

Risk of Breast Cancer-Related Lymphedema Following Locoregional Treatment among Breast Cancer Patients at Suez Canal University Hospital

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Abstract:

Background: Breast cancer-related lymphedema (BCRL) constitutes one of the most prevalent treatment sequelae among long-term survivors. Several risk factors have been suggested to be associated with BCRL, such as obesity, adjuvant radiotherapy, and taxane-based chemotherapy. **Patients and Methods:** Thirty-seven patients with BCRL and 74 patients without BCRL were recruited at the clinical oncology and nuclear medicine department, Suez Canal University (SCU) hospital, and their sociodemographic, cancer-related, and treatment-related data were obtained. The presence of lymphedema was assessed using limb volume difference. **Results:** BCRL was significantly higher in patients with advanced disease stage ($p=0.019$), extra-nodal extension (ENE) ($p=0.009$), increased number of positive lymph nodes ($p=0.001$), conventional radiotherapy ($p=0.042$), taxane-containing chemotherapy ($p=0.002$), and lack of proper health education on limb care ($p<0.001$). **Conclusion:** Health education programs are very valuable tools in lowering BCRL risk. Therefore, breast cancer patients should be provided with frequent assessments for arm lymphedema and proper health education programs.

Keywords: lymphedema, breast cancer, Egypt.

Introduction:

The number of long-term survivors of breast cancer has increased as a result of the outstanding progress achieved in breast cancer management. Unfortunately, breast cancer patients nowadays face a number of long-term post-treatment adverse events affecting their quality of life (QoL) ⁽¹⁾, such as arm lymphedema, which is one of the most disturbing complications ⁽²⁾. In fact, it has been estimated that 1 in 5 patients will suffer from BCRL, and even though most BCRL cases develop within the first 2 years after surgery, such a complication can still occur in patients twenty years later ^(3,4).

In BCRL, the lymphatic system is disrupted, preventing adequate drainage from lymphatic vessels, causing the accumulation of protein-rich lymph fluid in the interstitial space, and eventually

leading to abnormal swelling in the upper extremity, breast, or trunk on the side of locoregional treatment ⁽⁵⁾. Although lymphedema was classically defined by swelling, it has been established early in this century that lymphedema does not only refer to swelling but also to tissue tone and texture as described in the guidelines of the United States (US) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) ^(6,7). Needless to say, the impact of BCRL is not limited to physical impairment, but can also lead to anxiety and depression. ⁽⁸⁻¹⁰⁾. Therefore, an in-depth understanding of BCRL, its management, and its prevention is becoming a priority for all healthcare providers ⁽⁸⁾.

For years, it has been assumed that BCRL resulted solely from axillary lymph node removal. However, current data suggest

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a multifactorial nature of BCRL⁽¹¹⁾, being associated with several risk factors, such as adjuvant radiotherapy, taxane-based chemotherapy, lack of breast reconstruction after mastectomy, advanced disease stage, obesity, and physical inactivity⁽²⁾. The current study has thoroughly assessed most of the previously investigated risk factors of BCRL, including the socio-demographic, clinicopathologic, and treatment-related factors among patients in Ismailia city, Egypt as a step toward achieving better outcomes for Egyptian breast cancer survivors.

Patients and Methods:

This case-control study was conducted at the clinical oncology and nuclear medicine department, at SCU Hospital, Ismailia city, Egypt from June 2021 to January 2022. We recruited breast cancer patients who were adult females, with pathologically confirmed breast cancer, and had complete data in their medical records. We excluded patients with a recent diagnosis (<6 months) in whom BCRL may have not been evident yet⁽¹²⁾, patients with bilateral breast cancer; as an unaffected arm is needed for comparison, patients with arm swelling due to other causes, such as DVT, and patients with mental disorders rendering them uncooperative. Patients who met our selection criteria were assigned to either the BCRL group (37 patients) or the non-BCRL group (74 patients). The enrolled patients were interviewed using a structured checklist and their medical records were reviewed to collect data regarding their disease stage, histopathology, and treatment details.

Patients' BMI was assessed and compared to their baseline BMI at diagnosis. Sequential limb circumference measurements were performed at four

predefined levels—metacarpophalangeal joints, wrist, 10 cm distal to the lateral epicondyle, and 15 cm proximal to the lateral epicondyle—resulting in segmentation of the upper limb into five regions. The length of each segment was also measured and limb volume was calculated for each segment by the truncated cone formula⁽¹³⁾. According to the CTC v5.0, lymphedema is graded as absent (<5% difference between both arms), mild (5-10% difference), moderate (10-30% difference), or severe (>30% difference)⁽¹⁴⁾. Notably, the enrolled patients were also subjected to a thorough clinical examination and additional investigations, if needed, to exclude other causes of arm swelling.

Statistical analysis: Patients' data were analyzed using the Statistical Package for Social Sciences (SPSS) software program version 25.0. The Mann-Whitney U test was used to compare continuous data between BCRL and non-BCRL groups, whereas Chi-square and Fisher Exact tests were used to compare categorical data between BCRL and non-BCRL groups. Univariate and multivariate logistic regression analyses were conducted to identify the effects of different factors on the development of BCRL. Results were considered statistically significant at a p-value less than 0.05.

Results:

Of the 37 women diagnosed with BCRL, 13 (11.7%) presented with mild lymphedema, 12 (10.8%) with moderate lymphedema, and 12 (10.8%) with severe lymphedema. The BCRL group had a mean age of 48.14 years, and 56.8% were premenopausal. Notably, almost all our patients were obese, with a mean BMI at diagnosis of 31.71 for the BCRL group and 33.22 for the non-BCRL group. However, BCRL was not significantly associated

with the patient's age, menopausal status, marital status, level of education,

occupation, residency, smoking, or their BMI (Table 1).

Table 1. Socio-demographic characteristics of the study participants (n= 111)

Variables	BCRL (n=37)	Non-BCRL (n=74)	p-value
Age at diagnosis, mean $\pm$ SD	48.14 $\pm$ 12.7	49.28 $\pm$ 10.59	0.54 ^a
Menopausal status, n (%)			
Premenopausal	21 (56.8)	39 (52.7)	0.69 ^c
Postmenopausal	16 (43.3)	35 (47.3)	
Marital status, n (%)			
Single	2 (5.4)	2 (2.7)	0.199 ^b
Married	21 (56.8)	55 (74.3)	
Divorced/Separated	4 (10.8)	3 (4.1)	
Widowed	10 (27)	14 (18.9)	
Education, n (%)			
Illiterate	15 (40.5)	27 (36.5)	0.125 ^b
Can read and write	4 (10.8)	9 (12.2)	
Primary school	2 (5.4)	7 (9.5)	
Middle school	0 (0)	5 (6.8)	
High school	8 (21.6)	22 (29.7)	
College	7 (18.9)	4 (5.4)	
Post-graduate degree	1 (2.7)	0 (0)	
Occupation, n (%)			
Unemployed	31 (83.8)	66 (89.2)	0.75 ^b
Manual work	3 (8.1)	5 (6.8)	
Office work	3 (8.1)	3 (4.1)	
Residency, n (%)			
Urban	16 (43.2)	29 (39.2)	0.68 ^b
Rural	21 (56.8)	45 (60.8)	
Smoking, n (%)			
No	33 (89.2)	71 (95.9)	0.22 ^b
Yes	4 (10.8)	3 (4.1)	
BMI (at diagnosis), mean $\pm$ SD	31.71 $\pm$ 5.98	33.22 $\pm$ 6.84	0.24 ^a
BMI (current), mean $\pm$ SD	33.19 $\pm$ 6.09	33.35 $\pm$ 6.05	0.7 ^a

BCRL: breast cancer-related lymphedema, BMI: body mass index, SD: standard deviation.

^a P-values were calculated using the Mann-Whitney U test, with statistical significance defined as $p < 0.05$.

^b P-values were calculated using the Fisher Exact test, with statistical significance defined as $p < 0.05$.

^c P-values were calculated using the Chi square test, with statistical significance defined as $p < 0.05$.

Most of the patients reported that they used their ipsilateral arm very often in daily life activities (70.3% of the BCRL group and 74.3% of non-the BCRL group, $p=0.4$). They also did not recall any history of ipsilateral arm injury (62.2% of the BCRL group and 70.3% of the non-BCRL group, $p=0.39$) and did not have any medical procedures done to their ipsilateral arm, including blood pressure

measurements, IV injections, blood draw, or hand surgeries (91.9% of the BCRL group and 94.6% of the non-BCRL group, $p=0.68$). More importantly, most of the included women had an education program on ipsilateral arm care. Unfortunately, only 18.9% of the BCRL group were compliant with the given instructions, compared to 66.2% of the non-BCRL group ($p<0.001$) (Table 2).

Table 2. Comparison of limb care among the study participants (n= 111)

Variables	BCRL (n=37)	Non-BCRL (n=74)	p-value
Ipsilateral arm use in daily life activities, n (%)			
Very often	26 (70.3)	55 (74.3)	0.40 ^a
Sometimes	7 (18.9)	16 (21.6)	
Seldom	4 (10.8)	3 (4.1)	
Never	0 (0)	0 (0)	
Ipsilateral limb injury, n (%)			
No	23 (62.2)	52 (70.3)	0.39 ^b
Yes	14 (37.8)	22 (29.7)	
Medical procedures on ipsilateral arm, n (%)			
Blood pressure	2 (5.4)	0 (0)	0.68 ^a
IV injections	3 (8.1)	1 (1.4)	
Blood draw	2 (5.4)	2 (2.7)	
Hand surgery	0 (0)	1 (1.4)	
None	34 (91.9)	70 (94.6)	
Health education program, n (%)			
Yes, and compliant	7 (18.9)	49 (66.2)	<0.001 ^b
Yes, but uncompliant	19 (51.4)	6 (8.1)	
No	11 (29.7)	19 (25.7)	

BCRL: breast cancer-related lymphedema, IV: intravenous.

^a p-values were calculated using the Chi square test, with statistical significance defined as $p < 0.05$.

^b p-values were calculated using the Fisher Exact test, with statistical significance defined as $p < 0.05$.

BCRL was not significantly associated with the tumor grade, histologic type, hormonal receptors status, HER2 receptor status, or local recurrence (Table 3). Although lymphovascular invasion (LVI) was more prevalent among BCRL patients (51.4%) than in the comparison group (31.1%), the difference failed to achieve statistical significance ($p = 0.07$). Nevertheless, advanced disease stage and the presence of ENE were significantly more common in patients with BCRL compared to the non-BCRL group ($p=0.019$ and $p=0.009$, respectively).

Most of the enrolled women had undergone modified radical mastectomy (MRM) (91.9% of the BCRL group and 87.8% of the non-BCRL group) with axillary lymph node dissection (ALND) (100% of the BCRL group and 95.9% of the non-BCRL group), and over half of the patients had the surgery on the non-dominant arm side (Table 4). Only two

patients had reconstructive surgery (2.7% of the non-BCRL group). Notably, BCRL was not significantly correlated with the type of breast surgery, type of axillary surgery, side of surgery or breast reconstruction. Even though the mean number of the dissected lymph nodes was similar within both groups (17.78 ± 7.46 in the BCRL group vs 16.36 ± 7.13 in the non-BCRL group, $p=0.31$); however, the mean number of positive lymph nodes was significantly higher in the BCRL group as compared to the other group (7.35 ± 7.2 vs 4.16 ± 6.86 , respectively, $p=0.001$). Postoperative complications were not common among the studied patients and there was no significant difference between both groups regarding the frequency of such complications ($p=0.9$).

Table 3. Comparison of clinicopathological data of the study participants (n= 111).

Variables	BCRL (n=37)	Non-BCRL (n=74)	p-value
Histology, n (%)			
IDC	33 (89.2)	65 (87.8)	1 ^a
DCIS	0 (0)	2 (2.7)	
ILC	2 (5.4)	4 (5.4)	
Mixed	2 (5.4)	3 (4.1)	
Grade, n (%)			
I	0 (0)	4 (5.4)	0.44 ^a
II	32 (86.5)	62 (83.8)	
III	5 (13.5)	8 (10.8)	
LVI, n (%)	19 (51.4)	23 (31.1)	0.07 ^a
ENE, n (%)	16 (43.2)	25 (33.8)	0.009 ^a
ER receptor, n (%)			
Positive	28 (75.7)	66 (89.2)	0.09 ^b
Negative	9 (24.3)	8 (10.8)	
PR receptor, n (%)			
Positive	28 (75.7)	59 (79.7)	0.75 ^a
Negative	9 (24.3)	14 (18.9)	
Unknown	0 (0)	1 (1.4)	
Her2/neu receptor, n (%)			
Positive	9 (24.3)	14 (18.9)	0.51 ^b
Negative	24 (64.9)	46 (62.2)	
Unknown	4 (10.8)	14 (18.9)	
Stage, n (%)			
0	0 (0)	2 (2.7)	0.019 ^a
I	1 (2.7)	4 (5.4)	
II	8 (21.6)	34 (45.9)	
III	17 (45.9)	23 (31.1)	
IV	11 (29.7)	9 (12.2)	
NA	0 (0)	2 (2.7)	
T, n (%)			
is	0 (0)	2 (2.7)	0.017 ^a
1	5 (13.5)	15 (20.3)	
2	20 (54.1)	43 (58.1)	
3	7 (18.9)	14 (18.9)	
4	5 (13.5)	0 (0)	
N, n (%)			
0	5 (13.5)	31 (41.9)	0.016 ^a
1	11 (29.7)	16 (21.6)	
2	11 (29.7)	15 (20.3)	
3	10 (27)	10 (13.5)	
X	0 (0)	2 (2.7)	
M, n (%)			
0	26 (70.3)	65 (87.8)	0.035 ^b
1	11 (29.7)	9 (12.2)	
Local recurrence, n (%)			
Yes	2 (5.4)	1 (1.4)	0.56 ^a
No	35 (94.6)	73 (98.6)	

BCRL: breast cancer-related lymphedema, DCIS: ductal carcinoma in situ, ENE: extra-nodal extension, ER: estrogen receptor, HER/neu: human epidermal growth factor Receptor, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, N: nodal status, M: metastasis, PR: progesterone receptor, T: tumor size.

^a p-values were calculated using the Fisher Exact test, with statistical significance defined as $p < 0.05$.

^b p-values were calculated using the Chi square test, with statistical significance defined as $p < 0.05$.

Only 3 women (8.1%) in the BCRL group and 8 women (10.8%) in the other group did not receive radiotherapy as they missed follow-ups. Importantly, BCRL was significantly associated with radiotherapy dose ($p=0.042$) (Table 4). However, it was not significantly associated with the irradiated volume ($p= 0.14$) or boost dose over the

operative bed ($p=0.75$). As for systemic therapies, paclitaxel use was significantly more common among BCRL patients as compared to the other group (67.6% vs 36.5%, respectively, $p=0.002$). However, anthracyclines, docetaxel, hormonal therapy and trastuzumab were not significantly associated with BCRL.

Table 4. Treatment-related factors among the study participants (n= 111).			
Variables	BCRL (n=37)	Non-BCRL (n=74)	p-value
Type of breast surgery, n (%)			
MRM	34 (91.9)	65 (87.8)	0.75 ^a
CBS	3 (8.1)	9 (12.2)	
Type of axillary surgery, n (%)			
ALND	37 (100)	71 (95.9)	0.7 ^a
SLNB	0 (0)	2 (2.7)	
No axillary surgery	0 (0)	1 (1.4)	
Number of lymph nodes, n (%)			
≤10 dissected LNs	4 (10.8%)	9 (12.2%)	0.33 ^c
11-20 dissected LNs	20 (54.1%)	49 (66.2%)	
>20 dissected LNs	13 (35.1%)	16 (21.6%)	
Mean of dissected LNs, mean ± SD	17.78 ± 7.46	16.36 ± 7.13	0.31 ^b
Mean of Positive LNs, mean ± SD	7.35 ± 7.2	4.16 ± 6.86	0.001 ^b
Side of surgery, n (%)			
Dominant arm	14 (37.8)	33 (44.6)	0.49 ^c
The other arm	23 (62.2)	41 (55.4)	
Reconstructive surgery, n (%)			
Yes	0 (0)	2 (2.7)	0.52 ^a
No	37 (100)	72 (97.3)	
Post-operative complications, n (%)			
Sinus	0 (0)	1 (1.4)	0.9 ^a
Failed graft	0 (0)	1 (1.4)	
Seroma	0 (0)	5 (6.8)	
Wound infection	5 (13.5)	2 (2.7)	
None	32 (86.5)	65 (87.8)	
Received Radiotherapy, n (%)			
Yes	34 (91.9)	66 (89.2)	0.75 ^a
No	3 (8.1)	8 (10.8)	
Dose of Radiotherapy, n (%)			
40.05Gy/15#	1 (2.9)	10 (15.2)	0.042 ^a
45Gy/18#	1 (2.9)	1 (1.5)	
45Gy/20#	2 (5.9)	0 (0)	
50Gy/25#	30 (88.2)	55 (83.3)	
Boost, n (%)			
Yes	3 (8.1)	8 (10.8)	0.75 ^a
No	34 (91.9)	66 (89.2)	

Irradiated volume, n (%)			
Chest wall only	7 (20.6)	26 (39.4)	0.14 ^c
Chest wall and SCLN	16 (47.1)	22 (33.3)	
Chest wall, SCLN, axillary field	11 (32.4)	18 (27.3)	
Chemotherapy, n (%)			
Anthracyclines	33 (89.2)	72 (97.3)	0.09 ^a
Docetaxel	7 (18.9)	6 (8.1)	0.12 ^a
Paclitaxel	25 (67.6)	27 (36.5)	0.002 ^b
Hormonal therapy, n (%)			
Tamoxifen	22 (59.5)	42 (56.8)	0.84 ^b
AI	20 (54.1)	46 (62.2)	0.41 ^b
Goserelin	14 (37.8)	20 (27)	0.34 ^b
Trastuzumab, n (%)			
Yes	9 (24.3)	9 (12.2)	0.1 ^b
No	28 (75.7)	65 (87.8)	

ALND: axillary lymph node dissection, BCRL: breast cancer-related lymphedema, CBS: conservative breast surgery, Gy: gray, LN: lymph node, MRM: modified radical mastectomy, SLNB: sentinel lymph node dissection, SCLN: supraclavicular lymph node, #: fraction.

^a P-values were calculated using the Fisher's Exact test; statistical significance was defined as $p < 0.05$.

^b P-values were calculated using the Mann-Whitney U test; statistical significance was defined as $p < 0.05$.

^c P-values were calculated using the Chi-square test; statistical significance was defined as $p < 0.05$.

On univariate logistic regression, significant predictors of BCRL included lack of patient education ($p = 0.003$), ENE ($p = 0.004$), higher T ($p = 0.04$), N ($p = 0.017$), and M stage ($p = 0.027$), increased positive lymph nodes ($p = 0.03$), and paclitaxel use ($p = 0.003$) (Table 5).

Interestingly, by multivariate analysis, lower BMI at diagnosis, higher current BMI, lack of proper patient education and use of paclitaxel and docetaxel also significantly increased the risk of BCRL (Table 6).

Table 5. Univariate logistic regression analysis for risk factors of BCRL.

Variables	B	Odds Ratio	CI (95%)	p-value
Age	0.01	1.01	0.97 – 1.06	0.61
BMI (at diagnosis)	-0.04	0.96	0.90 – 1.03	0.26
BMI (current)	-0.005	0.99	0.94 – 1.07	0.89
Health education	-0.72	0.49	0.30 – 0.79	0.003
LVI	0.15	1.40	0.84 – 2.33	0.39
ENE	0.66	1.94	1.24 – 3.02	0.004
ER	0.97	2.65	0.93 – 7.58	0.69
Stage	0.13	1.14	0.93 – 1.40	0.22
T	0.51	1.67	1.02 – 2.74	0.04
N	0.43	1.54	1.08 – 2.19	0.017
M	1.12	3.06	1.13 – 8.23	0.027
Lymph nodes (dissected)	0.03	1.03	0.97 – 1.08	0.33
Lymph nodes (positive)	0.06	1.06	1.005 – 1.12	0.03
Axillary surgery	0.52	1.69	0.13 – 21.13	0.68
Side of surgery	0.28	1.32	0.59 – 2.96	0.50
Wound infection	1.72	5.62	1.04 – 30.54	0.04
Surgery to RT interval	-0.08	0.92	0.68 – 1.25	0.59
RT field	0.39	1.36	0.89 – 2.09	0.15
RT dose	0.33	1.03	0.63 – 1.70	0.90
Paclitaxel	1.29	3.63	1.57 – 8.36	0.003

Docetaxel	0.97	2.64	0.82 – 8.54	0.10
Tamoxifen	0.11	1.12	0.5 – 2.49	0.78

^a p-values were calculated using the Wald test, with statistical significance defined as $p < 0.05$.

Table 6. Multivariate logistic regression analysis for risk factors of BCRL.

Variables	B	Odds Ratio	CI (95%)	p-value
BMI (at diagnosis)	-0.20	0.97	0.71 – 0.95	0.009
BMI (current)	0.16	1.22	1.01 – 1.37	0.03
Health education	-1.01	0.86	0.20 – 0.65	0.001
Paclitaxel	1.55	4.72	1.79 – 12.46	0.002
Docetaxel	1.51	4.52	1.12 – 18.23	0.03

^a p-values were calculated using the Wald test, with statistical significance defined as $p < 0.05$.

Discussion:

Nowadays, it is believed that BCRL is a multifactorial condition. This case-control study included 111 breast cancer patients who received locoregional treatment and presented to the clinical oncology outpatient clinics at SCU hospital. In the current study, BCRL was not significantly associated with any of the patients' sociodemographic characteristics. These results align with the findings reported in earlier studies (15–17). However, some studies have found a higher risk of BCRL among patients of older age, mostly due to the aging process that affects the lymphatic system (18–20). Also, an early study reported that well-educated women tend to seek medical help more frequently than less-educated women, resulting in additional BCRL diagnoses (6).

Our multivariate analysis revealed that a lower BMI at diagnosis and a higher current BMI were significantly linked to an elevated risk of BCRL. Similarly, a meta-analysis indicated that BCRL incidence increased at higher BMI levels, likely because obese individuals tend to have a reduced muscle pumping efficiency within loose tissues (21). More interestingly, some evidence suggests that the risk of developing BCRL is associated with weight fluctuations

during or after treatment, rather than elevated BMI levels (8).

In the current study, BCRL was not significantly associated with frequency of ipsilateral arm use in daily life activities. Women at risk of BCRL were traditionally cautioned against strenuous activity. In contrast, it is now recognized that appropriately performed exercise can contribute to reducing BCRL risk (22). Surprisingly and despite being a common belief, having medical procedures done to the ipsilateral arm or experiencing arm injury was not significantly correlated with increased BCRL risk. A recent systematic review indicated that blood pressure measurement, injections, blood draw, and hand surgeries were not correlated with an increased risk of BCRL nor did they aggravate its severity in patients with established BCRL (23). More importantly, we found that receiving proper education on limb care and being compliant with the given instruction had significantly reduced BCRL risk. Unfortunately, a recent Egyptian study evaluated 50 women with BCRL and found that most of them had inadequate levels of knowledge regarding their condition and did not follow the lymphedema self-care advice (24).

It has been repeatedly reported that the presence of LVI and ENE were associated with an increased risk of BCRL (18,25). Even

though we found that LVI was more frequently seen in BCRL patients, this difference was not statistically significant. However, we found that ENE and advanced disease stage were significantly associated with higher risk of BCRL, which is similar to the previous studies ^(26,27).

Breast surgery is believed to cause tissue adhesion and fibrosis, along with subsequent lymphatic flow obstruction, whereas, breast reconstruction reduces postoperative fibrosis ⁽²⁸⁾. Furthermore, a meta-analysis estimated that BCRL risk becomes four times higher in patients undergoing ALND compared to those who have SLNB ⁽²⁹⁾. However, it is now clearly understood that BCRL risk depends on the amount of damage to the lymphatic system, and hence the number of removed lymph nodes and the subsequent need for multimodality therapy rather than the type of axillary surgery itself ⁽⁸⁾. Kim et al ⁽³⁰⁾ observed significantly lower rates of BCRL in patients with less than 10 axillary lymph nodes removed (6% vs 27%, respectively). In the current study, BCRL was not significantly associated with the type of breast surgery, type of axillary surgery, or breast reconstruction, mostly due to the small number of patients who had breast conservative surgery, SLNB, or reconstruction.

As for radiotherapy, BCRL was significantly associated with conventional radiotherapy dose, but not with the irradiated volume, boost dose over the operative bed, or the location of primary tumors in patients receiving a boost. Such an outcome may be explained by the limited sample size and it comes in concordance with the findings of two previous Egyptian studies ^(18,31). Yet, regional lymph node irradiation has been repeatedly identified in the literature as an

important contributor to the risk of BCRL ^(32,33).

In the present study, taxane-based chemotherapy demonstrated a significant association with BCRL, corroborating evidence reported in prior studies ⁽³⁵⁻³⁷⁾, and mostly attributed to the fluid retention effect of taxanes, especially in the extremities ⁽³⁴⁾. Moreover, it is believed that 17 β estradiol enhances lymphatic function and drainage and also promotes lymphatic angiogenesis after healing ⁽³⁸⁾. Thus, it was suggested that long-term use of anti-estrogen therapy can actually aggravate BCRL ⁽³⁹⁾. Yet, BCRL was not significantly associated with tamoxifen use in the current study. Furthermore, a few studies found that receiving trastuzumab was associated with an increased risk of BCRL ^(40,41). However, this association was not significant in the current study, and the findings of the previous studies could be due to a carry-over effect of the combined treatment with taxanes.

The current study presents a comprehensive evaluation of most of the previously investigated risk factors of BCRL. However, this study was a unicentric study conducted on a small number of patients, thus, the treatment-related factors such as SLNB and breast reconstruction depended to a large extent on the clinical practice within a single hospital, which does not usually represent the clinical practice of different cancer centers across the country. Also, we used a convenience sampling method due to the time limit which is often biased and unrepresentative. Finally, data collected from the patients themselves such as data related to limb care were susceptible to recall bias.

Conclusions:

The current study found that BCRL was not associated with ipsilateral arm use in daily life activities, accidental ipsilateral arm injury, or medical procedures done to the ipsilateral arm. On the other hand, patient education on limb care and compliance with the given instructions were associated with a significant reduction in BCRL risk. Therefore, assurance and proper education should be continuously provided for patients and healthcare workers. Moreover, frequent assessment of breast cancer patients for lymphedema preoperatively and at regular intervals afterwards should be implemented at every oncology center to allow for early detection and management of BCRL.

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