

# Preventative Measures for Lymphedema: Separating Fact from Fiction

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Lymphedema is the accumulation of protein-rich fluid that occurs when the ability of the lymphatic system to transport interstitial fluid is exceeded. This devastating disorder affects an estimated 3 to 5 million Americans and a staggering 140 to 200 million people worldwide.<sup>1</sup> In the United States and Western countries, lymphedema occurs most commonly as a complication of lymph node dissection for cancer treatment. It is estimated that as many as 30% to 50% of patients who undergo lymph node dissection go on to develop lymphedema.<sup>2,3</sup> Lymphedema can occur even after less invasive procedures such as sentinel lymph node dissection, thereby putting nearly all cancer survivors at risk for this dreaded complication.<sup>4</sup> Although lymphedema occurs most commonly as a complication of breast cancer management, it is also seen frequently in patients treated for other solid malignancies. In fact, a recent meta-analysis of nearly 8,000 patients reported an overall incidence of 16% in patients treated for melanoma, sarcoma, and gynecologic, urologic, and head and neck malignancies.<sup>5</sup>

Patients with lymphedema have chronic, progressive swelling, pain, recurrent infections, and significantly decreased quality of life. The swelling can progress to gigantic proportions, causing gross disfigurement with severe detrimental effects. In addition, lymphedema is a significant source of biomedical expenditures, with one recent study demonstrating a more than \$10,000 increase in the annual treatment costs of cancer survivors with lymphedema as compared with those without lymphedema.<sup>6</sup>

Treatment for lymphedema remains suboptimal and is in most cases palliative, with a goal of preventing disease progression rather than a cure. Medical and surgical treatments have been reported, but in general these therapies have been disappointing and the results are sometimes difficult to reproduce. In most instances, patients are treated with life-long physical therapy with manual lymphatic drainage and require tight-fitting, uncomfortable elastic

garments. Due to the expense, time, and discomfort associated with these treatments, there is a high degree of non-compliance and associated disease progression.

Despite the morbidity and costs of lymphedema, the mechanisms that regulate its development remain largely unknown. It remains unclear, for instance, why some patients develop lymphedema and others who are identically treated do not. Similarly, it is unknown why certain risk factors such as radiation, obesity, or infection increase the risk of lymphedema. Perhaps the most perplexing aspect of lymphedema is the fact that it develops in a delayed manner, usually 1 to 5 years after surgery. Sometimes lymphedema can develop even decades after surgery after seemingly trivial trauma. This gap in our knowledge has prevented development of targeted treatment options. Similarly, our lack of understanding of the cellular and molecular mechanisms in development of lymphedema have complicated effective preventative strategies. In fact, many of the current recommendations for prevention of lymphedema are anecdotal with scant scientific evidence. The National Cancer Institutes<sup>7</sup> PDQ information summary about preventative steps for lymphedema states the risks succinctly as those of the current recommendation from<sup>7</sup> The Royal Marsden Hospital (UK),<sup>8</sup> and The National Lymphedema Network<sup>9</sup> presented in Table 1. However, the National Lymphedema Network states that there is little evidence-based literature with respect to many of these recommendations and the majority of them are based on what is known through decades of clinical experience and comprehension of the pathophysiology by experts in lymphedema.

The purpose of this systematic review was to evaluate the current recommendations for prevention of lymphedema and present current scientific evidence supporting or disputing these claims.

## METHODS

### Search strategy

A review of preventative measures for lymphedema was performed by using a search strategy that included the key terms: “lymphedema/lymphoedema, preventative measures, myths, advice, recommendations, air travel, venipuncture/blood drawing/phlebotomy, blood pressure measurement, blood pooling, exercise, burns, extreme temperatures or hot or cold or heat, obesity, leg crossing or venous pressure and lymphedema.”

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**Table 1.** Preventative Recommendations for Lymphedema

Keep skin and nails clean and cared for to prevent infection
Use cream or lotion to keep the skin moist.
Treat small cuts or breaks in skin with an antibacterial ointment.
Avoid needle sticks of any type into the limb (arm or leg) with lymphedema. This includes vaccinations, blood drawing, intravenous lines, and acupuncture.
Use a thimble for sewing.
Avoid testing bath or cooking water using the limb with lymphedema.
Wear gloves when gardening and cooking.
Wear sunscreen and shoes when outdoors.
Cut toenails straight across and see a podiatrist as needed.
Keep feet clean and dry and wear cotton socks.
Preferably use an electric razor to remove unwanted body hair (underarms and legs), do not use razor blades.
Use an insect repellent to avoid bites.
Avoid blocking the flow of fluids through the body
Do not cross legs when sitting.
Change sitting position at least every 30 minutes.
Wear only loose jewelry and clothes without tight bands or elastic.
Do not carry handbags on the arm with lymphedema.
Do not use a blood pressure cuff on the arm with lymphedema.
Do not use elastic bandages or stockings with tight bands.
Try to avoid extremes of heat such as saunas or ice packs.
Try to keep your weight within the normal range for your height.
Keep blood from pooling in the affected limb
Keep the limb with lymphedema raised higher than the heart when possible.
Do not swing the limb quickly in circles or let the limb hang down.
Do not apply heat to the limb.

(Adapted from: the National Cancer Institute, The Royal Marsden Hospital, and the National Lymphedema Network,<sup>7,8,9</sup> with permission).

The search terms were applied to electronic bibliographic databases (Medline, SCOPUS, and Google Scholar) to find all relevant studies. No limits were applied to year of study; however, we did exclude publications that were not in English. Only studies describing risk factors for lymphedema or suggestions to prevent lymphedema were included. Relevant articles not found in the electronic bibliographic search were sought by a hand search review of references, tables used, and abstracts from each article.

### Data extraction

Data were extracted into a database developed for this systematic review. The database was pilot tested on 5 randomly selected articles that were to be included, and was adjusted as necessary. The data extracted included author, year of publication, evidence level of study, and recommendations made or disputed. Studies were subsequently categorized as levels 1 to 5 scientific evidence based on the US Agency for Health Care Research and Quality (Table 2).<sup>10</sup>

**Table 2.** Description of Scientific Levels of Evidence and Corresponding Studies<sup>10</sup>

Level of evidence	Description
Level 1	Randomized controlled trials with adequate follow-up Meta-analysis of multiple randomized control trials
Level 2	Nonrandomized, controlled prospective trial Prospective cohort studies
Level 3	Well-designed observational studies (eg, comparative studies, correlation study, case control study)
Level 4	Retrospective observational studies without controls Case-series
Level 5	Expert opinions or committee recommendations

## RESULTS

Our literature search identified 763 papers, 49 of which met inclusion criteria for review. These studies were grouped into 7 broad categories related to their recommendations: avoid needle sticks, avoid limb constriction, elevate the limb, avoid air travel and wear compression garments when flying, maintain normal body weight, avoid extremes of temperature and sunburns, and avoid vigorous exercise.

### Avoid needle sticks

This is perhaps the most common preventative measure for patients at risk for developing lymphedema and is based on the concept that these injuries may lead to infection and therefore, development or exacerbation of lymphedema. Most hospitals recommend this even in patients who have undergone sentinel lymph node biopsy. Patients are often designated with armbands and other measures to avoid accidental or inadvertent blood draws or needle sticks. Patients and clinicians often go to great lengths to adhere to this recommendation by performing blood draws from foot veins or having central venous catheters placed.

The historical source of this recommendation probably dates back to Halstead, who, in 1921, hypothesized that postsurgical infection or infection was the underlying cause of swelling of the arm after breast cancer surgery.<sup>11</sup> Unfortunately, the vast majority of evidence that opposes or supports this recommendation is of poor scientific quality (level 4 or 5). Most reports are small series and anecdotal observations. For example, in a retrospective study of 79 patients treated with breast cancer, Villasor and Lewison's<sup>12</sup> level 3 study reported that 3 patients developed lymphedema immediately after venipuncture of the affected arm, and based on this finding, they proposed that venipuncture of the affected arm should be avoided. Similarly, Britton and Nelson,<sup>13</sup> in 1962, performed a level 4 retrospective study to identify etiologic factors for 114 patients who developed lymphedema after

radical mastectomy; they reported that 53% of these patients had a history of recurrent cellulitis after an insect bite, cat scratch, needle, or thorn prick, with a marked increase in swelling or pain in their arm.<sup>13</sup> They concluded that any mode of bacterial entry could trigger development of cellulitis and lymphedema, leading to the recommendation to avoid venipuncture and practice meticulous skin care to avoid development or exacerbation of lymphedema. Interestingly, this is the only reference in the literature that we encountered reporting a potential link between needle sticks and infection, and it appears to be the only evidence for the underlying rationale of this recommendation. A level 5 study by Smith<sup>14</sup> reported that 10 patients referred to the lymphedema service over a 2-year period reported a direct correlation with venipuncture and the onset of new swelling in their arms.<sup>14</sup> Similarly, in an unusual level 4 report, Brennan and Weitz<sup>15</sup> described a case of a 78-year-old woman who developed lymphedema 30 years after a left radical mastectomy after performing needle sticks for blood monitoring for her newly diagnosed diabetes.<sup>15</sup> Other studies have never been published but were only reported at scientific conventions. Foldi and Foldi<sup>1</sup> cited Harlow and colleagues at the 18<sup>th</sup> convention of the International Society of Lymphology in 2001; they reported a significantly increased rate of lymphedema in a group of 252 patients after venipuncture. No details or other data were provided.

Clark and colleagues<sup>16</sup> performed the only level 2 prospective observational study in 2004 examining the incidence and risk factors (including hospital skin puncture) for arm lymphedema in patients with breast cancer. They measured limb circumference preoperatively and at regular time periods postoperatively in 188 women who had undergone treatment for breast cancer. The authors reported that 8 of 18 (44%) patients who had any needle stick developed lymphedema as compared with 31 of 170 (18%) patients who did not have venipuncture, concluding that skin puncture statistically significantly increased the risk of lymphedema. The authors, however, did not report the timing of lymphedema development in relation to venipuncture and did not evaluate the effect of potential confounding variables that may alter the rate of lymphedema. In addition, although the measurements were made prospectively, the analysis was retrospective and no "randomization" was done.

Other retrospective case series have suggested that venipuncture does not increase the risk of lymphedema development after lymphadenectomy. Cole<sup>17</sup> reported no cases of lymphedema development in a level 4 retrospective audit of 14 patients who had "non-accidental skin puncturing," with a 2-month follow-up of the at-risk limb. Simi-

larly, in their level 4 study, Winge and associates<sup>18</sup> analyzed the results of a questionnaire administered to 348 patients treated for breast cancer. Of the 311 respondents, 88 reported a history of intravenous procedures on the affected side but only 4 developed swelling as a complication in relation to venipuncture. This finding led the authors to conclude that intravenous procedures on ipsilateral arms pose a very low risk of complications such as lymphedema, but they acknowledge that their sample size is small and the study is retrospective, advocating a need for larger multi-centered studies.

### **Avoid limb constriction**

Similar to the edict on avoidance of venipuncture, the general recommendation to avoid pressure on the affected limb also appears to be based on limited scientific data. The root of this recommendation can probably be traced back to Drury and Jones, who hypothesized that increased venous pressure resulted in edema.<sup>19</sup> More recently, Petrek and associates<sup>20</sup> and Loudon and Petrek<sup>21</sup> hypothesized that blood pressure monitoring, tight bands or clothing, or other interventions increased blood pressure in the at-risk limb and that this effect would lead to increased lymph production. They also hypothesized that tight garments could lead to fibrosis and stenosis of lymphatic vessels, thereby resulting in obstruction of lymphatic flow. Other authors have echoed these sentiments, hypothesizing that tight, constrictive clothing (especially bra straps, waistbands, or socks) constrict collateral circulation, so are risk factors for lymphedema, but this statement is made with no explanation.<sup>22</sup> However, there is little scientific evidence for these statements and the precise relationship between blood flow and lymphatic fluid production remains unknown.

Some groups have challenged the concept that pressure on the affected extremity should be avoided. For example, Greene and colleagues<sup>23</sup> suggested that the use of blood pressure cuffs in patients with established lymphedema should not be contraindicated because the management strategy for these patients relies primarily on compression.<sup>23</sup> Patients routinely use compression garments and pneumatic pumps with pressures between 40 and 200 mmHg for hours at a time over many months. Similarly, in a retrospective report of 47 patients with a history of breast cancer-associated lymphedema, Assmus and Staub<sup>24</sup> reported that short applications (10 minutes) of pneumatic tourniquets for treatment of flexor retinaculum release resulted in no adverse effects. Fulford and coworkers<sup>25</sup> conducted a level 4 online survey of hand surgeons, breast surgeons, and breast care nurses to determine if they believed that previous axillary lymph node dissection was a contraindication to hand surgery. Interestingly, 58% of

hand surgeons responded that lymphadenectomy was not a contraindication to elective hand surgery using a tourniquet. In contrast, 70% of breast surgeons and 90% of breast care nurses thought that elective hand surgery in these patients was contraindicated. Similarly, when asked about the use of compression tourniquets, 79% of hand surgeons reported that this usage was not contraindicated; only 57% of breast surgeons and 68% of breast care nurses advised against this use.<sup>25</sup> Similar findings were reported in another level 4 survey of hand surgeons in the American Society of the Hand. Of the 617 responders (1,200 questionnaires were mailed), the majority stated that they would operate on patients with a history of axillary dissection. Nearly all surgeons (98.7%) would operate on patients with axillary surgery who do not currently have lymphedema; the majority (85.4%) would do so even in patients with established lymphedema. Similarly, the majority (74.1%) believed there was no contraindication to the use of a pneumatic tourniquet in patients with lymphedema.<sup>26</sup> These studies highlight that the fact that professional opinions differ significantly, and this is likely related to the paucity of reliable scientific studies.

In an effort to better address this question, in their level 4 study, Dawson and colleagues<sup>27</sup> retrospectively reviewed 317 patients who had undergone elective carpal tunnel release. With a follow-up of 16 months, the authors reported no new cases of lymphedema, worsening lymphedema symptoms, or infections among the 15 patients in the cohort who had a history of breast or axillary surgery. This finding led the authors to conclude that patients with previous breast or axillary surgery should not be denied elective hand surgical procedures based on the idea that this puts them at increased risk of complications such as infection or lymphedema.<sup>27</sup> This concept was supported in a level 4 study by Hershko and Stahl,<sup>28</sup> who reported no new cases of lymphedema and no cases of long-term worsening of lymphedema symptoms after elective hand surgery in 25 patients with a history of axillary lymph node dissection. These findings support the concept that compression is not a significant risk factor for development of lymphedema in at-risk patients. In addition, given that hand surgery is an invasive procedure with skin incisions and subsequent wound healing, these findings can also be interpreted to suggest that loss of skin integrity in a controlled and sterile manner does not increase the risk of lymphedema.

### **Elevate the limb**

Recommendations concerning limb position are based on blood pooling and resultant increased venous pressure in the affected extremity. Similar to other commonly accepted preventative measures, there is little scientific evidence to support this recommendation. For example, keeping the

extremity elevated above the level of the heart is useful for edema in general, but is probably less helpful in the setting of lymphedema due to the high oncotic pressure of lymphatic fluid. Similarly, crossing the legs is thought to hinder venous return and increase venous pressure in the affected extremity.<sup>29-31</sup> It has been postulated that decreased activity of the calf-muscle pump or prolonged standing or sitting will result in pooling of blood in the lower extremity, resulting in increased venous pressure and interstitial fluid leakage. Chronically increased lymphatic fluid stasis resulting from these postural changes is then thought to promote tissue fibrosis and worsen lymphedema.<sup>29</sup> Although these hypotheses seem putatively possible, the exact relationship between venous pressures and lymphatic fluid accumulation remains unknown.

### **Avoid air travel and wear compressive garments on flights**

Patients with a history of lymph node dissection are often told to avoid air travel or wear compressive garments (even if they do not have lymphedema) when flying. Unfortunately, as with many other recommended preventative measures, this guideline appears to have little scientific evidence supporting it. Ward and colleagues<sup>32</sup> presented case reports (level 5) of lymphedema development after air travel and cited anecdotal rates of lymphedema development in 5% to 30% of at-risk patients by The National Breast Cancer Centre of Australia. Casley-Smith<sup>33</sup> (1996) reported a questionnaire-based retrospective study (level 4) in an effort to determine the triggers that lead to lymphedema development (infection/insect bite/plane flight/burn/other/unknown). There were 531 patients who responded (1,020 surveys were sent), and of these, 27 reported that their symptoms started after an aircraft flight. In addition, 67 patients reported worsening of existing lymphedema after flying. These findings led the authors to conclude that lymphedema can be triggered by travelling on aircrafts and may be due to reduced activity or lower cabin pressure for long periods of time, resulting in pooling of blood in the limbs. However, the authors acknowledge that this is merely speculation with no direct evidence.

Other retrospective studies have suggested that air travel has little effect on the development of lymphedema. For example, Graham<sup>34</sup> surveyed 293 breast cancer survivors about changes in arm circumference and airplane travel (level 3) and found no cases of permanent new onset lymphedema in this cohort. In fact, patients who had taken precautions when flying, such as using compression garments, were actually more likely to develop lymphedema or have progression of their existing lymphedema than those who had not. Similarly, Kilbreath and associates<sup>35</sup> prospectively assessed the impact of flying on at-risk limbs in breast

cancer patients (level 2) by evaluating patients who had flown from Canada to Australia to attend a dragon boat regatta. They found no adverse changes in impedance ratios comparing the normal limbs with the at-risk limbs in 95% of patients when comparing pre- and postflight measurements. The authors acknowledged that the subjects in this study had trained for dragon racing and that this exercise may have had a protective effect.<sup>35</sup>

### Maintain a normal body weight

The clinical evidence supporting this recommendation is strong and derived from multiple studies including level 1 evidence. Early case reports and retrospective studies demonstrated a significant increase in the rate of lymphedema development in obese patients.<sup>36-39</sup> In one of the largest early studies aiming to identify risk factors for development of lymphedema, Treves<sup>40</sup> evaluated 768 patients after mastectomy and axillary lymph node surgery over a 5-year period (level 3). The overall rate of lymphedema in the entire cohort was 41%. The rate of lymphedema in obese patients (defined as patients weighing more than 150 lbs) was nearly double that of nonobese patients (49% vs 28%) and highly statistically significant. Furthermore, the severity of lymphedema also correlated with obesity, leading the authors to conclude that obesity is a significant predisposing risk factor.<sup>40</sup>

In a more recent study, Werner and colleagues<sup>41</sup> set out to identify risk factors contributing to the development of arm edema after conservative management of breast cancer. Their prospective level 3 study found that the only significantly associated variable in the development of arm edema was increased body mass index (BMI); furthermore, increased BMI was associated with increased frequency and severity of lymphedema. These findings were supported by Helyer and coauthors<sup>42</sup> in their prospective level 3 study following 137 patients after diagnosis with early stage breast cancer and arm circumference measurements at 6-month intervals for a median of 20 months (range 6 to 36 months). Similar to Werner and colleagues' study,<sup>41</sup> this study demonstrated a significant increase in arm volume in patients with BMI as a continuous variable; patients with a BMI greater than 30 kg/m<sup>2</sup> had a more than 2-fold increased risk of lymphedema.<sup>42</sup> Ridner and colleagues<sup>43</sup> found an even higher risk of lymphedema (3.6-fold) in obese patients in a prospective longitudinal study (level 2) of 138 breast cancer patients followed for 30 months with arm volume and weight measurements at 3-month intervals. Long-term studies have also demonstrated significant increases in the risk of lymphedema development in obese patients. In another level 3 study of 263 breast cancer survivors followed for 20 years after initial treatment, Petrek and colleagues<sup>3</sup> found an astounding overall lymphedema

rate of 49% with a 13% rate of severe lymphedema. They demonstrated that obesity at the time of diagnosis and weight gain after diagnosis were significant risk factors for development of lymphedema. Similar results were demonstrated more recently by McLaughlin and colleagues<sup>4</sup> in a level 2, 5-year prospective study of nearly 1,000 patients treated with axillary lymph node dissection or sentinel lymph node biopsy. Even mild increases in body weight appear to increase the risk of lymphedema as evidenced by higher rates of lymphedema in patients with a BMI greater than 25 kg/m<sup>2</sup> in a prospective follow-up study of 240 patients with breast cancer.<sup>44</sup>

In an interesting, though small, level 1 randomized clinical trial of 21 patients, Shaw and colleagues<sup>45</sup> found that interventions designed to promote weight loss were associated with a significant decrease in excess arm volume (9% decrease overall). These findings led the authors to conclude that interventions designed to maintain or decrease body weight after surgery can be an effective means of decreasing arm volumes and by inference, lymphedema.

Although it is clear that obesity is a significant risk factor for development of lymphedema, the cellular and molecular mechanisms that are responsible for this effect remain unknown. It has been hypothesized that obese patients undergo more extensive surgery, resulting in more injury to the lymphatic system. Alternatively, it has been suggested that the heavier limb in obese patients may act as a reservoir for lymphatic fluid. It is also possible that obesity is associated with increased inflammation either with or without overt infection and that this effect may increase tissue fibrosis and lymphatic dysfunction. These are important clinical questions that warrant further study.

### Avoid extremes of temperature and sunburns

The National Lymphedema Network and the Lymphedema Framework in the UK advise patients at risk for developing lymphedema to avoid exposure to extreme cold, which can be associated with rebound swelling, to avoid prolonged (greater than 15 minutes) exposure to heat, particularly hot tubs and saunas, and to avoid placing limbs in water temperatures above 102°F (38.9°C).<sup>9,46</sup> In addition, patients are advised to apply sunscreen to the affected limb and avoid excessive sun exposure. These precautions are based on the concept that heat or rebound increased circulation from cold exposure may increase blood flow and as a consequence, increase lymphatic load.<sup>22</sup>

Interestingly, the few studies that have been done to study the effect of heat on lymphedema appear to show positive rather than negative results from heat exposure. Heat therapy is strongly advocated by traditional Chi-

nese medical literature for treatment of lower extremity elephantiasis.<sup>47</sup> For example, Zhang Ti-Sheng and co-workers<sup>47</sup> reported positive results in more than 1,000 patients treated with heat therapy for lower extremity lymphedema. Similarly, Chang and colleagues<sup>48</sup> reported that microwave heat therapy resulted in significant reductions in limb edema in 85 of 98 patients (level 2). More than three-quarters of patients had reductions of at least 50%. The authors confirmed their findings in a level 1 double blind randomized study.<sup>49</sup> Similar positive findings were reported in a level 2 study of 45 patients with upper extremity lymphedema secondary to breast cancer treatment.<sup>50</sup> Liu and Olszewski<sup>51</sup> used microwave and hot water immersion hyperthermia therapies on 12 patients with leg lymphedema (level 2) and reported that heating was associated with reduced girth and volume of affected legs, with near resolution of lymph lakes. They hypothesized that regional heating resulted in an altered immune response, changes in extracellular matrix protein composition, and greater pliability of tissues, leading to decreased edema.

The use of sunscreen is advocated because superficial burns can cause inflammation, vasodilatation, and potentially, infection. However, there appear to be no reports that have evaluated the effectiveness of sunscreen application in prevention of lymphedema. Disruption or injury to the superficial lymphatic plexus may occur with deep partial thickness or full thickness burns due to the location of the dermal lymphatics in the dermal-epidermal junction.<sup>52</sup> However, aside from case reports and anecdotal studies there is little scientific evidence supporting these hypothetical issues. Hettrick and associates<sup>52</sup> cited a case (level 4) by Balakrishnan of a 50-year-old man with a 25% total body surface area burn to his lower limbs, who developed lymphedema in his right leg after skin grafting. They hypothesized that lymphedema in this case was due to deep subcutaneous excisions and infections leading to loss of the lymphatic system. Hettrick and colleagues<sup>52</sup> also reported a prospective analysis of burn patients (level 4) and found a low rate (1%) of lymphedema in this population. Maheshwari and coauthors<sup>53</sup> reported a case (level 4) of severe lymphedema occurring 8 years after a severe third-degree acid burn. The relevance of these case reports is even less considering that patients reviewed in these series had no history of lymphatic injury before their burn.

### **Avoid vigorous exercise**

For years, patients at risk for lymphedema have been admonished to avoid vigorous exercise. This recommendation was based on studies by Petrek and colleagues,<sup>3</sup> who found, in their retrospective series, that vigorous exercise was associated with development of lymphedema. It was

rationalized that sports or exercise increased blood flow and as a consequence, lymphatic fluid production, thereby exceeding the transport capacity of the lymphatic system. As a result, patients were told to avoid sports like rowing, volleyball, tennis, golf, soccer, weight lifting, or running sports. This edict seemingly was supported by reports of increased risk of genital lymphedema in professional female cyclists.<sup>1</sup>

More recently, however, multiple studies have disproved this concept and the National Cancer Institute now recommends that carefully controlled exercise is safe for patients with lymphedema. McKenzie and Kalda<sup>54</sup> performed a level 1 randomized control trial on 14 breast cancer patients randomizing them to an exercise or control group. The exercise group underwent an 8-week upper-body exercise program and both groups were assessed for arm circumference changes repeatedly over the experimental period. They found that the exercise group reported an improved quality of life without an increase in arm circumference. These findings were supported by a larger level 1 study reported by Ahmed and colleagues<sup>55</sup> in which 45 breast cancer patients (13 of whom had lymphedema) were randomly assigned into an exercise or control group. The exercise group had twice-weekly weight training sessions for 6 months, and both groups underwent lymphedema assessment at baseline and 6 months after initiation of the study. Lymphedema was measured in 3 ways: arm circumference measurements, self-report of diagnosis, and self-report of symptoms.<sup>55</sup> This study also reported no changes in arm circumference and no exacerbations of lymphedema in the exercise group.

Schmitz and associates<sup>56</sup> performed an even larger and longer level 1 randomized trial in 141 breast cancer patients randomly assigned to an exercise group (progressive weight lifting twice a week for a year) or a control group, who did not exercise. Similar to the previous studies, this study found no increased incidence of lymphedema in the exercise group compared with the control group. More importantly, the authors found a reduced incidence of exacerbations of lymphedema, reduced symptoms of lymphedema, and increased strength in the exercise group.<sup>56</sup> Sagen and colleagues<sup>57</sup> also found, in their level 1 randomized controlled trial, unrestricted physical activity and moderate resistance exercises had no increased risk of lymphedema developing and suggested that there is no need to limit activity of the affected limb in fear of developing lymphedema in patients who have undergone breast cancer surgery.

The results of our review for each recommendation are summarized in Table 3.

**Table 3.** Preventive Measure and Evidence to Support Either Fact or Fiction

Preventive measure	Best scientific evidence for	Best scientific evidence against	Fact/fiction/to be determined
Avoid needle sticks of any type	Clark. <sup>16</sup> Level 2 prospective observational study (188 patients), found that 44% patients with needle stick developed lymphedema as compared with 18% of those without needle sticks.	Winge. <sup>18</sup> Level 3 questionnaire study (311 patients, of whom 88 had intravenous procedures in affected limb). Only 4 patients developed lymphedema in relation to venipuncture.	To be determined
Avoid pressure	Louden & Petrek. <sup>20,21</sup> Level 5, expert opinion hypothesising that blood pressure monitoring and tight clothing increase blood pressure in at-risk limbs, resulting in increased lymph production.	Dawson. <sup>27</sup> Level 3, retrospective cohort (317 patients), no new cases or exacerbations of lymphedema in 15 patients with a history of lymph node dissection who subsequently had elective hand surgery with tourniquet.	Probably fiction
Leg/limb precautions	Ryan. <sup>29</sup> Level 5, expert opinion, crossing legs hinders venous return, prolonged standing/sitting results in pooling of blood in legs and hence, increased interstitial fluid leakage.	None found	To be determined
Avoid air travel/wear compressive garments for air travel	Casley-Smith. <sup>33</sup> Level 4, questionnaire-based retrospective study (531 patients), 27 patients reported lymphedema symptoms started after aircraft flight and 67 patients reported worsening lymphedema symptoms after flying.	Graham. <sup>34</sup> Level 2 cohort study (293 patients), no cases of permanent or new onset lymphedema found after aircraft flight taken.	Probably fiction
Maintain a normal body weight	Shaw. <sup>45</sup> Level 1 randomized clinical trial (21 patients), interventions designed to promote weight loss after surgery significantly reduced excess arm volume and lymphedema.	Villasor. <sup>12</sup> Level 3 nonconsecutive cohort (51 patients); 47% of patients with lymphedema had normal weight, no correlation between lymphedema formation and obesity or weight found.	Fact
Avoid extremes of temperature/apply sunscreen/avoid burns	Hettrick. <sup>52</sup> Level 4 prospective analysis; 1% of burn population found to have lymphedema.	Chang. <sup>49</sup> Level 1 double blind randomized study (60 patients), heat added to placebo, or benzopyrone therapy significantly improved symptoms of lymphedema compared with placebo or benzopyrone alone.	Fiction
Avoid vigorous exercise	Petrek/Foldi [1]. Level 5 Expert opinion rationalizing that vigorous exercise increases blood flow and consequently, lymphatic fluid production.	Schmitz. <sup>56</sup> Level 1 randomized trial (141 patients); no increased incidence of lymphedema in exercise group compared with nonexercise control group.	Fiction

## DISCUSSION

Lymphedema is a devastating complication of cancer treatment. Unfortunately, the etiology of this disorder remains unknown and this gap in our knowledge has prevented development of effective treatment strategies. In addition, although the clinical risk factors for lymphedema have been identified, rational preventative strategies derived from high-level scientific evidence are lacking. In fact, some authors have suggested adopting a “common-sense” approach to lymphedema management, arguing that it is not always appropriate to seek randomized control trials in order to establish optimal prevention strategies.<sup>1</sup> Although randomized trials may not always be feasible (or ethical), well-designed prospective cohort studies are generally attainable.

## CONCLUSIONS

To summarize the findings of this systematic review, there is limited evidence to support the recommendation that venipuncture should be avoided in patients with a history of lymph node surgery. Similarly, there is a paucity of evidence to support the preventative measures regarding limb constriction, elevation, heat and cold, and air travel and use of compression garments when flying. On the other hand, we found good scientific evidence (level 1 and 2) to support the recommendation of maintaining normal body weight or avoiding weight gain in patients who are at risk for developing lymphedema. Similarly, there is strong scientific support for participation in a supervised exercise regimen both in patients with lymphedema and in those at risk for developing lymphedema.

The lack of clarity for effective preventative measures likely contributes significantly to patient fear and anxiety. In addition, arbitrary recommendations have significant effects on patient care resulting in unnecessary insertion of central catheters (to avoid venipuncture of the affected limb), blood draws from regions not routinely used for this purpose (eg, external jugular vein, femoral vein, or dorsal foot veins). Therefore, given the limitations in our knowledge and the important implications for patient care and quality of life, additional research is clearly required. Future studies with well-defined outcomes, adequate patient sample sizes, and prospective limb measurements would be helpful.

### Author Contributions

Study conception and design: Cemal, Mehrara

Acquisition of data: Cemal, Mehrara

Analysis and interpretation of data: Cemal, Pusic, Mehrara

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