Original Article

Risk factors for breast cancer–related lymphedema in patients undergoing 3 years of prospective surveillance with intervention

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BACKGROUND: To evaluate risk factors (treatment-related, comorbidities, and lifestyle) for breast cancer–related lymphedema (BCRL) within the context of a Prospective Surveillance and Early Intervention (PSEI) model of care for subclinical BCRL. **METHODS:** The parent randomized clinical trial assigned patients newly diagnosed with breast cancer to PSEI with either bioimpedance spectroscopy (BIS) or tape measurement (TM). Surgical, systemic and radiation treatments, comorbidities, and lifestyle factors were recorded. Detection of subclinical BCRL (change from baseline of either BIS L-Dex ≥6.5 or tape volume ≥5% and <10%) triggered an intervention with compression therapy. Volume change from baseline ≥10% indicated progression to chronic lymphedema and need for complex decongestive physiotherapy. In this secondary analysis, multinomial logistic regressions including main and interaction effects of the study group and risk factors were used to test for factor associations with outcomes (no lymphedema, subclinical lymphedema, progression to chronic lymphedema after intervention, progression to chronic lymphedema without intervention). Post hoc tests of significant interaction effects were conducted using Bonferroni-corrected alphas of .008; otherwise, an alpha of .05 was used for statistical significance. **RESULTS:** The sample (n = 918; TM = 457; BIS = 461) was female with a median age of 58.4 years. Factors associated with BCRL risk included axillary lymph node dissection (ALND) (p < .001), taxane-based chemotherapy (p < .001), regional nodal irradiation (RNI) (p ≤ .001), body mass index >30 (p = .002), and rurality (p = .037). Mastectomy, age, hypertension, diabetes, seroma, smoking, and air travel were not associated with BCRL risk. **CONCLUSIONS:** Within the context of 3 years of PSEI for subclinical lymphedema, variables of ALND, taxane-based chemotherapy, RNI, body mass index >30, and rurality increased risk. ***Cancer* 2022;128:3408-3415**. © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: bioimpedance spectroscopy, breast cancer, intervention, lymphedema, prospective surveillance.

INTRODUCTION

Breast cancer–related lymphedema (BCRL) affects an estimated 21% of breast cancer survivors (BCSs).[1,2] To reduce the risk of chronic BCRL (i.e., visible swelling in the arm), the Prospective Surveillance and Early Intervention (PSEI) model of care establishes a clinical pathway that commences with assessment of arm status at cancer diagnosis and proceeds with screening for subclinical BCRL (i.e., accumulation of extracellular fluid, no visible swelling) at regular intervals throughout cancer treatment and follow-up.[2-4] The PSEI model integrates routine measurement, risk assessment, risk-reduction education, and, ideally, compression therapy intervention for subclinical BCRL, all of which are key to reducing chronic BCRL risk.[5,6] Identification of change only in extracellular fluid using bioimpedance spectroscopy (BIS)–driven interventions for subclinical BCRL have been associated with less progression to chronic BCRL[7-9] than has identification of whole arm volume change (e.g., tape measurement [TM])[7-9] when following the PSEI model, which includes a short compression intervention.

Despite this success, inconsistencies prevail in the literature regarding risk factors for progression to chronic BCRL. There is no known research regarding risk factors in patients undergoing compression for subclinical lymphedema as part of the PSEI model of care. This lack of evidence has made it difficult for clinicians to provide reliable risk assessment and

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risk-reduction education to patients when implementing the PSEI model.

Treatment-related risk factors such as type of surgery (mastectomy vs. breast conservation surgery), axillary procedures (axillary lymph node dissection [ALND] vs. sentinel lymph node biopsy), radiotherapy (regional nodal irradiation [RNI]), and chemotherapy are well-documented risk factors for chronic BCRL.[10-17] Studies have consistently demonstrated that the greater the extent of breast surgery, axillary procedures, and radiotherapy, the higher the chronic BCRL risk. With respect to systemic therapy, taxane-based chemotherapy has been a suspected risk factor for almost a decade,[13] as has the combination of chemotherapy and ALND.[17] Seroma has also been associated with chronic BCRL.[18-22] Comorbidities such as age, body mass index (BMI), hypertension, and diabetes have been evaluated as risks factors for chronic BCRL with mixed results.[23-30] Finally, lifestyle behaviors such as smoking, air travel, and area of residence may also influence chronic BCRL risk.[31-36] Available literature regarding smoking is scant.[30-32] Despite limited prospective data available to evaluate the role of air travel,[34] up to 50% of BCSs avoid air travel because of the uncertain BCRL risk,[34] and a survey examining precipitating factors for chronic BCRL indicated 5.5% of patients reported air travel as the precipitating factor.[35] Additionally, rurality has been associated with increased postoperative symptoms, including lymphedema.[36]

Risk-reduction guidelines range from simple strategies (e.g., good skin care) to potentially lifestyle altering (e.g., prophylactic compression garment use), but implementation does not guarantee reduced BCRL risk.[37] Given the importance of PSEI and initiation of subclinical BCRL interventions, research is needed on risk factors for subclinical and chronic lymphedema and the influence of measurement methods combined with compression intervention on factors leading to chronic BCRL. Thus, the purpose of this study was to conduct a secondary analysis to evaluate individual risk factors (treatment-related, comorbidities, lifestyle) for BCRL and explore if PSEI plus a compression intervention for subclinical BCRL influences the factors leading to chronic BCRL.

METHODS

Study design and sample

A prospective, multisite, international randomized, controlled trial enrolled women with newly diagnosed breast cancer before surgery, eligibility, and exclusion criteria previously published.[7-9] Study approval from all local research review boards, protocol posting on www.ClinicalTrials.gov, and informed consent were all obtained before enrollment in the study.

Randomization and assessments

Baseline physical measurements and self-report data were collected presurgery. Patients were randomized postoperatively to surveillance with either BIS or TM, with procedures previously documented.[7-9,38,39] Both assessment methods have been previously validated by the principal investigator of the parent study along with other published validation studies.[40-44] Intensive training was provided to all research staff at each site by the study principal investigator, as well as annual fidelity checks, before enrolling participants. Training was also conducted at regular intervals throughout the study period at each site to reduce variation in measurements and increase interrater reliability between research staff. Patients were measured with both BIS and TM at baseline, any time subclinical lymphedema was detected, and at the end of study participation regardless of reason. Progression to chronic lymphedema was determined solely by TM for both groups.

For purposes of this study, the "no lymphedema" outcome group did not develop subclinical lymphedema, the "subclinical lymphedema" group developed subclinical lymphedema and received compression therapy intervention for 4 weeks and did not progress to chronic lymphedema after intervention, the "progression to chronic lymphedema postintervention" group developed chronic lymphedema following compression therapy intervention, and the "progression to chronic lymphedema without intervention" group developed chronic lymphedema before the opportunity of receiving compression therapy intervention. Data collection and medical record review were conducted individually at each site and directly entered into the REDCap research database/record by trained site staff.

Treatment data and comorbidities

Breast cancer medical history and treatment (type/extent of nodal procedures, breast surgery, chemotherapy, and radiation) were collected at baseline and updated at each follow-up. RNI was defined as radiation to chest wall or breast and any of the following: supraclavicular fossa, infraclavicular fossa, internal mammary chain, axilla level 3, or standard fractionation whole-breast irradiation with high tangential fields. Medical records were accessed to determine postoperative seroma development. In the rare instance when medical history was not accessible, self-reported presence of seroma was recorded. Weight and

height were collected at baseline. Each measurement was taken twice, and the average was used to calculate BMI. Medical history and current comorbidities (hypertension and diabetes) were collected at baseline via self-report and medical record review.

Demographics and lifestyle

Self-reported race, marital status, education level, employment, area of residence, age, and smoking history were collected at baseline. Air travel history was collected at each follow-up through self-report surveys. In addition to total number of flights taken with and without compression, for those patients who met the criteria for subclinical lymphedema, flights before and after intervention were also analyzed.

Statistical methods

Descriptive statistical summaries of demographic and treatment characteristics were generated for the entire randomized sample and for each study arm. Those distributions were compared using likelihood ratio χ^2 statistics (nominal, ordinal categories) or Mann–Whitney tests (continuous). Each of the proposed risk factors were summarized by outcome group (no lymphedema, subclinical lymphedema, progression to chronic lymphedema after intervention, progression to chronic lymphedema without intervention) for the entire randomized sample. Multinomial logistic regressions were used to test the association of each factor with the outcome. An interaction term of study arm and factor was included in those regression models to test whether the association differed between the two arms. Pairwise post hoc tests among the four outcome groups were conducted of statistically significant factor effects using a Bonferroni-corrected alpha of.008; otherwise, an alpha of.05 was used for determining statistical significance.

RESULTS

Sample

Overall, 963 women were randomized to either TM (481) or BIS (482) prospective surveillance (Fig. 1).[7] Of those, 45 had no postrandomization assessments; thus, a sample of 918 (457 TM, 461 BIS) patients was included in the outcome analyses. Almost one-half of all the patients (42.4%) had some type of chemotherapy and, if they did, 88.4% had taxane-based chemotherapy. Slightly more than 80% had some type of radiation therapy and, of those, 27.3% had RNI. Other than a slightly higher percentage of the patients in the BIS group reporting seroma (24.7% vs. 19.3%, $p = .045$), no statistically significant differences between the two study groups were observed in any of the key risk factors. Patients were a median 58.4 years of age, predominantly non-Hispanic (96.3%), well-educated (median, 16 years), and 78.2% identified as White race. Approximately one-half (53.3%) dwelled in suburban areas, with the remaining split equally between urban and rural.

Patients were assessed over a median of 32.8 months (interquartile range [IQR] = 21, 35) postoperatively. Within the sample outcome groups, 670 showed no indication of BCRL (no lymphedema, 73.0%), 179 (subclinical lymphedema, 19.5%), 30 (progressed to chronic lymphedema after intervention, 3.2%), and 39 (progressed to chronic lymphedema without intervention, 4.2%). Months on study were significantly different among the outcome groups because those who progressed with or without intervention were in the study for fewer months than those in the other two groups (median = 16.0 and 8.2, respectively, vs. 33.1 [no lymphedema] and 33.0 [subclinical lymphedema]).

Risk factor associations with outcome

Summaries of the proposed risk factors by outcome group are shown in Table 1.

Treatment-related factors

Statistically significant effects were observed for having ALND ($p < .001$) and taxane-based chemotherapy ($p < .001$) (Table 1). Detailed investigation of the ALND effect found a significantly lower percentage of patients in the no lymphedema group had ALND (13.3%) than those in any of the other three outcome groups. A lower percentage of those who developed subclinical lymphedema but did not progress to chronic lymphedema had ALND than either of the chronic lymphedema groups (25.1% vs. >55%, $p < .008$). A lower percentage (33.6%) of the patients who had no lymphedema received taxane-based chemotherapy than did those in the chronic lymphedema outcome groups (progression to chronic lymphedema after intervention, 70%; progression to chronic lymphedema with intervention, 70%; progression to chronic lymphedema without intervention, 59%, $p < .001$) (Table 1). Finally, within the treatment factors, if a patient had any radiation therapy, there were statistically significant differences in outcome for RNI. Again, within the group that did not have any evidence of lymphedema, the percentage of patients who had received RNI was significantly lower than the percentage in both of the chronic lymphedema outcome groups (23.6% [no lymphedema] vs. [chronic lymphedema] groups: 50.0% [following intervention], 47.8% [without intervention], $p < .008$). Notably, neither mastectomy nor

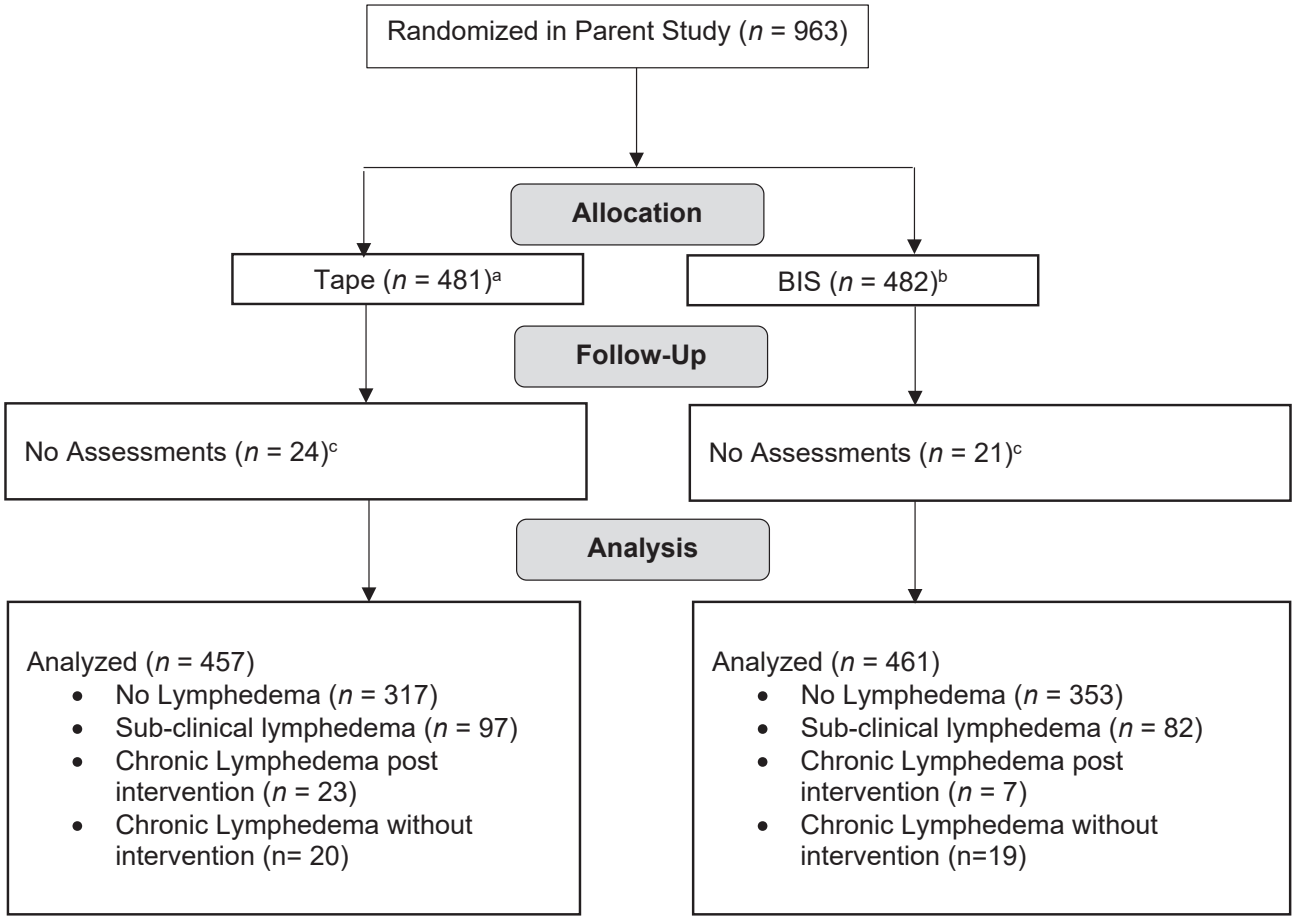

Figure 1. CONSORT flow diagram. BIS indicates bioimpedance spectroscopy. [a]All patients randomized to tape measurement after postoperative reassessment. [b]All patients randomized to BIS after postoperative reassessment. [c]Patients who had incomplete or missing assessments were removed from analysis.

postoperative seromas were statistically significantly associated with the outcome ($p > .05$) (Table 1).

Demographic, comorbid, and lifestyle factors

No statistically significant outcome associations were observed for age or for the comorbid factors of hypertension, diabetes, or smoking ($p > .20$) (Table 1). Compared with the other outcome groups, the highest BMI values were in the group who progressed to chronic lymphedema without receiving the compression intervention ($p = .002$). Rurality was significantly associated with outcome because a higher percentage of the patients who progressed to chronic lymphedema without the intervention lived in rural areas (46.2%) than those that had no lymphedema (22.2%) or those that received an intervention but did not progress to chronic lymphedema (21.9%) ($p < .008$) (Table 1).

Controlling for the opportunity for air travel before the end-of-study, no statistically significant association of simply flying (any air travel) was observed with the outcome ($p = .365$). However, if a patient did fly, the total number of flights (with or without prophylactic compression) was significantly associated with outcome. The direction of the effect, however, was not on increasing the likelihood of chronic lymphedema, rather it was in the direction of decreasing it ($p < .001$). The median number of flights before chronic lymphedema for both groups of patients who progressed was considerably lower (postintervention: median = 2.0, IQR = 1, 4; without intervention: median = 3.5, IQR = 2, 9) than those who underwent the intervention but did not progress to chronic lymphedema (median = 7.0, IQR = 4, 14) ($p < .008$). The number of flights without use of compression was lower in the group with chronic lymphedema after receiving the intervention than each of the other groups (median = 1.0, IQR = 0, 2; other groups: median $\geq$ 3.5) ($p < .008$) (Table 2). Furthermore, a

TABLE 1. Medical history and treatment factors by outcome group ($N = 918$)

	No lymphedema ($N = 670$)	Subclinical lymphedema ($N = 179$)	Chronic lymphedema after intervention ($N = 30$)	Chronic lymphedema without intervention ($N = 39$)	p
Factor					
		Median [IQR] (Min, Max)			
Age	58.4 [50, 66] (28, 93)	58.8 [51, 67] (34, 79)	60.7 [49, 70] (41, 79)	56.3 [47, 68] (43, 79)	.708
Missing	1	0	0	0	
BMI	27.7 [24, 32][a] (17, 61)	28.2 [24, 35] (16, 58)	29.6 [26, 35] (21, 47)	30.4 [26, 40][b] (24, 49)	.002
		No. (%)			
History/current hypertension	209 (31.2)	65 (36.5)	12 (40.0)	16 (41.0)	.300
Missing	1	1	0	0	
History/current diabetes	55 (8.2)	17 (9.6)	3 (10.0)	5 (12.8)	.766
Missing	3	2	0	0	
Area of residence					.037
City/urban	159 (23.9)	50 (28.1)	5 (16.7)	5 (12.8)	
Suburban	359 (53.9)	89 (50.0)	17 (56.7)	16 (41.0)	
Rural	148 (22.2)[a]	39 (21.9)[a]	8 (26.7)	18 (46.2)[b]	
Missing	4	1	0	0	
Seroma	142 (21.2)	44 (24.6)	8 (26.7)	8 (20.5)	.718
History of smoking	222 (33.2)	59 (33.0)	13 (43.3)	18 (46.2)	.277
Missing	1	0	0	0	
Mastectomy	135 (20.2)	48 (27.0)	11 (36.7)	9 (23.1)	.069
Missing	1	1	0	0	
ALND	89 (13.3)[a]	45 (25.1)[b]	17 (56.7)[c]	23 (59.0)[c]	<.001
Missing	2	0	0	0	
Chemotherapy					<.001
None	408 (61.0)[a]	98 (54.7)[a,b]	8 (26.7)[c]	14 (35.9)[b,c]	
Not taxane	36 (5.4)	6 (3.4)	1 (3.3)	2 (5.1)	
Taxane	225 (33.6)[a]	75 (41.9)[a,b]	21 (70.0)[c]	23 (59.0)[b,c]	
Missing	1	0	0	0	
RT (any)	560 (83.6)	152 (84.9)	23 (76.7)	26 (66.7)	.057
If RT, RNI[d]	128 (23.6) [a]	51 (34.2)	11 (50.0) [b]	11 (47.8) [b]	<.001
Missing	17	3	1	3	

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; IQR, interquartile range; RNI, regional node irradiation; RT, radiotherapy.
[a,b,c]Statistically significant differences between the outcome groups (Bonferroni-corrected, $p < .008$).
[d]Of cases for whom RNI could be determined. No lymphedema: $N = 543$, subclinical lymphedema only: $N = 149$, chronic lymphedema post intervention: $N = 22$; chronic lymphedema without intervention: $N = 23$.

drill-down within the two groups of patients who met the criteria for subclinical lymphedema revealed no statistically significant differences between them either in the total number of flights or in number of flights without compression before intervention nor after intervention ($p > .10$, Table 2).

DISCUSSION

To the best of our knowledge, this study represents the most comprehensive, prospective examination of BCRL risk factors to date. Findings should be considered in light of both the strengths and weaknesses of the study. Strengths include overall sample size, length of follow-up, international setting, and 22% rural representation. Limitations include insufficient sample size with small number progressing to complex decongestive physiotherapy (CDP) to conduct multivariate analyses. More frequent assessments may have led to more interventions for the 39 patients who progressed between visits; however, it is unknown if those patients met the criteria for intervention and bringing patients into clinical settings for more frequent lymphedema monitoring assessments is problematic because of patient and clinic burden and cost. Overall, the BIS group in the parent study had statistically significant less progression to CDP compared with TM,[7] and preliminary research has established that lymphedema home-based self-monitoring is feasible using BIS technology.[45,46] Future research should explore the use of various forms of home monitoring as a component of a PSEI model of care for individuals at higher risk.

Study findings relating to treatment modalities, comorbid conditions, and lifestyle practices as risk factors have significant implications for the PSEI model and clinical care. Regarding treatment, patients undergoing ALND, RNI, and taxane-based chemotherapy remain at higher risk for chronic lymphedema than others do, even after receiving a

TABLE 2. Air travel by outcome group ($N = 918$)

	No lymphedema ($N = 670$)	Subclinical lymphedema ($N = 179$)	Chronic lymphedema after intervention ($N = 30$)	Chronic lymphedema without intervention ($N = 39$)	p
			Median [IQR]		
Months on study	33.1 [25, 35] [a]	33.0 [23, 35][a]	16.0 [8, 25] [b]	8.2 [1, 27] [b]	<.001
			No. (%)		p^*
Any air travel	456 (68.2)	117 (65.4)	11 (36.7)	18 (47.4)	.365
Missing	1	0	0	1	
If travel:		Median [IQR] (Min, Max)			
No. of flights	6.0 [3, 11][a] (1, 78)	7.0 [4, 14][b] (1, 107)	2.0 [1, 4][a] (1, 6)	3.5 [2, 9][a] (2, 21)	<.001
Missing	0	1	0	0	
No. of flights without compression	5.0 [2, 10][a] (0, 78)	4.0 [1, 8][a] (0, 46)	1.0 [0, 2][b] (0, 4)	3.5 [2, 9][a] (0, 21)	<.001
Missing	1	1	0	0	
Before intervention					
		Median [IQR]			
Months to trigger		7.6 [1, 17]	3.7 [1, 8]		.007
		No. (%)			
Any air travel		70 (39.1)	4 (13.3)		.090
If travel:		Median [IQR] (Min, Max)			
No. of flights		4.0 [2, 8] (1, 89)	2.5 [1, 6] (1, 6)		.227
No. of flights without compression		4.0 [2, 7] (0, 34)	1.5 [1, 4] (1, 4)		.111
After intervention					
		Median [IQR]			
Months to last assessment		18.2 [5, 30]	9.6 [4, 17]		.026
		No. (%)			
Any air travel		91 (50.8)	7 (23.3)		.072
If travel:		Median [IQR] (Min, Max)			
No. of flights		6.0 [2, 11] (1, 73)	2.0 [1, 4] (1, 4)		.104
No. of flights without compression		2.0 [0, 4] (0, 40)	0.0 [0, 2] (0, 2)		.171

Abbreviation: IQR, interquartile range.
[a,b,c]Statistically significant differences between the outcome group (Bonferroni-corrected, $p < .008$).
*p value after controlling for months on study.

preventive compression intervention at onset of subclinical lymphedema. The ALND and RNI findings are consistent with previous research that found less treatment to the axilla (sentinel node biopsy alone) was associated with less incidence of subclinical BCRL than more extensive treatment (ALND or radiation that included level 3 of the axilla or supraclavicular fossa).[47] The taxane finding is not surprising because taxane-based chemotherapy was the predominant chemotherapy administered in this study, yet these results contrast with findings from another large prospective study in this population in which taxane-based chemotherapy was not found to be a risk factor.[48] The findings do, however, support other findings regarding taxanes as a risk factor.[13]

Comorbidities such as age, BMI, hypertension, smoking, or diabetes as risk factors in the presence of identified and immediately treated subclinical BCRL were minimal. Only BMI emerged as a risk factor, and the highest BMI values were in the group that progressed to chronic lymphedema without receiving the compression intervention.

Lifestyle factor findings are also informative. Rurality was found to be a risk factor. As with BMI, the highest number of rural dwellers were in the group that progressed to chronic lymphedema without receiving the compression intervention. These findings suggest that obesity and rurality should be considered high risk factors for chronic lymphedema development within the first year postoperatively. To afford these individuals an option for a preventive intervention likely requires more frequent monitoring than every 3 months, as was done in this study. These findings suggest that the PSEI with subclinical BCRL intervention may serve as a vital safety net for BCS residing in underresourced rural areas. Smoking was not found to be a protective lifestyle factor, and this finding in our large sample stands in contrast with a previous study that suggested smoking might be protective against chronic BCRL.[32] Our findings also provided new evidence to support clinicians when addressing air travel/flying as a risk factor. In this study of women participating in PSEI, air travel was not a

lymphedema risk factor (statistical significance in favor of flying). It is unknown however if patients who received the intervention subsequently limited flying out of concern for increased risk of developing chronic BCRL. Behavioral research regarding self-restrictive behaviors after intervention in the PSEI process would be illuminating. However, the need to restrict air travel in this distinct patient population was not reinforced in this study and, as such, does lend support to the National Comprehensive Cancer Network's Lymphedema Guidelines that suggest flying is not likely a risk factor.[49] Caution is warranted, however, when considering whether to advise patients without lymphedema to wear prophylactic compression garments when flying because our findings do not demonstrate patient benefit.

In general, patients who have any of the high-risk factors identified in this study may benefit from lymphedema assessment between routine cancer follow-up appointments, perhaps in the form of home self-monitoring. This is especially true for obese and rural dwelling patients. Risk reduction education should be targeted according to the current evidence and level of risk and encourage active patient participation in PSEI for the duration of the monitoring period. Finally, patients in this study were seen in high-volume cancer clinics by trained research staff who performed the measures and initiated an intervention.[6-9] This demonstrates that the PSEI model is not dependent on trained lymphedema therapists for successful outcomes and that referrals to certified lymphedema therapists when patients progress after subclinical intervention may be best practice. The breast cancer multidisciplinary treatment team is well positioned to be trained to independently conduct prospective surveillance and implement compression interventions for subclinical BCRL and thus improve patient outcomes.

In conclusion, within 3 years of PSEI with compression intervention for subclinical BCRL, treatment-related variables of ALND, taxane-based chemotherapy, and RNI increased lymphedema risk. A BMI >30 or residing in rural areas may place individuals at risk for very early development of chronic lymphedema. The study findings support the value of the PSEI model of care for successful management of subclinical BCRL not only to lymphedema prevention, but also in risk reduction education and as galvanizing for quality of life and empowerment in BCS.

AUTHOR CONTRIBUTIONS

Louise A. Koelmeyer: Methodology, resources, writing–review and editing, conceptualization and original draft, investigation, and project administration. **Katrina Gaitatzis:** Conceptualization and original draft, methodology, resources, writing–review and editing, investigation, and project administration. **Mary S. Dietrich:** Conceptualization and original draft, validation, methodology, resources, verification of underlying data, data curation, formal analysis, and writing–review and editing. **Chirag S. Shah:** Methodology, resources, writing–review and editing, and validation. **John Boyages:** Methodology, resources, writing–review and editing, investigation, and project administration. **Sarah A. McLaughlin:** Methodology, resources, writing–review and editing, investigation, and project administration. **Bret Taback:** Methodology, resources, writing–review and editing, investigation, and project administration. **Deonni P. Stolldorf:** Methodology, resources, writing–review and editing, investigation, and project administration. **Elisabeth Elder:** Methodology, resources, and writing–review and editing. **T. Michael Hughes:** Methodology, resources, and writing–review and editing. **James R. French:** Methodology, resources, and writing–review and editing. **Nicholas Ngui:** Methodology, resources, and writing–review and editing. **Jeremy M. Hsu:** Methodology, resources, and writing–review and editing. **Andrew Moore:** Methodology, resources, writing–review and editing, investigation, and project administration. **Sheila H. Ridner:** Conceptualization and writing original draft, methodology, resources, writing–review and editing, verification of underlying data, data curation, formal analysis, validation, investigation, and project administration.

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CONFLICTS OF INTEREST

Louise A. Koelmeyer reports serving as an education consultant for ImpediMed. Chirag S. Shah reports serving as a consultant for ImpediMed, PreludeDX, and Evicore and receiving grants from Varian Medical Systems and PreludeDX. John Boyages is a stockholder in ImpediMed.

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