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ORIGINAL ARTICLE – BREAST ONCOLOGY

Impact of Breast Cancer-Related Lymphedema on Cancer Care Costs: Longitudinal and Age-Based Analyses

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ABSTRACT

Purpose. How breast cancer-related lymphedema (BCRL) costs evolve over time, especially for younger patients, is poorly understood. We sought to characterize BCRL-associated costs by age and treatment phase.

Methods. Using Massachusetts All-Payer Claims data, we compiled costs for patients aged ≤61 years who received surgery for stage I–III breast cancer between January 1, 2016, and December 31, 2016, then, postoperatively through December 31, 2020. Treatment costs were compared annually by BCRL status (two or more vs. no BCRL diagnosis codes within 2 years of surgery). BCRL and non-BCRL cohorts were propensity-matched, accounting for surgery types, chemotherapy, and radiation. Sensitivity analyses determined cost differences by age at diagnosis (18–44 vs. 45–61 years).

Results. Of 2141 patients, 244 (11.4%) had BCRL. BCRL incidence was similar across ages: 46 of 434 (10.6%) aged 18–44 years versus 198 of 1707 (11.6%) aged 45–61 years; $p = 0.612$. Before matching, patients with BCRL had higher copayment ($US1200 vs. $US610 non-BCRL; $p < 0.001$) and payer costs ($US140,000 vs. $US76,000 non-BCRL; $p < 0.001$). After matching, copayment differences persisted ($US1200 BCRL vs. $US850 non-BCRL; $p < 0.001$). Among those aged 18–44 years, BCRL conferred lower out-of-pocket costs ($US2900 vs. $US23,000 non-BCRL; $p = 0.031$) but no difference in copayment/payer costs in years 1–2 or costs thereafter. Among those aged 45–61 years, only copayment costs were significant in year 3 ($p = 0.014$). Heat map analysis revealed that costs concentrated around chemotherapy for all ages; among younger women, BCRL represented the highest source of out-of-pocket spending after chemotherapy and reconstruction.

Conclusion. Patients with BCRL incurred higher payer and copayment costs than those without. As differences may not emerge until survivorship, strategies to reduce financial toxicity should continue after cancer treatment.

Keywords Breast cancer · Lymphedema · Healthcare costs · Young adults · Financial toxicity

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Breast cancer treatment represents a significant financial burden to the US economy, with $US30 billion spent in

annual cancer-attributable costs.[1,2] Out-of-pocket expenses alone totaled $US3.14 billion in 2019, conferring substantial expense for patients.[3] These costs can contribute to financial toxicity (FT), resulting in psychological distress and economizing behaviors that may lead to worse quality of life and clinical outcomes.[4,5]

Although multiple factors contribute to FT, treatment-related adverse events are an under-investigated and potentially modifiable source of expense.[6] Among these, breast cancer-related lymphedema (BCRL) is an irreversible chronic condition that occurs in up to 30% of patients with breast cancer.[7,8] Protracted treatment, including compression therapy, physical therapy, and surgery, contributes to direct costs. Indirect costs, such as lost income and reduced earning potential, perpetuate financial strain. These costs may disproportionately impact young adults (YAs) aged 18–44 years at high risk for financial toxicity[9,10] due to advanced disease and aggressive tumor subtypes at diagnosis that require expensive multimodality treatment,[11,12] limited financial reserves, high caregiving demands, and high-deductible insurance plans.[13,14]

Even though existing literature emphasizes BCRL as a source of cancer-related expense, little data are available on how these costs evolve over time and whether YAs who are particularly susceptible to vocational disruption and financial hardship are affected to a greater extent than older women. To inform strategies to mitigate long-term financial toxicity and to define populations in whom these interventions might be most helpful, we conducted a claims-based analysis to clarify how BCRL contributes to costs by age and over time, hypothesizing that these costs are most pronounced among younger patients and after treatment completion.

METHODS

Inclusion and Exclusion Criteria

This retrospective cohort study utilized the Massachusetts All-Payer Claims Database (MA APCD) data from 2016 to 2020 (Fig. 1). The MA APCD captures health-related claims data from all private and public payers serving Massachusetts residents. These data include patients who are dual eligible but does not take into account supplemental payments or self-pay spending outside of coverage plans. Out-of-pocket costs are calculated using deductibles, copayments, and coinsurance cost-sharing elements. Patients with International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS), and International Classification of Diseases, Tenth Revision—Clinical Modification (ICD-10-CM) diagnosis codes for invasive breast cancer who also had a Current Procedural Terminology code for breast-conserving surgery (BCS) or mastectomy between January 1 and December 31, 2016, were identified. The BCRL cohort was defined as patients with two ICD-10-PCS/IDC-10-CM codes related to BCRL within 2 years of index surgery; those with only a single BCRL diagnosis code and those who developed BCRL after the 2-year window from their index surgery were excluded.[15] Diagnosis and procedure codes considered in this study are reported in Supplementary Table 1. To understand whether

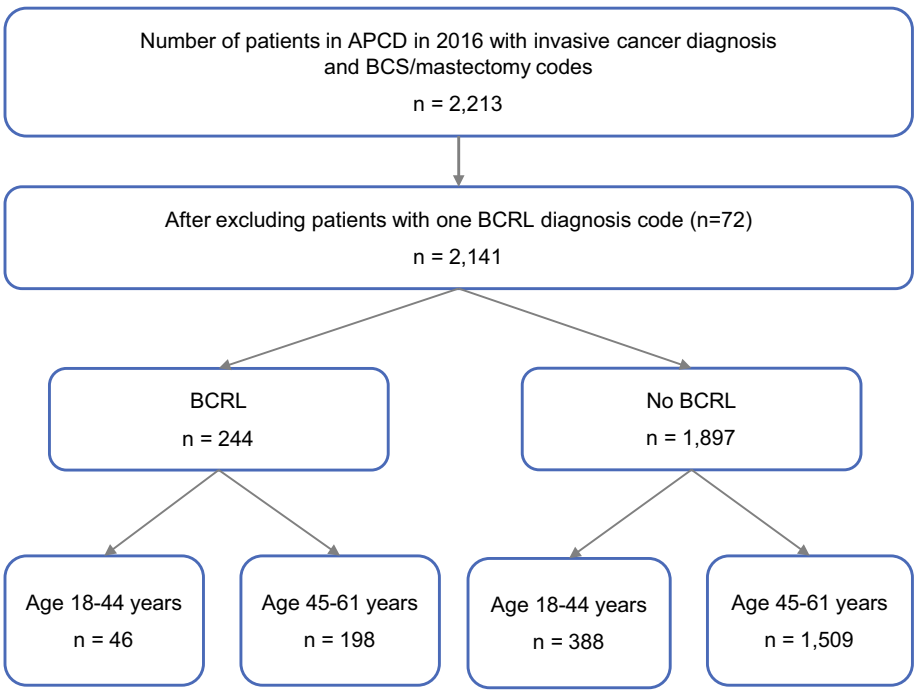

FIG. 1 Study flow diagram. APCD, all-payer claims database; BCRL, breast cancer-related lymphedema; BCS, breast-conserving surgery

costs differed by YA status, participants were divided into two cohorts based on age at time of surgery (2016): YAs aged 18–44 years and non-YAs aged 45–61 years. Although the traditional definition of young adulthood in oncology typically includes cancer diagnoses before the age of 40,[16] this study applied an expanded criterion to reflect two key realities: first, the rising incidence of early-onset breast cancers more broadly[17] and, second, the fact that many leading comprehensive cancer programs have adopted broader age parameters in their clinical programming.[18,19] The upper limit of age was chosen to ensure that the 5-year data period did not encompass age-based eligibility for Medicare enrollment. Study procedures were approved by the Massachusetts General Brigham institutional review board (2021A018772).

Variables and Outcomes of Interest

The primary outcome of interest was treatment-related costs, sub-classified as copayment, out-of-pocket expenses, and payers' costs. Cost data were identified and quantified using Current Procedural Terminology and Healthcare Common Procedure Coding System codes. These costs were reported as a total cumulative amount over the 5-year period, as well as captured separately for the active treatment phase (years 1 and 2) and annually after the transition to survivorship (years 3, 4, and 5). Breast cancer-specific costs included those related to diagnostic testing, such as mammography and ultrasound, treatments including chemotherapy, radiation therapy, endocrine therapy, and surgery, as well as oncology specialty visits. Costs specific to BCRL included expenses for diagnostic procedures such as lymphoscintigraphy, lymphangiography, and bioimpedance; treatment costs such as compression therapy, physical therapy, and surgical procedures; and the management of complications such as cellulitis.

Statistical Analysis

After applying a structured data processing pipeline to format variables and define cohorts as previously described, healthcare costs were compared between BCRL and non-BCRL cohorts overall and by treatment phase (i.e., years 1–2 considered as active treatment and years 3–5 considered as survivorship) using the Wilcoxon rank-sum test for unadjusted comparisons and generalized linear models for adjusted analyses. To adjust for potential confounding due to clinical disease characteristics, propensity score matching was performed based on treatment modalities available through the MA APCD. Age was intentionally excluded from the propensity score matching algorithm as the objective was to examine cost differences associated with BCRL across distinct age cohorts; therefore, age was considered a primary stratification variable rather than a potential confounder. Specifically, variables included in the matching process were breast surgery type (BCS vs. mastectomy), chemotherapy receipt, radiation therapy receipt, and axillary staging procedure (no axillary staging, sentinel lymph node biopsy alone, axillary lymph node dissection). A 1:2 nearest neighbor propensity score matching approach was applied to balance the aforementioned clinically relevant factors between the BCRL and non-BCRL groups, ensuring comparability of the cohorts on the basis of breast cancer treatment costs. Sensitivity analyses were performed by stratifying costs by age group. To visually explore cost distribution, a heat map was generated to display mean costs by treatment modality and BCRL-related spending across age cohorts. This two-dimensional grid used a warm-to-cool color scale, with warmer colors (red) indicating higher costs and cooler colors (blue) indicating lower costs. Statistical analyses were performed using R Statistical Software (v4.1.2; R Core Team, 2021), with p-values <0.05 reaching the threshold for statistical significance.

RESULTS

Of 2141 patients included in the analysis, 244 (11.4%) had BCRL. YAs accounted for 20.0% (434) of the overall cohort. BCRL incidence was similar across ages (46/434 [10.6%] aged 18–44 years vs. 198/1707 [11.6%] aged 45–61 years; $p=0.612$). Most patients underwent BCS, received radiation, and received axillary staging, whereas the minority received chemotherapy (Table 1). YA patients were more likely to undergo mastectomy (218/434 [50.2%] YA vs. 573/1707 [33.6%] non-YA; $p<0.001$), reconstruction (154/434 [35.5%] YA vs. 333/1707 [19.5%] non-YA; $p<0.001$), and receive chemotherapy (243/434 [56.0%] YA

TABLE 1 Overall patient and treatment characteristics, unmatched

Characteristic	Total cohort (N=2141)	BCRL (N=244)	No BCRL (N=1897)	p-Value
Age, years				
18–44	434 (20.27)	46 (18.85)	388 (20.45)	0.616
45–61	1707 (79.73)	198 (81.15)	1509 (79.55)	
BCS	1490 (69.59)	131 (53.69)	1359 (71.64)	<0.001
Mastectomy	791 (36.95)	141 (57.79)	650 (34.26)	<0.001
Chemotherapy	873 (40.78)	163 (66.80)	710 (37.43)	<0.001
Radiation	1363 (63.66)	183 (75.00)	1180 (62.20)	<0.001
Axillary staging	1844 (86.13)	227 (93.03)	1617 (85.24)	0.001
Breast reconstruction surgery	487 (22.75)	75 (30.74)	412 (21.72)	0.002

Data are presented as n (%) unless otherwise indicated.

BCRL, breast cancer-related lymphedema; BCS, breast-conserving surgery

vs. 630/1707 [36.9% non-YA]; $p < 0.001$) (Supplementary Table 2).

The final matched cohort included 727 patients, including 164 patients aged 18–44 years and 563 aged 45–61 years. After matching, treatment characteristics were balanced between patients with and without BCRL (Supplementary Table 2). As age was not included in the matching algorithm, in the matched cohorts, rates of mastectomy and chemotherapy were higher among YAs (mastectomy 122/164 [74.4%] YAs vs. 295/563 [52.4%] non-YAs, $p < 0.001$; chemotherapy 131/164 [79.9%] YAs vs. 353/563 [62.7%] non-YAs, $p < 0.001$). Breast reconstruction remained more common among younger patients (77/164 [47.0%] YA vs. 158/563 [28.1%] non-YA, $p < 0.001$).

Before matching, copayments and payer costs were significantly higher for patients with BCRL than for those without BCRL ($US1200 vs. $US610; $p < 0.001$; $US140,000 vs. $US76,000; $p < 0.001$; Table 2). There was no significant difference in out-of-pocket costs between patients with and without BCRL in the unmatched cohorts ($p = 0.791$). After propensity score matching, mean copayments were significantly higher in patients with BCRL ($US1200 vs. $US850; $p < 0.001$), but out-of-pocket and payer costs were similar (Table 2). When considering costs over time by year, there were no significant differences in out-of-pocket spending, copayments, or payer costs between patients with and without BCRL during active treatment (years 1–2). However, during survivorship, cost differences emerged; specifically, patients with BCRL with 4 years of complete data had significantly higher copayments ($US1600 vs. $US1000; $p = 0.043$, Table 3).

In the sensitivity analysis stratified by age, patients with BCRL in both the YA and THE older cohorts consistently trended towards higher copayments and payer costs. For older patients, these differences reached statistical significance for copayments in year 3 ($US1500 vs. $US700;

TABLE 2 Overall costs by breast cancer-related lymphedema (BCRL) status in the non-matched and matched cohorts

Costs	Unmatched cohort				Matched cohort			
	Total (N=2141)	BCRL (N=244)	No BCRL (N=1897)	*p*-Value	Total (N= 727)	BCRL (N=244)	No BCRL (N=483)	*p*-Value
OOP	13,000 ± 62,000	14,000 ± 86,000	12,000 ± 58,000	0.791	13,000 ± 67,000	14,000 ± 86,000	13,000 ± 55,000	0.893
Copay	670 ± 990	1200 ± 1400	610 ± 900	< 0.001	960 ± 1200	1200 ± 1400	850 ± 1100	< 0.001
Payer cost	83,000 ± 120,000	140,000 ± 200,000	76,000 ± 100,000	< 0.001	130,000 ± 170,000	140,000 ± 200,000	120,000 ± 150,000	0.167

All costs are presented as mean ± standard deviation, in $US.

OOP, out-of-pocket costs; copay, copayments

TABLE 3 Costs by breast cancer-related lymphodema (BCRL) status in the matched cohort for all patients and per age group

Costs	All patients (N = 727)			18–44 years (N = 164)			45–61 years (N = 563)		
Years 1–2	BCRL (N = 84)	No BCRL (N = 209)	*P*	BCRL (N = 16)	No BCRL (N = 56)	*P*	BCRL (N = 68)	No BCRL (N = 153)	*P*
OOP	16,000 ± 61,000	14,000 ± 48,000	0.77	2900 ± 6200	23,000 ± 68,000	0.031	19,000 ± 68,000	10,000 ± 37,000	0.32
Copay	570 ± 760	430 ± 680	0.139	690 ± 940	410 ± 690	0.278	540 ± 720	430 ± 680	0.304
Payer cost	120,000 ± 110,000	100,000 ± 110,000	0.246	170,000 ± 100,000	130,000 ± 110,000	0.232	110,000 ± 110,000	93,000 ± 100,000	0.333
Year 3	BCRL (N = 40)	No BCRL (N = 59)	*P*	BCRL (N = 6)	No BCRL (N = 17)	*P*	BCRL (N = 34)	No BCRL (N = 42)	*P*
OOP	36,000 ± 190,000	9600 ± 50,000	0.39	200,000 ± 490,000	24,000 ± 91,000	0.417	7100 ± 26,000	3600 ± 12,000	0.47
Copay	1400 ± 1600	870 ± 1100	0.074	750 ± 850	1300 ± 1500	0.296	1500 ± 1700	700 ± 860	0.014
Payer cost	140,000 ± 110,000	120,000 ± 120,000	0.374	220,000 ± 190,000	150,000 ± 130,000	0.483	120,000 ± 88,000	100,000 ± 110,000	0.35
Year 4	BCRL (N = 41)	No BCRL (N = 77)	P	BCRL (N = 9)	No BCRL (N = 17)	*P*	BCRL (N = 32)	No BCRL (N = 60)	*P*
OOP	8200 ± 29,000	12,000 ± 57,000	0.589	2600 ± 2800	17,000 ± 39,000	0.14	9700 ± 32,000	11,000 ± 62,000	0.89
Copay	1600 ± 1700	1000 ± 1200	0.043	1200 ± 920	600 ± 730	0.091	1800 ± 1800	1100 ± 1300	0.105
Payer cost	140,000 ± 120,000	130,000 ± 200,000	0.698	200,000 ± 130,000	120,000 ± 160,000	0.162	130,000 ± 110,000	140,000 ± 210,000	0.778
Year 5	BCRL (N = 79)	No BCRL (N = 138)	*P*	BCRL (N = 15)	No BCRL (N = 28)	*P*	BCRL (N = 64)	No BCRL (N=110)	*P*
OOP	3800 ± 5800	14,000 ± 66,000	0.06	4500 ± 6900	38,000 ± 130,000	0.181	3600 ± 5600	8500 ± 34,000	0.145
Copay	1500 ± 1400	1400 ± 1400	0.425	1300 ± 1400	1100 ± 1900	0.684	1600 ± 1400	1400 ± 1200	0.506
Payer cost	170,000 ± 320,000	150,000 ± 170,000	0.592	200,000 ± 170,000	170,000 ± 150,000	0.477	160,000 ± 340,000	140,000 ± 180,000	0.712

All costs are presented as mean ± standard deviation in $US

Copay, copayment; OOP, out-of-pocket costs

$p = 0.014$; Table 3). In the YA cohort, patients with BCRL had significantly lower out-of-pocket costs during years 1–2 than did those without BCRL ($US2900 vs. $US23,000; $p = 0.031$). During survivorship, costs for YA patients with BCRL trended higher than for those without BCRL; however, this did not reach statistical significance at any time point.

Heat map analysis (Fig. 2) showed that costs for all ages were concentrated around chemotherapy receipt. Warmer colors indicated higher patterns of out-of-pocket spending and copayments among YA women with BCRL compared with older women who developed the condition. For YA women, BCRL represented the highest source of out-of-pocket spending after chemotherapy and reconstruction.

DISCUSSION

In this study investigating how BCRL impacts healthcare costs over time and by age in patients undergoing surgical treatment for breast cancer in calendar year 2016 as captured by the MA APCD, payer and copayment costs were significantly higher for patients with breast cancer who developed BCRL within 2 years of their index surgery. When considering costs over time, those with BCRL also had higher copayments and payer spending during survivorship. Age-based sensitivity analyses did not demonstrate statistically significant differences in spending during survivorship (years 3–5) between those with and without BCRL in the YA cohorts but did show higher copayments for older women with BCRL. Not surprisingly, the costs of chemotherapy and reconstruction were significant sources of healthcare expenditure for patients of all ages and YA individuals, respectively. Yet,

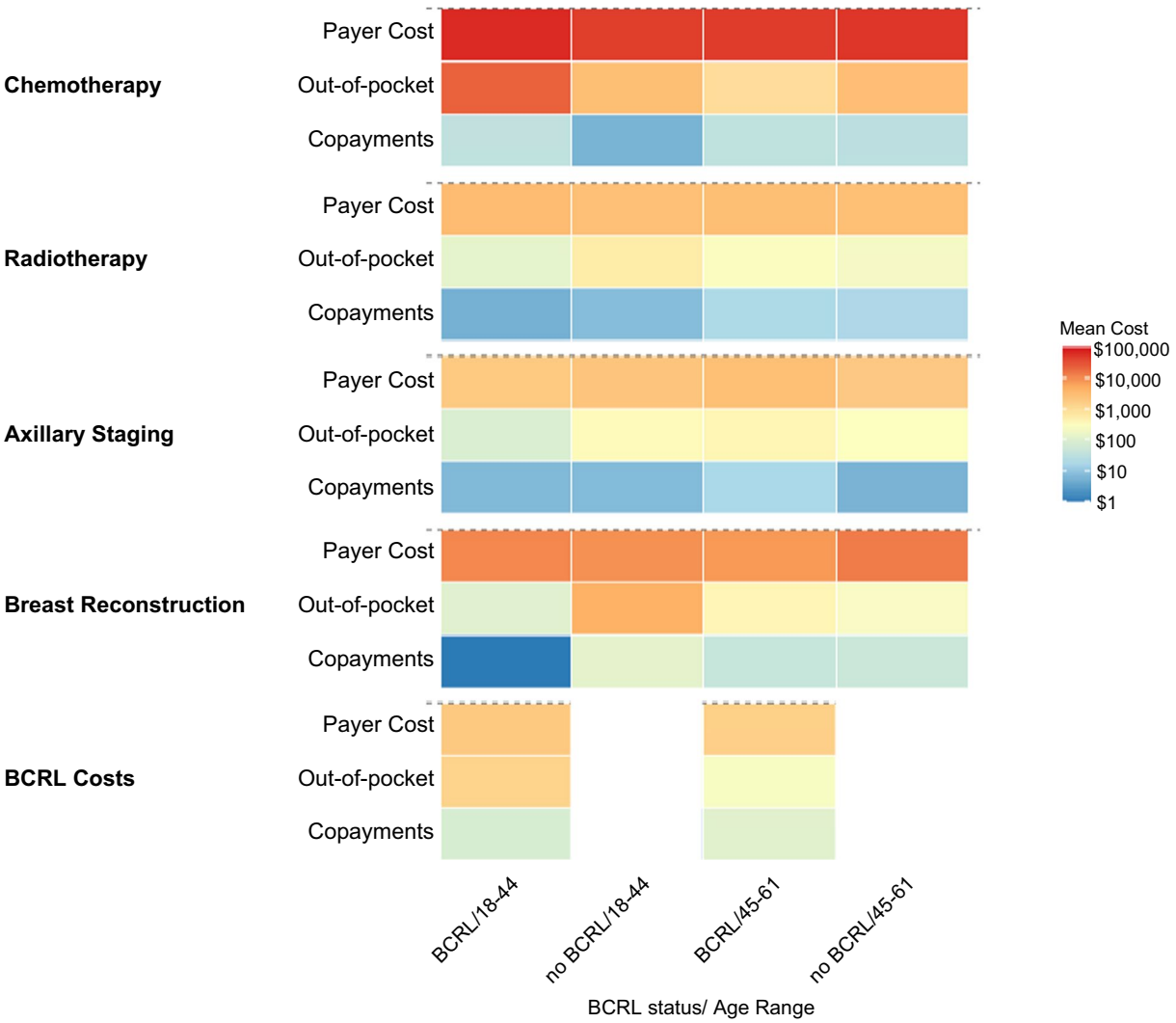

FIG. 2 Heat map depicting breast cancer-associated costs in matched cohorts. BCRL, breast cancer-related lymphedema

our findings demonstrated the unrecognized major expense of BCRL for young women with breast cancer, presenting initially in the survivorship phase. These data contribute to our understanding of how BCRL might impact long-term financial hardship and how patterns of spending might differ by age.

Although the financial burden associated with BCRL has been well-documented, few studies have focused on how the delayed onset of this adverse event affects treatment costs during active treatment versus survivorship.[15,20–22] Our findings provide further insight by illustrating that differences in spending among patients who develop BCRL compared with those without BCRL may not become pronounced until after cancer treatment is complete. Further, costs related to diagnosis and acute management represent only a fraction of costs when considering that these compound over time.[23] Early BCRL costs typically involve diagnostic testing along with first-line conservative treatments, including compression garments and physical therapy.[24] As BCRL progresses, patients may require more expensive interventions, including surgical procedures (e.g., lymphovenous bypass or lipectomy) that are rarely covered by insurance.[25] Although these procedures substantially increase treatment costs, primarily due to operating room time and specialized microsurgical expertise, their precise contribution to overall medical expenses is difficult to quantify because of substantial variability in institutional pricing and insurance coverage.[26] Beyond direct costs such as those captured in the current study, indirect costs from lost productivity also accumulate over time, with 42% of employed women with BCRL reporting an impact on work performance and annual absenteeism increasing from 1.4 days for women with mild lymphedema to 8.1 days for those with moderate/severe disease.[27] Taken together, these findings demonstrate that arm morbidity is a significant contributor to long-term financial difficulty and support the need for improved BCRL surveillance, health policy reform to increase reimbursement for treatment, and financial navigation during survivorship.

Our study indicated that spending for BCRL may differ by age, but further investigation is needed to understand how variations in incidence, severity, treatment, and treatment adherence between YAs versus older adults affect BCRL-associated costs. As YAs have been shown to be at elevated risk for experiencing financial toxicity, the economic consequences of BCRL may perpetuate hardship. In a multi-institutional cohort of more than 1100 young women with breast cancer, arm morbidity was associated with trajectories of greater financial difficulty.[6] Interestingly, in our study, we found that YA patients with BCRL had *lower* out-of-pocket costs than YA patients without BCRL. As younger patients more frequently present with advanced disease and aggressive tumor biology than do older patients,[11,28–30] we postulate that the majority of the YAs who were not diagnosed with BCRL in the first 2 years of analyzed data warranted preoperative chemotherapy, the primary driver of cancer-related costs.[12] Therefore, development of BCRL may occur later in these patients than in those undergoing upfront surgery. Additionally, in this study, older but not YA patients with BCRL experienced greater spending than non-BCRL cohorts during survivorship. These differences in cost patterns among younger and older patients may reflect underuse of lymphedema-related care among YAs because of insurance-related barriers or competing work and life responsibilities. Further, treatment nonadherence, a well-recognized coping behavior used to offset expenses, has been shown to be more pronounced among YA patients with breast cancer because of financial hardship.[4] Despite only observing statistically significant differences in cancer-related costs among older adults on the basis of BCRL, the heatmap generated from our data does indicate that costs related to reconstruction and BCRL are a high source of expense in younger patients. Additional research is needed to better understand the financial impact of BCRL and reconstructive procedures in this population.

This study has several limitations. First, claims data under-capture BCRL, particularly in mild cases. Our observed BCRL prevalence of 11.4%,[7] albeit lower than the expected ~ 30% reported in previous literature, is comparable to rates reported in claims-based analyses.[21,31] Underdiagnosis and inability to account for patients who did not pursue treatment may also have contributed to our smaller BCRL cohort. In this study, the BCRL cohort was identified using 10-PCS/ICD-10-CM codes associated with BCRL within 2 years of the index surgery. For patients whose diagnosis occurred closer to the 2-year postoperative mark, BCRL-related costs would have had little to no impact on the overall treatment costs.The latter is especially salient considering that data suggesting that risk for BCRL may not peak until over 2 years after surgery. For example, in those receiving sentinel lymph node biopsy with regional nodal irradiation, BCRL risk peaks at 36–48 months postoperatively.[32] Further, our reliance on claims data precluded adjustment for important confounders such as tumor biology, stage, recurrence, and detailed treatment plans, all of which might influence cost trajectories. Use of claims data also limited our ability to include granular data, including lymphedema severity; it is unclear whether these data are generalizable to the broader population of patients with BCRL. Additionally, out-of-pocket expense assessment is unreliable as claims data reflect expected rather than actual patient liability, may not account for secondary insurance coverage, and may be missing reconciliations.[13] Insurance factors (e.g., high-deductible plans, supplemental coverage), socioeconomic determinants, and behavioral factors such as treatment nonadherence linked to financial hardship were also unavailable. Despite these limitations, the strengths

of this study include our novel approach to understanding how patient age and time from diagnosis may contribute to the effects of treatment-related adverse events on financial hardship. Our findings provide a framework for real-world expenses related to BCRL.

CONCLUSIONS

In this claims-based analysis, patients with BCRL incurred higher payer and copayment costs than those without BCRL. Our observation that differences may not become apparent until survivorship emphasizes the ongoing, and presently lacking, need for financial resources and navigation after completion of breast cancer treatment.

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AUTHOR CONTRIBUTIONS Myers, Broyles, Dey, and Jain had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Myers, Broyles, Keating, Greenup, King, and Mittendorf. *Acquisition, analysis, or interpretation of data:* All authors. *Drafting of the manuscript:* Raymakers, Myers, and Broyles. *Critical review of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Jain, Dey. *Administrative, technical, or material support:* Myers, King, Mittendorf. *Supervision:* Myers.

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DATA AVAILABILITY The data in this article were obtained from the Massachusetts All-Payer Claims Database (MA APCD) under a data use agreement. Due to the terms of the data use agreement with the Massachusetts Center for Health Information and Analysis, the raw claims data cannot be shared publicly or with other researchers, but qualified researchers may request access to MA APCD data directly from the Massachusetts Center for Health Information and Analysis. Data access requires completion of a formal application process, approval by the data steward, execution of a data use agreement, and payment of applicable fees.

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