Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis

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Precautionary recommendations conveyed to survivors of cancer by health-care practitioners to reduce the risk of breast cancer-related lymphoedema are indispensable aspects of clinical care, yet remain unsubstantiated by high-level scientific evidence. By reviewing the literature, we identified 31 original research articles that examined whether lifestyle-associated risk factors (air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and skin infections—eg, cellulitis) increase the risk of breast cancer-related lymphoedema. Among the few studies that lend support to precautionary guidelines, most provide low-level (levels 3–5) or inconclusive evidence of an association between lymphoedema and these risk factors, and only four level 2 studies show a significant association. Skin infections and previous infection or inflammation on the ipsilateral arm were among the most clearly defined and well-established risk factors for lymphoedema. The paucity of high-level evidence and the conflicting nature of the existing literature make it difficult to establish definitive predictive factors for breast cancer-related lymphoedema, which could be a considerable source of patient distress and anxiety. Along with further research into these risk factors, continued discussion regarding modification of the guidelines and adoption of a risk-adjusted approach is needed.

Introduction

Since the 1990s, advances in targeted breast cancer therapies have led to notable improvements in survival, shifting the clinical focus to the alleviation of disease burden and the often chronic complications of treatment, one of which is lymphoedema. Patients might experience a range of symptoms in the affected limb, including swelling, heaviness, pain, tightness, changes in skin quality, a decreased range of motion, and a higher risk of infection. These symptoms not only compromise patients’ functional wellbeing and overall quality of life, but also unfavourably affect self-esteem and body image.

Patients with breast cancer who undergo axillary lymph node dissection (ALND), regional lymph node radiation, or to a lesser extent, sentinel lymph node biopsy (SLNB), have a lifelong risk of developing lymphoedema, which can occur years after the completion of all treatments.8,9 Because of variations in the clinical definition of breast cancer-related lymphoedema, the diagnostic modality, type of surgery and therapy, and the length of follow-up, no consensus exists about the incidence of lymphoedema, with studies reporting an approximate range of 5–50% worldwide.5,9 A broad array of lymphoedema-associated risk factors have been reported in the published literature, with varying contributory risks, including mastectomy8–10 (risk ratio [RR] of mastectomy vs lumpectomy, 1·42; 95% CI 1·15–1·76), regional lymph node radiation,11 (RR of axillary radiotherapy vs no axillary radiotherapy, 2·97; 2·06–4·28), axillary lymph node dissection,8–10,16–18 (RR of axillary lymph node dissection vs sentinel lymph node biopsy, 3·07; 2·20–4·29), and number of pathologically involved lymph nodes8,13,14 (RR of positive nodes vs no positive nodes, 1·54; 1·32–1·80).4 Having a high body-mass index (BMI) at the time of diagnosis or undergoing large weight fluctuations after surgery also represent significant risk factors7,8,10–12,14,16–18 (odds ratio of being overweight [BMI ≥25 kg/m²] vs not overweight [BMI <25 kg/m²], 5·58; 1·29–4·23).11

Very little is known, however, about the pathophysiology and underlying mechanisms that contribute to the development of breast cancer-related lymphoedema. This paucity of knowledge has hindered the development of any effective preventive or curative treatment options, and management of breast cancer-related lymphoedema remains largely palliative.20,21 Standard interventions include compression, exercise, skin care, and manual lymphatic drainage.21 As the prevention of lymphoedema is preferable to the mitigation of chronic symptoms, patients with breast cancer also receive advice regarding precautionary behaviours that they can adopt to reduce their life-long risk of lymphoedema development.22–26 Historically, risk-reduction strategies have been intended to minimise stressing the lymphatic system of the at-risk limb (the limb ipsilateral to the side of axillary surgery or radiation) in the hope of preventing lymphatic overload.21,26 The position statement of the National Lymphedema Network25 details several of the most salient recommendations, including the use of compression garments during air travel, the avoidance of any sort of trauma to the at-risk or affected arm, including skin and venous puncture (ie, blood draws, and intravenous sticks), and avoidance of limb constriction by blood pressure cuffs or tourniquets. Also of key importance is preventing the development of any skin infections. Although these and other risk-reduction guidelines are based on clinical reasoning, their potential benefits remain without definitive scientific backing. Many of the studies that have tried to answer their utility...
are restricted in scope, and are predominantly small, retrospective, and single-site reports.\textsuperscript{7,23,26–28} With scarce data supporting their efficacy, rigid adherence to these measures could contribute to further stress and anxiety, and needlessly heighten patients’ concern about their condition.\textsuperscript{20,21,26}

The goal of this Review is to examine the literature of studies that have tried to elucidate the aforementioned precautionary behaviours and lifestyle risk factors. We will pay particular attention to highlighting the strength of evidence (panel) in each study and whether or not it bolsters the National Lymphedema Network recommendations that are provided to the public. We further hope to underscore the importance of prospective trials in strengthening the breast cancer-related lymphoedema literature, and discuss the implications of existing and ongoing research in terms of patient individualisation.

**Air travel and compression garments**

The relation between air travel and the development or worsening of lymphoedema is unclear, as is the effect of use of compression garments on flights by at-risk or affected women.\textsuperscript{24–26} The National Lymphedema Network does not give a definitive recommendation for the use of prophylactic arm compression during air travel, as the majority of accounts of arm swelling after air travel are anecdotal and provide conflicting evidence. Studies have shown an association between long-haul flights and the worsening of oedema in the lower extremities of individuals with and without lymphoedema.\textsuperscript{23,24}

In people with compromised lymphatic systems, the hypobaric–hypoxic environment inside the aircraft, coupled with low cabin pressure, and the protracted reduced movement and dehydration experienced on flights, might be sufficient to incite or exacerbate lymphoedema.\textsuperscript{24,26,27–29} A few studies, most of which are retrospective and anecdotal, have focused on women at risk of developing breast cancer-related lymphoedema. A questionnaire-based study (level 4 evidence) by Casley-Smith\textsuperscript{32} is the only study to report a significant correlation between air travel and the onset of lymphoedema. A small proportion of patients with breast cancer-related lymphoedema (27 [6%] of 490) linked the onset of their swelling to air travel. These results were based on patient perception and so were susceptible to recall and selection bias, coming from individuals who were members of the same lymphoedema association. Nonetheless, they provided the initial groundwork for suggesting a link between air travel and lymphoedema, and prompted the authors to postulate that the physiological mechanism resulting in blood pooling in the limbs might be due to decreased on-flight cabin pressure.\textsuperscript{33} Another retrospective observational study by Hayes and colleagues (level 4),\textsuperscript{34} analysing a cohort in which 154 (88%) of 176 patients had undergone axillary lymph node dissection, found that the prevalence of lymphoedema was 2.5-times higher following air travel than in individuals who did not undergo air travel, where lymphoedema was defined as a greater than 5 cm difference between the sum of arm circumferences. The result, however, was not statistically significant.

There have also been studies that have shown no relation between air travel and lymphoedema. A study by Kilbreath and colleagues\textsuperscript{35} (level 2) set out to examine the effect of air travel on extracellular fluid content as measured by bioimpedance analysis, with 53 (74%) of 72 individuals having had axillary lymph node dissection. In 68 (94%) women, the researchers did not find a change in impedance ratios after flying. The population examined was not representative of the general population, however, because all the women were athletes attending a dragon boat regatta. Similarly, in another prospective analysis by Ferguson and colleagues\textsuperscript{36} (level 2) using perometry to assess arm volume in a cohort of 632 patients with breast cancer (total of 760 breasts treated) who had undergone sentinel lymph node biopsy (541 [71%] of 760 breasts), axillary lymph node dissection (159 [21%]), or no axillary surgery (60 [8%]), no significant association was found between air travel and arm volume increase by multivariate analysis. In a study by Graham\textsuperscript{37} (level 3), a group of survivors of breast cancer (with 246 [86%] of 287 patients having undergone axillary lymph node dissection) responded to a survey asking about their exposure to various lymphoedema risk factors. No individuals reported the development or worsening of permanent lymphoedema after air travel, and only...
nine (3%) participants reported cases of transient swelling linked to overseas flights. Among individuals who did fly, the authors found that the practice of precautionary behaviours (such as the use of compression garments) were associated with an increased risk of lymphoedema. This increased risk might have been due to more visits to doctors or other health practitioners among the individuals who practised precautionary behaviours than in those who did not, resulting in a higher incidence of breast cancer-related lymphoedema diagnosis.27,29 In another study (multisite, case control; level 3) Swenson and colleagues10 examined the possible contributors to lymphoedema as a prophylaxis on flights. The authors found that air travel was significantly associated with lower lymphoedema occurrence on univariate analysis than those who did not undergo air travel. This association, however, was not maintained on multivariate analysis. Similarly, no association was found between air travel and lymphoedema in patients with mild and moderate-to-severe breast cancer-related lymphoedema in a case-control study by Mak and colleagues (level 3),30 with the entirety of the cohort having undergone unilateral axillary lymph node dissection.

Evidently, no consensus exists among the few existing studies regarding the risk conferred by air travel on the development of lymphoedema and the utility of compression garments as a prophylaxis on flights. Because only a single study so far has shown a significant correlation between air travel and lymphoedema in a small number of patients,35 there is little reason to restrict air travel following breast cancer surgery. Even among the studies that included cohorts in which a high proportion had undergone axillary lymph node dissection, no association between air travel and lymphoedema was reported.36–40 Despite the study by Graham37 that calls into doubt the safety and efficacy of compression garments, many practitioners still recommend their use during flights, and in our clinical experience, patients have commented on their usefulness during long periods of air travel. Although prophylactic compression sleeve use during flights could mitigate fear, there is no evidence to show that their use is or is not of benefit to at-risk women (table 1).

**Temperature extremes**

The National Lymphedema Network and the American Cancer Society recommendation to those at-risk of lymphoedema and those with lymphoedema is to proceed with caution when facing sudden or prolonged temperature changes in the environment, and to make sure to avoid any sun or skin burns, exposure to extreme cold, and submersion of at-risk limbs in water temperatures above 38.9°C.38–40 If these temperature changes are drastic enough to damage tissues, inflammation and increased blood flow to the affected area can result in more lymph production.41–44 Patients are also advised to avoid any thermal-based heat or cold therapies on the affected arm, although local heat therapy for the management of lymphoedema has been shown by several level 1 and level 2 studies from China to represent a safe and effective treatment option for lower and upper extremity lymphoedema.45–46

A study by Showalter and colleagues41 (level 2) assessed sauna use and the risk of lymphoedema. The authors examined the exposure of survivors of breast cancer (with at least one lymph node removed) to 30 lifestyle behaviours (including the use of saunas) that are possibly associated with arm swelling. Participants were surveyed at 3-month intervals for 1 year. Among temperature-related risk factors, the authors included vigorous exercise in hot weather, travel to hot or humid areas, the use of hot tubs and saunas, and the development of sunburns or skin burns in their analysis. Despite a small number of participants reporting sauna use (13 [4%] of 295), this was the only risk factor among all 30 factors that was significantly associated with incident arm swelling (defined as ≥5% increase in interlimb volume difference).

In this study, however, the authors also reported a significant association between sauna use and having a cut on the affected arm, so exposure to the hot environment of the sauna per se might not have been the sole cause of incident arm swelling. Local inflammation due to an infected skin cut in such a humid, microorganism-rich environment could potentially play a part. More research is needed, however, to establish whether temperature extremes represent a risk factor for lymphoedema (table 2).

**Limb constriction: blood pressure measurements and tourniquets on the ipsilateral arm**

Several groups have postulated that an increase in venous pressure resulting from excessive constriction (eg, through the use of blood pressure cuffs or pneumatic tourniquets on the ipsilateral arm) might contribute to increased lymph production and precipitate swelling of the affected limb.45–46 In the absence of studies demonstrating a causative relationship, the National Lymphedema Network maintains that such instruments are to be applied on an unaffected extremity whenever necessary.47 By contrast, some practitioners contend that the pressure exerted by blood pressure cuffs is therapeutic for a lymphoedematous arm, since compression is an essential component of the treatment for upper and lower extremity lymphoedema.48–51 Lymphatic function does not seem to be impaired with transient increases in pressure, even in patients with a compromised lymphatic system.52–54 However, blood pressure cuffs exert a far greater amount of pressure on a localised area than compression garments or bandages, which could potentially damage lymphatic vessels.49,51
Table 1: Studies of air travel and risk of lymphoedema

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Study population</th>
<th>Risk factor composition of cohort</th>
<th>Main relevant findings</th>
<th>Conclusions</th>
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<tr>
<td>Kilbreath et al, 2010&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Level 2: prospective study</td>
<td>72 women who had breast and axillary surgery, attending a dragon boat regatta in Australia</td>
<td>Air travel did not cause an adverse change in the biopsychometric ratio in the at-risk arm among 94% of the women attending the regatta regardless of flight length or compression garment use</td>
<td>Air travel does not contribute to lymphoedema development</td>
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<td>Showalter et al, 2013&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Level 2: prospective subanalysis of the PAL trial&lt;sup&gt;32&lt;/sup&gt;</td>
<td>295 survivors of breast cancer participating in the PAL trial (54.4% at risk of lymphoedema and 141 with established lymphoedema)</td>
<td>Mean BMI at baseline, 29.2 kg/m², 229 (78%) patients received radiation (type unknown); all patients had at least one lymph node removed</td>
<td>268 patients (91%) did not have incident arm swelling whereas 27 (9%) did; among 30 potential risk factors for lymphoedema, air travel and travel to different altitudes were not found to be significant predictors of incident arm swelling</td>
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<td>Ferguson et al, 2016&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Level 2: prospective cohort study</td>
<td>62/2 patients with either unilateral or bilateral breast cancer surgery</td>
<td>Median BMI at baseline, 25.4 kg/m²; based on 760 treated breasts, 159 (21%) had ALND, 54/1 (71%) had SLNB, 60 (8%) had no axillary dissection; 160 (21%) received RNLN</td>
<td>By univariate and multivariate analysis, number and duration of flights taken was not a significant predictor of arm volume increase</td>
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<td>Graham, 2002&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Level 3: survey-based retrospective study</td>
<td>287 survivors of breast cancer with prospectively measured arm circumferences</td>
<td>24/6 (89%) of patients had ALND, 54 (19%) of patients received radiation to the supraclavicular fossa only, or both the supraclavicular fossa and axilla</td>
<td>No significant difference in the incidence of lymphoedema between fliers (11.2%) and non-fliers (8.3%); and no cases of permanent swelling occurred after a flight; among fliers, the practice of precautionary behaviours was associated with an increased risk of lymphoedema (OR 6.16 [95% CI 1.82–20.87])</td>
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<td>Swenson et al, 2009&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Level 3: multistate, case-control study</td>
<td>188 patients with breast cancer who had axillary surgery (94 patients with lymphoedema and 94 controls without lymphoedema, matched on type and date of axillary surgery)</td>
<td>In each of the two groups, 86 (91%) patients had ALND and 8 (9%) had SLNB. 65 (69%) patients with lymphoedema and 47 (55%) controls had a BMI of ≥ 25 kg/m². 64 (68%) patients with lymphoedema received radiation therapy, 21 (22%) received axillary radiation, and 26 (28%) received radiation to the supraclavicular area; 64 (68%) controls received radiation therapy, 8 (9%) received axillary radiation, and 23 (24%) received radiation to the supraclavicular area</td>
<td>On univariate analysis, air travel was associated with less lymphoedema occurrence; on multivariate analysis, the only factor significantly associated with lymphoedema was high BMI (OR 5.58 [95% CI 1.29–24.23])</td>
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<td>Mak et al, 2009&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Level 3: matched case-control study</td>
<td>202 women with unilateral breast cancer surgery (103 with lymphoedema and 101 matched controls without lymphoedema)</td>
<td>BMI at baseline, 23.5 kg/m² in patients with lymphoedema, 22.4 kg/m² in controls; all patients had ALND (in both groups)</td>
<td>Air travel was not associated with the development or worsening of lymphoedema in either the controls without lymphoedema or patients with lymphoedema</td>
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<td>Casley-Smith, 1996&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Level 4: questionnaire-based retrospective study</td>
<td>537 questionnaire respondents with lymphoedema (490 cases of secondary lymphoedema)</td>
<td>33% of patients with secondary lymphoedema had undergone a previous mastectomy; 20% of patients noted the start of lymphoedema following surgery or radiotherapy</td>
<td>27 (6%) of 490 patients with lymphoedema (16) of whom were patients with breast cancer-related lymphoedema noted the onset of swelling after air travel</td>
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<td>Hayes et al, 2005&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Level 4: retrospective observational study</td>
<td>176 patients with unilateral breast cancer surgery</td>
<td>154 (87.5%) patients had ALND, 22 (12.5%) had no axillary dissection</td>
<td>Air travel within 6 months was non-significantly associated with a 2.5-times higher prevalence of lymphoedema, when lymphoedema was defined as a difference of &gt;5 cm between the sum of arm circumferences</td>
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ALND=axillary lymph node dissection. SLNB=sentinel lymph node biopsy. RNLN=regional lymph node radiation. PAL=Physical Activity and Lymphedema. BMI=body-mass index. OR=odds ratio.

Few studies reveal whether blood pressure readings or other forms of constriction on the at-risk arm confer a significant risk of lymphoedema. The matched case-control study by Mak and colleagues<sup>39</sup> found that blood pressure monitoring was among the medical procedures that did not incite lymphoedema or worsen mild lymphoedema (<3 cm difference between sum of arm circumferences) among patients who had undergone axillary lymph node dissection. The previously discussed prospective study by Showalter and colleagues<sup>33</sup> also did not find a significant association between ipsilateral blood pressure measurements and arm swelling, nor did the prospective analysis by Ferguson and colleagues (level 2),<sup>38</sup> in which the majority of cases (601 [79%] of 760 treated breasts) had sentinel lymph node biopsy or no axillary surgery as opposed to axillary lymph node dissection (159 [21%] of 760 treated breasts). Notably, in the study by Hayes and...
colleagues\textsuperscript{66} (level 4; 88% of the cohort had axillary lymph node dissection), blood pressure measurements on the affected arm were associated with a 3.4-fold increase in the prevalence of lymphoedema, as defined by a more than 5 cm difference between sum of arm circumferences.

Few studies have shown a relation between arm morbidity and the use of extremity tourniquets, which exert high pressures to block all blood flow in an extremity during surgery.\textsuperscript{51,58} In a series of retrospective studies (level 4) examining the use of pneumatic tourniquets during elective hand surgery in women with a history of breast or axillary surgery, there was no permanent development or worsening of arm lymphoedema.\textsuperscript{63–69} Although the follow-up time of these studies was at least 1 year after surgery, larger cohorts are needed to substantiate these conclusions.

Survey-based level 4 studies have also been done to assess the professional opinion of health-care providers regarding the use of extremity tourniquets during elective hand surgery in patients with a history of ipsilateral axillary surgery. In an online survey, Fulford and colleagues\textsuperscript{73} (level 4) found that an overwhelming majority of hand surgeons, and a smaller majority of breast oncology nurses and breast surgeons, did not feel that the use of compression tourniquets should be contraindicated in patients who had previously undergone axillary lymph node dissection. Similarly, among hand surgeons responding to a survey provided by Gharbaoui and colleagues,\textsuperscript{60} it was found that the majority of surgeons routinely use tourniquets in women with and without lymphoedema.

No level 1 or level 2 evidence was found to suggest a relation between ipsilateral blood pressure measurements and arm swelling, nor any long-term adverse effects of tourniquet use on limb volume. Furthermore, surgeons and clinicians that were surveyed showed a willingness to use tourniquets on the ipsilateral arm during hand surgeries.\textsuperscript{73,74} Until larger, higher-level studies can resolve this ambiguity about the potential relation between ipsilateral blood pressure measurements and arm swelling, use of the uninvolved arm for blood pressure measurements whenever possible is reasonable, as per the National Lymphedema Network guidelines.\textsuperscript{24} Isolated blood pressure measurements taken on the at-risk arm have been shown not to be associated with arm swelling in two prospective studies that analysed this risk.\textsuperscript{75,76} which when discussed with the population of patients at risk of breast cancer-related lymphoedema might help to mitigate some fear about their risk of lymphoedema.

Table 3 shows the results from studies of blood pressure measurement and lymphoedema risk, and table 4 presents the findings from studies on tourniquet use and risk of lymphoedema.

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<tr>
<td>Chang et al, 1996\textsuperscript{46}</td>
<td>Level 1: double-blind randomised study</td>
<td>60 patients with leg lymphoedema (randomly assigned into two groups) and matched based on demographic and clinical characteristics</td>
<td>Among the 55 cases of secondary lymphoedema, 4 (7%) were caused by trauma, 3 (5%) from cancer surgery, and none by axillary surgery or radiation therapy</td>
<td>To a major extent, patients in both treatment groups (randomly assigned to either treatment with coumarin or a placebo, with both groups also receiving a regimen of microwave heat therapy) had greater symptom relief and limb volume reductions when given the heat therapy than when given only the coumarin or placebo</td>
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<td>Chang et al, 1989\textsuperscript{49}</td>
<td>Level 2: prospective trial</td>
<td>98 patients with peripheral oedema (23 with bilateral lymphoedema)</td>
<td>Patients had lymphatic filariasis of the legs (n=61) or arms (n=7); none had axillary surgery and radiation therapy</td>
<td>85 (87%) of 98 patients with peripheral lymphoedema had significant reductions in swelling after receiving microwave heat therapy; three-quarters of the cohort had reductions of at least 50%</td>
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<td>Liu and Olszewski, 1993\textsuperscript{47}</td>
<td>Level 2: prospective trial</td>
<td>12 patients with leg lymphoedema</td>
<td>33% (4/12) had removal of inguinal lymph nodes and underwent radiation for carcinoma</td>
<td>Hot water and microwave therapy promoted a significant reduction in limb girth and volume; lymphoscintigraphy did not detect alterations in lymph flow following treatment</td>
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<td>Gan et al, 1996\textsuperscript{48}</td>
<td>Level 2: prospective trial</td>
<td>45 patients with unilateral arm lymphoedema following radical mastectomy</td>
<td>Patients underwent radical mastectomy; details on type of axillary surgery and radiation therapy not noted, although patients probably underwent ALND</td>
<td>After two microwave treatment courses, all patients showed a significant reduction in the extent of peripheral oedema, with restoration of soft tissue elasticity</td>
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<tr>
<td>Showalter et al, 2012\textsuperscript{41}</td>
<td>Level 2: prospective subanalysis of the PAL trial\textsuperscript{40}</td>
<td>295 survivors of breast cancer participating in the PAL trial</td>
<td>Mean BMI at baseline, 29.2 kg/m\textsuperscript{2}; 229 (78%) patients received radiation (type unknown); 48 patients had at least one lymph node removed</td>
<td>Among potential risk factors for lymphoedema, sauna use was the only exposure found to be significantly predictive of incident arm swelling (OR 5.77 [95% CI 1.00–33.82]); hot tub use, exercise in hot weather, travel to humid areas, having a fever, sunburns, and skin burns were not significantly predictive of swelling</td>
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Table 2: Studies of temperature extremes and risk of lymphoedema

ALND=axillary lymph node dissection. PAL=Physical Activity and Lymphedema. BMI=body-mass index. OR=odds ratio.
Blood draws, infusions, and skin puncture

The avoidance of skin puncture on the ipsilateral arm for medical procedures is one of the most discussed precautionary measures for preventing lymphoedema, although several high-level studies have demonstrated that there is no risk among cohorts with varying levels of nodal surgery.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\) Puncturing the skin and veins is thought to increase the risk of infection and inflammation in the arm, which could incite or worsen existing lymphoedema in at-risk or affected patients.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)

Many authors have noted a connection between needleless, infections, and lymphoedema,\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\) especially in earlier studies examining the risk factors for breast cancer-related lymphoedema.\(^1\)\(^2\)\(^3\) In a retrospective study by Villasor and Lewis\(^1\)\(^2\)\(^3\) (level 3), four (5%) of 79 patients who had radical mastectomy either developed or had worsened lymphoedema after venepuncture. Similarly, a retrospective study by Britton and Nelson (level 4)\(^4\) reviewing 114 patients with breast cancer-related lymphoedema (post-radical mastectomy) over a 4-year period found that more than half of patients reported recurrent cellulitis caused by skin breaks as being the precipitator for pain or swelling in their arm. These studies concluded that those with breast cancer surgery should avoid any exposure to sources of skin puncture that might result in infection.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\) This conclusion was provided despite the fact that the investigators did not present a causative relation between venepuncture and infection. Other case reports (level 5) describe a woman who had previously undergone axillary lymph node dissection who experienced transient arm swelling after getting a vaccination in her ipsilateral arm,\(^1\)\(^2\) and a case of a woman who noticed the onset of lymphoedema 30 years after a radical mastectomy and ALND that developed 10 days after she began finger-prick testing for diabetes.\(^1\)\(^2\) However, the authors did not discuss whether having a high BMI could have been a contributing factor for the development of arm swelling.\(^1\)\(^2\)

The only prospective study that found a connection between hospital skin puncture and lymphoedema is a study by Clark and colleagues (level 2).\(^4\) The researchers prospectively measured the arm circumferences of 188 women, all of whom had level II axillary lymph node dissection, for a period of 3 years. The relative risk of developing lymphoedema was calculated by univariate analysis and was 2.44 (95% CI 1.33–4.47) for women having a hospital skin puncture. Notably, despite these striking results, this study was subject to recall bias, as patients who went on to develop lymphoedema were more likely to recall having skin punctures than those who did not. The authors also did not look into the temporal relationship between the time of skin puncture and lymphoedema development.\(^4\)

The tenuous link between skin puncture and lymphoedema is made evident by other conflicting reports that show no relation between skin puncture and lymphoedema risk. In their analysis, Showalter and colleagues\(^1\) included several forms of skin puncture (eg, blood draws, surgery) but found no significant association between these forms of skin puncture and incident arm swelling. Ferguson and colleagues\(^6\) also concluded in their study that there was no evidence of a relation between blood draws and lymphoedema risk, as did Mak and colleagues.\(^1\) A study by Cole\(^1\) (level 4)
reported no swelling of the ipsilateral limb in 14 patients with previous axillary lymph node dissection and a history of non-accidental skin puncture. Similarly, in their questionnaire-based study, Winge and colleagues30 (level 4) reported that in 88 patients with breast cancer surgery and who had reported a needle puncture in the presence of skin breaks might precipitate arm swelling.

In reviewing current clinical guidelines, several groups underscore the importance of avoiding skin puncture on the ipsilateral arm whenever possible.34,47,72 Even among the predominantly low-level studies suggesting a risk of lymphoedema, there is no direct evidence correlating the process of skin or venous puncture itself to the development of lymphoedema. Loss of skin integrity in the presence of sterile and controlled conditions might not increase the risk of lymphoedema;34 rather, cellulitis and other infections arising from skin breaks might precipitate arm swelling. Table 5 presents the main findings on studies of skin and venous puncture and their potential associations with lymphoedema.

### Cellulitis

Monitoring for skin infections and maintaining proper skin integrity are among the most emphasised recommendations in current guidelines. The National Lymphedema Network advises survivors of breast cancer to treat skin infections (eg, cellulitis) as urgent medical situations, since cellulitis episodes in the at-risk limb could spread quickly and lead to the onset of lymphoedema.24 Lymphatic stasis in patients with lymphoedema provides an optimal environment for cellulitis to develop, worsening the severity of arm oedema and increasing the risk for future infections.46,47

Even in the early 20th century, post-surgical infection or inflammation of the ipsilateral arm was thought to contribute to limb swelling.53 With the advent of breast conservation therapy and whole-breast radiotherapy, breast and trunk cellulitis have become increasingly problematic complications.24 In view of the reciprocal association between infection and lymphoedema, several groups have looked into the risk of developing lymphoedema after

<table>
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<th>Study population</th>
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<th>Main relevant findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dawson et al, 1995d</td>
<td>317 women undergoing carpal tunnel release (15 of whom had undergone previous breast cancer surgery)</td>
<td>35 (5%) patients who had breast cancer surgery had ALND on same arm as planned carpal tunnel release</td>
<td>Patients who had undergone ALND did not have the onset or exacerbation of lymphoedema symptoms and did not develop postoperative infections following ipsilateral hand surgery for up to 16 months after surgery</td>
</tr>
<tr>
<td>Assmus and Staub, 2004d</td>
<td>52 post-mastectomy survivors of breast cancer having carpal tunnel release (three patients with pre-existing lymphoedema)</td>
<td>47 (90%) of patients had ALND or SLNB</td>
<td>In the 49 (94%) patients without pre-existing lymphoedema, four developed postoperative swelling that had resolved by 3 months after surgery, in the three patients (6%) with pre-existing lymphoedema, only one had temporary worsening of symptoms</td>
</tr>
<tr>
<td>Gharabouhi et al, 2005d</td>
<td>665 surgeons (members of the American Society for Surgery of the Hand)</td>
<td>Not applicable (survey of health-care practitioners)</td>
<td>85% of surgeons surveyed would be willing to operate on patients with established lymphoedema, 74% and 94% of surgeons routinely use tourniquets in women with and without lymphoedema, respectively</td>
</tr>
<tr>
<td>Herholz and Stahl, 2007d</td>
<td>25 women having surgery for various hand conditions (four with existing lymphoedema) with previous breast cancer surgery</td>
<td>All patients had ALND and breast radiotherapy</td>
<td>Although prophylactic antibiotics were not given to any of the patients, there were no postoperative infections following surgery and no incitement of permanent swelling with 1 year of follow-up; two patients with pre-existing lymphoedema developed a transient worsening of their condition that resolved within a few months</td>
</tr>
<tr>
<td>Fulford et al, 2010d</td>
<td>101 hand surgeons, 136 breast surgeons, and 102 breast oncology nurses</td>
<td>Not applicable (survey of health-care practitioners)</td>
<td>79% of hand surgeons, 68% of breast oncology nurses, and 57% of breast surgeons did not feel that the use of compression tourniquets should be contraindicated in patients who had undergone previous ALND; the most commonly cited reason for avoiding hand surgery on the ipsilateral arm was the increased risk of postoperative lymphoedema</td>
</tr>
</tbody>
</table>

ALND=axillary lymph node dissection. SLNB=sentinel lymph node biopsy.

Table 4: Studies of pneumatic tourniquets and risk of lymphoedema

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Data from: Stahl, 200758 et al, 200560 Staub, 200457 Dawson et al, 201059 Fulford et al, 2010d
Studies of skin and venous puncture and risk of lymphoedema

ALND = axillary lymph node dissection. BMI = body-mass index. PAL = Physical Activity and Lymphedema. SLNB = sentinel lymph node biopsy. RLNR = regional lymph node radiation.

<table>
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<tbody>
<tr>
<td>Clark et al, 2005&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Level 2: prospective cohort study</td>
<td>188 patients with breast cancer who had undergone axillary biopsy, excision, or sampling</td>
<td>All patients had undergone level II ALND, 526 (67%) of patients received radiotherapy, 11 (6%) received radiation to axilla or supraclavicular fossa, or both; 92 (49%) of cohort had a BMI of ≥26 kg/m²</td>
<td>18 (10%) patients reported having a hospital skin puncture in the form of intravenous catheter insertion, venepuncture for blood draws, or diabetic finger stick tests on the affected limb; eight of these 18 patients (44%) developed lymphoedema, compared with 31 of 17% (18%) who did not have skin puncture; the relative risk of developing lymphoedema after hospital skin puncture was 2.44 (95% CI 1.33–4.47)</td>
<td>Hospital skin puncture on the ipsilateral arm confers a significant risk for the development of lymphoedema and should be avoided in patients with previous axillary surgery</td>
</tr>
<tr>
<td>Showalter et al, 2013&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Level 2: prospective subanalysis of the PAL trial&lt;sup&gt;42&lt;/sup&gt;</td>
<td>295 breast cancer survivors participating in the PAL trial</td>
<td>Mean BMI at baseline, 29.2 kg/m²; 229 (78%) patients received radiation (type unknown), all patients had at least one lymph node removed</td>
<td>Among potential risk factors for lymphoedema, pet scratches, bug bites, cuts, blisters, hang nails, and blood draws on the at-risk arm were not significantly associated with arm swelling</td>
<td>Skin and venous puncture on the at-risk arm are not predictive of lymphoedema</td>
</tr>
<tr>
<td>Ferguson et al, 2016&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Level 2: prospective cohort study</td>
<td>632 patients with either unilateral or bilateral breast cancer surgery</td>
<td>Median BMI at baseline, 25.4 kg/m²; based on 760 treated breasts, 259 (21%) had ALND, 543 (71%) had SLNB, 60 (8%) had no axillary dissection; 160 (21%) received RLNR</td>
<td>Blood draws and intravenous infusions on the ipsilateral arm following axillary surgery do not significantly increase the risk for lymphoedema</td>
<td>Blood draws and intravenous infusions on the ipsilateral arm following axillary surgery do not significantly increase the risk for lymphoedema</td>
</tr>
<tr>
<td>Villasor and Lewison, 1955&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Level 3: retrospective observational study</td>
<td>79 survivors of breast cancer who had radical mastectomy (51 with arm swelling and 28 without swelling)</td>
<td>Patients underwent radical mastectomy</td>
<td>Four (5%) of 79 patients developed lymphoedema immediately following venepuncture, or had a worsening of existing lymphoedema</td>
<td>Venepuncture should be avoided in patients who had a radical mastectomy</td>
</tr>
<tr>
<td>Britton and Nelson, 1962&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Level 4: retrospective observational study</td>
<td>114 patients with moderate or severe arm lymphoedema following breast cancer surgery</td>
<td>Group 1 (20 patients with local cancer), 19 (95%) received radiotherapy, group 2 (94 patients without local cancer), 94 (100%) had radical mastectomy, 71 (76%) received radiotherapy</td>
<td>50 (53%) of 94 patients reported recurrent cellulitis caused by skin breaks (animal scratches, insect bites, thorn or needle pricks) as being the precipitator for pain or swelling in their arm</td>
<td>Patients who had radical mastectomy should avoid any exposure to sources that might result in infection (eg, venepuncture)</td>
</tr>
<tr>
<td>Smith, 1998&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Level 4: retrospective observational study</td>
<td>691 patients with breast cancer referred to local lymphoedema service</td>
<td>All patients citing venepuncture as relevant event for swelling had undergone ALND, three (30%) of ten of these patients received axillary radiation</td>
<td>Ten of the 691 patients (1.5%) developed lymphoedema and were referred to a lymphoedema clinic after venepuncture on the ipsilateral arm</td>
<td>Venepuncture might contribute to the risk of developing lymphoedema</td>
</tr>
<tr>
<td>Cole, 2006&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Level 4: retrospective observational study</td>
<td>14 patients with axillary surgery (nine of whom had undergone surgery as treatment of breast cancer)</td>
<td>All 14 patients had ALND (for treatment of breast cancer, lymphoma, or melanoma)</td>
<td>Hospital skin puncture did not initiate lymphoedema in any of the patients over a 2-month follow-up</td>
<td>Venepuncture can be done on the ipsilateral arm if necessary, with minimal associated risk</td>
</tr>
<tr>
<td>Winge et al, 2010&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Level 4: questionnaire-based retrospective study</td>
<td>348 patients with breast cancer surgery and axillary lymph node clearance</td>
<td>All patients with level I or II ALND</td>
<td>Four (5%) of 88 patients that reported having a needle puncture or intravenous injection on the ipsilateral arm developed arm swelling</td>
<td>A small but measurable risk association exists between skin or venous puncture and lymphoedema</td>
</tr>
<tr>
<td>Brennan and Weitz, 1992&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Level 5: single-subject case report</td>
<td>A survivor of breast cancer who had a radical mastectomy 30 years previously</td>
<td>Patient with ALND, received radiation to chest wall and axilla</td>
<td>Noticed the onset of swelling of her ipsilateral arm 10 days after she began finger prick testing for diabetes</td>
<td>The risk of developing arm lymphoedema after axillary surgery persists throughout the life of survivors of breast cancer, and immediate recognition and prompt intervention is key for managing the condition well and mitigating its severity</td>
</tr>
<tr>
<td>Lee and Baumgart, 2012&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Level 5: single-subject case report</td>
<td>A survivor of breast cancer who had a mastectomy 26 years before development of oedema</td>
<td>Patient with ALND, received chest wall radiotherapy</td>
<td>The patient developed extensive arm oedema 2 days after receiving a series of vaccinations on the ipsilateral arm; swelling resolved within 3 months after the initial presentation at the lymphoedema clinic and had not returned by the 1 year follow-up</td>
<td>The risk for lymphoedema exists even decades after axillary surgery; practitioners should ensure that patients are aware of this risk and seek out treatment at the earliest signs of swelling following vaccination or similar procedures on the ipsilateral arm</td>
</tr>
</tbody>
</table>

ALND = axillary lymph node dissection. BMI = body-mass index. PAL = Physical Activity and Lymphedema. SLNB = sentinel lymph node biopsy. RLNR = regional lymph node radiation.

Table 5: Studies of skin and venous puncture and risk of lymphoedema
cellulitis and similar infections. In a retrospective analysis (level 3) of 580 women undergoing breast-conserving surgery of whom 516 (89%) had axillary lymph node dissection, Indelicato and colleagues reported an 8% incidence of delayed breast cellulitis occurring at least 3 months after surgery and more than 3 weeks after completing radiotherapy. 11 (22%) of 50 patients went on to develop recurrent breast cellulitis, which was significantly more prevalent in women with arm swelling than in those without.

Several other studies have also shown a relation between lymphoedema and infection. In another retrospective study, Petrek and colleagues followed a group of 263 patients for two decades after breast mastectomy (100% of the cohort had axillary lymph node dissection) to get a better understanding of the causative factors associated with arm swelling. Among the 15 risk factors analysed, they found that only two were significantly associated with arm lymphoedema: weight gain after surgery, and arm infection or injury. Similar associations have been reported in another matched level 3 case-control study by Mak and colleagues, who found that previous inflammation or infection was a risk factor for the initiation and aggravation of lymphoedema in a cohort having undergone axillary lymph node dissection. A stratified case-control study by Soran and colleagues (level 3) showed that the risk and severity of lymphoedema in their cohort of patients with previous axillary lymph node dissection was statistically related to infection, BMI, and level of hand use (defined by occupation—e.g., manual workers have a high level of hand use, teachers have a medium level). 19 (37%) of 52 patients with lymphoedema and only two (2%) of 104 controls reported having an arm infection. In the prospective study by Ferguson and colleagues, the only factors found to be significantly associated with arm volume increase were cellulitis, a BMI of 25 kg/m² or higher, axillary lymph node dissection, and regional lymph node radiation. The analysis by Clark and colleagues showed a 2.44-fold increased risk of lymphoedema following hospital skin puncture, and, interestingly, the entire cohort had undergone level II axillary lymph node dissection, which might explain such disparate findings in comparison to other prospective studies that have shown no risk of skin and venous puncture, since axillary lymph node dissection contributes to an approximately four-fold increase in lymphoedema incidence compared with sentinel lymph node biopsy.

The National Lymphedema Network advises patients with breast cancer and patients at risk of lymphoedema to avoid skin puncture or trauma to the ipsilateral arm when possible. Yet, studies have shown that women with bilateral axillary lymph node dissection do not have an increased risk of lymphoedema compared with those undergoing unilateral axillary lymph node dissection. Furthermore, patients might experience great discomfort when having to continuously avoid routine procedures on the at-risk arm, reducing the number of veins available for use. In patients with bilateral risk, if at-risk
Table 6: Studies of skin infections, cellulitis, and risk of lymphoedema

<table>
<thead>
<tr>
<th>Level of evidence</th>
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<th>Risk factor composition of cohort</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Bevilacqua et al, 2012</td>
<td>Level 2: prospective cohort study</td>
<td>356 patients with unilateral breast cancer surgery and ALND</td>
<td>All patients had I, II, or III ALND; 716 (68%) had BMI of ≥25 kg/m²; 60/64% received radiotherapy, 377 (36%) received breast or chest wall radiation, 293 (28%) received lymph node radiation.</td>
<td>The 5-year cumulative incidence of lymphoedema was found to be 30.3%; postoperative infection was among the independent risk factors significantly associated with lymphoedema (p=0.0001)</td>
</tr>
<tr>
<td>Showalter et al, 2013</td>
<td>Level 2: prospective subanalysis of the PAL trial</td>
<td>295 survivors of breast cancer participating in the PAL trial</td>
<td>Mean BMI at baseline, 29.2 kg/m²; 229 (78%) of patients received radiation (type unknown); all patients had at least one lymph node removed.</td>
<td>Among potential risk factors for lymphoedema, arm infection was not significantly associated with incident arm swelling; there was a significant interaction between sauna use (associated with increased risk of incident arm swelling) and having a cut on the affected arm (OR 18.74 [95% CI 41–249.48])</td>
</tr>
<tr>
<td>Ferguson et al, 2016</td>
<td>Level 2: prospective cohort study</td>
<td>632 patients with unilateral or bilateral breast cancer surgery</td>
<td>Median BMI at baseline, 25.4 kg/m²; based on 760 treated breasts, 159 (21%) had ALND, 541 (72%) had SLNR, 60 (8%) had no axillary dissection; 160 (21%) received RLNR</td>
<td>By multivariate analysis, cellulitis infection was among the few risk factors significantly associated with arm volume increase (p=0.001; 95% CI 1.72–3.80), the others being a BMI of ≥25 kg/m², ALND, and RLNR.</td>
</tr>
<tr>
<td>Petrek et al, 2001</td>
<td>Level 3: retrospective observational study</td>
<td>263 patients with recurrence-free breast cancer in a larger cohort observed for 20 years after mastectomy</td>
<td>All patients had ALND; 88 (33%) patients were moderately overweight or obese at baseline</td>
<td>128 patients (49%) reported the sensation of lymphoedema at 20 years after treatment, of the 15 potential risk factors examined, only arm infection or injury (p=0.001) and weight gain since the operation (p&lt;0.02) were statistically significant predictors of lymphoedema.</td>
</tr>
<tr>
<td>Johansson et al, 2002</td>
<td>Level 3: matched-pair case-control study</td>
<td>103 breast cancer survivors (71 with lymphoedema lasting between 6 months and 2 years), matched to controls without lymphoedema</td>
<td>All patients had ALND; breast and axillary radiation received by 40 patients (56%) in each group</td>
<td>No statistically significant correlation existed between superficial skin infections and arm swelling in the lymphoedema study group. The lymphoedema study group had a higher BMI at the time of surgery.</td>
</tr>
<tr>
<td>Soran et al, 2006</td>
<td>Level 3: stratified case-control study</td>
<td>52 patients with breast cancer with lymphoedema and 104 controls without lymphoedema, matched based on axillary surgery, clinicopathological factors, and various comorbidities</td>
<td>All patients had ALND (in both groups); 79% of patients (82 out of 104 cases, 41 out of 52 controls) received radiotherapy; mean BMI 26.1 kg/m² in controls, 29.0 kg/m² in mild cases, and 30.9 kg/m² in moderate or severe cases.</td>
<td>Infection on the ipsilateral arm was reported by two patients (2%) in the control group, 14 patients (3%) with mild lymphoedema and five patients (5%) with moderate or severe lymphoedema; the risk and severity of lymphoedema were statistically associated with postoperative arm infection (OR 3.256 [95% CI 1.6–45–363.41])</td>
</tr>
<tr>
<td>Indelicato et al, 2006</td>
<td>Level 3: retrospective observational study</td>
<td>580 patients with stage T0–T2N0–1 breast cancer who underwent breast-conserving therapy</td>
<td>All patients had ALND; among these, 316 (89%) had ALND; among these, 316 (89%) had more than five nodes removed</td>
<td>Arm lymphoedema was significantly associated with delayed breast cellulitis, and 11 (22%) of these 50 patients went on to develop recurrent episodes of cellulitis.</td>
</tr>
<tr>
<td>Mak et al, 2008</td>
<td>Level 3: matched case-control study</td>
<td>202 women who had unilateral breast cancer surgery (101 cases with lymphoedema and 101 matched controls without lymphoedema)</td>
<td>All patients had ALND (in both groups); 81% of patients received axillary radiotherapy (81 of 101 cases, 82 of 101 controls); mean BMI at surgery, 21.8 kg/m² in controls, 22.9 kg/m² in cases.</td>
<td>Previous inflammation and infection was among the risk factors associated with the development of lymphoedema, with an OR of 3.21 (95% CI 1.57–6.55)</td>
</tr>
</tbody>
</table>

PAL=Physical Activity and Lymphoedema. BMI=body-mass index. ALND=axillary lymph node dissection. OR=odds ratio. RLNR=regional lymph node radiation.

is therefore sensible in their recommendation to use the unaffected arm for blood draws and related medical procedures when possible, but patients should be reminded that isolated medical procedures or surgical treatment on the at-risk arm have been frequently shown to not increase the risk of lymphoedema, even in patients with previous axillary lymph node dissection. Given the alternatives, we do not agree with the

limbs are avoided, central venous catheters could be inserted and veins in the foot needed for blood draws and intravenous infusions, which are much more invasive and quite painful. Unfortunately, randomised controlled trials aimed at prospectively assessing the risk of medical procedures on the at-risk arm have been attempted in the past, but have not progressed beyond the concept phase. The National Lymphedema Network

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recommendation to avoid at-risk limbs in patients with bilateral surgery, but suggest using the arm with fewer or no nodes removed.

Only one piece of level 4 evidence exists demonstrating that the use of the ipsilateral arm for blood pressure measurements significantly increases the risk of lymphoedema.85 Notably, this association was only found when using one of three different diagnostic criteria for lymphoedema (<5 cm inter-sum of arm circumference difference), and is therefore inconclusive because it is based on the type of diagnostic modality. Provided that practitioners take blood pressure measurements according to the American Heart Association guidelines,86 isolated measurements on the ipsilateral arm should not increase the risk for lymphoedema. For patients who express concern following bilateral axillary lymph node dissection, a manual blood pressure cuff can be considered on the arm with fewer or no lymph nodes removed, since using the leg to obtain blood pressure measurements introduces calculation needs and potential error because of the effects of position and gravity.87

The controversy and scarcity of high-quality studies surrounding air travel and the prophylactic use of compression sleeves is another source of distress for patients. Among eight studies that analysed flight risk, only one level 4 questionnaire-based study has showed that air travel increases the risk of lymphoedema.88 Air travel necessitates reassessment as a presumed risk-increasing exposure, and considering the evidence base, practitioners should remind at-risk patients that several objective studies have neither identified a direct link between air travel and lymphoedema,89 nor have they shown whether compression does or does not confer a benefit to at-risk women.

Sudden or prolonged exposure to temperature extremes can engender tissue damage, inflammation, and precipitate oedema in a patient with an already impaired lymphatic system.90,91 Because of a commonly reported loss of sensation in the breast, chest wall, or axilla (or a combination of these) following surgery,13 individuals should remain mindful when it comes to saunas or other sources of topical heat or cold. Although one piece of prospective evidence supports the avoidance of saunas,92 there are few data supporting temperature-related recommendations for survivors who permanently live in areas with hot or humid temperatures. More research is needed to identify the extent of the risk conferred by increased temperatures on lymphoedema.

The recommendation to avoid infection and maintain proper skin integrity is the most prevalent of the risk-reduction practices. Ipsilateral arm infections (eg, cellulitis) and previous infection or inflammation were found in all35,63,64,93 but one study to represent a significant risk factor for breast cancer-related lymphoedema, especially for those studies that had cohorts who predominantly or entirely underwent axillary lymph node dissection. This was also the case in patients at low risk of breast cancer-related lymphoedema based on axillary surgery.94 As the relation between cellulitis and lymphoedema is quite a vicious cycle (ie, cellulitis damages the lymphatic vasculature, worsening oedema; lymphoedema causes stagnation of lymphatic fluid, preventing the transport of immune molecules to affected regions creating optimal conditions for infection and inflammation),95–71 more research is needed to explore preventive options that can lower the risk of lymphoedema in patients having recurrent episodes of cellulitis, such as prophylactic antibiotic use.96 As it stands, the importance of avoiding infection and maintaining proper skin integrity cannot be understated.

**Future directions**

Although existing precautionary guidelines are based on sound physiological rationale, there is a paucity of high-level scientific evidence supporting or refuting them, and conflicting results among the studies that have been published. Despite distinguishing between individuals who are at risk and those with established lymphoedema, the organisations who publish these recommendations instruct patients in essentially the same arm-care and hand-care precautions irrespective of risk,97 and they are certainly not in the wrong for striving to be thorough in their guidelines. However, we propose a move towards risk stratification of patients, which would allow practitioners to present individualised risk-reduction guidelines. Although we are unable to comprehensively stratify patient risk by taking into account the combination of all possible risk factors, there are demographic, surgical, and treatment-related factors whose contributory risks have been well substantiated in the literature,98 and can be used as a starting point. Some of these include axillary lymph node dissection99–110 and regional lymph node radiation,99–110 as well as high BMI.110–112 Based on the above studies,7–18 we suggest the following risk groups: patients with axillary lymph node dissection (estimated lymphoedema incidence of 7–20%),113 axillary lymph node dissection and regional lymph node radiation (estimated lymphoedema incidence of >20%),114 BMI of 30 kg/m² or higher (estimated lymphoedema incidence of 9%),115 or previous episodes of oedema resolved either with or without treatment116 (or a combination of these) could comprise the highest-risk group, to whom the importance of complying with precautionary guidelines should be continually reinforced with vigilance; the moderate-risk group could include those individuals with sentinel lymph node biopsy and regional lymph node radiation (estimated lymphoedema incidence of 5–15%);117 and the low-risk group could include, in part, those patients with sentinel lymph node biopsy only or no nodes removed (estimated lymphoedema incidence of 0–6%118 and with BMI below 25 kg/m² (estimated lymphoedema incidence of 3%).119 Patients at moderate risk and low risk should be advised that they have more flexibility in the
Review

Search strategy and selection criteria

A comprehensive literature search was done from Feb 1, 2016, to March 1, 2016 using PubMed and Google Scholar to identify potential studies discussing lifestyle-related risk factors and risk-reduction practices associated with breast cancer-related lymphoedema. The search terms used were “breast cancer-related lymphoedema” OR “lymphoedema”; “risk factors”; “precautionary behaviours”; “risk reduction”; “air travel”; “temperature extremes”; “venipuncture”; “skin puncture”; “blood draws”; “intravenous infusions”; “vaccines”; “limb constrictions”; “blood pressure readings”; “tourniquets”; “infections”; and “cellulitis.” Several websites that provided information to patients and health-care providers were also referenced. To highlight the articles’ strength of evidence, the most pertinent studies are presented along with their level of scientific evidence ranging from levels 1 to 5 (panel). All relevant articles found, irrespective of publication date, were included in this Review.

degree with which they adhere to these recommendations. Notably, even among the lowest-risk population, patients should be aware that the risk of lymphoedema might not be entirely eliminated irrespective of their practice of precautionary behaviours.8,11,18 Genetic variation and intrinsic differences in lymphatic function might also contribute a certain degree of risk.82 Further research and discussion is therefore greatly needed before guidelines can be reassessed accurately and adjusted accordingly towards individualisation. As a preliminary step, we suggest making the guidelines less stringent for the lowest-risk groups (eg, those having SLNB, those with low BMI), since there may be little tangible benefit for them to follow all the guidelines, as they are already at a lower risk than those patients having ALND.

Previous studies effectively identify skin infections and inflammation as significant risk factors for lymphoedema,14,15,18–20 but scarce high-level evidence lends support to many of the other lifestyle risk factors, such as air travel, blood pressure measurements, and venepuncture, especially in view of the fact that most studies were published more than 5 years ago, and consisted of patients with axillary lymph node dissection. Since sentinel lymph node biopsy has come to replace axillary lymph node dissection as the standard assessment of lymph node status in clinically node-negative breast cancer,2 the proportion of low-risk patients in the population is increasing. Practitioners should endeavour to challenge the status quo and implement clinical practice changes in lymphoedema risk reduction and education, starting with the lowest-risk group, so that these survivors are not left to adopt rigid lifestyle modifications with no guarantee as to their efficacy, and experience fear should they be unable to do so. Patients should be educated about lymphoedema and the associated risk factors so that they are made aware that current risk-reduction guidelines are not set in stone, and they should be given the opportunity to make informed decisions about the course of action perceived as most preferable and feasible.2 In the meantime, we hope to continue the dialogue about breast cancer-related lymphoedema and stress the importance of high-quality, prospective studies to identify the merit of existing precautionary guidelines and greatly improve patient quality of life during survivorship.

Contributors

MSA, MNS, CB, CES, LS, and AGT did the concept design and editing for the Review; and MSA did the literature search and writing.

Declaration of interests

We declare no competing interests.

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