Published in final edited form as:

Curr Breast Cancer Rep. 2017 June ; 9(2): 111–121. doi:10.1007/s12609-017-0237-8.

Diagnostic Methods, Risk Factors, Prevention, and Management of Breast Cancer-Related Lymphedema: Past, Present, and Future Directions

Hoda E. Sayegh¹, Maria S. Asdourian¹, Meyha N. Swaroop¹, Cheryl L. Brunelle², Melissa N. Skolny¹, Laura Salama¹, and Alphonse G. Taghian¹

¹Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

²Department of Physical Therapy, Massachusetts General Hospital, Boston, MA, USA

Abstract

Purpose of Review—Breast cancer-related lymphedema (BCRL) is a chronic, adverse, and much feared complication of breast cancer treatment, which affects approximately 20% of patients following breast cancer treatment. BCRL has a tremendous impact on breast cancer survivors, including physical impairments and significant psychological consequences. The intent of this review is to discuss recent studies and analyses regarding the risk factors, diagnosis, prevention through early screening and intervention, and management of BCRL.

Recent Findings—Highly-evidenced risk factors for BCRL include axillary lymph node dissection, lack of reconstruction, radiation to the lymph nodes, high BMI at diagnosis, weight fluctuations during and after treatment, subclinical edema within and beyond 3 months after surgery, and cellulitis in the at-risk arm. Avoidance of potential risk factors can serve as a method of prevention. Through establishing a screening program by which breast cancer patients are measured pre-operatively and at follow-ups, are objectively assessed through a weight-adjusted analysis, and are clinically assessed for signs and symptoms, BCRL can be tracked accurately and treated effectively. Management of BCRL is done by a trained professional, with research mounting towards the use of compression bandaging as a first line intervention against BCRL. Finally, exercise is safe for breast cancer patients with and without BCRL and does not incite or exacerbate symptoms of BCRL.

Summary—Recent research has shed light on BCRL risk factors, diagnosis, prevention, and management. We hope that education on these aspects of BCRL will promote an informed, consistent approach and encourage additional research in this field to improve patient outcomes and quality of life in breast cancer survivors.

Correspondence to: Alphonse G. Taghian.

Compliance with Ethical Standards

Conflict of Interest Hoda Sayegh, Maria Asdourian, Meyha Swaroop, Cheryl Brunelle, Melissa Skolny, and Laura Salama declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Breast cancer-related lymphedema; Risk factors; Prevention; Management; Diagnosis; Survivorship

Introduction

With the steady increase in the number of long-term survivors of early breast cancer due to ongoing medical advancements [1], emphasis on treating the chronic complications of treatment, including breast cancer-related lymphedema (BCRL), has increased [2]. Reported BCRL incidence in the literature ranges from 5 to 50% [3•]. A recent meta-analysis estimates that approximately one in five breast cancer survivors will develop BCRL [4] with a median onset of 14–18 months after surgery [5]. The pathophysiology and related processes contributing to BCRL are largely unknown [6]. Although there is no definitive cure for lymphedema, early intervention can limit progression of edema and significantly improve signs and symptoms [7••].

BCRL is characterized by improper drainage from lymphatic vessels [2, 8] and the subsequent accumulation of protein-rich fluid in the interstitial space [9]. Such fluid accumulation can result in abnormal swelling of the arm, shoulder, hand, breast, and/or trunk on the side treated for breast cancer [2, 4, 10–12]. Symptoms of lymphedema include arm tightness, heaviness, and in later stages, impaired limb function [10]. BCRL also negatively impacts a patient's body image and quality of life (QOL), contributing to increased rates of anxiety and depression amongst breast cancer survivors [2, 13, 14]. The risk of developing BCRL persists throughout a patient's lifetime, which may explain why BCRL causes considerable distress amongst patients [7••].

The multi-dimensional impact that BCRL can have on a patient's well-being has led to research focused on the prevention and treatment of this condition. Screening programs and research targeted at identifying potential preventative methods have continued to evolve. As a result of ongoing research regarding patient outcomes from radiation and lymph node surgery, physicians have shifted away from more invasive, high-risk surgical and treatment approaches [1–17]. There are several studies that have identified risk factors for BCRL, allowing practitioners to identify those at the highest risk for developing BCRL [3•, 4, 5, 18–27, 28•]. Lastly, research in the management and treatment of BCRL has allowed for significant improvements in patient outcomes. This review explores the risk factors, diagnosis, prevention, and management of BCRL, in an effort to ultimately improve the QOL of breast cancer survivors.

Diagnosis

Methods

Several notable advances in the diagnosis of BCRL are due to new measurement techniques, which have supplemented the more traditional methods such as water displacement and circumferential tape measurement (see Table 1) [8, 29, 30]. Water displacement, though accurate and inexpensive, comes at the cost of time-intensive cleaning to meet hygienic

standards and the need for a strict protocol to ensure accuracy [30]. Additionally, this technique cannot be used to localize swelling in a specific segment of the arm [31]. Circumferential tape measurement is also an inexpensive, reliable, and highly accessible measurement tool in a variety of healthcare settings [32, 33]. However, since the measurement process takes substantial time for both patient and provider, the perceived low cost of this technique needs to be reconsidered in the context of these important disadvantages [34]. Furthermore, it is common for multiple providers to measure the arm for lymphedema screening purposes [7••]. As such, inter-rater variability can generate error with the tape measurement without significant training and provider experience, reducing the consistency and accuracy of values obtained [35].

The disadvantages associated with the aforementioned methods in measuring BCRL have led to well-validated and more efficient measurement devices. One such device for measurement is the Perometer, which calculates total limb volume utilizing infrared sensors [30, 36]. Measurements are highly reproducible [37] and are completed within 2–3 min for both arms, the device can be wiped clean in seconds between patients, and a well-established measurement protocol is available [7••]. The Perometer is a valid and reliable measure of limb volume, and it is highly sensitive, allowing for subclinical detection of BCRL in patients [5, 33, 36, 38]. Perometry also allows for specific segments of the limb to be measured, which is helpful for detecting isolated edema in a section of the arm or hand. Drawbacks of the Perometer include its cost and large size [39].

Another modern measurement technique is bioimpedance spectroscopy (BIS). This machine passes an electrical current through the limb to establish impedance scores and ratios between arms which reflect the amount of extracellular fluid in the arm [40]. Recommendations for measurement methodology are published and available to the user [41]. There are several advantages to this method, including its portability and ability to complete measurements within 4–5 min [39, 42]. A limitation to this technique is that it measures only patients who have undergone unilateral breast surgery, excluding those who receive bilateral breast surgery. Jain et al. demonstrated that inter- and intra-rater reliability for BIS is high in a study involving ten patients [43]. The literature also suggests that BIS can detect subclinical lymphedema [29,44,45•]. Bundred et al. compared BIS to perometry and found moderate correlation between the methods at both 3 and 6 months [45•], though further studies with a longer follow-up time are needed to evaluate the sensitivity and specificity of the BIS method in detecting subclinical BCRL [46].

It is important to note that diagnosis of BCRL should not be made through volumetric methods or through BIS alone. A clinical examination as well as subjective information, including patient-related outcome measures, signs, and symptoms, should be included in any screening and diagnosis of BCRL [11, 47–51]. There are several comprehensive, well-validated outcome measures available to evaluate breast cancer-related lymphedema [48–50, 52].

Quantification

Though sensitivity has improved with recent developments in measurement and detection, Sun et al. analyzed 1028 patients and reported that without a baseline measurement prior to

surgery, diagnoses of subclinical and clinical lymphedema are missed 40–50% of the time. Furthermore, this study found that roughly half of lymphedema cases that are diagnosed without a baseline measurement are most likely over-diagnoses. This is largely because arms are rarely symmetrical at baseline. 2.9 and 28.3% of patients had >10 or >5% asymmetry, respectively, at their baseline measurement (Fig. 1). From these findings, it is clear that pre-operative measurements for at-risk patients must be implemented for accurate BCRL diagnosis [53•, 54]. Furthermore, research presented on BCRL that does not include a pre-operative measurement must be reviewed closely for inaccuracies in the diagnosis of lymphedema.

Ancukiewicz et al. demonstrated that absolute volume changes as a quantification method for BCRL is flawed. As seen in Fig. 2, specificity depends highly on the patient's body size. The arm size of patients diagnosed with breast cancer varies within a broad range: the ratio of largest to smallest arm volume in this patient sample was more than 5:1. With such variation, the visual—and likely the functional—impact of the same absolute increase in arm size (200 mL or 2 cm) is very different in patients with small and large arms. For example, Fig. 2 depicts that an increase of 200 mL in arm volume corresponds to a 15.4 and 3.3% increase in relative arm volume for arms of 1300 and 6000 mL volumes, respectively. Thus, the absolute and relative criteria for diagnosis of BCRL are mutually inconsistent in populations with heterogeneous arm sizes. Absolute volume change correlates with pre-operative arm volume, patient weight, and BMI but relative volume change is independent of patient weight. As such, relative volume change, which incorporates baseline volume, is better suited than absolute volume change as the standard quantification method for BCRL [55].

For unilateral breast surgery, Ancukiewicz et al. established a method for measuring relative volume change (RVC) by taking into account the pre-operative and post-operative follow-up volumes on the ipsilateral arm (A1 and A2, respectively) and the pre-operative and post-operative follow-up volumes (U1 and U2) on the contralateral arm. RVC is thus modeled as $RVC = [(A2 \cdot U1) / (U2 \cdot A1) - 1]$. The contralateral arm operates as a control as it assumes any weight gained equally distributes amongst the arms [56].

Since patients undergoing bilateral breast surgery do not have a contralateral arm to use as a control, Miller et al. formulated a revised model for this subset of patients, which incorporates a patient's weight at each arm measurement. This study demonstrated a 1:1 linear relationship between change in patient weight and contralateral arm volume in unilateral breast surgery patients, thus proposing a weight-adjusted change (WAC) formula to quantify arm volume in patients treated with bilateral breast surgery [57]. Furthermore, the WAC formula was validated by demonstrating that the RVC formula [56] and the WAC formula quantified BCRL similarly in unilateral breast surgery patients, defined as 10% arm volume change from baseline. The WAC formula takes into account the pre-operative and postoperative arm volumes on the surgical side (A1 and A2) as well as the pre-operative and post-operative weights of the patient (W1 and W2), as $WAC = [(A2 \cdot W1) / (W2 \cdot A1) - 1]$. It should be noted that arm volume calculated from tape measurement, perometry, or water displacement may be entered into the RVC or WAC formulas for unilateral or bilateral patients, respectively [51].

There is no universal definition for lymphedema diagnosis, and consequently, there exists no universal diagnostic method for the condition [58]. However, there has been a general consensus in the literature that an arm volume change of 10% is indicative of lymphedema. Some studies, however, have used an arm volume change of >3% as an appropriate threshold for intervention with compression [59] and certainly edema <10% is worthy of attention in those at risk. When utilizing BIS for measurement, the impedance value generated is converted to an L-Dex score [60]. Patients with an L-Dex score of greater than 10 units above pre-operative baseline or greater than 3 standard deviations above normative data are considered to have BCRL [60].

It has been suggested to choose one method of measurement which includes a pre-operative measurement whenever possible and to measure at set intervals throughout and beyond treatment as part of a screening program. This would allow for calculation of volume change as compared to baseline in order to successfully screen for, diagnose, and treat lymphedema as early as possible [7•, 53•].

Risk Factors

Numerous risk factors have been reported in the literature for BCRL, including regional lymph node radiation, method of breast and axillary surgery, high BMI at time of diagnosis, weight fluctuations during breast cancer treatment, subclinical edema, and cellulitis [4, 5, 18–27, 28•, 61–63].

Radiation Therapy

Tsai et al. found that any type of radiation therapy (relative risk (RR) = 1.92; 95% CI 1.61–2.28) was an independent risk factor for lymphedema development, as compared to no radiotherapy [18]. Warren et al. sought to determine the risk associated with several radiation therapy (RT) methods on BCRL development. A cohort of 1476 breast cancer patients was subdivided into the five treatment categories: no radiation, partial breast irradiation (PBI), whole breast (WBI)/chest wall irradiation alone, or WBI/chest wall radiation with regional lymph node radiation (RLNR). Patients who received RLNR were further differentiated into patients receiving a posterior axillary boost (PAB) along with the supraclavicular irradiation (SC) versus patients who only received SC. Analysis showed that the 2-year cumulative incidences of BCRL were 3.0% in the no radiation cohort, 3.1% in the breast or chest wall alone cohort, 21.9% in the SC cohort, and 21.1% in the SC and PAB cohort. RLNR was found to be an independent risk factor for BCRL development, though the BCRL risk between SC only and SC with PAB did not differ. Following these results, Warren et al. recommend that this high-risk population of breast cancer patients receiving RLNR should be prospectively screened for BCRL [28•].

In an effort to further assess the effect of RT on BCRL, Leong et al. compared hypofractionated nodal RT (defined as >2Gy/fraction) and conventional fractionated nodal RT (defined as 2Gy/fraction). The study cohort consisted of 708 patients whose self-reported arm symptoms were comprised of arm and hand swelling, stiffness, pain, numbness, and immobility. There was no difference in patient-reported arm symptoms or

disability when comparing hypofractionated nodal RT to conventional fractionated nodal RT. Arm and shoulder function, however, was impaired in the conventional RT group [61].

Axillary Surgery Type

Axillary lymph node dissection (ALND) has consistently been identified as an independent risk factor for the development of BCRL. Miller et al. examined a cohort of 627 patients who underwent 664 mastectomies for a median follow-up of 23 months. For mastectomy patients, a positive sentinel lymph node biopsy (SLNB) and radiation therapy (RT) resulted in a lower than 10% incidence of lymphedema compared to ALND with or without radiation (30.1 and 19.3%, respectively). Results indicate that avoiding ALND would significantly reduce lymphedema risk in those with a positive SLNB [63]. Tsai et al. published a comprehensive report calculating the relative risk of several treatment-related factors from 98 independent studies. They found that ALND increased the risk of lymphedema compared to no ALND (RR = 3.47; 95% CI 2.34–5.15) as well as compared to SLNB (RR = 3.07; 95% CI 2.20–4.29) [18].

Lack of Breast Reconstruction

The risk of lymphedema after breast reconstruction has been a topic of recent interest; Miller et al. compared immediate reconstruction to immediate autologous reconstruction through multivariate analysis with a prospective cohort of breast cancer patients screened pre-operatively and post-operatively via perometry. The cohort consisted of 616 individual patients with 891 total mastectomies. After 2 years, 26.7% of patients without an implant developed BCRL, 9.9% of patients opting for the immediate autologous developed BCRL, and only 4% of patients who opted for the immediate implant developed BCRL [62]. These results demonstrate that reconstruction, specifically immediate reconstruction, can result in a lower BCRL risk when compared to no breast reconstruction following a mastectomy. Basta et al., however, found that reconstruction does not modify lymphedema risk. It is important to note that there was no diagnostic consensus for BCRL as well as no indication of preoperative measurements in Basta's study, which limits the study's findings [64].

High BMI and Weight Fluctuations

Apart from treatment-related risk factors, high BMI at diagnosis ($> 30 \text{ kg/m}^2$) is a frequently published risk factor for lymphedema development [4, 18–23, 25, 26, 65]. Jammallo et al. reported on a cohort of 787 patients who were prospectively screened for BCRL via perometry. The study showed that BMI > 30 was an independent risk factor for BCRL. Weight fluctuations (loss or gain) greater than 10 lbs per month post-operatively also resulted in a higher risk of BCRL [19]. Fu et al. screened women via BIS and found similar results. Women who were obese were more likely to develop lymphedema—defined as an L-Dex ratio > 7.1 —than women who were in the normal/underweight group and the overweight group pre-operatively, 4–8 weeks post-operatively, and 12 months post-operatively [65].

Subclinical Edema

Studies on subclinical edema have elucidated other risk factors of BCRL. Specht et al. assessed whether arm volume changes at various time intervals influenced the risk of

developing BCRL. The group prospectively screened 1173 patients via perometry and found that low-level volume changes (RVC of 3 and <5, and 5 and <10%) within 3 months of surgery were significantly associated with BCRL development. Additionally, volume changes of RVC 5 and <10% were significantly associated with BCRL development greater than 3 months post-operatively, while an RVC of 3 and <5% greater than 3 months post-operatively was not associated with BCRL development. Results of this study suggest that patients with an RVC from 3 to <5% within 3 months of surgery and 5 to <10% at any point should be monitored closely and may greatly benefit from early intervention [5].

Cellulitis

Finally, Ferguson et al. found, through multivariate analysis, that cellulitis significantly increased the risk of BCRL [24•]. Indelicato et al. found that those with BCRL were more likely to develop delayed breast cellulitis. In this study, 22% of the patients with cellulitis developed recurrent episodes of cellulitis, which was more prevalent in patients with BCRL. Thus, cellulitis may increase the risk for developing BCRL, and vice versa [3•, 24•, 27], but further exploration is needed to understand the relationship between lymphedema development and cellulitis [24•].

Screening and Prevention

Routine screening allows for subclinical detection and therefore early treatment of lymphedema, which can aid in preventing further progression of edema [44, 45•, 66]. Brunelle et al. described the establishment and feasibility of a screening program at Massachusetts General Hospital (MGH), where all breast cancer patients are monitored for BCRL throughout their treatment and at follow-up visits with their treating oncologist. To date, over 4500 patients have been screened with pre-operative baseline perometry measurements and routine post-operative measurements with an accompanying survey for at least 5 years. Patients are screened for signs and symptoms of BCRL and a clinical exam ensues to confirm a diagnosis. Additionally, those at higher risk of BCRL are more frequently monitored [67]. In order to maximize consistency, the group implemented a well-defined measurement protocol [7].

Stout et al. prospectively measured 196 women via perometry pre-operatively and at 3-month intervals after surgery. Upon the diagnosis of lymphedema, defined in this study as a >3% increase in limb volume, patients received compression garments as treatment. Significant volume reduction was attained from the 4-week intervention and results were maintained at the average follow-up time 4.8 months after the completion of the intervention. This study again supports screening and early intervention but is limited by its small sample size and non-randomized design [54].

Screening and early prevention may have financial benefits. By estimating costs using the 2009 Medicare physician fee schedule, Stout et al. found the cost per year to manage early-stage BCRL through a prospective screening model is \$636.19. The cost per year to manage late-stage BCRL through the traditional model is \$3124.92 [68]. Though more research is necessary to determine the cost-effectiveness of screening and early intervention, this study provides compelling preliminary evidence.

Precautionary Guidelines

Ferguson et al. sought to determine the relationship between non-treatment-related risk factors and development of BCRL. The group prospectively screened 632 patients via perometry who had undergone unilateral or bilateral breast surgery. Data on the number of blood draws, blood pressure readings, injections, and incidence of infection in the at-risk arm as well as the number of flights taken since the last measurement was collected via patient self-report. Multivariate analysis showed no significant association between lymphedema development and undergoing one or more blood draws, blood pressure readings, infection to the ipsilateral arm, or air travel [24•]. It should be noted that the number of events within the cohort was low, and more research is needed to definitively establish the effect on BCRL risk of these precautionary behaviors.

The National Lymphedema Network provides several precautionary lifestyle recommendations for at-risk patients [69]. These include avoiding the constriction of the at-risk arm (i.e., blood pressure cuffs, tourniquets, and tight clothing), avoiding venous puncture (i.e., blood draws and intravenous sticks), and wearing a compression sleeve during air travel. There exists limited high-level data supporting or refuting their efficacy [3•, 70]. Therefore, Asdourian et al. have advocated for a more rigorous and evidence-based analysis of the lifestyle risk exposures for BCRL, with the goal of minimizing the risk of developing BCRL while maximizing QOL [3•].

Management

Treatment

Driven by the need to ensure best practice for BCRL intervention amongst healthcare professionals, the Lymphology Association of North America (LANA) has devised recommended standards for a certified lymphedema therapist. A practitioner must complete at least 135 hours of complete decongestive therapy (CDT) coursework, which involves the following: an in-depth understanding of the pathophysiology of lymphatic function, manual lymph drainage (MLD), compression bandaging (CB), lymphatic exercise, skin care, and education on the self-management of lymphedema. Practitioners must also be currently licensed as a physical therapist, occupational therapist, or another related medical profession [71].

There is neither high-level evidence for nor consensus on the appropriate threshold to initiate intervention for BCRL. Close screening is recommended for patients with elevated arm volume $>3\text{--}5\%$ in the 3 months after surgery, but these patients do not appear to progress to volume $>10\%$, and intervention at $3\text{--}5\%$ is not warranted [5]. However, further investigation of a $5\text{--}10\%$ threshold is indicated, as these patients may tend to progress to volume $>10\%$. Justification for early intervention should be a focus in the literature.

Treatment of BCRL involves two main phases: the first is reductive CDT and the second is maintenance therapy. Reductive CDT involves individualized therapy administered by a certified lymphedema therapist. Patients are seen frequently until the limb volume reaches a stable state, usually within a few weeks. The maintenance phase follows, emphasizing self-

care, including some or all of self-lymphatic drainage, compression garments, exercise, and a skin care routine [72].

In its entirety, CDT has been the main treatment for BCRL for many years. It has been found to effectively treat BCRL; however, parameters and protocols of CDT programs vary, making it difficult to establish best practice guidelines for frequency and duration [11, 73]. Studies generally look at CDT in its entirety, but there is less literature and poorer quality of studies on the role of each of its components, including exercise, skin care, compression, and MLD.

There exists increasingly more evidence for utilizing CB as the first-line intervention for BCRL. Stout et al. found that wearing a compression sleeve for a 4-week period successfully treated subclinical lymphedema (LE) [54]. In patients with established BCRL, McNeely et al. conducted a randomized controlled trial to assess whether the addition of MLD to CB reduced BCRL. Fifty women were measured via water displacement and circumferential tape measurement. CB reduced arm volume successfully, with or without the addition of MLD [74]. In a randomized trial, Andersen et al. assessed 42 patients with BCRL who were treated with CDT with or without MLD. The group found that edema volume, measured by circumferential tape measurement, and LE symptoms did not significantly differ between the two groups [75]. Finally, Dayes et al. conducted a randomized trial comparing CB to daily manual lymphatic drainage and CB. The trial measured 103 women via circumferential tape measurement and arm function and QOL was assessed. The group found no significant difference in volume reduction, arm function, and QOL measures between the two groups [76]. These studies assessing CB are all limited by their small sample size; however, because CDT is resource intensive for the patient and the healthcare system, these data provide invaluable insight into management of BCRL. In a recent editorial, Javid et al. follows this research to suggest that early LE should not be treated first with MLD [77], but rather with compression.

Intermittent pneumatic compression (IPC) technology has improved significantly over the past few decades [78]. Several studies have assessed the efficacy of IPC. Uzkeser et al. conducted a randomized controlled trial with 31 LE patients comparing CDT alone to CDT with the addition of IPC. The study found volume reduction in both groups with no significant difference between the groups [79]. Shao et al. conducted a meta-analysis of the published randomized controlled studies assessing IPC efficacy in BCRL management. The group found that recent studies, though lacking in quality, have not demonstrated IPC's efficacy in LE treatment [80].

Some studies evaluating IPC, however, have demonstrated its usefulness in BCRL management. Szolnoky et al. sought to assess the use of IPC in conjunction with CDT involving MLD. Twenty-seven women were randomly placed in either cohort and LE was measured via circumferential arm measurement and a self-reported symptom questionnaire at the beginning and end of therapy, and 1 and 2 months after the initiation of therapy. Though both groups exhibited volume reduction, there was significantly more reduction in the IPC cohort at all time points [81]. Gurdal et al. found similar results in their study comparing MLD + CB and IPC + self-lymphatic drainage (SLD). All patients, no matter the

treatment method, experienced volume reduction with no significant difference between the two cohorts. They further noted that IPC may be preferential to patients with BCRL as the treatment can be done while at home [82]. The use of IPC remains controversial and more high-level evidence is needed to assess its true efficacy. This method should be individualized and may supplement a patient's treatment by a certified lymphedema therapist.

It is important to note that management as discussed in this review is non-surgical. Techniques such as liposuction, lymph node transfers, and lympho-venous anastomoses [8, 83] are also aimed at BCRL prevention or management. Research is evolving quickly in this area; however, this is beyond the scope of this review.

Exercise

Exercise is an integral part of care for patients at risk for lymphedema development as well as those with a confirmed breast cancer diagnosis. The American College of Sports Medicine has issued exercise guidelines for breast cancer survivors. This panel urges cancer patients to remain active, maintaining daily activity during adjuvant therapies as well as resuming daily activity as soon as possible following surgery. Patients are recommended to complete 150 min/week of moderate level activity (e.g., walking) or 75 min/week of vigorous level activity (e.g., running). These recommendations should be included in the plan of care for every breast cancer survivor [84].

There exists a misconception that breast cancer survivors should limit the use of the at-risk arm to avoid BCRL development. However, this avoidance could lead to adverse effects such as increased risk of injury or subsequent weight gain [85], which itself has been shown to be a risk factor for BCRL [19]. Several exercise trials in patients with breast cancer have demonstrated that a progressive program of regular aerobic and resistance exercise is safe and does not incite BCRL [86–88].

Schmitz et al. performed a randomized controlled trial with 141 patients with stable BCRL, in which arm volume was measured using water displacement. The group sought to assess the effect of progressive weight lifting on LE exacerbation, and severity and number of symptoms, as well as muscle strength. After 1 year, patients with lymphedema in the weight lifting cohort were shown to have no change in limb swelling compared to the control group. The weight lifting cohort showed a decreased incidence of BCRL exacerbation and symptoms, as well as an increase in strength. Schmitz et al.'s work has also demonstrated that there is no upper limit for the amount of weight used, if weight addition is progressive [85].

Cormie et al. sought to measure the acute inflammatory response before and after low-, moderate-, and high-load resistance exercise of the upper body in a randomized, crossover study. Twenty-one patients with a BCRL diagnosis were measured via BIS. Symptoms were assessed and venous blood samples were taken in order to determine levels of inflammatory and exercise-induced muscle markers. The group found that regardless of the resistance load, there was no significant difference in inflammatory response, arm swelling, or symptom scores [89•].

Finally, a recent meta-analysis by Rogan et al. evaluated the current literature on the effects of exercise as well as treatment success. The group evaluated four different randomized controlled trials with four unique protocols for the exercise regimen. All four studies showed a reduction in limb fluid, and the group's meta-analysis demonstrated a 200-mL fluid reduction from exercise alone. It is essential to emphasize that exercise, under close supervision [8], is safe and beneficial for patients at risk of BCRL development, as well as for those with a confirmed diagnosis of BCRL [85, 90, 91].

Recently, a growing number of studies investigated the efficacy of other modes of exercise on BCRL. Fisher et al. reported that when six women with a confirmed BCRL diagnosis practiced Hatha Yoga three times per week for 8 weeks, arm volume significantly decreased while QOL and self-reported arm function remained stable [92]. Letellier et al. conducted a randomized controlled pilot and reported that when 25 women took part in a 12-week aqua lymphatic therapy (ALT) intervention, there was no change in limb volume, though grip strength improved, in both groups [93], and only the ALT group demonstrated a significant reduction in pain and an overall higher QOL. Studies are evolving quickly, supporting exercise for patients with BCRL. Larger randomized controlled trials are necessary to gain high-level evidence for alternative exercise interventions.

Future Directions

While current research and advances are promising, there is much to be done in BCRL research. Treatment and prevention of lymphedema must be a team approach, involving certified lymphedema therapists as well as treating oncologists and surgeons. In order to efficiently collaborate with one another, there must be universal agreement in defining, measuring, and quantifying lymphedema. Shifting from an impairment-based model towards a screening-based model will allow for increasingly early diagnosis and intervention and will allow the development of high-level evidence in support of screening and early intervention for BCRL. Finally, high-level research to define the role of precautionary behaviors in the risk of BCRL development is imperative.

Conclusion

The tremendous physical and psychosocial impact of BCRL on a breast cancer survivor is clear [2, 7•, 13, 14]. Practitioners must approach this condition with a full understanding of which patients are at risk, effective prevention, routine screening, early diagnosis, and management.

There exists no diagnostic consensus for defining BCRL, largely due to the multitude of measurement techniques available [58]. This will likely continue, given varying resources between healthcare systems and facilities. Of utmost importance, however, is establishing a screening program where newly diagnosed breast cancer patients are measured pre-operatively and post-operatively—at regularly scheduled follow-up visits—and are monitored clinically in order to screen for signs and symptoms of BCRL [7•]. Paired with an accurate analysis technique that controls for weight fluctuations, lymphedema development can be tracked accurately and effectively [53•, 54–57].

Well-substantiated treatment-related risk factors for BCRL include ALND, lack of reconstruction, and RLNR [18, 28, 63]. Non-treatment-related risk factors include high BMI at time of diagnosis (>30), weight fluctuations of ± 10 lbs per month post-operatively, subclinical edema within and beyond 3 months after surgery, and cellulitis in the at-risk arm [4, 5, 18–27, 65]. Identifying individual risk factors and educating patients of their individual risk are essential for BCRL prevention.

As BCRL is a highly feared complication [94] amongst breast cancer survivors, it is essential that well-substantiated precautionary guidelines be specified [3•, 24•]. More rigorous research must be done in this field to ensure that precautionary guidelines given to patients are backed by high-level scientific evidence.

In today's patient-centered healthcare environment, the patient's quality of life after cancer treatment must be prioritized. This means addressing a patient's physical and psychological well-being, which are both affected by BCRL. We believe that prevention, diagnosis, and management of breast cancer-related lymphedema operate most effectively in concert as part of an effective lymphedema screening and treatment program offered from diagnosis throughout survivorship.

Acknowledgments

The project was supported by Award Number R01CA139118 (AGT) and Award Number P50CA08393 (AGT) from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. This program is supported by the Adele McKinnon Research Fund for Breast Cancer-Related Lymphedema.

Alphonse G. Taghian is supported by the National Cancer Institute and has served as a consultant for VisionRT.

References

Paper of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogundimu OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP. CONCORD Working Group Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet*. 2015; 385:977–1010. [PubMed: 25467588]
2. Erickson VS, Pearson ML, Ganz PA, Adams J, Kahn KL. Arm edema in breast cancer patients. *J Natl Cancer Inst*. 2001; 93:96–111. [PubMed: 11208879]
- 3•. Asdourian MS, Skolny MN, Brunelle C, Seward CE, Salama L, Taghian AG. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. *Lancet Oncol*. 2016; 17:e392–405. This review examines the literature on lifestyle-associated risk factors for lymphedema (such as air travel, ipsilateral arm blood pressure measurements, skin puncture, cellulitis, and extreme temperatures). They found little high-level evidence and conflicting results, thereby advocating for further research and discussion on these risk factors. [PubMed: 27599144]
4. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and metaanalysis. *The Lancet Oncology*. 14:500–15.

5. Specht MC, Miller CL, Russell TA, Horick N, Skolny MN, O'Toole JA, Jammallo LS, Niemierko A, Sadek BT, Shenouda MN, Finkelstein DM, Smith BL, Taghian AG. Defining a threshold for intervention in breast cancer-related lymphedema: what level of arm volume increase predicts progression? *Breast Cancer Res Treat.* 2013; 140:485–94. [PubMed: 23912961]
6. Cemal Y, Pusic A, Mehrara BJ. Preventative measures for lymphedema: separating fact from fiction. *J Am Coll Surg.* 2011; 213:543–51. [PubMed: 21802319]
- 7•• Brunelle C, Skolny M, Ferguson C, Swaroop M, O'Toole J, Taghian AG. Establishing and sustaining a prospective screening program for breast cancer-related lymphedema at the massachusetts general hospital: lessons learned. *J Pers Med.* 2015; 5:153–64. This paper describes the establishment of a BCRL screening program at Massachusetts General Hospital. The clinicians' experiences, struggles, and improvements are carefully detailed in order for other institutions to learn from and develop screening programs of their own. [PubMed: 26011383]
8. Shaitelman SF, Cromwell KD, Rasmussen JC, Stout NL, Armer JM, Lasinski BB, Cormier JN. Recent progress in the treatment and prevention of cancer-related lymphedema. *CA Cancer J Clin.* 2015; 65:55–81. [PubMed: 25410402]
9. Cheville AL, McGarvey CL, Petrek JA, Russo SA, Taylor ME, Thiadens SR. Lymphedema management. *Semin Radiat Oncol.* 2003; 13:290–301. [PubMed: 12903017]
10. Cheville AL, McGarvey CL, Petrek JA, Russo SA, Thiadens SR, Taylor ME. The grading of lymphedema in oncology clinical trials. *Semin Radiat Oncol.* 2003; 13:214–25. [PubMed: 12903011]
11. Armer JM, Radina ME, Porock D, Culbertson SD. Predicting breast cancer-related lymphedema using self-reported symptoms. *Nurs Res.* 2003; 52:370–9. [PubMed: 14639083]
12. Armer JM, Stewart BR. Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. *Lymphology.* 2010; 43:118–27. [PubMed: 21226414]
13. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. *J Clin Oncol.* 2008; 26:5689–96. [PubMed: 19001331]
14. Cormier JN, Xing Y, Zaniletti I, Askew RL, Stewart BR, Armer JM. Minimal limb volume change has a significant impact on breast cancer survivors. *Lymphology.* 2009; 42:161–75. [PubMed: 20218084]
15. Canavese G, Bruzzi P, Catturich A, Tomei D, Carli F, Garrone E, Spinaci S, Lacopo F, Tinterri C, Dozin B. Sentinel lymph node biopsy versus axillary dissection in node-negative early-stage breast cancer: 15-year follow-up update of a randomized clinical trial. *Ann Surg Oncol.* 2016; 23:2494–500. [PubMed: 26975739]
16. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, Mansel RE, Cataliotti L, Westenberg AH, Klinkenbijn JHG, Orzalesi L, Bouma WH, van der Mijle HCI, Nieuwenhuijzen GAP, Veltkamp SC, Slaets L, Duez NJ, de Graaf PW, van Dalen T, Marinelli A, Rijna H. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *LANCET ONCOL.* 2014; 15:1303–10. [PubMed: 25439688]
17. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, Leitch AM, Saha S, Hunt KK, Giuliano AE. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol.* 2007; 25:3657–63. [PubMed: 17485711]
18. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GKD, Scott-Conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. *Ann Surg Oncol.* 2009; 16:1959–72. [PubMed: 19365624]
19. Jammallo LS, Miller CL, Singer M, Horick NK, Skolny MN, Specht MC, O'Toole J, Taghian AG. Impact of body mass index and weight fluctuation on lymphedema risk in patients treated for breast cancer. *Breast Cancer Res Treat.* 2013; 142:59–67. [PubMed: 24122390]
20. McLaughlin SA, Wright MJ, Morris KT, Giron GL, Sampson MR, Brockway JP, Hurley KE, Riedel ER, Van Zee KJ. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. *J Clin Oncol.* 2008; 26:5213–9. [PubMed: 18838709]

21. Swenson KK, Nissen MJ, Leach JW, Post-White J. Case-control study to evaluate predictors of lymphedema after breast cancer surgery. *Oncol Nurs Forum*. 2009; 36:185–93. [PubMed: 19273407]
22. Park JH, Lee WH, Chung HS. Incidence and risk factors of breast cancer lymphoedema. *J Clin Nurs*. 2008; 17:1450–9. [PubMed: 18482142]
23. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer*. 2001; 92:1368–77. [PubMed: 11745212]
24. Ferguson CM, Swaroop MN, Horick N, Skolny MN, Miller CL, Jammallo LS, Brunelle C, O'Toole JA, Salama L, Specht MC, Taghian AG. Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer. *J Clin Oncol*. 2016; 34:691–8. This prospective study investigated the impact of precautionary risk factors on BCRL development. The analysis demonstrated that cellulitis increases the risk of BCRL while blood pressure readings, air travel, injections, and ipsilateral blood draws do not. [PubMed: 26644530]
25. Bar, Ad V., Cheville, A., Solin, LJ., Dutta, P., Both, S., Harris, EE. Time course of mild arm lymphedema after breast conservation treatment for early-stage breast cancer. *Int J Radiat Oncol Biol Phys*. 2010; 76:85–90. [PubMed: 19427748]
26. Bevilacqua JL, Kattan MW, Changhong Y, Koifman S, Mattos IE, Koifman RJ, Bergmann A. Nomograms for predicting the risk of arm lymphedema after axillary dissection in breast cancer. *Ann Surg Oncol*. 2012; 19:2580–9. [PubMed: 22395997]
27. Shih YC, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, Perkins GH, Elting LS. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. *J Clin Oncol*. 2009; 27:2007–14. [PubMed: 19289624]
28. Warren L, Miller C, Horick N, Skolny M, Jammallo L, Sadek B, Shenouda M, O'Toole J, MacDonald S, Specht M, Taghian A. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: A prospective cohort study. *Int J Radiat Oncol Biol Phys*. 2014; 88:565–71. This prospective study investigated the impact of radiation therapy on BCRL development to find that regional lymph node radiation significantly increased the risk. [PubMed: 24411624]
29. Shah C, Arthur DW, Wazer D, Khan A, Ridner S, Vicini F. The impact of early detection and intervention of breast cancer-related lymphedema: a systematic review. *Cancer Med*. 2016; 5:1154–62. [PubMed: 26993371]
30. Ridner SH, Montgomery LD, Hepworth JT, Stewart BR, Armer JM. Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema. *Lymphology*. 2007; 40:35–46. [PubMed: 17539463]
31. Meijer RS, Rietman JS, Geertzen JH, Bosmans JC, Dijkstra PU. Validity and intra- and interobserver reliability of an indirect volume measurements in patients with upper extremity lymphedema. *Lymphology*. 2004; 37:127–33. [PubMed: 15560108]
32. Tewari N, Gill PG, Bochner MA, Kollias J. Comparison of volume displacement versus circumferential arm measurements for lymphoedema: Implications for the SNAC trial. *ANZ J Surg*. 2008; 78:889–93. [PubMed: 18959643]
33. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. *Phys Ther*. 2006; 86:205–14. [PubMed: 16445334]
34. Armer JM, Ridner SH. Measurement techniques in assessment of lymphedema. *National Lymphedema Network*. 2006; 18:1–4.
35. Tidhar D, Armer JM, Deutscher D, Shyu CR, Azuri J, Madsen R. Measurement issues in anthropometric measures of limb volume change in persons at risk for and living with lymphedema: a reliability study. *J Pers Med*. 2015; 5:341–53. [PubMed: 26437431]
36. Tierney S, Aslam M, Rennie K, Grace P. Infrared optoelectronic volumetry, the ideal way to measure limb volume. *Eur J Vasc Endovasc Surg*. 1996; 12:412–7. [PubMed: 8980428]
37. Stanton AW, Northfield JW, Holroyd B, Mortimer PS, Levick JR. Validation of an optoelectronic limb volumeter (Perometer). *Lymphology*. 1997; 30:77–97. [PubMed: 9215977]

38. Deltombe T, Jamart J, Recloux S, Legrand C, Vandenbroeck N, Theys S, Hanson P. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. *Lymphology*. 2007; 40:26–34. [PubMed: 17539462]
39. Ridner SH, Dietrich MS, Deng J, Bonner CM, Kidd N. Bioelectrical impedance for detecting upper limb lymphedema in nonlaboratory settings. *Lymphat Res Biol*. 2009; 7:11–5. [PubMed: 19231915]
40. Hayes S, Di Sipio T, Rye S, Lopez JA, Saunders C, Pyke C, Bashford J, Battistutta D, Newman B. Prevalence and prognostic significance of secondary lymphedema following breast cancer. *Lymphat Res Biol*. 2011; 9:135–41. [PubMed: 22066743]
41. Swaroop MN, Brunelle CL, Asdourian MS, Sayegh HE, Skolny MN, Salama L, Taghian AG. In Response to: Letter to the Editor by Kilbreath et al. *J Surg Oncol*. 2016
42. ImpediMed. [Accessed 01/31 2017] Measurement guide: assessment of unilateral arm lymphoedema. 2013. https://www.impedimed.com/wp-content/products/u400/L_Dex_Measurement_Guide_Arms.pdf
43. Jain MS, Danoff JV, Paul SM. Correlation between bioelectrical spectroscopy and perometry in assessment of upper extremity swelling. *Lymphology*. 2010; 43:85–94. [PubMed: 20848996]
44. Erdogan Iyigun Z, Selamoglu D, Alco G, Pilanci KN, Ordu C, Agacayak F, Elbiken F, Bozdogan A, Ilgun S, Guler Uysal F, Ozmen V. Bioelectrical impedance for detecting, monitoring lymphedema in patients with breast cancer Preliminary results of the florence nightingale breast study group. *Lymphat Res Biol*. 2015; 13:40–5. [PubMed: 25526543]
45. Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, Skene A, Purushotham A, Bramley M, Hodgkiss T. Investigators of BEA/PLACE studies. Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat*. 2015; 151:121–9. This study compared the measurement techniques of BIS and perometry. Correlation was found between the methods at 3 and 6 months. [PubMed: 25850535]
46. Ward LC, Kilbreath SL, Dylke E, et al. Letter to the Editor Re: Bundred “Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphoedema after axillary node clearance for breast cancer”. *Breast Cancer Res Treat*. 2015; 152:227–8. [PubMed: 25975953]
47. Armer JM, Whitman M. The problem of lymphedema following breast cancer treatment: prevalence, symptoms, and self management. *Lymphology*. 2002; 35(Suppl):153–9. [PubMed: 12570324]
48. Weiss J, Daniel T Validation of the Lymphedema Life Impact Scale (Llis): a condition-specific measurement tool for persons with lymphedema. *Lymphology*. 2015; 48:128–38. [PubMed: 26939160]
49. Viehoff PB, van Genderen FR, Wittink H. Upper limb lymphedema 27 (ULL27): Dutch translation and validation of an illness-specific health-related quality of life questionnaire for patients with upper limb lymphedema. *Lymphology*. 2008; 41:131–8. [PubMed: 19013881]
50. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphoedema fFunctioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. *Phys Ther*. 2011; 91:944–57. [PubMed: 21493748]
51. Jeffs E, Purushotham A. The prevalence of lymphoedema in women who attended an information and exercise class to reduce the risk of breast cancer-related upper limb lymphoedema. *Spring*. 2016; 5:21. 015-1629-8. eCollection 2016.
52. Radina E, Armer J, Daunt D, Dusold J, Culbertson S. Self-reported management of breast cancer-related lymphoedema. *J Lymphoedema*. 2007; 2:12–21. [PubMed: 20535235]
53. Sun F, Skolny MN, Swaroop MN, Rawal B, Catalano PJ, Brunelle CL, Miller CL, Taghian AG. The need for preoperative baseline arm measurement to accurately quantify breast cancer-related lymphedema. *Breast Cancer Res Treat*. 2016; 157:229–40. This study was the first to demonstrate that a baseline preoperative measurement is necessary when diagnosing BCRL accurately. Natural asymmetries exist between the arms and therefore assuming a perfectly symmetrical baseline is incorrect. [PubMed: 27154787]

54. Stout Gergich NL, Pflazer LA, McGarvey C, Springer B, Gerber LH, Soballe P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer*. 2008; 112:2809–19. [PubMed: 18428212]
55. Ancukiewicz M, Miller CL, Skolny MN, O'Toole J, Warren LE, Jammallo LS, Specht MC, Taghian AG. Comparison of relative versus absolute arm size change as criteria for quantifying breast cancer-related lymphedema: the flaws in current studies and need for universal methodology. *Breast Cancer Res Treat*. 2012; 135:145–52. [PubMed: 22710706]
56. Ancukiewicz M, Russell TA, Otoole J, Specht M, Singer M, Kelada A, Murphy CD, Pogachar J, Gioioso V, Patel M, Skolny M, Smith BL, Taghian AG. Standardized method for quantification of developing lymphedema in patients treated for breast cancer. *Int J Radiat Oncol Biol Phys*. 2011; 79:1436–43. [PubMed: 20605339]
57. Miller CL, Specht MC, Horick N, Skolny MN, Jammallo LS, O'Toole J, Taghian AG. A novel, validated method to quantify breast cancer-related lymphedema (BCRL) following bilateral breast surgery. *Lymphology*. 2013; 46:64–74. [PubMed: 24354105]
58. O'Toole J, Jammallo L, Skolny M, Miller C, Elliott K, Specht M, Taghian AG. Lymphedema following treatment for breast cancer: a new approach to an old problem. *Crit Rev Oncol*. 2013; 88:437–46.
59. Stout NL, Pflazer LA, Levy E, McGarvey C, Springer B, Gerber LH, Soballe P. Segmental limb volume change as a predictor of the onset of lymphedema in women with early breast cancer. *PM R*. 2011; 3:1098–105. [PubMed: 21974905]
60. Shah C, Vicini FA, Arthur D. Bioimpedance spectroscopy for breast cancer related lymphedema assessment: Clinical practice guidelines. *Breast J*. 2016; 22:645–50. [PubMed: 27487985]
61. Leong, N., Truong, P., Tankel, K., Kwan, W., Weir, L., Olivotto, I. Hypofractionated nodal radiotherapy (RT) did not increase arm morbidity compared to conventional fractionated nodal RT; San Antonio Breast Conference; 2016.
62. Miller CL, Colwell AS, Horick N, Skolny MN, Jammallo LS, O'Toole JA, Shenouda MN, Sadek BT, Swaroop MN, Ferguson CM, Smith BL, Specht MC, Taghian AG. Immediate implant reconstruction is associated with a reduced risk of lymphedema compared to mastectomy alone: a prospective cohort study. *Ann Surg*. 2016; 263:399–405. [PubMed: 25607768]
63. Miller CL, Specht MC, Skolny MN, Horick N, Jammallo LS, O'Toole J, Shenouda MN, Sadek BT, Smith BL, Taghian AG. Risk of lymphedema after mastectomy: potential benefit of applying ACOSOG Z0011 protocol to mastectomy patients. *Breast Cancer Res Treat*. 2014; 144:71–7. [PubMed: 24500108]
64. Basta MN, Fischer JP, Kanchwala SK, Silvestre J, Wu LC, Serletti JM, Tchou JC, Kovach SJ, Fosnot J. A propensity-matched analysis of the influence of breast reconstruction on subsequent development of lymphedema. *Plast Reconstr Surg*. 2015; 136:134e–43e. [PubMed: 26397660]
65. Fu MR, Axelrod D, Guth AA, Fletcher J, Qiu JM, Scagliola J, Kleinman R, Ryan CE, Chan N, Haber J. Patterns of obesity and lymph fluid level during the first year of breast cancer treatment: a prospective study. *Journal of Personalized Medicine*. 2015; 5:326–40. [PubMed: 26404383]
66. Soran A, Ozmen T, McGuire KP, Diego EJ, McAuliffe PF, Bonaventura M, Ahrendt GM, DeGore L, Johnson R. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection; a prospective observational study. *Lymphat Res Biol*. 2014; 12:289–94. [PubMed: 25495384]
67. Togawa K, Ma H, Sullivan-Halley J, Neuhaus ML, Imayama I, Baumgartner KB, Smith AW, Alfano CM, McTiernan A, Ballard-Barbash R, Bernstein L. Risk factors for self-reported arm lymph-edema among female breast cancer survivors: a prospective cohort study. *Breast Cancer Res*. 2014; 16:414. [PubMed: 25145603]
68. Stout NL, Pflazer LA, Springer B, Levy E, McGarvey CL, Danoff JV, Gerber LH, Soballe PW. Breast cancer-related lymphedema: comparing direct costs of a prospective surveillance model and a traditional model of care. *Phys Ther*. 2012; 152. [PubMed: 21921254]
69. National Lymphedema Network. [Accessed 01/22 2017] Position statement of the National Lymphedema Network: lymphedema risk reduction practices. 2012. <http://www.lymphnet.org/pdfDocs/nlnriskreduction.pdf>

70. Ahn S, Port ER. Lymphedema precautions: time to abandon old practices? *J Clin Oncol*. 2016; 34:655–8. [PubMed: 26712226]
71. National Lymphedema Network. [Accessed 01/22 2017] Position statement of the National Lymphedema Network: training of lymphedema therapists. 2013. <http://www.lymphnet.org/pdfDocs/nlntraining.pdf>
72. National Lymphedema Network. [Accessed 01/22 2017] Position statement of the National Lymphedema Network: the diagnosis and treatment of lymphedema. 2011. <http://www.lymphnet.org/pdfDocs/nlntreatment.pdf>
73. Lasinski BB, McKillip Thrift K, Squire D, Austin MK, Smith KM, Wanchai A, Green JM, Stewart BR, Cormier JN, Armer JM. A systematic review of the evidence for complete decongestive therapy in the treatment of lymphedema from 2004 to 2011. *PM R*. 2012; 4:580–601. [PubMed: 22920313]
74. McNeely ML, Magee DJ, Lees AW, Bagnall KM, Haykowsky M, Hanson J. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial. *Breast Cancer Res Treat*. 2004; 86:95–106. [PubMed: 15319562]
75. Andersen L, Hojris I, Erlandsen M, Andersen J. Treatment of breast-cancer-related lymphedema with or without manual lymphatic drainage—a randomized study. *Acta Oncol*. 2000; 39:399–405. [PubMed: 10987238]
76. Dayes IS, Whelan TJ, Julian JA, Parpia S, Pritchard KI, D'Souza DP, Kligman L, Reise D, LeBlanc L, McNeely ML, Manchul L, Wiernikowski J, Levine MN. Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in women with breast cancer. *J Clin Oncol*. 2013; 31:3758–63. [PubMed: 24043733]
77. Javid SH, Anderson BO. Mounting evidence against complex decongestive therapy as a first-line treatment for early lymphedema. *J Clin Oncol*. 2013; 31:3737–8. [PubMed: 24043744]
78. Feldman JL, Stout NL, Wanchai A, Stewart BR, Cormier JN, Armer JM. Intermittent pneumatic compression therapy: a systematic review. *Lymphology*. 2012; 45:13–25. [PubMed: 22768469]
79. Uzkeser H, Karatay S, Erdemci B, Koc M, Senel K. Efficacy of manual lymphatic drainage and intermittent pneumatic compression pump use in the treatment of lymphedema after mastectomy: a randomized controlled trial. *Breast Cancer*. 2015; 22:300–7. [PubMed: 23925581]
80. Shao Y, Qi K, Zhou QH, Zhong DS. Intermittent pneumatic compression pump for breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. *Oncol Res Treat*. 2014; 37:170–4. [PubMed: 24732640]
81. Szolnok G, Lakatos B, Keskeny T, Varga E, Varga M, Dobozy A, Kemeny L. Intermittent pneumatic compression acts synergistically with manual lymphatic drainage in complex decongestive physiotherapy for breast cancer treatment-related lymphedema. *Lymphology*. 2009; 42:188–94. [PubMed: 20218087]
82. Gurdal SO, Kostanoglu A, Cavdar I, Ozbas A, Cabioglu N, Ozcinar B, Igci A, Muslumanoglu M, Ozmen V. Comparison of intermittent pneumatic compression with manual lymphatic drainage for treatment of breast cancer-related lymphedema. *Lymphat Res Biol*. 2012; 10:129–35. [PubMed: 22984910]
83. Boccardo F, Casabona F, De Cian F, Friedman D, Villa G, Bogliolo S, Ferrero S, Murelli F, Campisi C. Lymphedema microsurgical preventive healing approach: a new technique for primary prevention of arm lymphedema after mastectomy. *Ann Surg Oncol*. 2009; 16:703–8. [PubMed: 19139964]
84. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, Schwartz AL. American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors *Med Sci Sports Exerc*. 2010; 42:1409–26. [PubMed: 20559064]
85. Schmitz K, Troxel A, Cheville A, Grant L, Bryan C, Gross C, Lytle L, Ahmed R. Physical activity and lymphedema (the PAL trial): assessing the safety of progressive strength training in breast cancer survivors. *Contemporary clinical trials*. 2009; 30:233–45. [PubMed: 19171204]
86. Ahmed RL, Thomas W, Yee D, Schmitz KH. Randomized controlled trial of weight training and lymphedema in breast cancer survivors. *J Clin Oncol*. 2006; 24:2765–72. [PubMed: 16702582]

87. Schmitz KH, Ahmed RL, Troxel AB, Cheville A, Lewis-Grant L, Smith R, Bryan CJ, Williams-Smith CT, Chittams J. Weight lifting for women at risk for breast cancer-related lymphedema: a randomized trial. *JAMA*. 2010; 304:2699–705. [PubMed: 21148134]
88. Sagen A, Karesen R, Risberg MA. Physical activity for the affected limb, arm lymphedema after breast cancer surgery. A prospective, randomized controlled trial with two years follow-up. *Acta Oncol*. 2009; 48:1102–10. [PubMed: 19863217]
89. Cormie P, Singh B, Hayes S, Peake JM, Galvao DA, Taaffe DR, Spry N, Nosaka K, Cornish B, Schmitz KH, Newton RU. Acute inflammatory response to low-, moderate-, and high-load resistance exercise in women with breast cancer-related lymphedema. *Integr Cancer Ther*. 2016; 15:308–17. This study sought to determine the impact of low-, moderate-, and high-load resistance exercise in women with pre-existing BCRL. Findings showed that levels of certain exercise-induced markers, arm swelling, and symptom severity remained constant across the three resistance conditions. [PubMed: 26582633]
90. Morris C, Wonders KY. Concise review on the safety of exercise on symptoms of lymphedema. *World J Clin Oncol*. 2015; 6:43–4. [PubMed: 26266100]
91. Keilani M, Hasenoehrl T, Neubauer M, Crevenna R. Resistance exercise and secondary lymphedema in breast cancer survivors-a systematic review. *Support Care Cancer*. 2016; 24:1907–16. [PubMed: 26715294]
92. Fisher MI, Donahoe-Fillmore B, Leach L, O'Malley C, Paeplow C, Prescott T, Merriman H. Effects of yoga on arm volume among women with breast cancer related lymphedema: a pilot study. *J Bodyw Mov Ther*. 2014; 18:559–65. [PubMed: 25440207]
93. Letellier ME, Towers A, Shimony A, Tidhar D. Breast cancer-related lymphedema: randomized controlled pilot and feasibility study. *Am J Phys Med Rehabil*. 2014; 93:751–9. quiz 760-1. [PubMed: 24743455]
94. Jammallo LS, Miller CL, Horick NK, Skolny MN, O'Toole J, Specht MC, Taghian AG. Factors associated with fear of lymphedema after treatment for breast cancer. *Oncol Nurs Forum*. 2014; 41:473–83. [PubMed: 25158653]

Fig. 1.
Histogram of arm asymmetry. Baseline asymmetries of >5 and 10% are shaded *light* and *dark pink*, respectively

Fig. 2.
Relative volume change after a 200-mL arm volume increase

Table 1

BCRL diagnostic method advantages and disadvantages

Diagnosis method	Advantages	Disadvantages
Water displacement	<ul style="list-style-type: none"> • Accurate • Inexpensive 	<ul style="list-style-type: none"> • Time consuming • Required strict protocol
Circumferential tape measurement	<ul style="list-style-type: none"> • Inexpensive • Reliable • Highly accessible 	<ul style="list-style-type: none"> • Time consuming • Low inter-rater reliability without significant training
Perometry	<ul style="list-style-type: none"> • Quick • Highly reproducible • Accurate • Segmental volumes • Identifies subclinical BCRL 	<ul style="list-style-type: none"> • Expensive • Large size
Bioimpedance spectroscopy	<ul style="list-style-type: none"> • Quick • Portable • Potentially identifies subclinical BCRL 	<ul style="list-style-type: none"> • Limited to unilateral patients • Expensive