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Effects of weight reduction on the breast cancer-related lymphedema: A systematic review and meta-analysis

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ABSTRACT

Background: Obesity has long been considered a risk factor for breast cancer–related lymphedema (BCRL), but the benefits of weight reduction in managing BCRL have not been clearly established.
Objective: To evaluate the beneficial effects of weight loss interventions (WLIs) on the reduction and prevention of BCRL.
Methods: We conducted a systematic review and meta-analysis by searching the PubMed, Scopus, and Embase databases from their earliest record to October 1st, 2019. We included randomized and non-randomized controlled trials involving adult patients with a history of breast cancer, that compared WLI groups with no-WLI groups, and provided quantitative measurements of lymphedema.
Results: Initial literature search yielded 461 nonduplicate records. After exclusion based on title, abstract, and full-text review, four randomized controlled trials involving 460 participants were included for quantitative analysis. Our meta-analysis revealed a significant between-group mean difference (MD) regarding the volume of affected arm (MD = 244.7 mL, 95% confidence interval [CI]: 145.3–344.0) and volume of unaffected arm (MD = 234.5 mL, 95% CI: 146.9–322.1). However, a nonsignificant between-group MD of −0.07% (95% CI: 1.22–1.08) was observed regarding the interlimb volume difference at the end of the WLIs.
Conclusions: In patients with BCRL, WLIs are associated with decreased volume of the affected and unaffected arms but not with decreased severity of BCRL measured by interlimb difference in arm volume.

1. Introduction

Lymphedema is defined as the accumulation of protein-rich lymph fluid in the interstitial space caused by a disruption in lymphatic flow [1]. It is not uncommon in patients with breast cancer who have received surgical treatment with adjuvant or neoadjuvant chemoradiotherapy. The reported incidence of breast cancer-related lymphedema (BCRL) varies widely, depending on the definition of BCRL, type of surgery received, and type of adjuvant treatment (e.g., radiotherapy and chemotherapy) [2]. A systematic review and meta-analysis including 72 studies and 29,612 women reported an overall BCRL incidence of 16.6%, which varied from 12.6% based on clinical diagnosis, 14.8% based on arm circumference measurement, and up to 20.4% based on self-report [3].

BCRL is often chronic, progressive, and incurable [4]. The symptoms of BCRL include arm stiffness, heaviness or fullness, pain, numbness, and impaired limb function [4,5]. It also affects a patient's emotional well-being, causing depression and anxiety and reducing the quality of life [6–8]. BCRL treatment mostly involves complete decongestive therapy, which encompasses manual lymphatic drainage, compression garment use, exercise, and self-care to reduce the limb swelling and maintain a decongested state [9,10]. However, the management of BCRL is often frustrating because of the incurable nature of the condition, and the need for long-term care places financial burden on affected individuals [11,12]. Therefore, identifying the modifiable risk factors associated

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with BCRL is of particular importance when addressing BCRL.

Many studies associated obesity with BCRL [13], [-16] but the mechanism is so far unclear. It has been hypothesized that obesity increases the risk of lymphedema as a result of increased production of lymph from adipose tissue which overwhelms the capacity of the lymphatic system, as a consequence of external compression of lymphatics by adipose tissues, or even as a result of direct injury to the lymphatic endothelium [17]. Several other risk factors for BCRL have also been established, including a greater number of axillary lymph nodes resected [3,4,18], the use of taxane-based chemotherapy [14], total mastectomy [14], and axillary regional nodal irradiation [19]. Among these risk factors, obesity is the only factor which can be modified to combat BCRL without changing the treatment plans for breast cancer. Therefore, it is reasonable trying to understand whether weight loss in such a population would be beneficial to the management of BCRL.

Consequently, we conducted the present review to answer the following two questions: (1) do weight loss interventions (WLIs) decrease the incidence of BCRL, and (2) do WLIs reduce the severity of existing BCRL.

2. Methods

2.1. Design

This study was conducted in accordance with the PRISMA guidelines. Two distinct cohorts were targeted: (1) the breast cancer cohort, which refers to patients without BCRL at baseline; and (2) the BCRL cohort, which refers to patients with baseline BCRL. The breast cancer cohort was used to investigate the effect of WLIs on reducing the incidence of BCRL compared to the control group (ie, preventive effect); and the BCRL cohort was used to investigate the effect of WLIs on reducing BCRL severity compared to the control group (ie, treatment effect). All types of WLIs including diet control interventions, exercise training, medications, and surgery were considered. A WLI had to fulfill two criteria to be included in the present study: (1) weight loss $\geq$3% of the baseline body weight or body mass index (BMI) was achieved after the intervention; (2) the percentile difference of weight loss between the WLI group and control group was $\geq$3%.

The authors searched for all relevant articles in the PubMed, Scopus, and Embase databases from their earliest record to October 1st, 2019. The Cochrane Library and Google Scholar were scrutinized for additional references. The main search terms were [(breast cancer) AND (exercise OR diet OR bariatric surgery) AND (weight)] (please refer to the Supplementary file for the search plan). Additional studies were obtained from the references of relevant reviewed articles.

2.2. Study selection

We included randomized and non-randomized control trials

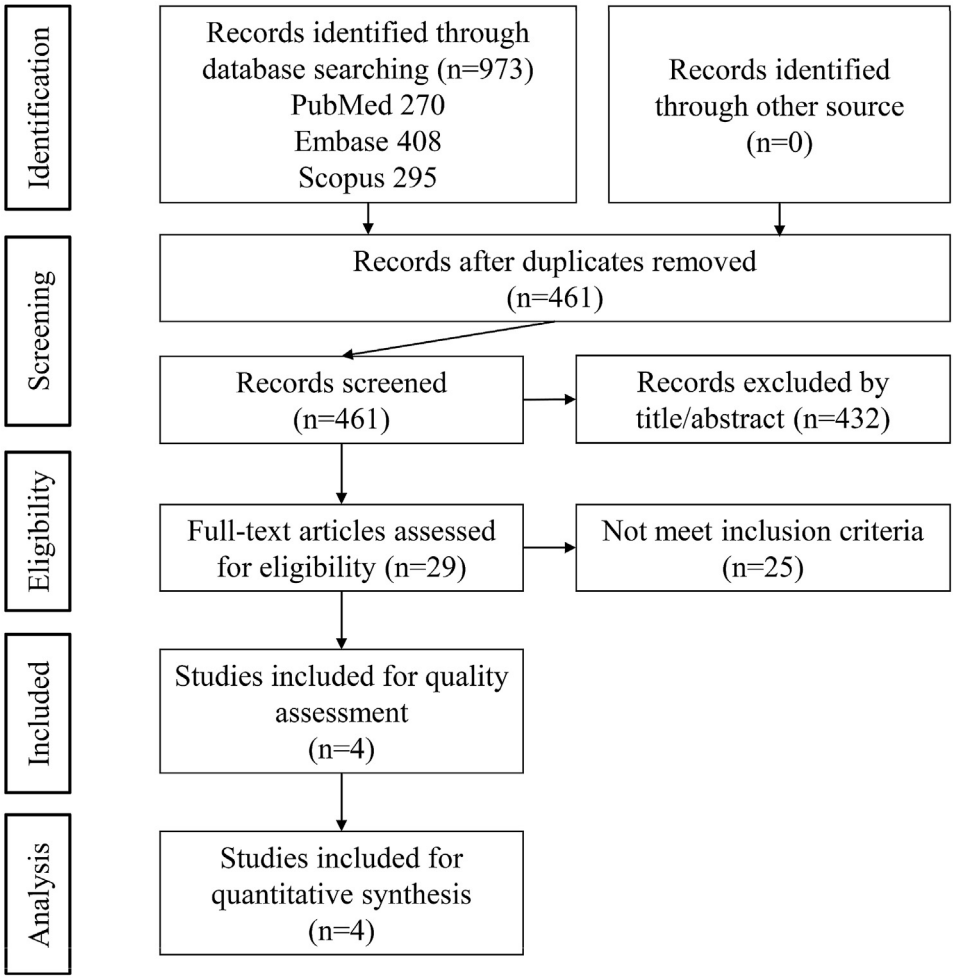

Fig. 1. Flowchart of the study selection.

Table 1
Summary of the studies included in the review.

Study	Study type	PEDro score	Participants	Definition of lymphedema
Shaw et al. (2007a, UK) [21]	3-arm RCT	6	(1) with BCRL; (2) with cancer in remission; (3) did not receive chemotherapy or radiotherapy in preceding 12 months	Affected arm volume at least 20% larger than unaffected arm volume.
Shaw et al. (2007b, UK) [22]	2-arm RCT	6	(1) with BCRL; (2) with cancer in remission; (3) did not receive chemotherapy or radiotherapy in preceding 12 months; (4) BMI >25 kg/m^2	Affected arm volume at least 15% larger than unaffected arm volume.
Schmitz et al. (2009, USA) [23]	2-arm RCT	7	(1) with BCRL; (2) had at least one lymph node removed; (3) BMI <50 kg/m^2; (4) with cancer in remission	(1) Interlimb difference in volume or circumference $\geq$ 10%; or (2) diagnosed according to the Common Toxicity Criteria for Adverse Events.
Schmitz et al. (2019, USA) [24]	4-arm RCT	7	(1) with BCRL; (2) with cancer in remission; (3) >6 months posttreatment; (4) BMI = 25–50 kg/m^2 All participants were provided with lymphedema care from lymphedema therapists throughout the trial	(1) Diagnosed according to the Common Toxicity Criteria for Adverse Events; or (2) previous diagnosis of lymphedema.

BCRL, breast cancer-related lymphedema; BMI, body mass index; BW body weight; RCT, randomized controlled trial; WLI, weight loss interventions.
[a] The primary outcome measure in all four studies includes the percentage of interlimb volume difference.
[b] The Norman Lymphedema Survey was used for participant self-reporting, which included 14 possible symptoms with possible values ranging from 0 (no symptoms) to 4 (very severe symptoms) for each item.

that (1) involved adult patients with a history of breast cancer; (2) compared WLI groups with no-WLI groups or groups having received interventions not relevant to weight reduction; and (3) provided quantitative measurements of lymphedema. Baseline interventions (e.g., BCRL management) other than WLIs had to be conducted under the same conditions between treatment arms. If several studies involved the same study sample, only one was included for analysis unless said studies provided additional information regarding study outcomes.

Three authors (CLT, CYH, and WWC) searched and evaluated the literature for relevant studies based on titles and abstracts. After pooling the studies obtained from different sources and removing duplicates, the full text of potentially relevant articles was retrieved, and each article was independently evaluated by CLT, CYH, and WWC for its eligibility.

2.3. Quality assessments

CJT and YNL assessed the quality of the included studies using the PEDro scale and Cochrane risk-of-bias tool. For the PEDro scale, methodological quality was assessed using eight items regarding random allocation, blinding procedures, and the dropout rate. Two items were related to statistical reporting. Aggregate scores ranged from 0 to 10 points with a higher score indicating higher quality. Quality was categorized as high (6–10), fair (4 or 5), or poor ($\leq$3). Using the Cochrane risk-of-bias tool, we assessed seven domains of bias and stratified the risk of bias into low, high, and unclear risk. Discrepancies between reviewers at any stage were resolved through discussion until a consensus was reached.

2.4. Data extraction

We extracted the relevant data from each study using a standard data recording form, which included the number of participants, inclusion and exclusion criteria, intervention protocol (i.e., intervention duration, comparators, number of sessions, additional interventions, and outcome measures), information regarding the study quality, and the final results. The goal was to evaluate the effects of WLIs after their completion. We extracted the corresponding mean, mean change, and standard deviation (SD) for the outcomes of interest. If a single trial contained multiple WLI groups, we synthesized the overall mean and SD for the WLI groups regarding the outcome of interest [15].

2.5. Outcome measurements

The incidence of lymphedema after the end of the intervention period was investigated using the breast cancer cohorts. For the BCRL cohorts, all objective measures of BCRL (e.g., absolute or relative interlimb difference) were considered. We also investigated the absolute volume of the affected and unaffected arms. Other relevant outcomes such as self-reported severity of BCRL and arm circumference were collected when available.

2.6. Meta-analysis

Our meta-analysis focused on the comparison "WLI versus no WLI." The mean difference (MD) was obtained to assess the treatment effect. A fixed effect model was used, and a point estimate with 95% confidence interval (CI) was selected. Heterogeneity across studies was tested using the I [2] test. I [2] values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively [20]. The meta-analysis was performed using Review Manager 5.3.

3. Results

Our searches yielded 461 non-duplicate records. After exclusion based on the title, abstract, and full-text review, four randomized controlled trials were included in this review. No breast cancer cohorts reporting the effects of a WLI on the incidence of BCRL were available. A total of four BCRL cohorts [21–24] involving 460 participants were used for the meta-analysis (Fig. 1).

Table 1 presents the characteristics of the four included studies. All studies recruited patients with BCRL and overweight or obesity, but their inclusion criteria and definition of BCRL and overweight

Number, weight loss		Intervention period	Therapy		Relevant outcome measures	Assessment timing
Control group	WLI group		Control group	WLI group		
n = 15 BW loss by 1.1%	n = 19 BW loss by 5.8%	24 weeks	Continue habitual diet	Advised to reduce intake to 1000–1200 kcal per day	Arm volume measured using perometry or derived from arm circumference[a]	Before dietary intervention and after 24 weeks of intervention
n = 10 No BW change	n = 11 BW loss by 3.8%	12 weeks	No specific dietary intervention advice	Individualized dietary advice aimed to generate an energy deficit of 1000 kcal per day from habitual intake	Arm volume derived from arm circumference[a]	Before and after treatment
n = 70 No BMI change	n = 71 BMI loss by 3.2%	12 months	Continue baseline exercise level	Weight lifting exercise: 90-min supervised group session, twice weekly, for 13 weeks, followed by twice-weekly unsupervised exercise for 39 weeks	(1) Limb volume measured by submerging the arm and hand in water and measuring the displaced water volume[a]; (2) self-reported symptoms obtained through a standardized survey[b]	At baseline and after 12 months of intervention
n = 90 BW loss by 0.55%	WLI group 1 (diet control): *n* = 87 BW loss of 7.37% WLI group 2 (diet control + exercise): *n* = 87 BW loss of 8.06%	12 months	No WLI	WLI group 1 (diet control): 24 week dietitian-led sessions followed by monthly group meetings for additional behavioral modification in weeks 25 through 52 WLI group 2 (diet control + exercise): 6 weeks of exercise instruction with additional weight loss intervention from week 7	Percentage of interlimb volume differences measured using perometry[a]; (2) self-reported symptoms obtained through a standardized survey[b]	At baseline and after12 months of intervention

and obesity varied. The WLIs also differed between studies. Participants from two studies received dietary advice with the aim of generating an energy deficit in their habitual intake [21,22]; in one study, intensive weight lifting was employed [23]; and one four-armed study had two WLI groups, namely the diet control group and a combination of diet control and exercise training [24]. The WLI groups exhibited 6.26% weight loss from baseline (weighted by participant number) compared with 0.36% in the control groups. Despite the different techniques used to measure arm volume, all included studies reported a relative interlimb difference (i.e.,

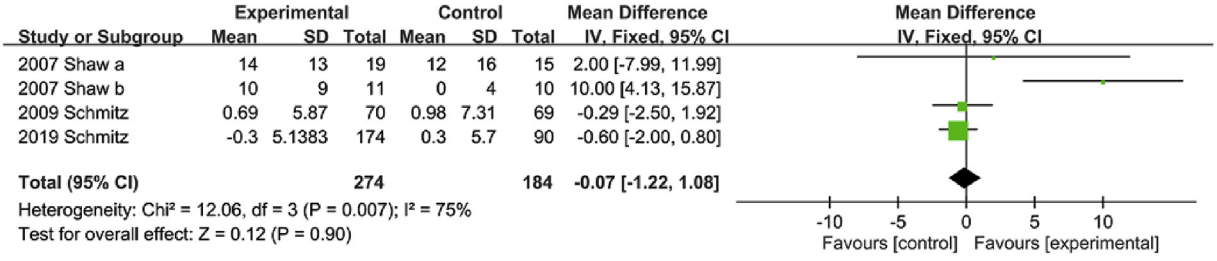

Fig. 2. Forest plot of the effects of weight loss intervention on lymphedema based on interlimb difference (%).

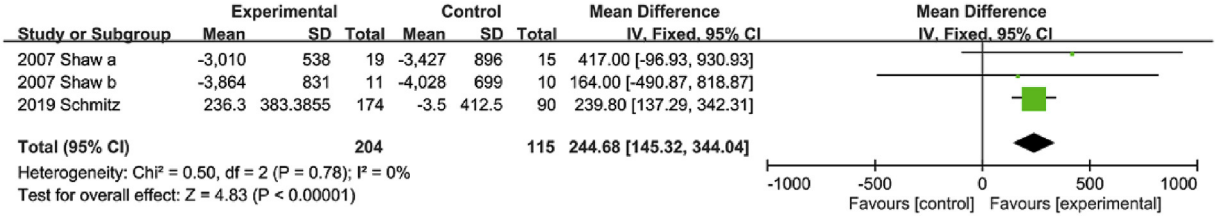

Fig. 3. Forest plot of effects of weight loss intervention on reduced volume (mL) of affected arm.

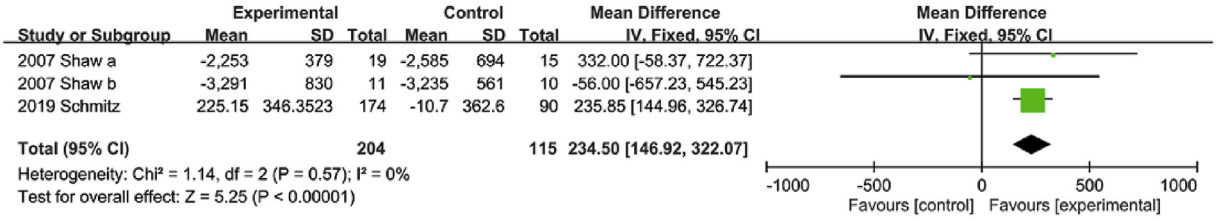

Fig. 4. Forest plot of effects of weight loss intervention on reduced volume (mL) of unaffected arm.

percentage of excess arm volume).

The PEDro scores of included studies ranged from 6 to 7 (Table 1 and the Supplementary file). Based on the Cochrane risk-of-bias assessment, all studies exhibited significant bias in terms of the personnel blinding process because of the nature of the interventions (Supplementary file). Considering that all the included studies were contributed by only 2 research teams, particular attention was devoted to detecting duplicate publication bias. We found low risk of duplicate studies due to the distinct characteristics of the included studies. Two studies were published in the same year by the same research team [21,22], and we contacted the author to confirm that the two studies did not involve overlapping patients.

Our meta-analysis revealed, at the end of interventions, a nonsignificant MD of −0.07% between the WLI and control groups regarding interlimb volume difference (Fig. 2), a significant between-group MD of 244.7 mL regarding volume of the affected arm (Fig. 3), and a significant between-group MD of 234.5 mL regarding volume of the unaffected arm (Fig. 4). Two studies explored the effects of WLIs on subjective BCRL severity [23,24]. Our meta-analysis revealed a significant MD of 0.55 (95% CI: 0.03 to 1.06, $I^2 = 0\%$) and a significant MD of 0.18 (95% CI: 0.00 to 0.35, $I^2 = 32\%$), regarding the number of symptoms and severity of symptoms, respectively, favoring the WLI group.

4. Discussion

The present study aimed to assess the beneficial effects of WLIs on BCRL. We initially planned to investigate both the preventive and treatment effects of WLIs on BCRL by searching for two different types of cohorts. However, only four BCRL cohorts and no breast cancer cohorts were available for analysis, which enabled us to evaluate only the treatment effects. The results of our meta-analysis indicated that weight loss effectively reduces the limb volume of both affected and unaffected arms but is ineffective at improving BCRL as measured by the interlimb difference in arm volume. Given that obesity is a risk factor for BCRL, WLIs should have some potential to either prevent or improve BCRL. However, the present study provides a somewhat contradictory result, which raises a broad range of implications.

Lymphatic insufficiency occurs when the lymphatic drainage system is either overloaded with fluid or fails mechanically [11]. Obesity has been reported to cause the collapse of lymphatic vessels, resulting in insufficient drainage. Under such conditions, lymphatic drainage would be expected to improve following weight loss. However, a non-breast-cancer-related lymphedema study revealed that substantial weight loss corresponding to a BMI decrease from 80 to 36 kg/m^2 did not improve lymphedema as defined by lymphoscintigraphy [25]. The findings of our meta-analysis are in agreement with this study.

Lymphedema can be the result of chronic inflammation with subsequent progressive fibrosis and lymphatic system dysfunction in the subcutaneous tissue of the affected limb [26,27]. Histological studies of clinical specimens in patients with BCRL have reported that lymphatic vessels were progressively encased in and replaced by fibrous tissues, resulting in the loss of functional lymphatics and luminal obliteration of the collected vessels [28]. Therefore, once fibrosis of the lymphatic system has begun, the disease has probably already become irreversible. This might explain why WLIs were discovered to be ineffective in treating preexisting lymphedema.

The methods used to evaluate the severity of BCRL may also be of concern. As opposed studies obtaining nonsignificant results by using objective measures, the present study indicates that WLIs resulted in fewer symptoms and decreased severity of symptoms of BCRL, both of which are subjective measures of BCRL. The existing evidence indicates a closer correlation of obesity to subjective measures of BCRL than to objective measures [3,13]. These findings imply that obesity or weight loss may influence the subjective evaluation of BCRL through unclear mechanisms. Further studies are needed to understand the mechanism underlying the discrepancies observed between subjective and objective measures of BCRL.

Although numerous studies have reported a statistical association between obesity and BCRL [13], [-16] the causal relation and underlying mechanisms remain unclear. Given that studies have reported that obesity increases patients' risks of larger tumors and axillary lymph node invasion and is considered a negative prognostic factor [29,30], patients with obesity could have received more treatments associated with subsequent occurrence of BCRL. Thus, obesity could in fact be indirectly connected to BCRL. In this case, targeting obesity to treat BCRL would be less effective.

Finally, given that BCRL is intractable, it is perhaps even more crucial to understand whether BCRL can be prevented through weight reduction. However, no existing WLI trial has reported the incidence of BCRL in their outcomes to address such an issue. Although many ongoing trials registered on clinicaltrials.gov evaluating the benefits of weight reduction among patients with breast cancer, none included the incidence of BCRL as an outcome measurement. Future trials should focus on the high-risk population of BCRL and include the incidence of BCRL as an outcome. More well-designed randomized controlled trials are needed to determine whether weight reduction can prevent BCRL in a high-risk population.

4.1. Limitations

Several limitations need to be addressed. First, no relevant studies were available for evaluating the preventive effects of WLIs on BCRL. Second, only four trials with a BCRL cohort were included, resulting in a relatively small sample size. Third, the included studies differed in terms of intervention setting, definition of BCRL, degree of obesity, and extent of weight loss after the intervention, which potentially contributed to the evident heterogeneity.

5. Conclusions

Among patients with BCRL, WLIs decreased the volume of both the affected and unaffected arms. However, WLIs did not reduce the severity of BCRL measured by the interlimb difference in arm volume. Clinical trials are warranted to further investigate the efficacy of weight reduction in preventing BCRL in those surviving breast cancer.

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None.

Declaration of competing interest

Nil.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.05.007.

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