lymphedema, if they reported ever receiving a diagnosis of lymphedema; having arm symptoms related to lymphedema without diagnosed lymphedema, if they answered yes to any of the questions about arm symptoms and did not have diagnosed lymphedema; or without lymphedema or arm symptoms, if they answered no to all questions.

HRQOL. The 2004 follow-up questionnaire included the Medical Outcomes Study Short Form-36 Version 2 (SF-36). This validated self-report measure includes 36 questions that evaluate the following eight health concepts: physical functioning, role limitations physical, bodily pain, general health, vitality, social functioning, role limitations emotional, and mental health.[24-26] Each subscale is standardized on a 0 to 100 scale; higher scores indicate more favorable health status. Normalized composite scores representing overall physical and mental functioning are calculated from individual scales.[24]

Analysis and Statistical Methods

Three groups of BrCa survivors (n = 1,287) were defined for analysis based on the lymphedema survey, as follows: with diagnosed lymphedema (n = 104); with arm symptoms without diagnosed lymphedema (n = 475); and without diagnosed lymphedema or arm symptoms (n = 708). SAS software (version 8.02; SAS Institute Inc, Cary, NC) was used. *P* values were adjusted using the Bonferroni correction;[27] tests were two sided. Raw SF-36 scores were converted to standardized T-scores (mean = 50, standard deviation [SD] = 10) using 1998 US general population norms.[28] A score of 40 represents 1 SD below the US population mean.[28] The effect size, a distribution-based method used to benchmark important HRQOL differences, was computed by dividing the difference in means between groups by the SD for both groups combined.[29] An effect size is small if it equals 0.2, medium if it equals 0.5, and large if it equals 0.8.[30,31] The minimally clinically important difference indicates the smallest difference in a score believed to be clinically relevant. SF-36 literature generally shows effect sizes in the range of 0.3 to 0.5 representing minimally clinically important differences.[32]

SF-36 scores are presented as means ± SE. PROC GLM with the LSMEANS option was used to calculate and compare scores between groups using age- and multivariate-adjusted linear regression. Potential confounders were individually examined and retained if they changed age-adjusted parameter estimates for physical or mental summary scores by 10% (baseline BMI and comorbidity index). The comorbidity index is the sum of self-reported illnesses (diabetes, heart disease, and hypertension) and was modeled categorically (none, one, or two to three comorbidities). Additional variables that were evaluated but not added to final models because they did not change age-adjusted parameter estimates by 10% or alter interpretation of the results included time since BrCa diagnosis, BMI in 2004, education, marital status, pack-years of smoking, tumor stage, tumor estrogen/progesterone receptor status, surgery, radiation, chemotherapy, and number of examined or positive lymph nodes.

Mean HRQOL scores were also computed by the number of arm symptoms experienced by women with arm symptoms without diagnosed lymphedema (n = 475); tests for linear trend were conducted using coefficients of orthogonal polynomials. To compare HRQOL in BrCa survivors to the overall cohort, proportions of participants with HRQOL scores more than 1 SD below the mean for the entire IWHS cohort were determined.

RESULTS

Population

Nonrespondents (n = 1,283), compared with respondents (n = 1,287), of the 2004 follow-up survey were more likely to be older

than 62 years (59.5% *v* 45.1%, respectively), to have a BMI of more than 25 kg/m^2 (66.8% *v* 63.9%, respectively), to have regional or distant disease (28.6% *v* 13.9%, respectively), and to have positive lymph nodes (24.7% *v* 15.5%, respectively); other characteristics did not differ between respondents and nonrespondents (Appendix Table A1, online only). Mean time (± SE) between BrCa diagnosis and the 2004 follow-up survey was 8.1 ± 0.2 years. Table 1 lists lymphedema survey data. Of participants, 8.1% reported having diagnosed lymphedema, and 37% reported arm symptoms without diagnosed lymphedema. Forty-three percent of participants reported arm symptoms over the last 3 months, including arm swelling (30.3%), pain/discomfort (21.3%), and functional limitations (17.6%). Of the 708 women without lymphedema or arm symptoms, 37.6% had heard of lymphedema. Of the 475 women with arm symptoms without diagnosed lymphedema, 39.8% had heard of lymphedema; 1.7% (n = 8) of these women had ever received treatment for arm symptoms compared with 51.9% (n = 54) of women with diagnosed lymphedema.

Table 2 lists IWHS baseline and 2004 follow-up survey data, as well as BrCa and treatment data from SEER. Participants with diagnosed lymphedema or arm symptoms without diagnosed lymphedema were more likely to have a positive comorbidity index than women without lymphedema or arm symptoms. Compared with other participants, women with diagnosed lymphedema had higher BMI at baseline and in 2004 and more often had distant metastases, larger tumor size, more advanced surgery, more lymph nodes examined, tumor-positive nodes, radiation treatment, and chemotherapy use.

HRQOL

Table 3 lists multivariate-adjusted HRQOL scores. Women with diagnosed lymphedema had statistically significantly lower mean SF-36 scores compared with women without lymphedema or arm symptoms for all scales except the mental summary scale, mental health subscale, and role limitations emotional subscale after age adjustment (data not shown) or multivariate adjustment; effect sizes between these groups ranged from negligible (mental health) to medium (physical health). After age and multivariate adjustment, mean scores for all SF-36 scales were statistically significantly lower for women with arm symptoms without diagnosed lymphedema compared with women without lymphedema or arm symptoms; effect sizes ranged from small (mental health) to medium (physical health). Women with lymphedema or arm symptoms without diagnosed lymphedema had mean physical summary scale, physical functioning, and role limitations physical subscale scores that averaged 1 SD below US population norms.[28]

For women with arm symptoms without diagnosed lymphedema (n = 475), after multivariate adjustment, there was a statistically significant linear trend of decreasing mean score by increasing number of arm symptoms for each SF-36 component and subscale ($P_{trend} < .0001$; Table 4). Table 5 lists the multivariate-adjusted proportions of participants with mean scores more than 1 SD below the mean for the remaining IWHS cohort (including non-BrCa participants). Compared with women without lymphedema or arm symptoms, more women with diagnosed lymphedema had physical health scores more than 1 SD below corresponding scores for the IWHS

Table 1. Self-Reported Diagnosis of Lymphedema and Arm Symptoms Among Women With Unilateral Breast Cancer Between 1986 and 2003 Who Responded to the 2004 Follow-Up Survey from the Iowa Women's Health Study

Parameter	All Women With Unilateral Breast Cancer (n = 1,287)		Women Without Lymphedema or Symptoms (n = 708)		Women With Lymphedema* (n = 104)		Women With Arm Symptoms Without Lymphedema† (n = 475)	
	No.	%	No.	%	No.	%	No.	%
Diagnosed lymphedema	104	8.1	0	0	104	100	0	0
Any symptoms over the last 3 months	553	43.0	0	0	78	75.0	475	100
Ever heard of lymphedema	558	43.4	266	37.6	103	99.0	189	39.8
Ever talked to practitioner about hand/arm appearing different from the other side	117	9.1	2	0.3	66	63.4	49	10.3
Ever received treatment for one limb larger than the other‡	62	4.8	0	0	54	51.9	8	1.7
Symptoms (experienced in the hand or arm of one upper extremity compared with the other during the last 3 months)								
No. of symptoms experienced								
Mean	2.6		0		3.3		2.4	
SE	0.1		0		0.3		0.1	
Swelling§	390	30.3	0	0	67	64.4	323	68.0
Functional changes‖	227	17.6	0	0	33	31.7	194	40.8
Pain or discomfort¶	275	21.3	0	0	41	39.4	239	50.3

*Women with diagnosed lymphedema include all participants with unilateral breast cancer who self-reported having had a diagnosis of lymphedema on the 2004 follow-up survey.
†Women with arm symptoms include all participants with unilateral breast cancer without diagnosed lymphedema who reported arm symptoms during the last 3 months on the 2004 follow-up survey.
‡No. and percentage presented for those participants who talked with a practitioner about limb swelling.
§Swelling occurred if a participant experienced any of the following on one side compared with the other: rings, bracelet, watch, or clothing felt too tight; puffiness; swelling after exercise; knuckles or veins were not visible; indentations were noted in the skin; or hand or arm was larger.
‖Functional changes occurred if a participant experienced any of the following on one side compared with the other: difficulty writing or limited range of motion.
¶Pain or discomfort occurred if a participant experienced any of the following on one side compared with the other: skin felt different; limb felt tired, thick, or heavy on one side; or pain.

Table 2. Selected Baseline, 2004, or Breast Cancer Characteristics in Participants With Unilateral Breast Cancer Between 1986 and 2003 Who Responded to the 2004 Follow-Up Survey

Characteristic	% of Women		
	Without Lymphedema or Arm Symptoms (n = 708)	Diagnosed Lymphedema (n = 104)	Arm Symptoms Without Lymphedema (n = 475)
Age at baseline, years			
Mean	61.0	60.5	61.1
SE	0.2	0.4	0.2
Age at breast cancer diagnosis, years			
Mean	71.0	70.8	71.1
SE	0.2	0.5	0.3
Time since breast cancer diagnosis, years			
Mean	8.1	7.8	8.2
SE	0.2	0.5	0.2
BMI			
Baseline, $\geq$ 25 kg/m^2	60.3	78.9	65.9
2004, $\geq$ 25 kg/m^2	59.1	80.4	64.5
Comorbidity index*	55.1	60.6	59.6
Tumor size (SEER), mm			
< 10	31.9	23.1	27.4
10-20	34.2	41.4	39.6
> 20	23.6	27.9	21.9
Unknown	10.3	7.7	11.2
Cancer stage (SEER)			
In situ	13.2	5.8	14.6
Local	58.4	58.3	57.4
Regional/distant	12.0	21.4	15.1
Unknown	16.4	14.6	12.9
Surgery (SEER)			
No surgery	1.0	0.8	0.6
Lumpectomy	34.6	31.6	36.7
Simple mastectomy	2.9	3.6	4.8
Radical mastectomy	61.5	64.0	57.9
No. of nodes examined (SEER)†			
Mean	10.3	13.3	11.8
SE	0.3	0.8	0.4
Positive lymph nodes (SEER)†	11.7	21.2	16.9
Radiation treatment (2004 follow-up)			
Ever to axilla	7.9	13.5	11.8
Ever to breast	32.9	41.4	32.8
Ever received chemotherapy (2004 follow-up)	9.8	22.1	11.2
Ever received tamoxifen (2004 follow-up)	43.8	55.8	42.7

Abbreviations: BMI, body mass index; SEER, Surveillance, Epidemiology, and End Results.
*Derived from baseline and follow-up questionnaires; participants with a history of hypertension, heart disease, and/or diabetes.
†No. of nodes only available since 1988; women diagnosed with unilateral breast cancer during or after 1988 (n = 1,209) are included (participants without lymphedema or arm symptoms, n = 666; participants with lymphedema, n = 94; participants with arm symptoms without diagnosed, n = 449).

cohort; more women with arm symptoms without diagnosed lymphedema had HRQOL scores more than 1 SD below the IWHS cohort for all scales.

DISCUSSION

In this study of unilateral BrCa survivors in Iowa, 45% had either diagnosed lymphedema (8%) or arm symptoms without diagnosed lymphedema (37%), consistent with other reports.[1,2,8] HRQOL was significantly lower in BrCa survivors with diagnosed lymphedema or with arm symptoms without diagnosed lymphedema compared with survivors without lymphedema or arm symptoms. Only 40% of survivors with arm symptoms without diagnosed lymphedema had previously heard of lymphedema; less than 2% had ever received treatment compared with 52% of women with diagnosed lymphedema. These data highlight the lack of knowledge about lymphedema among BrCa survivors, which may have prevented women with arm symptoms from seeking evaluation or treatment. Although women with known lymphedema experienced more arm symptoms on average, women with arm symptoms without diagnosed lymphedema had altered HRQOL in more domains of physical and mental HRQOL. Perhaps not surprisingly, there was a significant dose-response relationship for decreasing SF-36 scores by number of arm symptoms.

Our findings build on two smaller studies that compared the SF-36 in BrCa survivors with and without lymphedema. In unadjusted analyses, Velanovich and Szymanski[16] reported that women

Table 3. Multivariate-Adjusted Normalized Scores for the SF-36 in Participants With Unilateral Breast Cancer Between 1986 and 2003 Who Responded to the 2004 Follow-Up Survey

SF-36 Summary and Subscales	Women With Unilateral Breast Cancer (n = 1,287)		Women Without Lymphedema or Arm Symptoms (n = 708)		Women Diagnosed With Lymphedema (n = 104)*			Arm Symptoms Without Lymphedema (n = 475)‡					
	Mean Score	SE	Mean Score	SE	Mean Score	SE	Effect Size†	Mean Score	SE	Effect Size§	*P*‖	*P*¶	*P*#
Physical component summary	40.2	0.3	41.9	0.4	38.5	1.0	0.3	38.0	0.5	0.4	.01	< .0001	1.00
Mental component summary	53.0	0.3	54.1	0.4	53.5	1.0	0.1	51.3	0.5	0.3	1.00	< .0001	.17
Vitality/fatigue	48.3	0.3	49.9	0.4	46.4	0.9	0.3	46.3	0.4	0.3	.002	< .0001	1.00
Physical functioning	39.0	0.3	40.3	0.4	37.6	1.0	0.25	37.3	0.5	0.3	.04	< .0001	1.00
Role limitations, physical	41.2	0.3	43.0	0.4	39.9	1.1	0.3	38.8	0.5	0.4	.03	< .0001	.98
Mental health	52.0	0.2	53.0	0.3	52.2	0.9	0.1	50.5	0.4	0.3	1.00	< .0001	.21
Role limitations, emotional	46.8	0.3	48.2	0.5	46.5	1.2	0.2	44.9	0.6	0.3	.54	< .0001	.65
Social functioning	48.9	0.3	50.5	0.4	47.5	1.0	0.3	46.7	0.5	0.35	.02	< .0001	1.00
Bodily pain	45.9	0.3	47.8	0.4	44.2	1.0	0.3	43.4	0.5	0.4	.003	< .0001	1.00
General health	46.4	0.2	47.9	0.3	44.8	0.9	0.4	44.5	0.4	0.5	.002	< .0001	1.00

Abbreviation: SF-36, Medical Outcomes Study Short Form-36.
*Participants with unilateral breast cancer who self-reported a diagnosis of lymphedema on the 2004 survey.
†Effect size comparing women with diagnosed lymphedema with women without lymphedema or symptoms.
‡Participants with unilateral breast cancer who experienced any arm symptoms on the 2004 survey.
§Effect size comparing women with arm symptoms with women without lymphedema or symptoms.
‖Pairwise *t*-test with Bonferroni adjustment comparing women with diagnosed lymphedema *v* women without lymphedema or arm symptoms, adjusted for age, body mass index, and comorbidity index.
¶Pairwise *t*-test with Bonferroni adjustment comparing women with arm symptoms *v* women without lymphedema/arm symptoms, adjusted for age, body mass index, and comorbidity index.
#Pairwise *t*-test with Bonferroni adjustment comparing women with arm symptoms *v* women with lymphedema, adjusted for age, body mass index, and comorbidity index.

with lymphedema (n = 11) had lower median bodily pain ($P = .03$) and role emotional ($P = .08$) scores compared with women without lymphedema (n = 90).[16] Wilson et al[15] reported lower unadjusted physical component summary scores in BrCa survivors with (n = 32) versus without (n = 78) lymphedema ($P < .005$) and nonsignificant differences in mental component summary scores. BrCa survivors with lymphedema had statistically significantly ($P < .005$) lower scores for each SF-36 subscale, except mental health. Between-group effect sizes were larger than in our study.[15] Participants with lymphedema had average scores that were 1 SD below national norms for physical but not mental health, as was seen in the IWHS, as well as in another report of 48 women with lymphedema,[33] but not in the study by Velanovich and Szymanski.[16]

Our results also add to those from authors who reported decreased HRQOL in BrCa survivors with, versus without, lymphedema using other HRQOL measures.[9,12,15,17-19] The SF-12 was used

Table 4. Multivariate-Adjusted SF-36 Scores by Number of Arm Symptoms in Participants With Unilateral Breast Cancer Without Diagnosed Lymphedema

SF-36 Summary and Subscales*	No Symptoms (n = 708)†		1 Symptom (n = 214)‡		2 Symptoms (n = 101)‡		3 or 4 Symptoms (n = 98)‡		5+ Symptoms (n = 62)‡	
	Mean Score	SE	Mean Score	SE	Mean Score	SE	Mean Score	SE	Mean Score	SE
Physical component summary	41.9	0.4	38.4	0.7	38.1	1.0	37.8	1.0	35.3	1.3
Mental component summary	53.1	0.4	53.0	0.7	52.9	0.7	48.7	1.0	47.0	1.2
Vitality/fatigue	49.9	0.4	47.6	0.7	46.4	1.0	44.8	1.0	44.0	1.2
Physical functioning	40.3	0.4	37.6	0.7	36.7	1.0	36.5	1.0	35.1	1.3
Role limitations, physical	43.0	0.4	39.5	0.7	40.3	1.1	37.7	1.1	35.6	1.3
Mental health	53.0	0.3	51.5	0.6	51.6	0.9	49.2	0.9	47.2	1.1
Role limitations, emotional	48.2	0.4	46.7	0.8	47.2	1.2	42.0	1.2	39.1	1.5
Social functioning	50.5	0.4	48.2	0.7	45.8	1.1	44.5	1.1	44.8	1.4
Bodily pain	47.8	0.4	44.4	0.7	44.1	1.0	41.9	1.0	41.3	1.3
General health	47.9	0.3	45.1	0.6	44.3	0.9	43.8	0.9	41.1	1.1

Abbreviation: SF-36, Medical Outcomes Study Short Form-36.
*$P_{trend} < .0001$ for each component summary and subscale, adjusted for age, baseline body mass index, and comorbidity index.
†Women without lymphedema or arm symptoms include all participants with unilateral breast cancer who denied a history of lymphedema and did not experience any symptoms of lymphedema in the last 3 months on the 2004 survey.
‡Women with arm symptoms without diagnosed lymphedema include all participants with unilateral breast cancer who reported any symptoms of lymphedema (in the last 3 months) on the 2004 survey.

Table 5. Multivariate-Adjusted Proportions of Unilateral Breast Cancer Survivors With SF-36 Scores 1 SD Below the Mean SF-36 Scores for the IWHS Cohort

SF-36 Summary and Subscales	IWHS Cohort (n = 20,844)		% of Women				
	Mean Score	SE	Women Without Lymphedema or Arm Symptoms (n = 708) %	Women With Diagnosed Lymphedema (n = 104)* %	Women With Arm Symptoms Without Lymphedema (n = 475)† %	*P*‡	*P*§
Physical component summary	41.4	0.07	25.3	40.4	34.4	.005	.003
Mental component summary	53.0	0.07	21.5	27.9	31.8	.48	.0002
Vitality/fatigue	49.0	0.06	16.5	25.0	22.3	.12	.04
Physical functioning	40.1	0.07	18.6	29.8	26.1	.03	.007
Role limitations, physical	41.8	0.08	18.8	28.8	27.6	.06	.001
Mental health	51.8	0.06	14.8	15.4	23.8	1.00	.0003
Role limitations, emotional	47.1	0.08	19.2	27.9	31.4	.16	< .0001
Social functioning	49.0	0.07	15.4	22.1	25.9	.32	< .0001
Bodily pain	46.4	0.07	21.2	29.8	31.8	.18	.0001
General health	47.5	0.06	17.0	27.9	28.6	.03	< .0001

Abbreviations: SF-36, Medical Outcomes Study Short Form-36; SD, standard deviation; IWHS, Iowa Women's Health Study.

*Women with lymphedema include participants who self-reported having had a diagnosis of lymphedema on the 2004 survey.

†Women with arm symptoms without diagnosed lymphedema include participants who denied having a known diagnosis of lymphedema and who experienced any symptoms of lymphedema (in the last 3 months) on the 2004 survey.

‡Pairwise *t*-test with Bonferroni adjustment comparing women with diagnosed lymphedema to women without either lymphedema or arm symptoms, adjusted for age, baseline body mass index, and comorbidity index.

§Pairwise *t*-test with Bonferroni adjustment comparing women with arm symptoms only to women without either lymphedema or arm symptoms, adjusted for age, baseline body mass index, and comorbidity index.

to compare HRQOL in 622 premenopausal BrCa survivors observed prospectively for 3 years; after adjustment for potential covariates, physical and mental HRQOL were lower for survivors with lymphedema versus without.[17] In two studies, BrCa survivors with arm symptoms without edema were included.[9,18] Kwan et al[9] reported that women with lymphedema (n = 14) or arm symptoms without edema (n = 51) had lower ($P < .01$) unadjusted mean HRQOL scores compared with asymptomatic/no-edema women (n = 47) for physical functioning, social functioning, and pain symptoms, but not for global QOL. Women with arm symptoms had HRQOL reductions at least as great in magnitude as women with lymphedema, similar to IWHS; however, in IWHS, women with arm symptoms without diagnosed lymphedema had reductions in mental health that were not observed in women with diagnosed lymphedema. Engel et al[18] observed 990 BrCa survivors prospectively for 5 years and surveyed them annually to assess HRQOL and arm problems. The majority of annual unadjusted mean HRQOL scores, including the global score, were statistically significantly lower for participants with arm problems compared with BrCa survivors without arm problems. From years 1 to 5, the percentage of participants with arm problems decreased from 47% to 38%; participants whose arm problems improved from years 1 to 2 (n = 87) reported improvements in several HRQOL domains.[18]

Although there have been some differences across studies in specific domains of HRQOL affected, the general consensus is that HRQOL is lower in BrCa survivors with lymphedema or related arm symptoms compared with BrCa survivors without lymphedema or arm symptoms. Differences in participant age, length of follow-up, surveys, or other aspects of study design may contribute to differences among studies. Women in our study were generally older and further out from cancer diagnosis than in other studies. However, we did not observe confounding or interaction by time since BrCa diagnosis. Because studies have used different methods to present HRQOL data, we chose to present the data in varied ways (means between groups, effect sizes, and proportions of participants 1 SD below the means for US norms and the overall IWHS cohort) to aid in comparison across studies.

Lymphedema improves with complete decongestive therapy, which includes manual lymphatic drainage, compression therapy exercises, and skin/nail care.[1] There have been a few, generally small and nonrandomized, interventions that have demonstrated improved mood or HRQOL after intensive reductive therapy.[11,34-39] Improved emotional function, sleep quality, dyspnea, and altered sensations (eg, pain and heaviness) were reported in BrCa survivors after one randomized intervention of manual lymphatic drainage.[39] Interestingly, some authors have reported that change in limb volume was not statistically correlated with change in HRQOL[11,34] or mood.[35] However, participants reported greater comfort and strength and reduced limb size at the same time as improved HRQOL.[11,34] Swelling is a defining characteristic of lymphedema, but it is not the only symptom; the results of the IWHS suggest that other aspects of lymphedema in addition to swelling, such as pain and altered function or perhaps even knowledge of lymphedema and use of treatment, may impact HRQOL.

In the IWHS, women with arm symptoms without diagnosed lymphedema had lower mental health scores than women with diagnosed lymphedema. The difference may be attributable to bias from cross-sectional methodology or a result of the relatively few women with diagnosed lymphedema compared with women with arm symptoms without diagnosed lymphedema. Alternatively, it is possible that women with known lymphedema had developed adaptation mechanisms to learn to cope with persistent lymphedema and that these mechanisms affect mental health differently from physical health; by comparison, women with arm symptoms without diagnosed lymphedema had poor knowledge about lymphedema. In IWHS, women with diagnosed lymphedema knew of and had used lymphedema therapies to a much greater extent than women with arm symptoms without diagnosed lymphedema (Table 1); although they

had more symptoms on average, perhaps their lymphedema symptoms were under better control or they were more used to having the symptoms or understood the symptoms in a way that affected mental health.

Strengths of this study include the numbers of participants with lymphedema and arm symptoms within a large population-based sample and the ability to study several potential covariates. Limitations include that analyses were cross-sectional, HRQOL data before BrCa were not available, and lymphedema and arm symptoms data were self-reported. Given the lack of knowledge about lymphedema in women with arm symptoms but without diagnosed lymphedema, these women may have truly had lymphedema and not known it, thereby resulting in a misclassification bias. Data regarding use of lymphedema therapy are limited, and the date of lymphedema diagnosis was unknown, preventing evaluation of the effect of time since lymphedema development on HRQOL. We studied women who survived an average of 8.1 years after BrCa; given the differences between responders compared with nonresponders, findings for the 52% of participants who had previously died or refused the survey could differ and raise the possibility of a response bias in this study.

In summary, both women with diagnosed lymphedema and women with arm symptoms without diagnosed lymphedema had substantially lowered HRQOL compared with BrCa survivors without lymphedema or arm symptoms. Lymphedema had an impact on HRQOL several years after diagnosis (mean, 8.1 years). There was a dose-response relation between the number of symptoms present and lower HRQOL. Knowledge about lymphedema and treatment use was low in survivors without diagnosed lymphedema. There is a growing consensus that women with lymphedema and related arm symptoms have lower HRQOL compared with other BrCa survivors. Further clinical trials will determine whether interventions to improve lymphedema impact HRQOL for BrCa survivors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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