

WJCO 5th Anniversary Special Issues (2): Breast cancer**Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and management**

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Abstract

The global burden of breast cancer continues to increase largely because of the aging and growth of the world population. More than 1.38 million women worldwide were estimated to be diagnosed with breast cancer in 2008, accounting for 23% of all diagnosed cancers in women. Given that the 5-year survival rate for breast cancer is now 90%, experiencing breast cancer is ultimately about quality of life. Women treated for breast cancer are facing a life-time risk of developing lymphedema, a chronic condition that occurs in up to 40% of this population and negatively affects breast cancer survivors' quality of life. This review offers an insightful understanding of the condition by providing clinically relevant and evidence based knowledge regarding lymphedema symptoms, diagnosis, risk reduction, and management with the intent to inform health care professionals so that they might be better equipped to care for patients.

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Key words: Lymphedema; Breast cancer; Symptoms; Diagnosis; Risk reduction; Management

Core tip: Lymphedema is one of the most dreaded and

unfortunate outcomes of breast cancer treatment. Up to 40% of the women treated for breast cancer had lymphedema. Currently, there is no cure for this chronic condition. Even more distressing is that women who treated for breast cancer are facing a life-time risk of developing lymphedema. Lymphedema elicits daily stress and negative impact on breast cancer survivors' the quality of life. This paper offers an insightful understanding of the condition by providing clinically relevant and evidence based knowledge regarding lymphedema symptoms, diagnosis, risk reduction, and management with the intent to inform health care professionals so that they can be better equipped to care for patients.

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INTRODUCTION

The global burden of breast cancer continues to increase largely because of the aging and growth of the world population. More than 1.38 million women worldwide were estimated to be diagnosed with breast cancer in 2008, accounting for 23% of all diagnosed cancers in women^[1]. Given that the 5-year survival rate for breast cancer is now 90% and currently there are more than 2.9 million breast cancer survivors in the United States^[2], experiencing breast cancer is ultimately about quality of life. Women treated for breast cancer are facing a life-time risk of developing lymphedema, a chronic condition that occurs in up to 40% of this population^[3-6].

Breast cancer-related lymphedema results from obstruction or disruption of the lymphatic system associated with cancer treatment (removal of lymph nodes and radiotherapy); patient personal factors [obesity or

Table 1 Bivariate association between each symptom and lymphedema

Symptom	OR	95%CI	P-value
Arm swelling	561	76.04-71644.49	< 0.0001
Arm heaviness	17.46	8.22-39.25	< 0.0001
Arm firmness	10.33	5.04-22.16	< 0.0001
Increased arm temperature	9.07	2.98-29.94	0.000
Seroma formation	8.61	3.54-21.54	< 0.0001
Arm tightness	7.78	3.84-16.84	< 0.0001
Limited arm movement	5.86	2.94-11.93	< 0.0001
Tingling in affected arm	5.54	2.79-11.26	< 0.0001
Arm aching	5.14	2.60-10.46	< 0.0001
Limited fingers movement	4.56	1.92-10.66	0.0008
Limited elbow movement	4.39	1.53-12.21	0.0069
Limited wrist movement	4.23	1.58-10.99	0.0049
Limited shoulder movement	3.84	1.94-7.64	0.0001
Stiffness in the affected arm	3.55	1.75-7.16	0.0005
Burning in the affected arm	2.86	1.11-6.93	0.0299
Arm Redness	2.47	1.02-5.66	0.0450
Numbness in the affected arm	2.4	1.21-4.71	0.0124
Tenderness	2.07	1.06-4.03	0.0320
Pain in the affected arm	1.99	1.01-3.89	0.0463

Modified from the publication Ref.[23].

higher body mass index (BMI)] can increase the risk of lymphedema^[4-6]; and infections or trauma can trigger lymphedema^[4-6]. Lymphedema has elicited psychosocial problems that affect breast cancer survivors' daily lives^[7,8]. Significantly lower quality of life is observed in breast cancer survivors with lymphedema than in those without the condition^[9-12]. Management of lymphedema remains a major challenge for patients and health care professionals. Routine check-ups for lymphedema management, long-term physical therapy, management equipment (compression garments, bandages, special lotions), and repeated cellulitis, infections, and lymphangitis create financial and economic burdens not only to survivors but also to the health care system^[11]. Breast cancer survivors with lymphedema have significantly higher health care costs than those without it, they spend more days annually either hospitalized or visiting physicians' offices; they also have more days absent from work, which could adversely affect employment^[11,12]. Women treated for breast cancer often report being unaware that lymphedema was a possible outcome of cancer treatment and that health care professionals are not well informed and/or not helpful in guiding them on how to reduce the risk of lymphedema and manage this debilitating condition^[8,13]. The purpose of this paper is to offer an insightful understanding of the condition by providing clinically relevant and evidence based knowledge regarding lymphedema symptom, diagnosis, risk reduction, and management with the intent to inform health care professionals so that they might be better equipped to care for patients.

LYMPHEDEMA SYMPTOMS

Symptom assessment is essential since very often observable swelling and measurable volume changes are absent

during the initial development of lymphedema^[14-16]. Breast cancer survivors with lymphedema in the ipsilateral upper extremity report experiencing multiple symptoms, including swelling, heaviness, tightness, firmness, pain/aching/soreness, numbness, tingling, stiffness, limb fatigue, limb weakness, and impaired limb mobility of shoulder, arm, elbow, wrist, and fingers^[8,13-16]. These symptoms may be the earliest indicator of increasing interstitial pressure changes associated with lymphedema^[15,16]. As the fluid increases, the limb may become visibly swollen with an observable increase in limb size. Recent research shows that limb volume change has significantly increased as breast cancer survivors' reports of swelling, heaviness, tenderness, firmness, tightness, and aching have increased^[17]. Clinicians and researchers have long recognized that lymphedema symptoms may indicate an early stage of lymphedema in which changes cannot be detected by objective measures^[8,15]. The early stage of lymphedema may exist months or years before overt swelling occurs^[14-16].

Recent research demonstrates significant bivariate associations between each symptom and lymphedema^[16] (Table 1). A significant relationship exists between an increased number of symptoms and an increase in survivors' limb volume measured by infra-red perimeter^[17]. On average, breast cancer survivors reported 4.2 mean numbers of symptoms for survivors with < 5.0% limb volume change (LVC); 5.5 mean numbers of symptoms for 5.0%-9.9% LVC, 7.0 mean numbers of symptoms for 10.0-14.9% LVC, and 12.5 mean numbers of symptoms for \geq 15% LVC^[17]. A count of lymphedema symptoms is able to differentiate healthy adults from breast cancer survivors with lymphedema and those at risk for lymphedema^[16]. A diagnostic cutoff of three symptoms discriminated breast cancer survivors with lymphedema from healthy women with sensitivity of 94% and specificity of 97% [AUC (area under the curve) = 0.98]. A diagnostic cutoff of nine symptoms discriminated at-risk survivors and survivors with lymphedema with sensitivity of 64% and specificity of 80% (AUC = 0.72)^[16].

Since swelling is one of the key observable signs of lymphedema, objective measures are usually considered superior to symptom assessment or patient's perception of lymphedema. Perhaps, from the patient's perspective it is only the symptom experience and the perception of lymphedema that matter clinically because it is symptom experience and the perception of lymphedema that elicit tremendous distress and impair survivors' quality of life more than a measurement of inter-limb volume or girth size^[8,15]. In the absence of objective measurements capable of detecting early development of lymphedema, assessing symptoms may be a useful and cost-effective screening tool for detecting lymphedema.

DIAGNOSING BREAST CANCER-RELATED LYMPHEDEMA

Breast cancer-related lymphedema is a chronic syndrome

of abnormal swelling and multiple symptoms, resulting from abnormal accumulation of protein-rich lymph fluid in the interstitial tissue spaces due to an imbalance between lymph fluid production and transport^[13,14]. Because swelling is the cardinal sign of lymphedema, traditionally, lymphedema has been clinically diagnosed by health care professionals' observations of swelling and has often arbitrarily been defined in research as a 2 centimeters increase in limb girth, a 200-mL or more increase in limb volume, or a 5% or greater limb volume change^[17-19]. Inconsistency in the criteria defining lymphedema and the use of different measures has presented tremendous difficulty in diagnosing lymphedema. Breast cancer-related lymphedema can also occur in the shoulder, breast, and thoracic regions, unfortunately, no epidemiological studies have explored the incidence of lymphedema in the shoulder, breast, and thoracic regions due to lack of instruments to quantify swelling in these difficult-to-measure areas. Quantification of lymphedema by measuring limb size or girth or limb volume has been a major objective measure in research and clinical practice for diagnosing lymphedema using sequential circumference limb measurement, water displacement, and infra-red Perometry^[16]. Bioelectrical impedance is emerging as a possible alternative^[20-23]. Emerging assessment tool such as sonagraph needs more research to determine its reliability, sensitivity, and specificity.

Sequential circumferential arm measurements

Measuring limb size or girth or limb volume has been the most widely used diagnostic method in research. A flexible non-stretch tape measure for circumferences is usually used to assure consistent tension over soft tissue, muscle, and bony prominences^[19]. Measurements are done on both affected and non-affected limbs at the hand proximal to the metacarpals, wrist, and then every 4 or 10 centimeters from the wrist to axilla. The most common criterion for diagnosis has been a finding of ≥ 2 centimeters or ≥ 200 mL difference in limb volume as compared to the non-affected limb or 5% or 10% volume difference in the affected limb^[19].

Water displacement

Water displacement is seldom used in clinical settings because of spillover and hygienic concerns. Patients submerge the affected arm in a container filled with water and the overflow of water is caught in another container and weighed or measured. This method does not provide data about localization of the edema or shape of the extremity^[19,23]. The method is contraindicated in patients with open skin lesions. Patients may find it difficult to hold the position for the time needed for the tank overflow to drain^[19,23].

Infrared perometry

The infrared perometer is an optoelectronic device that works similarly to computer-assisted tomography, but makes use of light instead of X-rays^[19,23]. The volume and

shape of the limb can be measured and volume changes can be calculated. Perometry and circumference are reliable measurement of limb volume change over time in individuals undergoing breast cancer treatment^[19].

Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) measures impedance and resistance of the extracellular fluid using a single frequency below 30 kHz^[20,21]. The device uses the impedance ratio values between the unaffected and affected limb to calculate a *Lymphedema Index*, termed as L-Dex ratio. A recent published study has demonstrated that the L-Dex ratio with a cutoff point of $> +7.1$ can discriminate between at-risk breast cancer survivors and those with lymphedema with 80% sensitivity and 90% specificity (AUC = 0.86)^[20]. In comparison, using the industrial recommended cutoff point of L-Dex $> +10$ can only identify 66% of true lymphedema cases among at-risk breast cancer survivors, that is, miss 34% of true lymphedema cases [AUC = 0.81 sensitivity = 0.66 (95%CI: 0.51-0.79)]. Since early treatment usually leads to better clinical outcomes, it is important to have higher sensitivity to avoid missing large number of true lymphedema cases. Since there are still about 20% of true lymphedema cases are missed by BIA with a cutoff point of $> +7.1$, it is critical for health care professionals to incorporate other assessment methods, including self-report, clinical observation, or perometry, to ensure the accurate detection of lymphedema^[20]. The BIA technique currently is not appropriate in assessing bilateral limb lymphedema.

LYMPHEDEMA RISK REDUCTION

Over 50% of breast cancer survivors were found to be exceptionally worried about their risk of developing lymphedema^[6]. Multiple factors may be associated with this fear, including symptom experience, type of cancer surgery, education level, earlier experiences, or the way that health care professionals educate and counsel survivors about risk reducing practices.

While lymphedema incidence has been reported less frequently in women who underwent sentinel lymph node biopsy only (SLNB), lymphedema has by no means become a minor or disappearing problem. A large number of women each year still face the life-time risk of developing this progressive and debilitating condition even with the most conservative estimates suggesting that 3% of women with sentinel lymph node biopsies and 20% of those who have axillary dissections develop lymphedema at 12 mo following breast cancer surgery^[6]. It is essential to note that surgical removal of lymph nodes and radiation remains the optimal choice for treating breast cancer with positive cancerous lymph nodes. As a result, current surgical approaches for diagnosis of and treatment for breast cancer continue to make patients with invasive cancer susceptible to the risk of lymphedema.

Risk factors that are directly related to breast cancer treatment may be mostly unavoidable for patients treated

for breast cancer, including breast surgery (lumpectomy and mastectomy), removal of lymph nodes (sentinel lymph node biopsy and axillary lymph node dissection), radiotherapy, or chemotherapy^[4-6]. There are also known risk factors that are not directly related to breast cancer treatment. These risk factors may actually be modified, such as obesity, weight gain after diagnosis, minor upper extremity infections, injury or trauma to the affected limb, or overuse of the limb^[4-6].

For decades, patient education has emphasized on precautionary lifestyle to avoid the modifiable risk factors. Breast cancer survivors are cautioned to avoid such activities as repetitive activity, lifting weighted objects, needle punctures, blood draw, as well as to use of compression garments for air travel^[24]. A recent systematic review evaluated the scientific evidence for current recommended risk reduction recommendations. The review concluded that some commonly practiced precautionary lifestyle recommendations were proved to be not true or “fiction”, such as avoid air travel/wear compression garment for air travel, avoid pressure, avoid extremes of temperature/apply sunscreen/avoid sun burn, avoid vigorous exercise; while precautionary recommendation of avoiding needle sticks/injection needs more research evidence. Only maintaining normal weight is an evidence based recommendation^[24]. Thus, to date, the insufficiency of high quality evidence is lacking to support these practices to reduce the risk of developing lymphedema and effective management of lymphedema.

Inflammation-infection and higher body mass index (BMI) are the main predictors of limb volume change and lymphedema besides treatment-related risk^[3-6]. Women who had previous inflammation-infection in the breast, chest, or arm were 3.8 times more likely to develop lymphedema^[5]; weight gain and obesity (BMI > 30 kg/m²) increases lymphedema risk: survivors with each increase of 1 kg/m² in their BMI were 1.11 times more at risk for developing lymphedema^[5,25].

Patient education focusing on risk reduction strategies is promising for lymphedema risk reduction. A recent study of 136 breast cancer survivors demonstrated patients who received lymphedema information reported significantly fewer symptoms and more frequent practice of risk reduction behaviors than those who did not^[26]. After controlling for confounding factors of treatment-related risk factors, patient education remains an important predictor of lymphedema outcome. While rigid prevention measures may promote fears and frustration, one essential risk reduction behavior under patient control is maintaining optimal body weight, because excess body weight is associated with decreased lymphatic function^[27-29].

Preventing infection and trauma that may trigger the onset of lymphedema is vital for lymphedema risk reduction^[5,27,28]. Infection is a significant risk factor and is the most frequently occurring complication of lymphedema^[5]. Risk increases with breaches in skin integrity. Daily skin care that maintain skin moisture and integrity

may be promising to preventing infection and trauma in the affected limb^[29,30]. Fluid accumulation can cause skin dryness and irritation, increasing the risk of cellulitis and skin infection. Water-based and low pH moisturizers are recommended to discourage infection^[30,31].

In the past, breast cancer survivors were cautioned to restrict physical exercises as a way to reduce their risk for lymphedema. A growing body of evidence suggests that exercises, including whole body exercises (walking, running), weight training, resistance training, do not necessarily increase lymphedema risk^[31,32]. Breast cancer survivors should be encouraged to perform all postoperative exercises, resume normal activities as tolerated, and be as fit as possible, while monitoring their affected limbs^[31]. In addition to a broad range of benefits, from weight control, physical fitness, positive emotion, and quality of life, physical exercise can promote lymph fluid drainage through large muscle movement. Survivors should be instructed to perform physical exercise according to the general exercise guidelines^[31,32] (Table 2).

To facilitate effective lymphedema risk reduction, health care professionals can assist patients by presenting or reinforcing risk reduction information. Emphasis on self-protection rather than rigid rules fosters patient empowerment^[26]. An empowered patient assumes responsibility for reminding health care professionals to avoid use of the affected arm rather than expecting health care professionals to remember to do so.

MANAGEMENT OF BREAST CANCER-RELATED LYMPHEDEMA

Once breast cancer-related lymphedema is established, there is no cure. Management of lymphedema focuses on swelling reduction and symptom alleviation while minimizing exacerbations of swelling. Treatments include pharmacological therapy, surgery, complete decongestive physiotherapy (CDT), mechanical pneumatic pumps, and infection prevention and treatment^[29-44]. Emerging treatment such as low-dose laser needs more research to determine its efficacy.

Pharmacological management of lymphedema uses benzopyrones, flavonoids, diuretics, hyaluronidase, pantothenic acid, and selenium^[35]. Poor quality of existing trials on pharmacological agents makes it impossible to draw conclusions about the effectiveness of pharmacological approach for lymphedema among breast cancer survivors^[35].

Surgical treatment for lymphedema includes microsurgical lymphovenous or lympholymphatic anastomoses, debulking, and liposuction^[34]. Surgical procedures aiming at enhancing lymphatic function by removing excess fluid or tissue in the affected area have been shown to be only marginally effective^[34]. Surgery does not cure lymphedema, use of compression is necessary after surgery^[34]. Potential complications may occur with surgical management, such as recurrence of swelling, poor wound healing, and infection; thus surgical treatment should only be

Table 2 General exercise guidelines for breast cancer survivors

	Suitability	
	Survivors at-risk for Lymphedema	Survivors with Lymphedema
(1) Initiate exercise at lower intensity gradually increasing intensity as tolerated, monitoring the affected limb for signs and symptoms of lymphedema	Yes	Yes
(2) Walking, swimming, cycling and low impact aerobics are recommended.	Yes	Yes
(3) Modify physical exercise to reduce the risk of trauma and injury. Exercise to the extent that the affected body part is not sore or fatigued	Yes	Yes
(4) Flexibility exercises should be performed to maintain range of movement	Yes	Yes
(5) Appropriate warming up and cooling down should be implemented as part of exercise regime	Yes	Yes
(6) Compression garments should be worn during exercise	Not established	Yes

considered when other treatments fail, and with careful consideration of the benefits to risks ratio.

Chronic lymphedema leads to formation of excess subcutaneous adipose tissue secondary to slow or absent lymph flow^[36]. Liposuction can help to remove excess fat tissue^[36-38]. Liposuction increases skin capillary blood flow without further damaging already compromised lymph transport capacity in breast cancer survivors with lymphedema^[36-38]. Patients are able to maintain limb size reduction with the use of compression garments after liposuction. Liposuction does not correct inadequate lymph drainage and is contradictory when pitting edema is present.

Complete decongestive therapy (CDT) is the standard care for lymphedema in the United States, but it is time-consuming, expensive, and requires lifelong maintenance. This approach includes manual lymph drainage, multi-layer, short-stretch compression bandaging, gentle exercise, meticulous skin care, education in lymphedema self-management, and elastic compression garments^[39-41]. In the treatment phase, patients generally receive 2-h treatments 5 d a week for 3 to 8 wk. Once treatment phase is completed, the patient continues self-management phase at home with skin care and exercise, self-massage, and use of a compressive sleeve and glove during the day and/or arm bandaging at night^[40,41]. Studies have shown long-term volume reduction as high as 50%-63% in up to 79% mean volume reduction of patients who are 100% adherent^[39,40]. Lifelong adherence to prescribed treatment regimen is required to prevent progression of disease. Adherence to the prescribed management routine can be difficult because even the most customized garments or sleeves sometimes are uncomfortable, unsightly, and laborious to put on^[39-41]. A constellation of complex factors (*e.g.*, physical, financial, aesthetic, time) can influence survivors' adherence with management routines. From the patient's perspective, the complete decongestive therapy itself is a constant reminder of cancer experience that prevents her from living a normal life^[8].

Mechanical pneumatic pumps use electricity to inflate a single-chamber or multi-chamber sleeve that produces external limb compression. A decreased tissue capillary filtration rate facilitates tissue fluid reduction and, consequently, limb volume decrease^[42]. Lymph formation decreases, but lymph transport is not improved. Pneumatic

pumps can reduce swelling, but concern exists regarding the way in which the rapid displacement of fluid in the other areas of the body. The use of pumps does not eliminate the need for compression garments and may not provide more benefit than garments alone^[42]. Using pumps may cause complications, including lymphatic congestion and injury proximal to the pump sleeve, and increased swelling adjacent to the pump cuff in up to 18% of patients^[42].

Infection prevention and treatment is another important aspect of lymphedema management. Infection is the most common lymphedema complication^[43]. Lymph stasis, decreased local immune response, tissue congestion, and accumulated proteins and other debris foster infection^[43]. Patients and health care professionals should be vigilant about any signs and symptoms of infection, such as fever, malaise, lethargy, and nausea. Prompt oral antibiotics are the first line of treatment for acute infection to prevent the need for intravenous therapy and hospitalization^[29-30,44]. Preventive antibiotics have been highly effective for patients who experience repeated serious infections or inflammatory episodes^[43,44]. Skin care optimizes the condition of the skin and prevents cellulitis and infection^[43,44]. Lymphedema can cause skin dryness and irritation, increasing the risk of cellulitis and skin infection. Water-based and low pH moisturizers are recommended to discourage infection^[31].

CONCLUSION

Lymphedema is one of the most important factors that elicit daily stress in breast cancer survivors since there is no cure for this condition^[6-7]. In addition, breast cancer survivors face a life-long risk of developing lymphedema since there is no defined period of time after cancer treatment when the risk no longer exists^[3]. To reduce the risk of lymphedema and maintain optimal lymphedema management, patient self-care is ultimately necessary to promote lymph drainage and prevent inflammation-infection. Optimal self-care typically includes adherence to risk reduction behaviors, optimal weight management, use of compression garments, exercises, healthy lifestyle practices, and seeking assistance for lymphedema-related problems. Health care professionals should focus on empowering patients with skills and knowledge that helps

patients to reduce lymphedema risk and achieve optimal management and risk reduction. Empowering patients for optimal self-care is a great impetus to long-term success of lymphedema risk reduction and management.

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