

Association Between Precautionary Behaviors and Breast Cancer–Related Lymphedema in Patients Undergoing Bilateral Surgery

Maria S. Asdourian, Meyha N. Swaroop, Hoda E. Sayegh, Cheryl L. Brunelle, Amir I. Mina, Hui Zheng, Melissa N. Skolny, and Alphonse G. Taghian

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on October 4, 2017.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Clinical trial information: NCT01521741.

Corresponding author: Alphonse G. Taghian, MD, PhD, Department of Radiation Oncology, Massachusetts General Hospital, 100 Blossom St, Boston, MA 02114; e-mail: ataghian@partners.org.

© 2017 by American Society of Clinical Oncology

0732-183X/17/3535w-3934w/\$20.00

ABSTRACT

Purpose

This study examined the lifestyle and clinical risk factors for lymphedema in a cohort of patients who underwent bilateral breast cancer surgery.

Patients and Methods

Between 2013 and 2016, 327 patients who underwent bilateral breast cancer surgery were prospectively screened for arm lymphedema as quantified by the weight-adjusted volume change (WAC) formula. Arm perometry and subjective data were collected preoperatively and at regular intervals postoperatively. At the time of each measurement, patients completed a risk assessment survey that reported the number of blood draws, injections, blood pressure readings, trauma to the at-risk arm, and number of flights since the previous measurement. Generalized estimating equations were applied to ascertain the association among arm volume changes, clinical factors, and risk exposures.

Results

The cohort comprised 327 patients and 654 at-risk arms, with a median postoperative follow-up that ranged from 6.1 to 68.2 months. Of the 654 arms, 83 developed lymphedema, defined as a WAC $\geq 10\%$ relative to baseline. On multivariable analysis, none of the lifestyle risk factors examined through the risk assessment survey were significantly associated with increased WAC. Multivariable analysis demonstrated that having a body mass index ≥ 25 kg/m² at the time of breast cancer diagnosis ($P = .0404$), having undergone axillary lymph node dissection ($P = .0464$), and receipt of adjuvant chemotherapy ($P = .0161$) were significantly associated with increased arm volume.

Conclusion

Blood pressure readings, blood draws, injections, and number or duration of flights were not significantly associated with increases in arm volume in this cohort. These findings may help to guide patient education about lymphedema risk reduction strategies for those who undergo bilateral breast cancer surgery.

J Clin Oncol 35:3934-3941. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Although surgical and targeted treatments for breast cancer have improved survival, treatment complications remain a significant concern for patients. Breast cancer–related lymphedema (BCRL) is one complication caused by damage to lymph nodes through surgical intervention and/or radiation, which may interrupt the circulation of lymph fluid and precipitate edema of the arm, breast, or trunk.¹⁻³ Associated symptoms, such as decreased arm functionality, pain, heaviness, changes in skin quality, and high rates of infection (eg, cellulitis),

may compromise overall quality of life (QOL) and are significant sources of distress in at-risk patients.^{4,5} Survivors of breast cancer have a lifelong risk of developing lymphedema.⁶⁻⁸

The etiologic factors that contribute to the development of BCRL and potential lifestyle strategies aimed at minimizing lymphedema risk after breast cancer surgery are frequent points of discussion and controversy in the literature.⁹ Well-defined risk factors include axillary lymph node dissection (ALND), regional lymph node radiation (RLNR), and high body mass index (BMI), with mastectomy, chemotherapy, and older age at diagnosis demonstrating an association on

DOI: <https://doi.org/10.1200/JCO.2017.73.7494>

occasion.^{7,8,10-13} Why some patients with the same demographic, surgical, and treatment-related characteristics develop lymphedema and others do not remains unclear. This lack of knowledge has prompted speculation about whether lifestyle-related risk exposures play a causative role.¹⁴ The position statement of the National Lymphedema Network¹⁵ outlines precautionary recommendations intended to reduce the risk of developing lymphedema in at-risk breast cancer survivors, which include the avoidance of trauma, temperature extremes, skin infections, venipuncture (eg, blood draws, intravenous infusions), and limb constriction (eg, blood pressure readings) on the ipsilateral arm. These guidelines play a significant role in patient education with regard to post-treatment lifestyle but have not evolved in the face of ongoing surgical and treatment advancements.⁹

With limited high-level evidence to support or refute the risk of blood pressure measurements and needle punctures in lymphedema development, patients may experience distress because of their risk for BCRL and their need to avoid such medical procedures throughout their life.^{9,16} These restrictions may prove especially problematic in patients who receive bilateral treatment of breast cancer and who are at bilateral risk for BCRL because optimal health care necessitates procedures in the at-risk arm, which make the evaluation of whether there is a sound scientific basis for precautionary behaviors imperative. Currently, > 20% of all patients with breast cancer undergo bilateral surgery,¹⁷⁻¹⁹ and a pressing need exists to provide high-level data and reassurance to these patients about the safety and efficacy of using their arms for medical procedures. Thus, we examined the association between lymphedema and the commonly discussed lifestyle risk exposures for BCRL, including blood pressure readings, blood draws, injections, infusions, and air travel, in a prospective cohort of patients who underwent bilateral breast cancer surgery.

PATIENTS AND METHODS

Study Design

Lymphedema screening program. With the approval of the Partners Healthcare Institutional Review Board, we used perometry to prospectively screen women with newly diagnosed breast cancer for lymphedema at our institution from 2010 to 2016.²⁰ The perometer is a reliable optoelectronic system that uses infrared lamp light-receiver pairs contained within a frame.²¹ All patients underwent a preoperative baseline measurement²² and were measured postoperatively and approximately every 3 to 8 months at regular follow-up oncology visits or more frequently at the request of the patient. Patients were also provided at each screening visit the Lymphedema Evaluation Following Treatment of Breast Cancer questionnaire,²³ which assesses QOL issues, changes in upper-extremity functionality and use, and fear perception and avoidance behaviors. Lymphedema diagnosis was contingent upon both clinical examination and perometry.²⁴⁻²⁶ The protocol for prospective lymphedema screening has been well established at our institution.²⁰

Risk assessment survey. On the basis of a component of the lymphedema screening program, patients were asked to complete a risk assessment survey at the time of every follow-up arm measurement. They reported risk exposures, including the number of blood pressure readings, blood draws, injections, trauma to the at-risk arm (eg, fractures), and number and length of flights since their previous visit. Patients who underwent bilateral breast cancer surgery began completing the risk assessment survey after 2013. The analysis includes patients who underwent bilateral surgery and completed the risk assessment survey during at least one follow-up appointment. Data was incorporated in which both a perometer measurement was obtained and a survey completed.

Quantifying arm volume changes. To quantitatively determine the percentage arm volume change compared with preoperative baseline, the previously validated weight-adjusted volume change (WAC) formula was used [$WAC = (A_2W_1) / (W_2A_1) - 1$] for patients who undergo bilateral breast surgery and thereby lack a contralateral control arm. A_1 is the preoperative and A_2 the postoperative at-risk arm volume, and W_1 and W_2 are the patient's weight that corresponds to these time points. The WAC formula allows for the calculation of independent left and right arm volumes and takes into account changes in the patient's weight, which can contribute to increases or decreases in arm volume unrelated to lymphedema.²⁷ Lymphedema was defined as a WAC of $\geq 10\%$ that occurred > 3 months after surgery.^{28,29}

Patient Population

This study included 327 patients who underwent bilateral surgery for a diagnosis of primary breast cancer between 2013 and 2016. A total of 654 at-risk arms were evaluated; 622 of these represented mastectomies (95.1%) and 32 lumpectomies (4.9%), of which 54% (355 of 654) were performed for the treatment of breast cancer and 46% (297 of 654) prophylactically. The number of at-risk arms was 654 because each breast was considered individually. Patients who undergo prophylactic contralateral mastectomy at our hospital typically have a sentinel lymph node biopsy (SLNB) performed on their contralateral breast to stage an occult breast cancer, which thus puts both arms at risk for lymphedema.

All patients had a preoperative perometer measurement and at least 6 months of postoperative follow-up. Only measurements that occurred ≥ 3 months after surgery were used to determine the incidence of BCRL because arm volume increases recorded within 3 months of surgery may be attributed to transient postsurgical swelling.^{2,14} Demographic, clinicopathologic, and treatment-related characteristics were obtained through medical record review. To avoid potential confounding factors, measurements obtained after local recurrence or distant metastases were excluded.

Statistical Analysis

Generalized estimating equations were used to assess the association among WAC measured as a continuous variable, clinical risk factors, and nonprecautionary behaviors. These models account for correlation within the same patient and for patients who underwent bilateral breast surgery, on the same side of the body. Longitudinal WAC measurement was used as the response variable. At each measurement, the number of blood draws, injections, blood pressure readings, and traumas were analyzed as binary variables categorized according to whether patients reported having had one or more events versus none. Number of flights and hours spent on flights in total since the last follow-up were analyzed as dichotomous and trichotomous variables, respectively. Univariable model results were used to estimate and plot the mean WAC within each subgroup for categorical clinical and risk factors along with the 95% CI for the mean and the P value associated with the comparison of means. The multivariable model was chosen in a backward selection fashion by starting with a full model that included all variables that had a $P < .10$ in the univariable analysis and variables considered to be known confounders and by removing one variable at a time until only variables with $P < .05$ remained.

The Kaplan-Meier method was used to estimate the 2-year cumulative incidence of lymphedema. Statistical analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC) and R programming language (www.R-project.org).

RESULTS

Patient Population

Median postoperative follow-up time in the cohort was 27 months (range, 6 to 68 months), whereas median age at diagnosis was 47 years (range, 25 to 72 years). Median BMI was 25 kg/m²

(range, 18 to 56 kg/m²). Medical record review indicated that of 654 treated breasts, 36 episodes of cellulitis in the breast and/or the arm required treatment with oral or intravenous antibiotics (Table 1). The 2-year cumulative incidence of BCRL, defined as WAC \geq 10%,^{28,29} was determined to be 11.8% (95% CI, 9.4% to 14.8%).

Precautionary Behaviors

Through the risk assessment survey, 1,795 events were reported over 4,104 responses. Of the total of 4,102 responses, 209 patients (5.1%) reported having one or more blood draws in their affected arms since their last measurement, 640 (15.6%) reported blood pressure readings, 120 (2.9%) reported injections, and 52 (1.3%) reported trauma events (eg, bruising, fractures). Nineteen

percent of responses (n = 774) indicated one or more flights since the patients' last measurement (Table 2).

Univariable and Multivariable Analysis Results

By univariable analysis, no significant association was found between an increased WAC and having undergone one or more blood draws versus no blood draws ($P = .4906$), one or more injections versus no injections ($P = .0928$), one or more incidents of trauma to the at-risk arms versus no trauma ($P = .5705$), and number ($P = .2756$) or duration (1 to 12 hours [$P = .5223$] and \geq 12 hours [$P = .2524$]) of flights versus none (Fig 1). In addition, cellulitis infections were not found to be significantly associated with increased WAC ($P = .1179$; Table 3). Factors significantly associated with increased WAC were ALND compared with SLNB ($P < .001$),

Table 1. Demographic and Clinicopathologic Characteristics of Bilateral Cohort

Characteristic	Lymphedema, No. (%)		Overall
	No	Yes	
No. of arms	571	83	654
Age at diagnosis, years*	47 (28-72)	46 (25-69)	47 (25-72)
BMI, kg/m ² *	24.7 (17.7-47.5)	28.8 (18-55.9)	25 (17.7-55.9)
Follow-up, months*	25.4 (6.1-68.2)	34.5 (7-65.7)	27.2 (6.1-68.2)
Postoperative visits*	4 (1-19)	6 (2-19)	4 (1-19)
Arm measurements*	5 (2-20)	7 (3-20)	5 (2-20)
Lymph nodes removed*	1 (0-33)	3 (0-41)	2 (0-41)
Tumor type			
DCIS	46 (8.1)	5 (6.0)	51 (7.8)
Invasive	255 (44.7)	49 (59.0)	304 (46.5)
Not available	268 (46.9)	29 (34.9)	297 (45.4)
Breast surgery			
Lumpectomy	30 (5.3)	2 (2.4)	32 (4.9)
Mastectomy	541 (94.7)	81 (97.6)	622 (95.1)
Axillary surgery			
None	90 (15.8)	10 (12.0)	100 (15.3)
SLNB	405 (70.9)	40 (48.2)	445 (68.0)
ALND	76 (13.3)	33 (39.8)	109 (16.7)
Neoadjuvant chemotherapy			
No	453 (79.3)	61 (73.5)	514 (78.6)
Yes	118 (20.7)	22 (26.5)	140 (21.4)
Adjuvant chemotherapy			
No	321 (56.2)	37 (44.6)	358 (54.7)
Yes	250 (43.8)	46 (55.4)	296 (45.3)
Hormonal therapy			
No	146 (25.6)	18 (21.7)	164 (25.1)
Yes	425 (74.4)	65 (78.3)	490 (74.9)
Radiation therapy			
None	459 (80.4)	49 (59)	508 (77.7)
Chest wall only	32 (5.6)	7 (8.4)	39 (6.0)
RLNR	80 (14.0)	27 (32.5)	107 (16.4)
Breast reconstruction			
No	40 (7.0)	6 (7.2)	46 (7.0)
Yes	503 (88.1)	75 (90.4)	578 (88.4)
Not available	28 (4.9)	2 (2.4)	30 (4.6)
Peripheral intravenous infusion			
No	357 (62.5)	43 (51.8)	400 (61.2)
Yes	214 (37.5)	40 (48.2)	254 (38.8)
Median No. of infusions	0	1	0
Cellulitis			
No	542 (94.9)	76 (91.6)	618 (94.5)
Yes	29 (5.1)	7 (8.4)	36 (5.5)

NOTE. Values are based on the number of treated breasts (n = 654).

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; DCIS, ductal carcinoma in situ; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy.

*Data are median (range).

Table 2. Summary of Reported Risk Events

Risk Event	Lymphedema, No. (%)		
No. of events	3,900 (No)	204 (No)	4,104 (Overall)
Blood pressure			
None	1,052 (27.0)	88 (43.1)	1,140 (27.8)
One or more	621 (15.9)	19 (9.3)	640 (15.6)
Blood draws			
None	1,469 (37.7)	102 (50.0)	1,571 (38.3)
One or more	204 (5.2)	5 (2.5)	209 (5.1)
Injections			
None	1,556 (39.9)	104 (51.0)	1,660 (40.4)
One or more	117 (3.0)	3 (1.5)	120 (2.9)
Trauma			
None	1,623 (41.6)	105 (51.5)	1,728 (42.1)
One or more	50 (1.3)	2 (1.0)	52 (1.3)
No. of flights			
None	938 (24.1)	68 (33.3)	1,006 (24.5)
One or more	735 (18.8)	39 (19.1)	774 (18.9)
Hours of flights			
None	934 (23.9)	68 (33.3)	1,006 (24.5)
1-12	389 (8.5)	23 (10.3)	412 (8.6)
> 12	406 (10.4)	18 (8.8)	424 (10.3)

NOTE. Values represent risk events reported by patients in the risk assessment survey.

analyzed were significantly associated with WAC in the multivariable analysis (Fig 2; Table 4).

DISCUSSION

This study examined the association between the risk of lymphedema in patients who underwent bilateral breast cancer surgery and lifestyle/clinical risk exposures for lymphedema. Precautionary strategies aimed at minimizing BCRL risk after breast cancer surgery are frequent discussion points in the literature. Although risk reduction guidelines as described in the National Lymphedema Network position statement¹⁵ are based on clinical reasoning, limited high-level research supports or refutes their effectiveness. Studies that sought answers about risk reduction guideline utility are restricted in scope and are predominantly small, retrospective, and single-site reports with cohorts that underwent mostly ALND.^{9,30-32} Historically, studies demonstrated that women who undergo bilateral ALND do not have an increased risk of BCRL compared with those with unilateral lymph node dissection.^{33,34}

To examine the current evidence, our team carried out a comprehensive review of 31 studies that examined the association between these exposures and BCRL. Only eight were prospective cohort studies,^{10,14,35-40} among which four demonstrated a statistically significant correlation between BCRL and commonly reported lifestyle-based risk factors, namely infections,^{10,14} sauna use,³⁹ and skin puncture.⁴⁰ In a small number of patients who developed lymphedema after skin puncture, Clark et al⁴⁰ found a correlation between skin puncture and lymphedema in patients who underwent ALND (n = 188). The authors did not look into the temporal relationship between skin puncture and lymphedema development, so the association could not be used to identify whether the punctures themselves were a risk factor for swelling. Clark et al noted in their discussion that replication of their work with a larger sample that includes patients with SLNB is needed. All

breast/chest wall radiation and RLNR compared with no radiation ($P < .001$), BMI $\geq 25 \text{ kg/m}^2$ compared with $< 25 \text{ kg/m}^2$ ($P = .0121$), and adjuvant chemotherapy versus no adjuvant chemotherapy ($P = .0168$; Table 3). Univariable analysis showed that having one or more blood pressure measurements versus none was significantly associated with decreased WAC ($P = .0109$; 95% CI, -1.26 to 0.03 ; Fig 1); this was no longer significant upon multivariable analysis.

The only variables that retained significance upon multivariable analysis were BMI $\geq 25 \text{ kg/m}^2$ ($P = .0404$), ALND ($P = .0464$), and adjuvant chemotherapy ($P = .0161$). None of the risk exposures

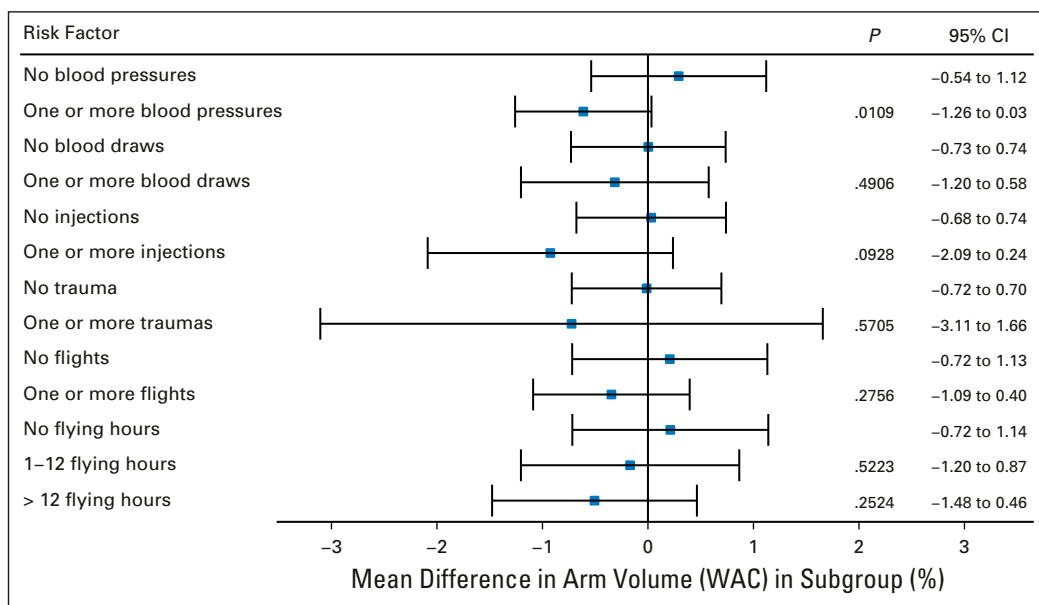


Fig 1. Univariable analysis. WAC, weight-adjusted volume change.

Table 3. Univariable Analysis of Categorical Treatment Factors

Patient or Treatment-Related Risk Factor	Mean WAC in Subgroup (%)	95% CI	P
Surgical characteristics			
Lumpectomy	-2.03	-4.89 to 0.82	*
Mastectomy v lumpectomy	0.14	-0.40 to 0.67	.1418
No nodal surgery	-0.32	-1.19 to 0.55	*
SLNB v none	-0.65	-1.19 to -0.11	.4803
ALND v SLNB	2.45	1.13 to 3.78	< .0010
Radiation therapy			
None	-0.55	-1.01 to -0.08	*
Breast/chest wall irradiation v none	1.11	-1.90 to 4.11	.2806
Breast/chest wall + RLNR v none	1.82	0.54 to 3.10	< .0010
BMI, kg/m²			
BMI < 25	-0.65	-1.19 to -0.12	*
BMI ≥ 25 v < 25	0.66	-0.22 to 1.53	.0121
BMI < 30	-0.17	-0.71 to 0.38	*
BMI ≥ 30 v < 30	0.84	-0.73 to 2.42	.2354
Systemic therapy			
Neoadjuvant chemotherapy			
No	-0.26	-0.86 to 0.34	*
Yes v no	0.93	-0.22 to 2.07	.0718
Adjuvant chemotherapy			
No	-0.61	-1.38 to 0.15	*
Yes v no	0.68	-0.06 to 1.43	.0168
Peripheral intravenous infusions			
No	-0.35	-1.05 to 0.36	*
Yes v no	0.52	-0.29 to 1.34	.1126
Hormone therapy			
No	0.66	-0.32 to 1.65	*
Yes v no	-0.14	-0.77 to 0.49	.1781
Reconstruction			
No	0.35	-1.59 to 2.28	*
Yes v no	0.13	-0.43 to 0.69	.8324
Cellulitis			
No	-0.09	-0.63 to 0.46	*
Yes v no	1.78	-0.51 to 4.07	.1179

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy; WAC, weight-adjusted volume change.
*Specified variable or comparison was not analyzed.

but one¹⁴ of the studies in our comprehensive review had cohorts that underwent predominantly ALND, which made them higher-risk populations because ALND contributes to an approximately

fourfold increased incidence of lymphedema compared with SLNB.⁸ Of note, other studies have demonstrated that ipsilateral skin puncture does not represent a risk factor for lymphedema;

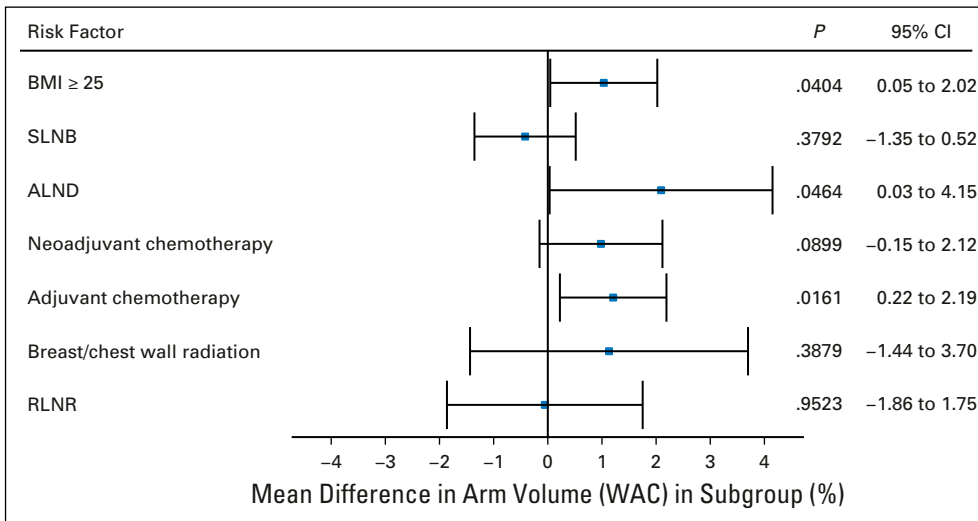


Fig 2. Multivariable analysis. ALND, axillary lymph node dissection; BMI, body mass index; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy; WAC, weight-adjusted volume change.

Table 4. Multivariable Linear Model

Risk Factor	Estimated Change in WAC, %	Estimated 95% CI	P
BMI \geq 25 kg/m ²	1.03	0.05 to 2.02	.0404
SLNB	-0.42	-1.35 to 0.52	.3792
ALND	2.09	0.03 to 4.15	.0464
Neoadjuvant chemotherapy	0.98	-0.15 to 2.12	.0899
Adjuvant chemotherapy	1.21	0.22 to 2.19	.0161
Breast/chest wall radiation	1.13	-1.44 to 3.70	.3879
RLNR	-0.06	-1.86 to 1.75	.9523

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy; WAC, weight-adjusted volume change.

furthermore, surgical procedures on the at-risk arm have been shown to not contribute to permanent arm swelling.^{14,39,41,42}

With regard to limb constriction through the use of blood pressure cuffs, no high-level scientific evidence suggests a relationship between ipsilateral blood pressure measurements and arm swelling or long-term adverse effects of tourniquet use on limb volume.⁴³ Surveyed breast oncology surgeons and clinicians have regularly demonstrated a willingness to use tourniquets on the ipsilateral arm during elective hand surgeries.^{44,45} This lack of evidential support extends to air travel. Among eight studies that analyzed flight risk to date, only one questionnaire-based study demonstrated that air travel increases the risk for lymphedema.⁴⁶ Several other objective studies have not identified a causative link between flights and lymphedema and have not demonstrated whether prophylactic compression confers a benefit to at-risk women.^{11,14,36,40,46,47}

In a recent prospective analysis, Ferguson et al¹⁴ assessed whether lifestyle and behavioral risk exposures, including air travel, blood draws, injections, blood pressure measurements, and cellulitis infections, on the ipsilateral arm confer a risk for the development of lymphedema. The analysis included 632 patients who had undergone unilateral or bilateral surgery, each with a preoperative baseline measurement and an overall median follow-up of 24 months. By multivariable analysis, none of the lifestyle risk factors examined were associated with increased arm volume. The only factors found to be significantly associated with arm volume increase were a BMI \geq 25 kg/m², ALND, RLNR, and cellulitis. Limitations of the study were a median follow-up time of 24 months, low incidence of risk events, potential for recall bias, and lack of information about patients' receipt of physical therapy.

In the current cohort of patients who underwent bilateral breast cancer surgery, although the univariable analysis showed that one or more blood pressure measurements had a significantly lower WAC than no blood pressure measurements, neither group independently demonstrated a significant arm volume change from baseline. Furthermore, the significant difference was no longer observed upon multivariable analysis. The factors found to be significantly associated with arm swelling by multivariable analysis were BMI \geq 25 kg/m² at diagnosis, ALND, and adjuvant chemotherapy. High BMI and ALND are well-substantiated risk factors for BCRL in the literature.^{5,7,8,10,11,23,48-53} In the current cohort, adjuvant chemotherapy also was found to be a significant risk factor for the development of arm swelling, which may be a reflection of transient fluctuations in arm swelling as a result of taxane-based chemotherapy

regimens that have been found to contribute to mild arm swelling.⁵⁴ Limitations of this study are similar to those of Ferguson et al,¹⁴ namely, the potential for recall bias as a result of the provision of the risk assessment survey at inconsistent intervals and low incidence of risk events. Our median postoperative follow-up, however, was longer at 25.4 months for patients who did not develop lymphedema and even longer (34.5 months) for patients who developed lymphedema. Furthermore, our study collected data on breast and/or arm cellulitis, which may play a causative role in the development or worsening of arm swelling.⁵⁵⁻⁶⁰ We found that cellulitis infections are not significantly associated with the development of BCRL. Some of these patients may not have had readings right around the time of their cellulitis (given the 3- to 8-month interval between measurements) and/or may have had their swelling recede as the infection cleared or as they received treatment by a certified lymphedema therapist before their next perometry reading. As Ferguson et al and other studies^{10,59-61} have found, cellulitis is significantly associated with the development of arm swelling, and the importance of maintaining skin integrity and avoiding infection is critical.

Unlike the study by Ferguson et al¹⁴ that only had a small proportion of patients who underwent bilateral breast cancer surgery, the current study represents an analysis of a large cohort of patients at bilateral risk for BCRL to determine whether an association between risk exposures and the development of lymphedema in this higher risk population exists. With consideration of current developments in the surgical treatment of breast cancer, specifically the increasing trend in younger women who undergo contralateral prophylactic mastectomy and that approximately 20% of all patients with breast cancer undergo bilateral mastectomy,¹⁷⁻¹⁹ we specifically analyzed this risk in a population where the practice of precautionary behaviors may be difficult to implement. For example, in patients with bilateral axillary surgery, if at-risk arms are to be avoided, blood pressure readings may need to be taken in the leg, which introduces potential inaccuracies.⁶²

Interpretation of Ferguson et al¹⁴ has prompted controversy and discussion. Some practitioners misinterpreted the study as evidence to support changes in clinical practice and the complete dismissal of all such precautions.⁶³⁻⁶⁸ Because the results of the current study also demonstrate a lack of association between these risk exposures and lymphedema development, we strongly emphasize that we do not consider these findings as sufficient data to do away with current precautions provided to patients, and we do not support changing clinical practice with regard to risk reduction patient education. Our goal is to add to the research base and bring reasonable doubt to current guidelines to ensure that any recommendations we give to patients are well-substantiated and individualized to prevent unnecessary distress in light of historical research and improved treatment modalities. Currently, the proportion of patients who undergo SLNB for the assessment of lymph node status in clinically node-negative breast cancer is increasing, and this low-risk group now comprises approximately 80% of this population.⁶⁹ Patients at different risk for BCRL should be provided different precautionary guidelines, and we hope to see a move toward a risk-adjusted approach in the application of these guidelines pending high-level research. This topic must be further studied prospectively through large-scale clinical trials. The goal of our work on precautionary measures is to foster a dialogue about these guidelines, but current guidelines should remain the standard

of care until definitive evidence is available. The generation of new studies and collaborative discussion will allow for progress in improving patient QOL throughout survivorship.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

REFERENCES

1. Erickson VS, Pearson ML, Ganz PA, et al: Arm edema in breast cancer patients. *J Natl Cancer Inst* 93:96-111, 2001
2. Armer JM, Radina ME, Porock D, et al: Predicting breast cancer-related lymphedema using self-reported symptoms. *Nurs Res* 52:370-379, 2003
3. Shih YC, Xu Y, Cormier JN, et al: Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: A 2-year follow-up study. *J Clin Oncol* 27:2007-2014, 2009
4. Ridner SH: Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. *Support Care Cancer* 13:904-911, 2005
5. Cormier JN, Xing Y, Zaniletti I, et al: Minimal limb volume change has a significant impact on breast cancer survivors. *Lymphology* 42:161-175, 2009
6. Armer JM, Stewart BR: Post-breast cancer lymphedema: Incidence increases from 12 to 30 to 60 months. *Lymphology* 43:118-127, 2010
7. Tsai RJ, Dennis LK, Lynch CF, et al: The risk of developing arm lymphedema among breast cancer survivors: A meta-analysis of treatment factors. *Ann Surg Oncol* 16:1959-1972, 2009
8. DiSipio T, Rye S, Newman B, et al: Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. *Lancet Oncol* 14:500-515, 2013
9. Asdourian MS, Skolny MN, Brunelle C, et al: Precautions for breast cancer-related lymphoedema: Risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. *Lancet Oncol* 17:e392-e405, 2016
10. Bevilacqua JL, Kattan MW, Changhong Y, et al: Nomograms for predicting the risk of arm lymphedema after axillary dissection in breast cancer. *Ann Surg Oncol* 19:2580-2589, 2012
11. Swenson KK, Nissen MJ, Leach JW, et al: Case-control study to evaluate predictors of lymphedema after breast cancer surgery. *Oncol Nurs Forum* 36:185-193, 2009
12. Warren LE, Miller CL, Horick N, et al: The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: A prospective cohort study. *Int J Radiat Oncol Biol Phys* 88:565-571, 2014
13. Jammallo LS, Miller CL, Singer M, et al: Impact of body mass index and weight fluctuation on lymphedema risk in patients treated for breast cancer. *Breast Cancer Res Treat* 142:59-67, 2013
14. Ferguson CM, Swaroop MN, Horick N, et al: Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer. *J Clin Oncol* 34:691-698, 2016
15. National Lymphedema Network: Lymphedema risk reduction practices, 2012. <http://www.lymphnet.org/pdfDocs/nlnriskreduction.pdf>

16. Nielsen I, Gordon S, Selby A: Breast cancer-related lymphoedema risk reduction advice: A challenge for health professionals. *Cancer Treat Rev* 34:621-628, 2008
17. Tuttle TM, Habermann EB, Grund EH, et al: Increasing use of contralateral prophylactic mastectomy for breast cancer patients: A trend toward more aggressive surgical treatment. *J Clin Oncol* 25:5203-5209, 2007
18. Mahmood U, Hanlon AL, Koshy M, et al: Increasing national mastectomy rates for the treatment of early stage breast cancer. *Ann Surg Oncol* 20:1436-1443, 2013
19. Kummerow KL, Du L, Penson DF, et al: Nationwide trends in mastectomy for early-stage breast cancer. *JAMA Surg* 150:9-16, 2015
20. Brunelle C, Skolny M, Ferguson C, et al: Establishing and sustaining a prospective screening program for breast cancer-related lymphedema at the Massachusetts General Hospital: Lessons learned. *J Pers Med* 5:153-164, 2015
21. Tierney S, Aslam M, Rennie K, et al: Infrared optoelectronic volumetry, the ideal way to measure limb volume. *Eur J Vasc Endovasc Surg* 12:412-417, 1996
22. Sun F, Skolny MN, Swaroop MN, et al: The need for preoperative baseline arm measurement to accurately quantify breast cancer-related lymphedema. *Breast Cancer Res Treat* 157:229-240, 2016
23. Jammallo LS, Miller CL, Horick NK, et al: Factors associated with fear of lymphedema after treatment for breast cancer. *Oncol Nurs Forum* 41:473-483, 2014
24. O'Toole J, Jammallo LS, Skolny MN, et al: Lymphedema following treatment for breast cancer: A new approach to an old problem. *Crit Rev Oncol Hematol* 88:437-446, 2013
25. O'Toole JA, Ferguson CM, Swaroop MN, et al: The impact of breast cancer-related lymphedema on the ability to perform upper extremity activities of daily living. *Breast Cancer Res Treat* 150:381-388, 2015
26. Miller CL, Specht MC, Skolny MN, et al: Sentinel lymph node biopsy at the time of mastectomy does not increase the risk of lymphedema: Implications for prophylactic surgery. *Breast Cancer Res Treat* 135:781-789, 2012
27. Miller CL, Specht MC, Horick N, et al: A novel, validated criteria to quantify breast cancer-related lymphedema (BCRL) following bilateral breast surgery. *Lymphology* 46:64-74, 2013
28. Armer JM, Stewart BR: A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphat Res Biol* 3:208-217, 2005
29. Armer JM, Stewart BR, Shook RP: 30-month post-breast cancer treatment lymphoedema. *J Lymphoedema* 4:14-18, 2009
30. Cemal Y, Pusic A, Mehrara BJ: Preventative measures for lymphedema: Separating fact from fiction. *J Am Coll Surg* 213:543-551, 2011

AUTHOR CONTRIBUTIONS

Conception and design: Maria S. Asdourian, Meyha N. Swaroop, Hoda E. Sayegh, Cheryl L. Brunelle, Melissa N. Skolny, Alphonse G. Taghian
Collection and assembly of data: Maria S. Asdourian, Meyha N. Swaroop, Hoda E. Sayegh, Melissa N. Skolny, Alphonse G. Taghian
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

31. Cheng CT, Deitch JM, Haines IE, et al: Do medical procedures in the arm increase the risk of lymphoedema after axillary surgery? A review. *ANZ J Surg* 84:510-514, 2014
32. Jakes AD, Twelves C: Breast cancer-related lymphoedema and venepuncture: A review and evidence-based recommendations. *Breast Cancer Res Treat* 154:455-461, 2015
33. Petrek JA, Heelan MC: Incidence of breast carcinoma-related lymphedema. *Cancer* 83:2776-2781, 1998 (suppl S12B)
34. Loudon L, Petrek J: Lymphedema in women treated for breast cancer. *Cancer Pract* 8:65-71, 2000
35. Kilbreath SL, Ward LC, Lane K, et al: Effect of air travel on lymphedema risk in women with history of breast cancer. *Breast Cancer Res Treat* 120:649-654, 2010
36. Chang TS, Han LY, Gan JL, et al: Microwave: An alternative to electric heating in the treatment of peripheral lymphedema. *Lymphology* 22:20-24, 1989
37. Liu NF, Olszewski W: The influence of local hyperthermia on lymphedema and lymphedematous skin of the human leg. *Lymphology* 26:28-37, 1993
38. Gan JL, Li SL, Cai RX, et al: Microwave heating in the management of postmastectomy upper limb lymphedema. *Ann Plast Surg* 36:576-580, 1996; discussion 580-581
39. Showalter SL, Brown JC, Cheville AL, et al: Lifestyle risk factors associated with arm swelling among women with breast cancer. *Ann Surg Oncol* 20:842-849, 2013
40. Clark B, Sitzia J, Harlow W: Incidence and risk of arm oedema following treatment for breast cancer: A three-year follow-up study. *QJM* 98:343-348, 2005
41. Dawson WJ, Elenz DR, Winchester DP, et al: Elective hand surgery in the breast cancer patient with prior ipsilateral axillary dissection. *Ann Surg Oncol* 2:132-137, 1995
42. Hershko DD, Stahl S: Safety of elective hand surgery following axillary lymph node dissection for breast cancer. *Breast J* 13:287-290, 2007
43. Assmus H, Staub F: Postmastectomy lymphedema and carpal tunnel syndrome. Surgical considerations and advice for patients [in German]. *Handchir Mikrochir Plast Chir* 36:237-240, 2004
44. Fulford D, Dalal S, Winstanley J, et al: Hand surgery after axillary lymph node clearance for breast cancer: Contra-indication to surgery? *Ann R Coll Surg Engl* 92:573-576, 2010
45. Gharbaoui IS, Netscher DT, Thornby J, et al: Safety of upper extremity surgery after prior treatment for ipsilateral breast cancer: Results of an American Society for Surgery of the Hand membership survey and literature review. *J Am Soc Surg Hand* 5:232-238, 2005
46. Casley-Smith JR, Casley-Smith JR: Lymphedema initiated by aircraft flights. *Aviat Space Environ Med* 67:52-56, 1996

47. Graham PH: Compression prophylaxis may increase the potential for flight-associated lymphoedema after breast cancer treatment. *Breast* 11:66-71, 2002
48. Mak SS, Yeo W, Lee YM, et al: Risk factors for the initiation and aggravation of lymphoedema after axillary lymph node dissection for breast cancer. *Hong Kong Med J* 15:8-12, 2009 (suppl 4)
49. Park JH, Lee WH, Chung HS: Incidence and risk factors of breast cancer lymphoedema. *J Clin Nurs* 17:1450-1459, 2008
50. Norman SA, Localio AR, Kallan MJ, et al: Risk factors for lymphedema after breast cancer treatment. *Cancer Epidemiol Biomarkers Prev* 19:2734-2746, 2010
51. Bar Ad V, Chevillat A, Solin LJ, et al: Time course of mild arm lymphedema after breast conservation treatment for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 76:85-90, 2010
52. McLaughlin SA, Wright MJ, Morris KT, et al: Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: Objective measurements. *J Clin Oncol* 26:5213-5219, 2008
53. Petrek JA, Senie RT, Peters M, et al: Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer* 92:1368-1377, 2001
54. Swaroop MN, Ferguson CM, Horick NK, et al: Impact of adjuvant taxane-based chemotherapy on development of breast cancer-related lymphedema: Results from a large prospective cohort. *Breast Cancer Res Treat* 151:393-403, 2015
55. Mallon E, Powell S, Mortimer P, et al: Evidence for altered cell-mediated immunity in post-mastectomy lymphoedema. *Br J Dermatol* 137:928-933, 1997
56. Woo PC, Lum PN, Wong SS, et al: Cellulitis complicating lymphoedema. *Eur J Clin Microbiol Infect Dis* 19:294-297, 2000
57. Al-Niimi F, Cox N: Cellulitis and lymphoedema: A vicious cycle. *J Lymphoedema* 4:38-42, 2009
58. Hughes LL, Styblo TM, Thoms WW, et al: Cellulitis of the breast as a complication of breast-conserving surgery and irradiation. *Am J Clin Oncol* 20:338-341, 1997
59. Soran A, D'Angelo G, Begovic M, et al: Breast cancer-related lymphedema—What are the significant predictors and how they affect the severity of lymphedema? *Breast J* 12:536-543, 2006
60. Indelicato DJ, Grobmyer SR, Newlin H, et al: Delayed breast cellulitis: An evolving complication of breast conservation. *Int J Radiat Oncol Biol Phys* 66:1339-1346, 2006
61. Mak SS, Yeo W, Lee YM, et al: Predictors of lymphedema in patients with breast cancer undergoing axillary lymph node dissection in Hong Kong. *Nurs Res* 57:416-425, 2008
62. Malhotra A, Cohen D, Syms C, et al: Blood pressure changes in the leg on standing. *J Clin Hypertens (Greenwich)* 4:350-354, 2002
63. Ahn S, Port ER: Lymphedema precautions: Time to abandon old practices? *J Clin Oncol* 34:655-658, 2016
64. Nudelman J: Do no harm: Lymphedema risk reduction behaviors. *J Clin Oncol* 34:3109-3110, 2016
65. Asdourian MS, Skolny MN, Brunelle C, et al: Reply to J. Nudelman. *J Clin Oncol* 34:3111-3112, 2016
66. Stout NL: #Lymphchat4: Risk reduction (recap) [National Lymphedema Network E-Channel Twitter Chat]. <https://storify.com/lymphnet/new-story-559d375c04ba787972fd8f8e>
67. Nudelman J: Debunking lymphedema risk-reduction behaviors: Risky conclusions. *Lymphat Res Biol* 14:124-126, 2016
68. Brunelle CL, Swaroop MN, Asdourian MS, et al: Precautionary behaviors and breast cancer-related lymphedema. *Lymphat Res Biol* 10.1089/lrb.2017.0016 [epub ahead of print on September 7, 2017]
69. Donker M, van Tienhoven G, Straver ME, et al: Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): A randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 15:1303-1310, 2014

Affiliations

All authors: Massachusetts General Hospital, Boston, MA.

Support

Supported by National Cancer Institute grants R01CA139118 and P50CA089393 (to A.G.T.) and the Adele McKinnon Research Fund for Breast Cancer-Related Lymphedema.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Association Between Precautionary Behaviors and Breast Cancer–Related Lymphedema in Patients Undergoing Bilateral Surgery

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Maria S. Asdourian

No relationship to disclose

Meyha N. Swaroop

No relationship to disclose

Hoda E. Sayegh

No relationship to disclose

Cheryl L. Brunelle

No relationship to disclose

Amir I. Mina

No relationship to disclose

Hui Zheng

No relationship to disclose

Melissa N. Skolny

No relationship to disclose

Alphonse G. Taghian

Honoraria: UpToDate

Consulting or Advisory Role: VisionRT