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ORIGINAL REPORT

Impact of Ipsilateral Blood Draws, Injections, Blood Pressure Measurements, and Air Travel on the Risk of Lymphedema for Patients Treated for Breast Cancer

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org

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ABSTRACT

Purpose
The goal of this study was to investigate the association between blood draws, injections, blood pressure readings, trauma, cellulitis in the at-risk arm, and air travel and increases in arm volume in a cohort of patients treated for breast cancer and screened for lymphedema.

Patients and Methods
Between 2005 and 2014, patients undergoing treatment of breast cancer at our institution were screened prospectively for lymphedema. Bilateral arm volume measurements were performed preoperatively and postoperatively using a Perometer. At each measurement, patients reported the number of blood draws, injections, blood pressure measurements, trauma to the at-risk arm(s), and number of flights taken since their last measurement. Arm volume was quantified using the relative volume change and weight-adjusted change formulas. Linear random effects models were used to assess the association between relative arm volume (as a continuous variable) and non-treatment risk factors, as well as clinical characteristics.

Results
In 3,041 measurements, there was no significant association between relative volume change or weight-adjusted change increase and undergoing one or more blood draws ($P = .62$), injections ($P = .77$), number of flights (one or two [$P = .77$] and three or more [$P = .91$] *v* none), or duration of flights (1 to 12 hours [$P = .43$] and 12 hours or more [$P = .54$] *v* none). By multivariate analysis, factors significantly associated with increases in arm volume included body mass index ≥ 25 ($P = .0236$), axillary lymph node dissection ($P < .001$), regional lymph node irradiation ($P = .0364$), and cellulitis ($P < .001$).

Conclusion
This study suggests that although cellulitis increases risk of lymphedema, ipsilateral blood draws, injections, blood pressure readings, and air travel may not be associated with arm volume increases. The results may help to educate clinicians and patients on posttreatment risk, prevention, and management of lymphedema.

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INTRODUCTION

Clinicians and national guidelines strongly advise patients with breast cancer to avoid blood draws, injections, blood pressure readings, and trauma to the at-risk arm during and after treatment to reduce the risk of developing cellulitis and breast cancer–related lymphedema (BCRL).[1-6] Patients are also advised to exercise caution when flying by wearing prophylactic compression sleeves.[1,3,5] These guidelines are based on anecdotal information, and comprehensive data demonstrating the efficacy of such precautionary behaviors do not exist, highlighted in a recent statement by the National Lymphedema Network.[5] The guidelines place a large amount of burden on patients and clinicians, who go to great lengths to exercise precautionary behaviors and face high levels of anxiety when they accidentally do not abide by the guidelines. Therefore, we sought to investigate the association between blood draws, injections, blood pressure readings, trauma, and cellulitis in the at-risk arm and flying on increases in arm volume in a large prospective cohort of patients undergoing treatment of breast cancer.

Lymphedema is a potential adverse effect of breast cancer treatment characterized by arm swelling, discomfort, and impaired upper extremity function in its later stages. The development of lymphedema is the result of a compromised lymphatic drainage system after the removal of lymph nodes or radiation to the axillary lymph nodes. Patients with breast cancer carry a lifelong risk of developing lymphedema; the average time to onset is 14.4 months after treatment completion.[7,8] Consequently, if patients comply with cautionary guidelines, they must exercise risk-reducing practices for the rest of their lives.

Well-defined risk factors for developing lymphedema include axillary lymph node dissection (ALND),[9-15] regional lymph node irradiation (RLNR),[8,16-19] higher body mass index (BMI), and older age at diagnosis.[7,8,11,14,20-30] It remains unclear why, among patients with similar demographic and treatment-related characteristics, some go on to develop lymphedema. This variation has prompted speculation that events including blood draws, injections, blood pressure readings, trauma to the arm, air travel, and cellulitis might incite lymphedema.[6,31] Despite the prevalence and persistence of recommendations to pursue precautionary behavior after breast cancer treatment, few data exist to support these practices, and investigation into the topic is warranted.[5]

PATIENTS AND METHODS

Study Design

Patients with newly diagnosed breast cancer between 2009 and 2014 who were prospectively screened for lymphedema at our institution were included in this analysis. Bilateral arm volume measurements were obtained using an optoelectric Perometer (Pero-system, Wuppertal, Germany), which uses infrared light to measure limb circumference and calculate arm volume. All patients had a preoperative baseline measurement, a postoperative measurement, a measurement after chemotherapy and/or radio therapy, and measurements at regular follow-up intervals corresponding with oncology visits.[32-35] Regular follow-up intervals correspond to time periods of between 3 and 7 months. Occasionally patients are measured more frequently at their request. The protocol for lymphedema screening has been previously published and approved by the institutional review board[33] (ClinicalTrials.gov identification number NCT01521741).

Arm volume changes were quantified using the relative volume change (RVC)[33] formula after unilateral breast surgery or the weight-adjusted volume change (WAC) formula after bilateral breast surgery.[34] The RVC equation accounts for preoperative differences in arm volume by using a baseline measurement and for nontreatment-related changes, including weight gain or loss, by comparing the surgical arm to the nonsurgical arm.[33,34] Briefly, RVC = $\{[A(2)U(1)/U(2)A(1)\} - 1)$, where $A(1)$ and $A(2)$ are arm volumes on the surgical or ipsilateral side at preoperative and postoperative measurements, and $U(1)$ and $U(2)$ are arm volumes on the contralateral side at corresponding time points.[33] The WAC calculates changes in arm volume compared with a preoperative arm measurement for each arm independently and accounts for weight changes that could influence arm size.[34] RVC and WAC have been shown to classify lymphedema similarly.[34] Lymphedema was defined as RVC or WAC $\geq$ 10%.[7,15,36]

At each Perometer measurement, patients were asked to complete a survey on which they reported the number of blood draws, injections, blood pressure readings, and trauma to the at-risk arm(s); number of flights and the length of the flight since their last measurement; and use of compression sleeve while flying. Self-reported trauma ranged from bruising to arm fractures.

This analysis includes information from each patient visit at which both an arm volume measurement and a survey were obtained.

Patient Population

All 632 patients included in this study had a new diagnosis of invasive breast cancer at their baseline measurement, more than 6 months of postsurgical follow-up, and at least one follow-up arm measurement. Patient and clinocopathologic characteristics were collected via medical record review. Patients who undergo sentinel lymph node biopsy are still at risk for developing lymphedema and are often advised to exercise risk reduction practices just like those who undergo ALND. Therefore, both groups were included in the study. Episodes of cellulitis were defined as clinical signs of infection in the ipsilateral arm and/or breast that required antibiotics. Each side was evaluated independently for patients who underwent bilateral breast surgery, resulting in a total of 760 at-risk arms available for analysis. In our hospital, the majority of patients who chose to undergo contralateral prophylactic mastectomy undergo sentinel lymph node biopsy on their unaffected breast to stage an occult breast cancer if discovered on final pathology. Therefore, the unaffected breasts for patients undergoing bilateral mastectomies were included in the analysis because they are also at risk for developing lymphedema. Patients were censored from the analysis after a diagnosis of distant metastases and recurrence and if they wore a compression sleeve while flying.

Statistical Analysis

The Kaplan-Meier method was used to estimate the 2-year cumulative incidence of lymphedema, defined by RVC/WAC $\geq$ 10%. Linear random effects models were used to assess the association between relative arm volume (as a continuous variable), clinical risk factors, and episodes of nonprecautionary behavior. These models account for the correlation between arm volume measurements obtained from the same patient and, for patients who underwent bilateral breast surgery, on the same side of the body. At each measurement, the number of blood draws, injections, blood pressure readings, trauma, and episodes of cellulitis were analyzed both as continuous variables and as dichotomous variables, categorized according to whether patients reported having had one or more events versus none. Number of and hours spent on flights in total since last follow-up were analyzed as both continuous and trichotomous variables. Model estimates give the mean change in RVC or WAC associated with a one-unit increase in a continuous risk factor and the mean difference in RVC or WAC between subgroups for categorical variables. Univariate model results were used to estimate and plot the mean RVC or WAC within each subgroup for categorical clinical and nontreatment-related variables, along with the 95% CI for the mean and the P value associated with the comparison of means. The multivariate model was chosen by starting with a model that included all variables that were significant at the .10 significance level in the univariate analysis, as well as all nonprecautionary behaviors, and removing one variable at a time until only significant ($P < .05$) variables remained. Because cellulitis is in the causal pathway between the risk events and arm volume increase, it was not included in the model selection process to avoid overadjustment bias.

Cox proportional hazards models were used to assess the association between risk of cellulitis and risk events. Patients who developed cellulitis in the postoperative period were excluded from this analysis because of lack of information on risk events. In addition, in analyzing the association between risk events and subsequent cellulitis, we evaluated the relationship between the risk of infection and the number of risk events reported before the cellulitis episode.

RESULTS

Patient Population

Six hundred thirty-two patients with a total of 3,041 postoperative measurements were included. Median age at diagnosis was 52 years (range, 28 to 81 years), and median BMI was 26 lb/in^2 (range, 16 to 59 lb/in^2; Table 1); 92.1% of the cohort was white, 0.6% Hispanic, 2% African American, 2.7% Asian, and 2.6% unknown. Patients were followed for a median of 24 months (6 to 60 months)

Table 1. Summary of Clinicopathologic Factors Stratified by Lymphedema (RVC/WAC ≥ 10%)

	Lymphedema		
	No (n = 697)	Yes (n = 63)	Overall (N = 760)
Age at diagnosis, years*	52	51	52
BMI, lb/in^2*	25.4	29.1	25.6
Follow-up, months*	23.59	34.31	24.03
No. of postoperative visits*	4	5	4
Months between visits*	7.14	6.45	7.09
Tumor type			
None			
No.	112	13	125
%	16.1	20.6	16.4
Invasive			
No.	583	50	633
%	83.6	79.4	83.3
Not available			
No.	2	0	2
%	0.3	0	0.3
Laterality			
Unilateral			
No.	473	31	504
%	67.9	49.2	66.3
Bilateral			
No.	224	32	256
%	32.1	50.8	33.7
Breast surgery			
Lumpectomy			
No.	359	18	377
%	51.5	28.6	49.6
Mastectomy			
No.	338	45	383
%	48.5	71.4	50.4
Axillary surgery			
None			
No.	53	7	60
%	7.6	11.1	7.9
SLNB			
No.	519	22	541
%	74.5	34.9	71.2
ALND			
No.	125	34	159
%	17.9	54	20.9
Neoadjuvant chemotherapy			
No			
No.	606	50	656
%	86.9	79.4	86.3
Yes			
No.	91	13	104
%	13.1	20.6	13.7
Adjuvant chemotherapy			
No			
No.	416	25	441
%	59.7	39.7	58
Yes			
No.	281	38	319
%	40.3	60.3	42
Hormonal therapy			
No			
No.	121	12	133
%	17.4	19	17.5
Yes			
No.	576	51	627
%	82.6	81	82.5
Radiation therapy			
None			
No.	248	17	265
%	35.6	27	34.9
Chest wall only			
No.	316	16	332
%	45.3	25.4	43.7
RLNR			
No.	130	30	160
%	18.7	47.6	21.1
Not available			
No.	3	0	3
%	0.4	0	0.4
Cellulitis			
No			
No.	659	56	715
%	94.5	88.9	94.1
Yes			
No.	38	7	45
%	5.5	11.1	5.9

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; RNLR, regional lymph node irradiation; RVC, relative volume change; SLNB, sentinel lymph node biopsy; WAC, weight-adjusted volume change.
*Values shown, median.

and had a median of four postoperative visits (one to 16). The median time between measurements was 7 months (interquartile range, 6.2 months). Thirteen percent of patients had one measurement, 34% had two to three measurements, 40% had four to six measurements, and 13% had seven to 16 measurements. By medical record review, 5.9% (45 of 760) of treated breasts had at least one episode of cellulitis any time after surgery requiring antibiotics (Table 1); 47% (21 of 45) of cellulitis episodes occurred in the immediate postoperative period and therefore before the first postoperative arm measurement. At 24 months, the cumulative incidence of BCRL as defined by an RVC or WAC ≥ 10% was 7.72% (95% CI, 5.82% to 10.22%).

Nonprecautionary Behaviors

In 8.5% (251 of 2,965) of responses, patients reported having one or more blood draw in their affected arm(s) since their last measurement, 2.1% (63 of 2,961) of responses reported having one or more injection, 16.3% (482 of 2,961) of responses reported having one or more blood pressure measurements taken, and 1.0% (37 of 2,999) of responses reported trauma to the at-risk arm (Table 2). Thirty percent (878 of 2,960) of patients had flown since their last measurement (Table 2).

Univariate and Multivariate Analyses

By univariate analysis, there was no significant association between an increased RVC or WAC and undergoing one or more blood draws ($P = .62$), injections ($P = .77$), trauma to the at-risk arm ($P = .08$), number of flights (one or two [$P = .77$] and three or more [$P = .91$] *v* none), or duration of flights (1 to 12 hours [$P = .43$] and 12 hours or more [$P = .54$] *v* none) (Fig 1). Having a BMI ≥ 25 lb/in^2 at time of diagnosis ($P = .0064$), undergoing ALND ($P = .0003$), having blood pressure readings ($P = .034$), RLNR ($P < .001$), and cellulitis ($P < .001$) were significantly associated with arm volume increases (Table 3; Fig 1). When

Table 2. Summary of Reported Risk Events

Risk Factor	No. of Measurements With Event		
	Lymphedema		
	No (n = 192)	Yes (n = 2,849)	Overall (N = 3,041)
Blood draws			
None			
No.	2,538	176	2,714
%	89.1	91.7	89.2
1+			
No.	241	10	251
%	8.5	5.2	8.3
Not available			
No.	70	6	76
%	2.5	3.1	2.5
Injections			
None			
No.	2,726	183	2,909
%	95.7	95.3	95.7
1+			
No.	60	3	63
%	2.1	1.6	2.1
Not available			
No.	63	6	69
%	2.2	3.1	2.3
Blood pressure			
None			
No.	2,305	174	2,479
%	80.9	90.6	81.5
1+			
No.	470	12	482
%	16.5	6.3	15.9
Not available			
No.	74	6	80
%	2.6	3.1	2.6
Trauma			
No			
No.	2,780	182	2,962
%	97.6	94.8	97.4
Yes			
No.	29	8	37
%	1	4.2	1.2
Not available			
No.	40	2	42
%	1.4	1	1.4
Flights, No.			
None			
No.	1,949	133	2,082
%	68.4	69.3	68.5
1-2			
No.	453	28	481
%	15.9	14.6	15.8
3+			
No.	389	8	397
%	13.7	4.2	13.1
Not available			
No.	58	23	81
%	2	12	2.7
Flights, hours			
None			
No.	1,946	132	2,078
%	68.3	68.8	68.3
1-12			
No.	429	23	452
%	15.1	12	14.9
12+			
No.	408	13	421
%	14.3	6.8	13.8
Not available			
No.	66	24	90
%	2.3	12.5	3

analyzed as continuous variables, age at diagnosis ($P = .25$), the number of ipsilateral blood draws ($P = .92$), injections ($P = .85$), blood pressure readings ($P = .15$), and number ($P = .34$) or duration of flights ($P = .98$) were not associated with an increase in RVC or WAC by univariate analysis. In a subset of patients who underwent ALND, BMI $\geq$ 25 lb/in^2 ($P = .0051$) and cellulitis ($P < .001$) remained significant, but blood draws ($P = .26$), injections ($P = .35$), blood pressures ($P = .39$), trauma ($P = .23$), and air travel (one or two [$P = .96$] and three or more [$P = .88$] *v* no flights) or duration of flights (1 to 12 hours [$P = .85$] and 12 hours or more [$P = .69$] *v* none) were not associated with increased arm swelling.

By multivariate analysis, factors significantly associated with increases in arm volume included BMI $\geq$ 25 lb/in^2 ($P = .0236$), ALND ($P < .001$), RLNR ($P = .0364$), and cellulitis ($P < .001$) (Fig 2). None of the nonprecautionary behaviors were significantly associated with arm volume change in the multivariate analysis.

Further investigation of the association between risk events and subsequent cellulitis revealed that blood draws (hazard ratio [HR], 0.977; $P = .91$), injections (HR, 1.101; $P = .5$), and blood pressure readings (HR, 0.943; $P = .1$) on the ipsilateral arm were not significantly associated with cellulitis.

DISCUSSION

A large, prospective cohort of patients with breast cancer was analyzed to investigate the association of nonprecautionary behaviors and the subsequent risk of lymphedema. No significant association was found between undergoing ipsilateral blood draws, injections, and blood pressure readings, and trauma to the at-risk arm, air travel, and arm swelling. Increase in arm swelling was associated with ALND, RLNR, BMI $\geq$ 25 lb/in^2, and cellulitis.

Previous reports postulate that blood draws, injections, blood pressure readings, and trauma can cause infection and injury to the at-risk arm.[3,6,37-39] The theory is that patients with surgically removed lymph nodes have compromised lymphatic systems that cannot clear fluid resulting from an immune response, leading to build-up of lymphatic fluid in the arm and subsequent lymphedema.[37] One of the first papers to recommend precautionary behaviors was published in 1992 as a case report of a woman who developed swelling 30 years after treatment in response to a finger pinprick.[40] Smith[37] advised avoidance of traumatic events to the at-risk arm after examining 10 patients with BCRL, four of whom reported blood draws as triggering their arm swelling. These studies are anecdotal and based on information from a small number of patients. Despite minimal data, the authors provided persistent recommendations to avoid blood draws, blood pressure readings, and injections in the at-risk arm to reduce the risk of lymphedema.[6,31,37,41] The results of our prospective study provide evidence-based data that call these guidelines into question.

Clark et al[41] evaluated 188 patients with breast cancer who underwent ALND and correlated skin punctures with risk of developing lymphedema. With a median follow-up of 3 years, 20.7% (39 of 188) of patients developed arm lymphedema, 9.6% (18 of 188) of all patients had a skin puncture, and therefore 44% (8 of 18) of patients with skin puncture developed lymphedema during the follow-up period.[41] This analysis performed a measurement for lymphedema at 6 months and 3 years after surgery

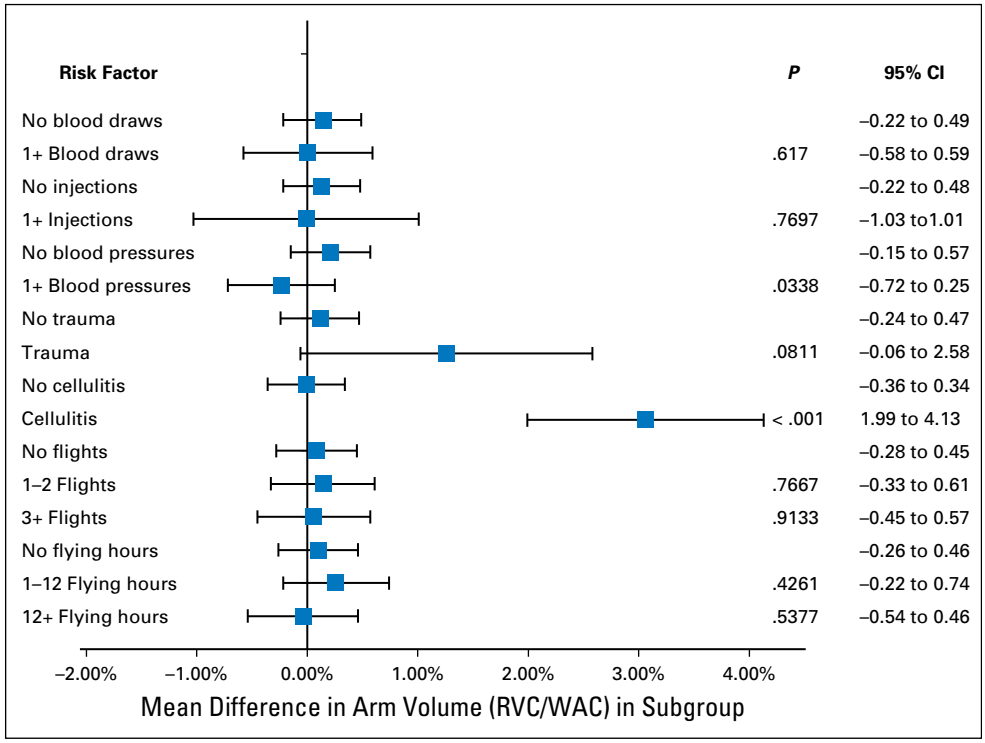

Fig 1. Univariate analysis of association between risk events and arm volume increases. RVC, relative volume change; WAC, weight-adjusted volume change.

and did not specify the timing of skin puncture; therefore, it did not take into account other events that could have contributed to lymphedema.[42] In our subset analysis of 159 patients undergoing ALND, nonprecautionary risk behaviors and specifically skin puncture were not correlated with increased arm swelling. By performing arm measurements at regularly timed intervals for as long as 5 years and recording the number of nonprecautionary events since the previous measurement, we were able to reduce the recall bias and more specifically evaluate effects of nonprecautionary behavior on arm swelling.

Table 3. Univariate Analysis of Categorical Treatment Factors

Patient- or Treatment-Related Risk Factor	Mean RVC/WAC in Subgroup (%)	95% CI	*P*
Surgical characteristics			
Lumpectomy	0.04	−0.42 to 0.51	—*
Mastectomy *v* lumpectomy	0.26	−0.28 to 0.79	.5542
No nodal surgery	−0.22	−1.22 to 0.78	—
SLNB *v* none	−0.35	−0.73 to 0.04	.8113
ALND *v* none	1.89	1.22 to 2.55	<.001
Radiation therapy			
None	−0.00	−0.43 to 0.43	—
Breast/chest wall irradiation *v* none	−0.20	−0.65 to 0.25	.42341
Breast/chest wall + RLNR *v* none	1.29	0.65 to 1.88	<.001
BMI, lb/in^2			
< 25	−0.43	−0.98 to 0.11	—
≥ 25	0.57	0.10 to 1.03	.0064

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; RLNR, regional lymph node irradiation; RVC, relative volume change; WAC, weight-adjusted volume change.
*Indicates the specified variable or comparison was not analyzed.

In contrast, McLaughlin et al[6] found no association in risk-reducing behaviors of patients with and without lymphedema when evaluated using tape measured circumferential arm measurements. Circumferential tape measurement is limited because the measurements can be subject to both inter- and intrapersonal variation.[43] Unlike tape measurements, measurements by the Perometer and use of the RVC and WAC formulas account for preexisting arm volume differences and detect small volume changes. In addition, obtaining reproducible, prospective arm measurements using the Perometer at the same time as collecting individual incidence of risk-related events could have biased our data to attribute small volume changes that may have not represented swelling detectable via circumferential tape measurement to risk events. Similarly, we found no association with nonprecautionary behavior and increase in arm volume.

The Physical Activity and Lymphedema (PAL) trial assessed the safety of progressive strength training in breast cancer survivors and investigated the association of 30 risk factors and arm swelling.[44,45] The authors reported no significant association between ipsilateral blood draws, blood pressure readings, and air travel and incident arm swelling.[44] The study included clinical evaluation of arm swelling using water displacement and patient-reported risk-reducing behaviors at 3, 6, and 12 months after enrollment.[44,45] Patients were given compression sleeves to wear during exercise and participated in a biweekly, year-long exercise program. The incidence of lymphedema as defined as interlimb difference increase of ≥ 5% was low, which may be due to wearing a compression sleeve or the exercise program.[44,45] In addition, the incidence of nonprecautionary behaviors was also low, which may be due to the education about lymphedema provided to participants. Patients in our cohort do not routinely receive recommendations to avoid blood draws, injections, or blood pressure readings or to wear a

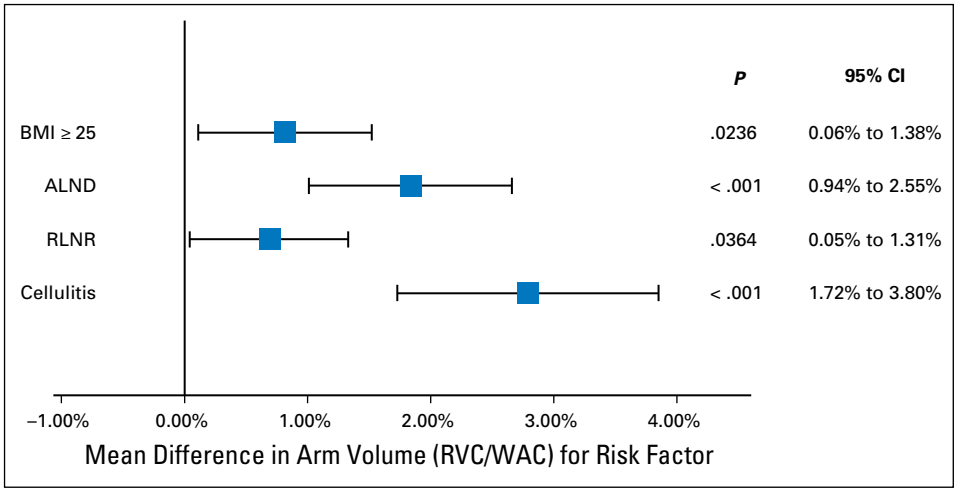

Fig 2. Multivariate analysis of risk factors associated with arm volume increases. ALND, axillary lymph node dissection; BMI, body mass index (in lb/in^2); RNLR, regional lymph node irradiation; RVC, relative volume change; WAC, weight-adjusted volume change.

compressive sleeve while flying. However, our incidence of risk events was low, and we enhanced our patient cohort to include patients with both unilateral and bilateral breast surgery, increasing both the number of risk events and the overall incidence of lymphedema.

It has been reported that flying incites the development of lymphedema because of changes in cabin air pressure.[6,46] Many clinicians recommend using risk-reducing compression sleeves when flying based on few, mostly retrospective, studies.[47] In these studies it is unclear if the reported lymphedema was preexisting or influenced by other factors. Kilbreath et al[48] evaluated changes in arm volume after short- and long-distance flights and found no change in arm volume as measured by bioimpedance. In our analysis, we prospectively collected information regarding air travel and quantified arm swelling with short intervals of follow-up. This design enabled the investigation of the immediate effects of flying on arm volume and minimized the risk of recall bias due to the shorter interval of follow up.

In our study, BMI $\geq$ 25 lb/in^2 at diagnosis, ALND, RLNR, and cellulitis were significantly associated with arm swelling. High BMI, RLNR, and ALND are consistently cited in the literature as risk factors for arm swelling and lymphedema, and our data further support these claims.[6,8,10,11,13-16,19,20,24,49,50] The increased risk for developing lymphedema after infection including cellulitis is also well documented in the literature,[2,6,22,51] and our results support these findings. Interestingly in our cohort, episodes of cellulitis were not associated with a risk event that occurred before the cellulitis. This may be due to a lower incidence of risk events or to an overall lower risk of infection after risk events in a modern era of attention to sterility.

Limitations of the study include a relatively short 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. As lymphedema has been shown to develop an average of 14.4 months after surgery,[8] longer follow-up time would strengthen the study. Although efforts were made to ensure regular follow-up visits, future studies using repeat questionnaires and sensitivity analyses might elucidate the effects of recall bias. In addition, our analysis did not adjust for the number of positive lymph nodes because we have not found it to be significant in a previous analysis; however, this is an important area for future investigation.[52] Finally, the study did not capture and therefore was not able to account for women who had physical therapy, which might have placed them at lower risk for developing swelling, even after risk events.

This study represents the largest cohort of patients with breast cancer prospectively screened for lymphedema using preoperative arm measurements to determine the impact of risk-reducing practices on arm swelling. We evaluated the association between risk events and changes in arm volume and found no significant associations between air travel, blood draws, injections, and blood pressure readings in the at-risk arm with arm volume increase. Patients who have a BMI $\geq$ 25 lb/in^2, underwent ALND or RLNR, and have had an episode of cellulitis should be more closely monitored for changes in arm volume because of the significant association with arm volume increases. The recommendations set forth in the studies discussed still persist today and unfortunately are supported with few evidence-based data. Although we cannot affirmatively state that risk-reduction practices have no effect on arm swelling, we hope to generate evidence that brings reasonable doubt to burdensome guidelines and encourage further investigation into nonprecautionary behaviors and the risk of lymphedema.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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REFERENCES

1. American Cancer Society: Lymphedema: What every woman with breast cancer should know—For women at risk for lymphedema. http://www.cancer.org/acs/groups/cid/documents/webcontent/002876-pdf.pdf
2. 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
3. Loudon L, Petrek J: Lymphedema in women treated for breast cancer. Cancer Pract 8:65-71, 2000
4. National Lymphedema Network: Supplement to NLN position breast cancer screening: Screening and early detection of breast cancer-related lymphedema—The imperative. http://www.lymphnet.org/pdfDocs/PP_Lymphedema_BC_Supplement.pdf
5. National Lymphedema Network: Position statement of the National Lymphedema Network: Lymphedema risk reduction practices. http://www.lymphnet.org/pdfDocs/nlnriskreduction.pdf
6. McLaughlin SA, Bagaria S, Gibson T, et al: Trends in risk reduction practices for the prevention of lymphedema in the first 12 months after breast cancer surgery. J Am Coll Surg 216:380-389, 2013; quiz 511-513
7. 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
8. Specht MC, Miller CL, Russell TA, et al: Defining a threshold for intervention in breast cancer-related lymphedema: What level of arm volume increase predicts progression? Breast Cancer Res Treat 140:485-494, 2013
9. 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
10. Mansel RE, Fallowfield L, Kissin M, et al: Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: The ALMANAC Trial. J Natl Cancer Inst 98: 599-609, 2006
11. Norman SA, Localio AR, Kallan MJ, et al: Risk factors for lymphedema after breast cancer treatment. Cancer Epidemiol Biomarkers Prev 19: 2734-2746, 2010
12. Yang EJ, Park WB, Seo KS, et al: Longitudinal change of treatment-related upper limb dysfunction and its impact on late dysfunction in breast cancer survivors: A prospective cohort study. J Surg Oncol 101:84-91, 2010
13. Lucci A, McCall LM, Beitsch PD, et al: American College of Surgeons Oncology Group: Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol 25:3657-3663, 2007
14. Park JH, Lee WH, Chung HS: Incidence and risk factors of breast cancer lymphoedema. J Clin Nurs 17:1450-1459, 2008
15. 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
16. 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
17. Coriddi M, Khansa I, Stephens J, et al: Analysis of factors contributing to severity of breast cancer-related lymphedema. Ann Plast Surg 74:22-25, 2015
18. Tiwari P, Coriddi M, Lamp S: Lymphedema strategies for investigation and treatment: A review. Plast Surg Nurs 32:173-177, 2012; quiz 178-179
19. Hayes SB, Freedman GM, Li T, et al: Does axillary boost increase lymphedema compared with supraclavicular radiation alone after breast conservation? Int J Radiat Oncol Biol Phys 72:1449-1455, 2008
20. 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
21. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR: Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast Cancer Res Treat 130:981-991, 2011
22. 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
23. Wilke LG, McCall LM, Posther KE, et al: Surgical complications associated with sentinel lymph node biopsy: Results from a prospective international cooperative group trial. Ann Surg Oncol 13:491-500, 2006
24. Soran A, Wu WC, Dirican A, et al: Estimating the probability of lymphedema after breast cancer surgery. Am J Clin Oncol 34:506-510, 2011
25. Swenson KK, Nissen MJ, et al: Case-control study to evaluate predictors of lymphedema after breast cancer surgery. Oncol Nurs Forum 36: 185-193, 2009
26. Nesvold IL, Dahl AA, Løkkevik E, et al: Arm and shoulder morbidity in breast cancer patients after breast-conserving therapy versus mastectomy. Acta Oncol 47:835-842, 2008
27. Hayes SC, Janda M, Cornish B, et al: Lymphedema after breast cancer: Incidence, risk factors, and effect on upper body function. J Clin Oncol 26: 3536-3542, 2008
28. Paskett ED, Naughton MJ, McCoy TP, et al: The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. Cancer Epidemiol Biomarkers Prev 16:775-782, 2007
29. Crosby MA, Card A, Liu J, et al: Immediate breast reconstruction and lymphedema incidence. Plast Reconstr Surg 129:789e-795e, 2012
30. Ozaslan C, Kuru B: Lymphedema after treatment of breast cancer. Am J Surg 187:69-72, 2004
31. Cole T: Risks and benefits of needle use in patients after axillary node surgery. Br J Nurs 15: 969-974, 976-979, 2006
32. Ancukiewicz M, Miller CL, Skolny MN, et al: Comparison of relative versus absolute arm size change as criteria for quantifying breast cancer-related lymphedema: The flaws in current studies and need for universal methodology. Breast Cancer Res Treat 135:145-152, 2012
33. Ancukiewicz M, Russell TA, Otoole J, et al: Standardized method for quantification of developing lymphedema in patients treated for breast cancer. Int J Radiat Oncol Biol Phys 79:1436-1443, 2011
34. Miller CL, Specht MC, Horick N, et al: A novel, validated method to quantify breast cancer-related lymphedema (BCRL) following bilateral breast surgery. Lymphology 46:64-74, 2013
35. O'Toole J, Russell T, Singer M, et al: A general hospital's multi-disciplinary approach to BCRL. J Lymphoedema 5:81-85, 2010
36. Armer JM, Heckathorn PW: Post-breast cancer lymphedema in aging women: Self-management and implications for nursing. J Gerontol Nurs 31: 29-39, 2005
37. Smith J: The practice of venepuncture in lymphoedema. Eur J Cancer Care (Engl) 7:97-98, 1998
38. Davis S: Lymphedema following breast cancer treatment. Radiol Technol 70:42-56, 1998; quiz 57-60
39. Drury AN, Jones NW: Observations upon the rate at which edema forms when the veins of the human limb are congested. Heart 2:580-581, 1927
40. Brennan MJ, Weitz J: Lymphedema 30 years after radical mastectomy. Am J Phys Med Rehabil 71:12-14, 1992
41. 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
42. Cemal Y, Pusic A, Mehrara BJ: Preventative measures for lymphedema: Separating fact from fiction. J Am Coll Surg 213:543-551, 2011
43. Deltombe T, Jamart J, Recloux S, et al: Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. Lymphology 40:26-34, 2007
44. 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
45. Schmitz KH, Troxel AB, Cheville A, et al: Physical Activity and Lymphedema (the PAL trial): Assessing the safety of progressive strength training in breast cancer survivors. Contemp Clin Trials 30: 233-245, 2009
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. 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
49. Shahpar H, Atieh A, Maryam A, et al: Risk factors of lymph edema in breast cancer patients. Int J Breast Cancer 2013:641818, 2013
50. Graham P, Jagavkar R, Browne L, et al: Supraclavicular radiotherapy must be limited laterally by the coracoid to avoid significant adjuvant breast nodal radiotherapy lymphoedema risk. Australas Radiol 50:578-582, 2006
51. 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
52. Miller CL, Skolny M, Ferguson C, et al: Does number of sentinel lymph nodes removed impact the risk of breast cancer- related lymphedema (BCRL)? The National Lymphedema Network Conference, 11th International Conference, Washington DC , September 3-7, 2014

GLOSSARY TERM

sentinel lymph node: the lymph node that is anatomically located such that it is the first site of lymph drainage from the location of the primary tumor. It is suspected and assumed that if a malignancy is going to disseminate via the lymphatic system, metastases will first be evident in the sentinel lymph node. In this manner, this lymph node is said to stand guard or sentinel over the metastatic state of the tumor. For many cancers, the sentinel lymph node is biopsied as part of the staging process and presence of macro- or micrometastases in the sentinel lymph node is a negative prognostic factor.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of Ipsilateral Blood Draws, Injections, Blood Pressure Measurements, and Air Travel on the Risk of Lymphedema for Patients Treated for Breast Cancer

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