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ORIGINAL REPORT

Incidence, Treatment Costs, and Complications of Lymphedema After Breast Cancer Among Women of Working Age: A 2-Year Follow-Up Study

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ABSTRACT

Purpose
This study estimated the economic burden of breast cancer–related lymphedema (BCRL) among working-age women, the incidence of lymphedema, and associated risk factors.

Methods
We used claims data to study an incident cohort of breast cancer patients for the 2 years after the initiation of cancer treatment. A logistic regression model was used to ascertain factors associated with lymphedema. We compared the medical costs and rate of infections likely associated with lymphedema between a woman with BCRL and a matched control. We performed nonparametric bootstrapping to compare the unadjusted cost differences and estimated the adjusted cost differences in regression analysis.

Results
Approximately 10% of the 1,877 patients had claims indicating treatment of lymphedema. Predictors included treatment with full axillary node dissection (odds ratio [OR] = 6.3, $P < .001$) and chemotherapy (OR = 1.6, $P = .01$). A geographic variation was observed; women who resided in the West were more likely to have lymphedema claims than those in the Northeast (OR = 2.05, $P = .01$). The matched cohort analysis demonstrated that the BCRL group had significantly higher medical costs ($14,877 to $23,167) and was twice as likely to have lymphangitis or cellulitis (OR = 2.02, $P = .009$). Outpatient care, especially mental health services, diagnostic imaging, and visits with moderate or high complexity, accounted for the majority of the difference.

Conclusion
Although the use of claims data may underestimate the true incidence of lymphedema, women with BCRL had a greater risk of infections and incurred higher medical costs. The substantial costs documented here suggest that further efforts should be made to elucidate reduction and prevention strategies for BCRL.

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INTRODUCTION

Upper extremity lymphedema is one of the most dreaded sequelae of breast cancer (BC) treatment.[1,2] The psychosocial impact of lymphedema has been described to be as distressing as the initial diagnosis of BC; patients with breast cancer–related lymphedema (BCRL) have been found to have a lower quality of life, a higher level of anxiety or depression, a higher likelihood of chronic pain and fatigue, and greater difficulty functioning socially and sexually compared with BC women without lymphedema.[3-10] Reported incidence rates of BCRL vary from 4% to 56%[2,4,11-20]; the true incidence is difficult to assess because of varying criteria used to define lymphedema and the duration of follow-up across studies.[21-23] Prior clinical series have found that risk factors include treatment with axillary node dissection, breast radiation, axillary radiation, or chemotherapy; an increased number of tumor-involved lymph nodes; and a high body mass index.[13,15,16,24-36]

The clinical management of lymphedema encompasses a wide variety of strategies, including manual lymphatic drainage, compression garments, pneumatic pumps, multilayer bandaging, and surgery.[2,37,38] To date, however, symptom control remains the mainstay of lymphedema treatments.[2,39] Complications secondary to lymphedema include repeated infections, discomfort, and functional impairment.[40] Although, the etiology of recurrent lymphedema-related infections is not entirely clear,

these episodes necessitate early antibiotic treatment and might require hospitalization for intravenous antibiotic therapy.

Current literature on the economic burden of BCRL is extremely limited. BCRL patients are likely to incur high medical costs as a result of frequent visits to physicians and/or physical therapists to seek symptom control. Additionally, poorly managed lymphedema may lead to complications needing medical attention, which increases the costs of care. This study estimated the costs of BCRL by comparing medical costs between BC patients with lymphedema and those without. We also examined the incidence of and risk factors associated with diagnosed BCRL among working-age women who received treatment for BC.

METHODS

Data

We used the 1997 to 2003 Medstat MarketScan Health and Productivity Management (HPM) database. The HPM contains productivity information for more than 550,000 employees and gathers medical and pharmacy claims data for the employees and their spouses and dependents from primarily self-insured plans.[41] The data have been processed to meet the Health Insurance Portability and Accountability Act requirements. We chose claims data because they allowed us to estimate costs and complications of lymphedema, which is the primary focus of our study. However, it should be noted that claims data are not ideal for reporting incidence and prevalence because lymphedema identified from claims would be limited to those with such a diagnosis who sought treatments covered by insurance (referred to as the DX_BCRL group hereafter). Therefore, lymphedema incidence reported herein is likely to be underestimated.

Study Population and Variables

The study population consisted of an incident cohort of BC patients identified using a validated algorithm.[42] We defined the index date as the earliest date a definitive treatment appeared in the patient's medical claims and observed each patient for 2 years. We selected a 2-year timeframe because of sample size considerations and also because earlier studies suggested that the majority of the first identifications of lymphedema occurred during the first 18 months after BC surgery.[43] When estimating costs and complication rates, we excluded patients with less than 27 months of continuous enrollment to ensure the completeness of claims in the 2-year follow-up duration and to include a 3-month washout period before the index date. Males and those with missing enrollee identifiers were also excluded. We

Table 1. Descriptive Statistics of the Incident Cohort of Women With Breast Cancer

Factor	All Women (N = 1,877)		Women With DX_BCRL (n = 180)		Women Without DX_BCRL (n = 1,697)		*P*
	No.	%	No.	%	No.	%	
Age, years							.95
Mean	48.8		48.9		48.8		
SD	8.0		7.1		8.0		
Comorbidity index							.76
Mean	0.11		0.10		0.11		
SD	0.36		0.34		0.36		
Relationship with employer							.062
Employee	805	42.9	89	40.4	716	42.2	
Spouse	1,072	57.1	91	50.6	981	57.8	
Geographic region in the United States							.023
Northeast	490	26.1	35	19.4	255	26.8	
North Central	568	30.3	62	34.4	506	29.8	
South	646	34.4	58	32.2	588	34.7	
West	173	9.2	25	13.9	148	8.7	
Treatment modality within the first 6 months of breast cancer diagnosis							.002
Mastectomy	838	44.7	100	55.6	738	43.5	
Lumpectomy only	1,039	55.3	80	44.4	959	56.5	
Lymph node dissection							< .001
Yes, SLND	110	5.9	4	2.2	106	6.3	
Yes, ALND	1,292	68.8	168	93.3	1,124	66.2	
No	475	25.3	8	4.5	467	28.5	
Radiation therapy							.724
Yes	732	39.0	68	37.8	664	39.1	
No	1,145	61.0	112	62.2	1,033	60.9	
Chemotherapy							< .001
Yes	900	48.0	124	68.9	776	45.7	
No	977	52.0	56	31.1	921	54.3	
Received definitive treatment in year 2							< .001
Yes	257	13.7	40	22.2	217	12.8	
No	1,620	86.3	140	77.8	1,480	87.2	

Abbreviations: DX_BCRL, diagnosed breast cancer–related lymphedema; SD, standard deviation; SLND, sentinel lymph node dissection; ALND, axillary lymph node dissection.

identified BCRL patients from the cohort using the International Classification of Diseases, ninth revision (ICD-9) codes indicative of lymphedema (457.0 and 457.1) after the index date. The ICD-9 codes were obtained from a coding guide to Medicare providers and coders at our institution.[44]

We characterized initial BC treatment (within the first 6 months of diagnosis) using several dichotomous variables to indicate mastectomy, lumpectomy, chemotherapy, radiation, or node dissection. The Current Procedural Terminology and ICD-9 procedure codes used to identify these treatment modalities were primarily obtained from Nattinger et al[42] and augmented with additional codes to capture sentinel lymph node dissection (38792 and 38500 to 38542). Complications were identified from the ICD-9 codes and classified as infections most likely associated with lymphedema versus other complications that may be related to lymphedema. Infections included lymphangitis (457.2x) and cellulitis (681.xx and 682.xx). Other complications included septicemia (038.xx), bacteremia (790.7x), phlebitis and thrombophlebitis (451.xx), venous embolism and thrombosis of the vena cava (453.2x), pulmonary embolism and infarction (415.1x), and other bacterial infections (041.xx). A dichotomous variable was used to represent the resumption of definitive BC treatment in year 2 after completing the initial treatment; this variable was included in analyses involving costs because patients who resumed treatment in year 2 incurred higher 2-year costs than patients who did not. Additionally, we constructed a comorbidity score for each patient using Klabunde's adaptation of the Charlson comorbidity index.[45]

Statistical Analyses

We analyzed the incident cohort of BC patients to compare the difference between women with DX_BCRL and those without and determined the statistical significance using χ^2 and two-sided t tests for categorical and continuous variables, respectively. We used multivariate logistic regression to ascertain factors associated with DX_BCRL; covariates included age, geographic region, relationship with the employer (employee *v* spouse), and clinical factors, such as treatment modalities and comorbidities.

We constructed a matched control group to compare the rate of complications and medical costs between BC patients with and without DX_BCRL. The control group was matched with the DX_BCRL group by the initial treatment modalities and treatment resumption status, using the frequency-matching method.[46,47] We used multivariate logistic regression to compare the rates of complications. Because medical costs were highly skewed, we used nonparametric bootstrapping to compare the unadjusted cost differences.[48] To obtain the adjusted cost differences, we used the logarithm transformation of costs as the dependent variable and then retransformed the estimated difference in log-transformed cost to the original scale.[49,50] All costs were updated to 2006 US dollars using the medical care component of the Consumer Price Index. All P values reported are two sided; statistical significance is defined as $P < .05$.

RESULTS

Descriptive statistics (Table 1) show that approximately 10% of the incident cohort of patients (180 of 1,877 patients) had claims data for a diagnosis of lymphedema (DX_BCRL) within 2 years of BC treatment initiation. A significantly higher proportion of the DX_BCRL group, compared with the non-DX_BCRL group who did not have a claim for a diagnosis of lymphedema, had undergone a mastectomy (55.6% *v* 43.5%, respectively; $P = .002$), full axillary lymph node dissection (93.3% *v* 66.2%, respectively; $P < .001$), or chemotherapy (68.9% *v* 45.7%, respectively; $P < .001$) or had resumed definitive treatment in year 2 (22.2% *v* 12.8%, respectively; $P < .001$), whereas a significantly lower proportion of the DX_BCRL group had sentinel node dissection (2.2% *v* 6.3%, respectively; $P < .001$). We also noted that a larger proportion of women with DX_BCRL, compared with non-DX_BCRL women, resided in the West of the United States (13.9% *v* 8.7%, respectively).

Table 2 lists the risk factors associated with DX_BCRL. Significant predictors were full axillary node dissection, chemotherapy, and residing in the West. Women with full axillary node dissection were 6.3 times (95% CI, 2.9 to 13.4 times) more likely to have a claim for treatment for lymphedema than women without node dissection. No statistically significant difference was found between women with sentinel node dissection and those without dissection. As an exploratory analysis, we extended the follow-up duration to 3 and 4 years to examine whether risk factors differed in longer term follow-ups. It should be noted that because of the requirement of continuous enrollment in health insurance plans to ensure complete information on covered services in claims data, the sample size reduced substantially as the duration of follow-up lengthened. Incidence of DX_BCRL increased from 9.6% in the 2-year follow-up to 12% in the 4-year

Table 2. Logistic Regression for Factors Associated With Incidence of Diagnosed Lymphedema After Breast Cancer Treatment

Factor	2-Year Follow-Up (N = 1,877)		3-Year Follow-Up (n = 1,260)		4-Year Follow-Up (n = 854)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age	1.00	0.98 to 1.02	1.00	0.97 to 1.02	1.00	0.97 to 1.02
Comorbidity	0.82	0.47 to 1.43	1.10	0.60 to 2.05	1.61	0.80 to 3.26
Employee *v* spouse	1.22	0.89 to 1.68	1.09	0.76 to 1.56	0.91	0.58 to 1.41
Geographic region in the United States (reference group: Northeast)						
North Central	1.40	0.90 to 2.18	1.55	0.96 to 2.51	2.20	1.18 to 4.10
South	1.01	0.64 to 1.58	0.93	0.56 to 1.54	1.17	0.60 to 2.28
West	2.05	1.16 to 3.61	1.62	0.83 to 3.20	2.79	1.23 to 6.31
Treatment modality within the first 6 months of breast cancer diagnosis						
Mastectomy *v* lumpectomy only	1.22	0.80 to 1.86	1.35	0.85 to 2.14	1.20	0.66 to 2.19
Radiation therapy	1.10	0.72 to 1.68	1.25	0.78 to 1.99	1.50	0.83 to 2.72
Sentinel node dissection *v* none	1.80	0.52 to 6.17	2.55	0.74 to 8.81	4.72	0.81 to 27.46
Full axillary node dissection *v* none	6.26	2.92 to 13.4	4.44	2.11 to 9.36	6.49	2.44 to 17.28
Chemotherapy	1.59	1.12 to 2.27	1.87	1.26 to 2.77	1.83	1.14 to 2.95

Abbreviation: OR, odds ratio.

Table 3. Logistic Regression for Factors Associated With Incidence of Complications in the Matched Sample (N = 680)

Factor	Cellulitis or Lymphangitis		Other Complications*	
	OR	95% CI	OR	95% CI
DX_BCRL	2.02	1.19 to 3.42	2.05	1.19 to 3.55
Age	1.00	0.98 to 1.05	0.99	0.96 to 1.03
Comorbidity	2.29	1.14 to 4.62	1.28	0.54 to 3.03
Employee	1.14	0.68 to 1.89	0.90	0.53 to 1.54
Geographic region in the United States (reference group: Northeast)				
North Central	1.34	0.65 to 2.77	0.74	0.35 to 1.54
South	1.18	0.58 to 2.41	1.04	0.54 to 2.03
West	1.28	0.50 to 3.25	0.60	0.21 to 1.77
Treatment modality within the first 6 months of breast cancer diagnosis				
Mastectomy	1.26	0.65 to 2.44	1.25	0.64 to 2.45
Radiation therapy	1.12	0.58 to 2.17	1.03	0.51 to 2.06
Node dissection	1.46	0.33 to 6.43	2.97	0.39 to 22.60
Chemotherapy	1.30	0.73 to 2.31	1.49	0.80 to 0.77

Abbreviations: OR, odds ratio; DX_BCRL, diagnosed breast-cancer–related lymphedema.
*Other complications include septicemia, bacteremia, phlebitis, thrombophlebitis, venous embolism and thrombosis of the vena cava, pulmonary embolism and infarction, and other bacterial infections.

follow-up. Full axillary node dissection and chemotherapy remained significant in the longer term follow-ups.

The frequency matching generated a one-to-three matched case-control cohort. Lymphangitis or cellulitis and other complications were found in 15.9% and 14.1% of patients, respectively, in the DX_BCRL group compared with 8.4% and 7.8% of patients, respectively, in the matched control group. Table 3 shows that women in the DX_BCRL group were significantly more likely to have complications possibly related to lymphedema. The odds ratio (OR) of lymphangitis or cellulitis was 2.02 (95% CI, 1.19 to 3.42) when comparing the DX_BCRL group with the non-DX_BCRL group, and the OR for other complications was 2.04 (95% CI, 1.19 to 3.55).

When examining medical costs, we first compared the unadjusted cost between the DX_BCRL and non-DX_BCRL groups by cost categories to ascertain the type(s) of services that contributed most to the observed difference, followed by regression analyses to obtain the adjusted cost difference. Table 4 shows that total medical costs within the 2-year follow-up were significantly higher in the DX_BCRL group ($22,153; $P < .001$). Two categories that accounted for more than 80% of the observed difference were cancer treatments ($8,560; $P = .0075$) and outpatient visits unrelated to cancer treatment, probable complications of lymphedema, or physical therapy ($9,463; $P < .001$). Significantly higher costs were also found for outpatient prescription drugs ($2,403; $P = .0063$) and physical therapies and supplies (eg, compression garments; $769; $P = .0035$). Regression analyses show that the adjusted cost difference was $23,167 (Fig 1). If we excluded cancer-related costs, the adjusted cost difference was $14,877, which can be viewed as the lower bound estimate.

We explored patterns of health care resource utilization that could possibly explain the higher BCRL costs reported earlier. Table 5 shows that the DX_BCRL group, compared with the non-DX_BCRL group, had more non–cancer-related office visits (73.1 *v* 56.1 visits in 2 years, respectively; $P < .001$) and outpatient drug prescriptions (48.7 *v* 36.0 prescriptions, respectively; $P < .001$). It also indicated that the higher outpatient costs could be attributed to (1) a larger proportion of patients with mental health–related services[51] (74.1% in DX_BCRL group *v* 65.9% in non-DX_BCRL group; $P = .046$) or who used

Table 4. Comparison of 2-Year Medical Costs for Women With and Without DX_BCRL by Cost Category

Cost Category	Cost ($)			*P**
	DX_BCRL	Non-DX_BCRL	Difference	
Total	86,707	64,554	22,153	.0002
Cancer related	47,908	39,348	8,560	.0075
Not cancer related	45,896	31,297	14,600	.0001
Infections	2,151	1,237	915	.3705
Physical therapy plus supplies	1,083	315	769	.0035
All others				
Inpatient	4,313	4,269	44	.9708
Outpatient	25,451	15,988	9,463	.0005
Outpatient prescription drugs	5,801	3,398	2,403	.0063

Abbreviation: DX_BCRL, diagnosed breast cancer–related lymphedema.
**P* value from 10,000 iterations using the nonparametric bootstrap method.

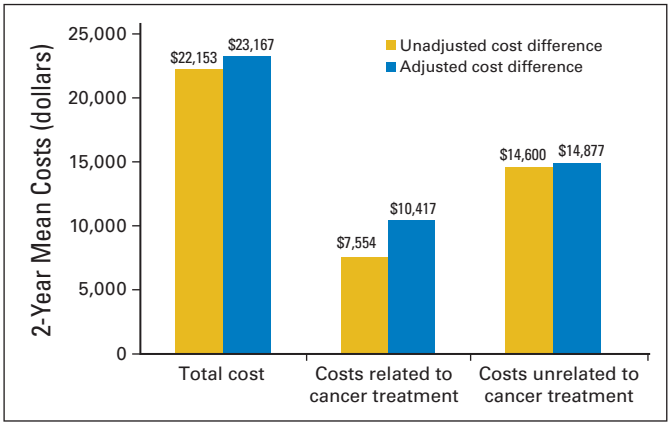

Fig 1. Differences in 2-year medical costs for women with breast cancer. Unadjusted and adjusted costs for women with versus women without diagnosed lymphedema are shown.

diagnostic imaging (98.8% in DX_BCRL group *v* 94.1% in non-DX_BCRL group; $P = .012$), and (2) a higher utilization of level IV and V office visits (visits involving patients with moderate or high complexity; 8.65 visits in DX_BCRL group *v* 7.21 visits in non-DX_BCRL group; $P = .014$) or imaging tests (6.13 tests in DX_BCRL group *v* 4.72 tests in non-DX_BCRL group; $P < .001$). The higher utilization of diagnostic imaging in the DX_BCRL group was driven primarily by three body sites—upper arms, chest, and abdomen. Using unique days of services, we estimated the number of days a patient's usual daily activities were interrupted by either hospitalization or office visits and found a significant difference between the two groups (58.7 days in DX_BCRL group *v* 46.5 days in non-DX_BCRL group, $P < .001$).

DISCUSSION

In this study of 1,877 BC patients identified from claims data, approximately 10% had one or more medical claims indicating lymphedema. Those treated with full axillary node dissection and chemotherapy were more likely to have a claim with a diagnosis of lymphedema but not those with sentinel node dissection. A matched-cohort analysis demonstrated that the DX_BCRL group was twice as likely to have encounters classified as infections as the non-DX_BCRL (eg, lymphangitis or cellulitis). This study was the first to report the substantial economic burden of BCRL; the estimated difference in the 2-year costs between women in the DX_BCRL and non-DX_BCRL groups ranged from $14,877 to $23,167, with outpatient visits accounting for the majority of the difference. Knowledge of the costs of BCRL not only provides a better understanding of the disease burden of this condition, but also establishes a baseline of comparison for future cost-effectiveness studies.

Claims data are increasingly recognized as valuable resources in oncology research. The benefits of claims data are that they represent the real world, allow a longer duration of follow-up, and provide a relatively inexpensive way to gather information on medical costs and treatment patterns.[52] However, because claims data are collected for billing purposes, they are not designed to estimate incidence or prevalence. Typically, the rate reported from claims will be underestimated. Indeed, the 2-year cumulative rate of lymphedema was approximately 10% in our study, whereas a recently published study reported a 50% 2-year cumulative incidence of arm and/or hand swelling and a 32% rate of persistent swelling up to 3 years after BC surgery.[16] We used ICD-9 codes to identify BCRL; this diagnosis would only appear in claims data after the utilization of medical services related to lymphedema and coded as such. It is possible that other patients expressed concerns

Table 5. Comparison of 2-Year Health Care Resource Utilization for Non–Cancer-Related Outpatient Care for Women With and Without DX_BCRL

Cost Category	DX_BCRL	Non-DX_BCRL	Difference	*P*
Total No. of office visits	73.1	56.1	17.0	< .001
Total No. of prescriptions	48.7	36.0	12.7	< .001
Patients with utilization, %				
Hospitalization	27.3	27.1	0.2	.997
Level IV and V visits*	97.1	95.5	1.6	.370
MH-related services†	74.1	65.9	8.2	.05
Diagnostic imaging‡	98.8	94.1	4.7	.012
Upper arms	20.6	13.2	7.4	.019
Chest	84.7	76.4	8.3	.023
Abdomen	49.4	32.4	17.0	< .001
Average counts per patient				
Level IV and V visits	8.7	7.2	1.4	.014
Diagnostic imaging	6.1	4.7	1.4	< .001
Average No. of days patients' usual activities were interrupted as a result of hospitalizations or physician office visits				
Total	58.7	46.5	12.2	< .001
Days in hospitals	2.6	2.4	0.2	.793
Days in office visits	56.1	44.1	12.0	< .001

Abbreviations: DX_BCRL, diagnosed breast cancer–related lymphedema; MH, mental health.
*Level IV and V visits are outpatient visits that involve medical decision making for patients with moderate or high complexity.
†Codes to identify mental health-related services were obtained from Larson et al.[50]
‡Diagnostic imaging included radiologic examinations, computed tomography, and magnetic resonance imaging.

about upper arm swelling at their physicians' offices but received no treatment. It is also possible that patients were treated for lymphedema but were not assigned such diagnosis. Furthermore, patients may not have realized that swelling was unnatural or a problem and thus did not seek treatment. For these reasons, lymphedema identified here is likely to underestimate the true incidence of lymphedema in BC patients and will probably represent more severe cases.

The risk factors of lymphedema reported in our study are similar to those reported by Paskett et al,[16] except for the type of node dissection and geographic region. We compared our study with that of Paskett et al[16] because of similarities in the study cohort (mean age, 38.5 years) and time period (1998 to 2005). Both studies reported chemotherapy as a significant risk factor but found neither radiation nor mastectomy to be significant. These conclusions seem to contradict findings from several previous reports.[27,32,33] Paskett et al[16] postulated that these findings were likely driven by the common use of more aggressive treatments for younger women with BC; the same reasoning should be applicable to our study. Although Paskett et al[16] did not examine the effect of the type of node dissection because only a small number of patients in their sample had sentinel lymph node dissection (4%, n = 26), information on the number of nodes surgically removed was available in that study but not in ours. Therefore, the highly significant OR associated with full axillary node dissection (compared with no dissection) in our study may have been insignificant if such information were available. The regional difference in the odds of lymphedema may be explained by geographic variations in treatment patterns, recognition of symptoms, or insurance coverage.[53] Although the Women's Health and Cancer Rights Act mandates coverage of treatment for lymphedema incident to BC,[54] suggesting that our study sample (patients with self-insured plans) should be governed by the act, insurance coverage of lymphedema may still vary as a result of differential level of compliance to this federal regulation or different health plan benefits, with economic barriers to care more likely to be observed among patients in plans with higher cost sharing.

To date, only one study discussed the economic impact of lymphedema. Moffatt et al[55] conducted a survey of lymphedema patients in the United Kingdom and concluded that lymphedema, both related to cancer and not, resulted in at least one acute infection in 29% of the patients and one or more hospital admissions in 15%. However, they did not estimate costs of lymphedema. We found significantly higher costs among women in the DX_BCRL group; the estimated difference in the 2-year medical costs ranged from $14,877 to $23,167, depending on whether noncancer costs or total costs were considered. A more conservative estimation would exclude the costs of cancer treatment, although one can argue that an estimate based on total costs is also meaningful because the early onset of lymphedema after surgery could lead to more intensive resource utilization during the remaining period of cancer treatment.

The major cost drivers for women with DX_BCRL were office visits and prescription drugs, primarily as a result of level IV and V office visits, mental health–related services, and diagnostic imaging of upper arms, chest, and abdomen. The higher use of level IV and V visits probably reflects added complexity resulting from lymphedema, whereas higher utilization of mental health services is likely to be associated with a higher level of psychological morbidity documented in the literature. Diagnostic imaging for the upper arms, chest, and abdomen are likely performed to rule out causes of swelling arms other than lymphedema. Specifically, imaging of upper arms and chest is likely used to exclude deep venous thrombosis, and computed tomography of chest and abdomen is used to rule out tumor recurrence in the axilla. Higher utilization of outpatient services also results in DX_BCRL patients having more number of days with usual activities interrupted by the receipt of care.

Furthermore, because the DX_BCRL and non-DX_BCRL groups were matched by initial treatment modalities, we initially anticipated similar costs of cancer treatment between the two groups but found a significant difference of $8,560. Additional analyses found that more than 50% of the discrepancy was a result of variations in chemotherapy regimens. A higher proportion of the DX_BCRL group, compared with the non-DX_BCRL group, received regimens containing more expensive agents such as taxanes (20% *v* 11%, respectively) and trastuzumab (3% *v* 1%, respectively). These analyses also confirmed our initial speculation of higher costs among patients who resumed treatment in year 2. Indeed, the 2-year medical costs were $109,000 and $61,000 for patients with and without treatment resumption, respectively. However, the higher proportion of patients with treatment resumption observed in the DX_BCRL group (Table 1) should not distort the overall cost profile in our cost comparison because treatment resumption status was one of the factors incorporated in the construction of the matched cohort.

This study likely underestimated the cost of BCRL. The onset of lymphedema varies in time; although we followed our study cohort for 2 years, the costs of BCRL for women who developed the condition late within that period would not reflect the total financial burden of BCRL. Therefore, it is important to recognize that the costs documented in our study represent the differences in medical costs between the DX_BCRL and non-DX_BCRL groups within the first 2 years after the initiation of BC treatment but not during the 2 years after the diagnosis of lymphedema. Estimating the latter costs will require a different study design. Additionally, we identified lymphedema from ICD-9 diagnosis codes in claims data. It is possible that some women in the non-DX_BCRL group suffered from lymphedema but that the diagnosis had not been added to their insurance claims; thus, we would have found a lower mean cost in the non-DX_BCRL group had such patients been recategorized to the DX_BCRL group. It is also possible that those women have mild disease and thus do not consume more health care resources. In that case, costs would be overestimated. Unfortunately, recategorization cannot be achieved with the information available in the claims data. Another limitation of our study pertains to the generalizability of the study findings. This study was limited to working-age women; therefore, our findings may not be generalizable to elderly women with BCRL, whose costs need to be assessed using Medicare claims data in future research.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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