UNIVERSITY OF NEW ENGLAND

INNOVATION FOR A HEALTHIER PLANET

# Literature Review of Causative and Non-Causative Risk Factors for Breast Cancer-Related Lymphedema

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## Known Causative Factors

### Axillary Lymph Node Dissection (ALND)

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Gillespie et al, 2018[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques. | There is strong evidence that ALND is an independent risk factor for BCRL and patients who undergo this treatment are at life-long risk for developing lymphedema. | Causative risk |
| DiSipio et al, 2013[2] | Meta-analysis that assessed incidence of breast cancer related lymphedema and associated risk in patients following axillary lymph node dissection. | 19.9% incidence of lymphedema in patients following ALND. There is strong evidence to support ALND is a risk factor for lymphedema. | Causative risk |
| Kilbreath et al, 2016[3] | Prospective cohort study that followed 450 women up to 18 months following surgery to assess risk for lymphedema. | 18.2% of patients with ≥5 axillary LNs removed developed BCRL compared to 3.3% of patients with <5 nodes removed. | Causative risk |

### Body Mass Index

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Gillespie et al, 2018[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques. | High BMI at the time of breast cancer diagnosis is a well-established risk factor for developing BCRL. | Causative risk |

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| Asdourian et al, 2016[4] | Systematic review that considered whether lifestyle risk factors, such as ipsilateral arm blood pressure measurements and air travel, and if they contribute to an increase risk of breast cancer-related lymphoedema. | High BMI at the time of diagnosis or undergoing large weight fluctuations after surgery represent significant risk. | Causative risk |
| Cemal et al[6] | Systematic review of 49 articles and their recommendations on needle sticks, limb constriction, limb elevation, air travel and compression garments, body weight management, extreme temperature, and vigorous exercise for lymphedema prevention. | Obesity is a significant risk factor for lymphedema development, but the mechanism is unknown. More extensive surgery, heavier limb, and increased inflammation are hypothesized mechanisms for which the risk may originate. | Causative risk |

**Cellulitis**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Gillespie et al[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques. | Cellulitis is a well-established BCRL risk factor in the literature. | Causative risk |
| Asdourian et al[4] | Systematic review that considered whether lifestyle risk factors, such as ipsilateral arm blood pressure measurements and air travel and if they contribute to an increase risk of breast cancer-related lymphoedema. | Ipsilateral arm infections and previous infection or inflammation were found in all but one study to represent a significant risk factor for BCRL. | Causative risk |
| National Lymphedema Network Medical Advisory Committee[7] | Standardized frameworks for clinical education and practiced published as resources for the community by the National Lymphedema Network and their Medical Advisory Committee. | Treat all episodes of cellulitis as an urgent medical situation. Cellulitis may lead to worsening lymphedema. If you have more than three episodes of cellulitis in a year, talk to your medical provider about the use of suppressive antibiotics. | Causative risk |

**Lack of Breast Reconstruction Surgery**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Gillespie et al[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques. | Patients who did not undergo reconstruction surgery were more likely to develop BCRL. | Causative risk |

**Timing of Breast Reconstruction Surgery**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Gillespie et al[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques. | Delayed breast reconstruction surgery increased the risk of BCRL compared to immediate breast reconstruction surgery. | Causative risk |

**Radiation Lymph Node Radiation (RLNR)**

| Study | Study Design | Results | Bottom Line |
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| Gillespie et al[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques. | Patients who undergo RLNR, even without ALND should be considered a high-risk group for developing lymphedema, and all patients undergoing ALND and/or RLNR should be prospectively screened. | Causative risk |

## Known Non-Causative Factors

**Air Travel**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Calsey Smith[8] | Retrospective questionnaire study with 531 respondents | 490 patients with lymphedema, 190 with breast cancer related lymphedema responded noting the onset of swelling after air travel, with 27 directly linking air travel with the onset of their swelling. | Causative risk |
| Gillespie et al[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques. | Air travel was determined to not be a significant risk factor for breast cancer related lymphedema. | Non-causative risk |
| Ferguson et al[12] | Prospective cohort study that investigated the association between blood draws, injections, blood pressure readings, trauma, cellulitis in the at-risk arm, air travel, and increases in arm volume in 632 patients with unilateral or bilateral breast cancer surgery. | The number of flights and the duration of the flights subjects took were not a significant indicator of arm volume increase. | Non-Causative risk |
| Co et al[9] | Performed a comprehensive literature review of Medline, Embase, CINAHL, and Cochrane databases to evaluate air travel safety in breast cancer patients. | Air travel is not associated with upper limb lymphedema following breast cancer surgery. Malignancy is a risk factor for DVT, and DVT is a known complication following air travel. | Non-Causative risk |
| Asdourian et al[4] | Systematic review that considered whether lifestyle risk factors, such as ipsilateral arm blood pressure measurements and air travel and if they contribute to an increase risk of breast cancer-related lymphoedema. | There was no direct evidence that flying increased lymphedema risk in patients with known lymphedema. Compression garments were shown to have no clear evidence if they effect symptoms or have any positive outcome. | Non-Causative risk |
| Showalter et al[13] | Prospective sub-analysis of the PAL trial which looked at 295 survivors of breast cancer who were either at risk for or with well-established lymphedema. | Found that air travel and travel to different altitudes were not significant risk factors or predictors of incidence of arm swelling. | Non-Causative risk |
| Graham[10] | Retrospective study that surveyed 287 breast cancer | There was no significance found in the relationship of | Non- |

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| | survivors who had prospective measurements of their arm circumference. | lymphedema and flying. There were also no cases of permanent swelling after flights. | Causative risk |
| Swenson et al[5] | Case control study of 188 patients with breast cancer who had axillary surgery. 94 patients had lymphedema and 94 did not have lymphedema. | Air travel was shown to not be associated with lymphedema occurrence. | Non-Causative risk |
| Mak et al[14] | A matched case-control study of 202 women with unilateral breast cancer surgery (101 with lymphoedema and 101 matched controls without lymphoedema). | Air travel was not linked to be associated with worsening lymphedema. | Non-Causative risk |
| Hayes et al[15] | Retrospective observational study of 176 patients with unilateral breast cancer surgery | Air travel within 6 months post unilateral surgery was not significantly related to higher prevalence of lymphedema. | Non-Causative risk |
| Kilbreath et al[11] | Prospective study of 72 women who had breast and axillary surgery | Air travel did not cause any adverse issues or change in arm circumference no matter the flight length or use of a compression garment. | Non-Causative risk |

**Blood Pressure Measurement**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Showalter et al[13] | Prospective sub-analysis of the PAL trial which looked at 295 survivors of breast cancer who were either at risk for or with well-established lymphedema. | BP measurements on at-risk arm are NOT predictive of lymphedema. | Non-Causative risk |
| Ferguson et al[12] | Prospective cohort study that investigated the association between blood draws, injections, blood pressure readings, trauma, cellulitis in the at-risk arm, air travel, and increases in arm volume in 632 patients with either unilateral or bilateral breast cancer surgery. | Limb constriction through the use of BP cuffs on the ipsilateral arm is NOT a risk factor for lymphedema. | Non-Causative risk |
| Mak et al[14] | A matched case-control study of 202 women with unilateral breast cancer surgery (101 with | Medical procedures on the affected arm such as BP measurements are not associated with an increased | Non-Causative |

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| | lymphoedema and 101 matched controls without lymphoedema) | lymphedema risk. | risk |
| Asdourian et al[16] | A prospective cohort study of 327 patients who underwent bilateral breast cancer surgery were screened for arm lymphedema | No high-level evidence to support ipsilateral BP cuffs and increased lymphedema. | Non-Causative risk |
| Greene et al[17] | Letters & Viewpoints from Plastic & Reconstructive Surgery Journal, *Vol. 116, No. 7 pgs. 2058-2059* | Suggested that the use of BP cuffs in patients with established lymphedema should not be contraindicated as the management strategy for these patients relies primarily on compression. | Non-Causative risk |
| Kilbreath et al[3] | Prospective cohort study that followed 450 women up to 18 months following surgery to assess risk for lymphedema | BP and arm use did NOT increase risk of BCRL in women with >/= 5 lymph nodes removed. | Non-Causative risk |
| Asdourian et al[4] | Systematic review that considered whether lifestyle risk factors, such as ipsilateral arm blood pressure measurements and air travel and if they contribute to an increase risk of breast cancer-related lymphoedema. | Isolated BP measurements on the ipsilateral arm should not increase the risk for lymphedema. | Non-Causative risk |
| National Lymphedema Network Medical Advisory Committee[7] | Standardized frameworks for clinical education and practiced published as resources for the community by the National Lymphedema Network and their Medical Advisory Committee. | While no studies have determined actual risk of having BP taken on the at-risk arm, NLN recommends using an uninvolved or not-at-risk extremity when taking BP measurements. | Non-Causative risk |

**Weight Training**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Schmitz K et. al[20] | Randomized Control Trial of 141 breast cancer survivors with stable lymphedema of the arm participated in slow/ progressive weight lifting intervention 2x/week (Physical Activity and Lymphedema Trial) | Slow/ progressive weight training with compression garments on arm and close supervision had no significant effect on limb swelling. Compared to the control group, those doing weight training had decreased incidence of lymphedema exacerbation, reduced arm/ hand symptoms, and increased strength. | Non-causative risk |

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| Johansson et al[18] | Randomized Control Trial of 31 breast cancer treated patients with small or moderate arm lymphedema | Low intensity resistance exercise can be performed by patients with arm lymphedema without risk of worsening edema. | Non-causative risk |
| Ahmed et al[22] | Randomized Control Trial of 45 female breast cancer survivors participated in a six-month exercise intervention | No participants in intervention group experienced change in arm circumference ≥ 2 cm after the six-month intervention. No intervention group participants reported symptom changes. | Non-causative risk |
| Johansson et al[21] | Match Pair Case-Control Study on the effects of supervised upper and lower body weight training on the incidence and symptoms of lymphedema in 45 breast cancer survivors | Women treated for breast cancer axillary node dissection can maintain physical activity after treatment without added risk of developing lymphedema. | Non-causative risk |
| Harris et al[23] | A series of case reports where arm circumference was measured in 20 women who received axillary dissection and were competing in vigorous upper body sport of dragon boat racing. | No women showed a clinically significant difference in arm circumference between ipsilateral and contralateral extremity. Only two women showed a measurably different change (5/8 inches). | Non-causative risk |
| Kwan et al[19] | Systematic Review of 19 articles selected for final review from an initial 1,303 potential articles | Exercise when completed with proper supervision can be safe for patients and not increase risk of lymphedema or exacerbate symptoms. | Non-causative risk |

**Insect Bites**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Showalter et al[13] | Prospective sub-analysis of the PAL trial which looked at 295 survivors of breast cancer who were either at risk for or with well-established lymphedema. | Infection is not a predictive factor of lymphedema. | Non-Causative risk |
| Petrek et al[36] | Level 3: retrospective observational study.<br>263 pts observed 20 years after mastectomy.<br>Developed an infection on their ipsilateral arm. | Infection on the arm after axillary surgery is a controllable risk factor for lymphedema | Causative risk |

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| Johansson et al[18] | Level 3: Matched pair case control study. 103 breast cancer survivors,71 with lymphedema, matched to controls without lymphedema. These patients reported having an infection on their ipsilateral arm. | Skin infections are not a significant risk for developing lymphedema | Non-Causative risk |
| Britton & Nelson[35] | Level 4 retrospective study. 114 pts with lymphedema after breast cancer surgery. | 114 pts developed lymphedema after radical mastectomy, 53% had recurrent cellulitis following an insect bit, cat scratch, needle, or thorn prick with marked swelling or pain in their arm. | Causative risk |

## Inconclusive Evidence

**Weight Loss**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Gillespie et al[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques | Weight fluctuations during and after treatment may be a risk factor for BCRL. More research regarding weight fluctuation is needed before optimal weight loss and/or management programs can be implemented to modify BCRL risk. | More evidence needed |
| Shaw et al[24] | Randomized control trial where 21 women with BCRL were given dietary advice for weight reduction or a booklet on general healthy eating and monitored over 12 weeks | Weight loss by dietary advice significantly reduced BCRL. | Non-causative risk |
| Jammallo et al[25] | Large prospective cohort study | Weight fluctuations greater than 10 pounds per month, lost or gained, from preoperative weight was associated with increased BCRL risk. | Causative risk (if greater than 10 pounds per month) |
| Rock et al[26] | Summary report of findings from a group of experts in nutrition, physical activity, and cancer survivorship of scientific evidence and best clinical practices related to optimal nutrition, physical activity following cancer diagnosis | Achieve and maintain a healthy weight, engage in regular physical activity, and achieve a dietary pattern that is high in vegetables, fruits, and whole grains | Not applicable |

**Extreme Temperature Exposure: Hot tubs, Saunas, Sun Damage**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Cemal et al[6] | Systematic review of 49 articles and their recommendations on needle sticks, limb constriction, limb elevation, air travel and compression garments, body weight management, extreme temperature, and vigorous exercise for lymphedema prevention. | Recommendations to avoid exposure to extreme temperatures are hypothesized due to the fact that heat or rebound increased circulation from cold exposure, will increases one's blow flow which may in turn increased lymphedema. Some studies suggest that heat exposure may have a positive effect on lymphedema, however more evidence is needed to classify extreme temperature exposure as a risk factor. | More evidence is needed |
| Asdourian et al[4] | Systematic review that considered whether lifestyle risk factors, such as ipsilateral arm blood pressure measurements and air travel and if they contribute to an increase risk of breast cancer-related lymphoedema. | More research is needed to determine if exposure to extreme temperatures is a risk factor for lymphedema. | More evidence is needed |
| Chang et al[40] | Level 1 double-blind randomized study that consisted of 60 patients with leg lymphoedema that matched based on demographics and clinical characteristics. | The study supports that microwave heat therapy could be beneficial in improving the extent of lymphoedema in conjunction with various other drug therapies. | Non-causative risk |
| Gan et al[41] | Level 2 prospective trial consisting of 45 patients with unilateral arm lymphoedema following radical mastectomy | All patients showed a significant improvement in tissue extensibility and lymphedema. Therefore, the study supports the use of microwave heat therapy as an effective and safe treatment option for arm lymphoedema. | Non-causative risk |
| Liu and Olszewski[42] | Level 2 prospective trial consisting of 12 patients with leg lymphoedema | Hot water and microwave therapy promoted a significant reduction in limb girth and volume during testing. The study supports the hypothesis that heat therapy can lead to a reduction in local inflammation and an alteration of the extracellular protein matrix. | Non-causative risk |

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| Showalter et al[13] | Prospective sub-analysis of the PAL trial which looked at 295 survivors of breast cancer who were either at risk for or with well-established lymphedema. | "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" | Extreme temperatures: Non-Causative risk<br><br>Sauna use: Causative risk |
| Baker PW[39] | Clinical Review on the theoretical use of contrast hydrotherapy for the prevention and management of lymphedema. | Contrast hydrotherapy involves the affected limb being alternately placed in hot and cold water to prompt reduction of symptoms. Contrast hydrotherapy may be an effective method in treating lymphedema. This is theoretically based off the similarities between the vascular and lymphatic systems. | Non-Causative risk |
| Kilbreath et al[3] | Prospective cohort study that followed 450 women up to 18 months following surgery to assess risk for lymphedema | Exposure to extreme heat is not a risk factor for developing lower extremity lymphedema at 18 months following surgery in women with ≥5 lymph nodes removed. | Non-Causative risk |

**Needle Sticks**

| Study | Study Design | Results | Bottom Line |
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| Winge et al[32] | Level 3 questionnaire:<br>348 pts who had breast cancer surgery and axillary lymph node clearance and received venipuncture on their ipsilateral arm. | 4/88 developed lymphedema in relation to venipuncture. There is a small risk associated. | Non-causative risk |
| Showalter et al[13] | Prospective sub-analysis of the PAL trial which looked at 295 survivors of breast cancer who were either at risk for or with well-established lymphedema. | Venous punctures on the at-risk arm are not predictive of lymphedema. | Non-Causative risk |
| Ferguson et al[12] | Prospective cohort study that investigated the association between blood draws, injections, blood pressure readings, trauma, cellulitis in the at-risk | Intravenous infusions on ipsilateral following axillary surgery do not significantly increase risk of lymphedema. | Non-Causative risk |

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| | arm, air travel, and increases in arm volume in 632 patients with either unilateral or bilateral breast cancer surgery. | | |
| Cole[30] | Level 4 retrospective observational study:<br>14 pts with axillary surgery who received venipuncture in their ipsilateral arm. | Venipuncture if necessary, can be done on ipsilateral arm with minimal risk. | Non-Causative risk |
| Cemal et al[6] | Systematic review of 49 articles and their recommendations on needle sticks, limb constriction, limb elevation, air travel and compression garments, body weight management, extreme temperature, and vigorous exercise for lymphedema prevention. | To be determined: Conflicting research study evidence<br>There is limited evidence to support the recommendation that venipuncture should be avoided in pts with a history of lymph node surgery. | Non-Causative risk |
| Asdourian et al[4] | Systematic review that considered whether lifestyle risk factors, such as ipsilateral arm blood pressure measurements and air travel and if they contribute to an increase risk of breast cancer-related lymphoedema. | There is limited/ conflicting evidence for injections/ blood draws. | Non-Causative risk |
| Villasor & Lewison[28] | Level 3 retrospective observational study:<br>79 breast cancer survivors with radical mastectomy and received venipuncture in their ipsilateral arm. | 3/79 patients lymphedema developed after venipuncture. Venipuncture should be avoided in affected arm, especially after radical mastectomy. | Causative risk |
| Britton & Nelson[35] | Level 4 retrospective study:<br>114 pts with lymphedema after breast cancer surgery and reported having a skin puncture. | 53% developed cellulitis or lymphedema after skin puncture. Patients should avoid venipuncture after radical mastectomy. | Causative risk |
| Smith[34] | Level 4 retrospective observational study:<br>691 pts who had breast cancer lymphedema and received venipuncture in their ipsilateral arm. | 10 patients reported direct correlation with venipuncture and onset of new swelling in arm. | Causative risk |

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| Clark et al[31] | Prospective observational study:<br>188 pts with breast cancer. All patients had level II ALND. 18 patients received non-accidental skin punctures on their ipsilateral arm. | 44% who had needle sticks developed lymphedema compared to 18% who did not. Non-accidental skin puncture (NASP) increases the likelihood of developing lymphedema by 40 %. There is a significant risk on ipsilateral arm. | Causative risk |
| Brennan & Weitz[27] | Level 5 single-subject case report: The patient is a breast cancer survivor who had a radical mastectomy. 30 years later, after a diabetes finger stick, she developed lymphedema. | Breast cancer survivor had a mastectomy, ALND, and radiation to her chest wall and axilla 30 years prior to diabetes finger stick and developed lymphedema from the finger stick. A risk of lymphedema after axillary surgery persists throughout lifetime. | Causative risk |
| Lee & Baumgart[29] | Level 5 single-subject case report: The patient is a breast cancer survivor that had a radical mastectomy and ALND and developed lymphedema 26 years after having a vaccination. | Breast cancer survivor who had a mastectomy 26 years prior to developing lymphedema. Pt had ALND and chest wall radiation. She developed lymphedema after vaccinations in ipsilateral arm. There is a risk of developing lymphedema decades after axillary surgery. | Causative risk |

**Limb Positioning**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Cemal et al[6] | Systematic review of 49 articles and their recommendations on needle sticks, limb constriction, limb elevation, air travel and compression garments, body weight management, extreme temperature, and vigorous exercise for lymphedema prevention. | Limb positioning recommendations are based on blood pooling and increased venous pressure. Crossing one's legs or prolonged sitting and standing are thought to increase venous pressure, which will result in an increase in lymphatic fluid stasis. However, the exact relationship between venous pressures and lymphatic fluid accumulation are unknown. | More evidence is needed |
| Ryan TJ[37] | Seminar Review on potential risk factors and management of lower extremity swelling due to compromised vascular and lymphatic systems. | Increase in venous pressure, new vessel formation, leakage of the capillary beds, and destruction of elastin could compromise the lymphatic system. | Causative factor if venous insufficiency present |

**Adjuvant and Neoadjuvant Chemotherapy**

| Study | Study Design | Results | Bottom Line |
|---|---|---|---|
| Gillespie et al, 2018[1] | Comprehensive review of current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, surgical and non-surgical treatment techniques. | More studies, using objective and standardized BCRL measurement techniques and definitions, are needed to define the role of neoadjuvant and adjuvant chemotherapy in BCRL risk. | More evidence is needed |
| DiSipio et al, 2013[2] | Meta-analysis that assessed incidence of breast cancer related lymphedema and associated risk in patients following axillary lymph node dissection. | There is moderate evidence that supports adjuvant chemotherapy as risk factors. | Causative risk |
| Kilbreath et al, 2016[3] | Prospective cohort study that followed 450 women up to 18 months following surgery to assess risk for lymphedema. | Arm swelling at 6 and 12 months was associated with adjuvant taxane therapy, and swelling at both time points were independent risk factors for lymphedema development. | Causative risk |

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