LE RISKS, WHAT ARE THEY AND HOW CAN THEY BE REDUCED?

Merinda Higton, Deborah Valadares

Lymphoedema can a long-term complication of breast cancer treatment (Mak et al, 2008), which, once established, is difficult to cure. Therefore, it is essential to prevent or minimise this condition. Factors that contribute to the development of breast cancer-related lymphoedema (BCRL) are not as yet fully elucidated. The common procedures of venepuncture and blood pressure measurement are a vital component of medical practice, but their impact on lymphoedema is unascertained. This article reviews current risk reduction advice and provides direction to ensure that the advice given to breast cancer patients is supported by the best evidence available.

Key words

Secondary arm lymphoedema
Risk prevention
Evidence-based practice
Self-care
Morbidity control

Lymphoedema is a serious long-term complication of breast cancer surgery and radiation therapy (Mak et al, 2008). The true incidence of lymphoedema is unknown, although estimates reported in previous studies ranged from 6.7–62.5% for different populations (Hardy and Baum, 1991; Passik and McDonald, 1998; Roh, 2002; Geller et al, 2003; Hinrichs et al, 2004; Ozaslan and Kuru, 2004). The variation in incidence may be attributed to the methods used to define and measure lymphoedema, the patient population studied and the interval between breast cancer diagnosis and the collection of data. The onset of breast cancer-related lymphoedema (BCRL) is most likely to occur during the initial two to three years postoperatively (Segerstrom et al, 1991). However, symptoms related to lymphoedema can start almost immediately after surgery, or even 30 years later (Geller et al, 2003). Patients with lymphoedema can experience a substantial degree of functional impairment, psychosocial morbidity and diminished quality of life (Morgan et al, 2005; Park et al, 2008; Towers et al, 2008). Therefore, the prevention of BCRL is of utmost importance.

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Lymphoedema occurs most frequently with axillary lymph node dissection (ALND) during breast cancer surgery (Park et al, 2008). Furthermore, the addition of radiation therapy to the dissected axilla has proven to be a strong predictor of lymphoedema. Radiation therapy promotes the development of lymphoedema by blocking lymph vessels or by compressing lymph vessels through radiation fibrosis (Tsai et al, 2009). Across several studies (Moffatt et al, 1992; Mortimer et al, 1996; Ozaslan and Kuru, 2004; Thomas-MacLean et al, 2008), lymphoedema has been reported to occur in approximately 41% of patients who undergo axillary radiation therapy in addition to surgery, as opposed to approximately 17% of patients treated only with surgery (Mak et al, 2008). As ALND increases the risk of lymphoedema, sentinel lymph node biopsy (SLNB) is of paramount importance to avoid unnecessary axillary dissection (Roh, 2002; Ozaslan and Kuru, 2004). Moreover, SLNB has been found to improve upper limb morbidity and reduce lymphoedema prevalence (Mansel et al, 2006). Findings from a large trial showed a significantly reduced risk of developing BCRL in the first year postoperatively following SLNB compared with ALND (5% vs 13%, respectively) (Sener et al, 2001). However, long-term differences in lymphoedema occurrence with SLNB have yet to be reported.

Since lymphoedema is difficult to cure, prevention is the major goal (Hull, 2000). However, this can be difficult as the aetiology of breast cancer-related lymphoedema is not fully elucidated and contributing factors, such as blood pressure measurement and venepuncture have not, in the authors' opinion, been well studied. Treatment factors, including the number of axillary nodes removed, number of positive nodes, radiation therapy (especially axillary radiation therapy), and infection in the ipsilateral arm, have been associated with an increased incidence rate of lymphoedema

after ALND (Louden and Petrik, 2000; Mellor et al, 2000). In the authors' opinion, delayed onset, variation in severity, and the limited number of patients treated appropriately (by trained clinicians with experience and knowledge of BCRL) who suffer from lymphoedema, indicate that there should be more patient and practitioner education on the causes of BCRL following breast cancer treatment.

Current risk reduction advice

The importance of educating breast cancer survivors about lymphoedema prevention and management has long been recognised with organisations such as the National Cancer Institute, the National Lymphoedema Network (NLN) and the Oncology Nursing Society publishing guidelines on follow-up care after breast cancer treatment (Bosompra et al, 2002). Box et al (2002) discovered a reduced incidence of BCRL in patients who received risk minimisation education. Therefore, advice regarding precautions and lifestyle modification that is aimed at reducing the life-long risk of BCRL development is an important aspect in the care of breast cancer survivors (Basen-Engquist et al, 2006). Unfortunately, this advice largely lacks a sound evidence base, being derived primarily from anecdotal information and reasoning based on an incomplete understanding of the condition's aetiology (Erickson et al, 2001; Harris et al, 2001; Nielsen et al, 2008; Cheifetz, 2010). Patient education and risk factors contributing to the development of lymphoedema should be acknowledged, as literature has found a positive association between preventive self-care activities and the incidence of lymphoedema (Didem et al, 2005; Park et al, 2008).

There is a multitude of BCRL risk reduction advice available on the internet for breast cancer survivors, including exercises and massage techniques, certain diets and weight targets and advice about skin care to prevent the development of lymphoedema (www.breastcancer.org/tips/lymphedema/ask_expert/2002_07/). Prominent lymphoedema, cancer and health organisations publish recommendations on the World Wide Web. The format of these range from prescriptive (a list of specific dos and don'ts), to a discussion of broader principles (i.e. The American Cancer Society; Breast Cancer Organisation UK; Breast Cancer Network Australia). Commonly, BCRL precautions include avoiding accidental and non-accidental skin trauma and infection, limb constriction, weight gain and exposure to extreme temperatures, in addition to promoting early diagnosis and management through self-surveillance (Lymphoedema Association of Australia, 1995; NLN, 2005; Breast cancer care, 2006; NHS direct, 2007). However, the literature is inconsistent and precautions vary between organisations on whether factors such as hypertension, obesity, exercise and exposure to airline travel play a role in the initiation or aggravation of lymphoedema (NLN, 2005; Breast Cancer Care, 2006).

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Specifically, most organisations advocate limiting strenuous exercise or advise the use of a compression garment if doing resistance training, and recommend avoiding or limiting activities such as vigorous gardening and lifting heavy shopping (NLN, 2005; Breast Cancer Care, 2006). Use of a compression garment when flying is stated as a requirement by some organisations (NHS Direct, 2007), but is less stringently mandated by others (NLN, 2005).

Women are often advised by medical practitioners and breast care nurses, based on the *Best Practice for the Management of Lymphoedema* (Lymphoedema Framework, 2006), to avoid constrictive pressures, such as blood pressure measurements on their affected arm, and activities that could lead to arm injury or infection (Mak et al, 2008). However, most of this advice is based on limited data.

Medical procedural advice

Medical procedures, such as intravenous procedures and blood pressure measurements, are vital components of medical practice. However, they have been promoted as post-treatment risk reduction procedures based purely on physiologic rationale (Cheifetz, 2010). Guidelines for arm precautions are based on the principle of not increasing blockage to lymph transport (Louden and Petrick, 2000). Literature has purported that wearing tight garments or blood pressure measurements result in fibrosis and stenosis of lymphatic vessels, which may, in turn, obstruct lymph flow (Petrek et al, 2000). However, there is limited data from clinical trials to support any of the recommendations. Importantly, studies have proven that women with bilateral axillary dissections have no increased reported risk of lymphoedema than those undergoing unilateral axillary dissection (Mose et al, 1997; Louden and Petrick, 2000). Contrary to popular belief, these findings do not support the implication that venepuncture, intravenous administration, blood pressure monitoring, and injections after axillary dissection accelerate the development of lymphoedema.

Blood pressure measurement and lymphoedema

The proposed causative role of limb constriction in lymphoedema, such as through blood pressure monitoring or wearing tight clothing on the ipsilateral arm, has not been systematically studied. Advice to avoid constriction is based on the physiological rationale that constriction may impede lymphatic flow which is already impaired (Petrek et al, 2000). It is thought that vascular occlusion caused by blood pressure measurement induces haemodynamic changes, which may adversely affect the lymphatic system, or even produce BCRL. A recent study by Mak et al (2008) found that lymphoedema was not initiated, nor was mild lymphoedema aggravated by medical procedures, such as venepuncture or blood pressure measurements on the ipsilateral arm of

cancer. However, it was established that moderate-to-severe lymphoedema was made significantly worse after medical procedures were performed on the ipsilateral side as the axillary clearance (Mak et al, 2008). This emerging data calls for further investigation and accurate determination of the stage and progression of the condition.

The current guideline for indirect blood pressure measurement is the auscultatory method, a mainstay in most general practices and tertiary hospitals (Pickering et al, 2005). This involves occlusion of the brachial artery and gradual inflation and deflation of the cuff. The required applied external pressure provided by the cuff to occlude the vessel must be greater than systolic pressure (Toi, 2007). The cuff can sometimes reach pressures of well above 140mmHg to occlude the brachial artery, higher than both venous (40mmHg) and interstitial fluid pressure (-1mmHg and -7mmHg) (Dennis, 2008). In addition, the large external cuff pressure occludes not only arterial and venous vessels, but is also capable of occluding lymphatic vessels, which are capable of pumping up to ~45 mmHg (Olszewski and Engeset, 1980). It has been previously determined that a bandage pressure or blood pressure cuff of 40–70mmHg was required to prevent the lymphatic transport of a tracer to the axilla (Howarth et al, 1994), thus indicating that lymph flow from the wrist to the axilla is prevented.

These figures alone would be enough to support the idea that 'normal' blood pressure measurement contributes to lymphoedema. However, the external pressure is not directly transmitted to the tissue in a linear fashion; whereby the interstitial fluid pressure reaches 60–65% of the externally applied pressure (Reddy et al, 1981). This would indicate that an external cuff pressure of 140mmHg would produce an interstitial fluid pressure of 84–91mmHg, which would cause increased hydrostatic capillary pressure, thus forcing fluid from the capillaries not the tissue. However, it is becoming known that it is not the hydrostatic and oncotic pressures in the Starling hypothesis that define fluid movement, but rather the pressures in subglycocalyx channels between endothelial cells (Michel, 1997; Levick, 2004; 2009). According to Dennis (2008), arterial pressure itself has little influence on capillary filtration, and what effects the increased pressure produced by the external cuff pressures has on the subglycocalyx is yet to be ascertained. Moreover, the increase in interstitial fluid pressure derived from the cuff would increase capillary filtration pressure, facilitating fluid exchange from the blood into the interstitium, thus preventing interstitial fluid accumulation which manifests as lymphoedema (Carati et al, 2010).

Furthermore, the mainstay of lymphoedema management is known as complex decongestive therapy (CDT) or complex lymphoedema therapy (CLT), which relies heavily on compression therapy, multilayer inelastic lymphoedema bandaging, manual lymphatic drainage (MLD) and intermittent pneumatic compression (IPC) (Lymphoedema Framework, 2006). These methods themselves are styled on the basis of stimulating the remaining patent lymphatic duct routes and clearing those pathways that are impaired (Lymphoedema Framework, 2006). Graduated compression garments can produce pressure of up to 40–80mmHg, and forces of up to 150mmHg with a pneumatic pump (Tiwari et al, 2003). However, the pressures that are used to produce beneficial effects are well below the compression applied by the cuff, which occludes and impairs venous drainage (Sarin et al, 1992). In fact, it has been identified that the venous closing pressure of 60mmHg, which is well below the standard pressures applied when measuring blood pressure, is enough to collapse the vessel and reduce lymph flow significantly (Miller and Seale, 1981). Therefore, while the basis of externally applied pressure is to improve fluid drainage through compression bandaging, it is possible that externally applied pressure from the cuff could cause some damage to the venous drainage of the affected limb.

Another query that requires investigating is length of time the inflated cuff should be applied to an arm to obtain an accurate blood pressure measurement. According to current practice guidelines, the average time that the cuff applies pressure is approximately 60–120 seconds in an average adult with a bp of 120/80mmHg (Pickering et al, 2005). In the management of lymphoedema, wearing compression garments daily for several months or the application of pneumatic pumps for a few hours, assists lymphatic drainage. How, therefore, does the use of pressure applied from the blood pressure cuff for a few minutes impact on the lymphatic system? Whether this limited period of time is sufficient to cause enough damage to both venous and lymphatic drainage systems to produce or exacerbate lymphoedema is uncertain. It has been demonstrated that the hand-to-axilla lymph transit time is approximately 10 minutes (Modi et al, 2007). Moreover, a congesting cuff applied at 60mmHg for 30 minutes arrests the lymph flow (Howarth et al, 1994), but whether an externally applied pressure of up to 140–150mmHg for a few minutes is likely to produce or exacerbate BCRL, is yet to be determined.

Venepuncture and lymphoedema

Research relating to venepuncture and intravenous procedures has conflicting conclusions. The advice to avoid venepuncture is based on the idea that puncturing the skin and veins increases the risk of infection or inflammation, which may produce lymphoedema in a patient with an impaired lymphatic system (Clark et al, 2005). Therefore, avoidance of venepuncture may minimise the risk of further damage to the lymphatics and prevent the formation of lymphoedema. Smith (1998) reported that 1.5% of patients who underwent an ALND, identified intravenous procedures as having a causative relation with their limb swelling within a two-year period. However, the time span between the intravenous procedure and the onset of arm swelling is not stated, and thus it is difficult to determine if there is a correlation.

In addition, Clark et al (2005) discovered that intentional skin puncture to the ipsilateral arm while in hospital was found to be associated with a significantly

increased risk of developing BCRL within the first three years post-operatively. The findings of Clark et al's prospective study support largely anecdotal findings from previous authors (Smith, 1998; Brennan and Weitz, 1992). Indications from Clark et al's small study prompted Cole (2006) to advise against blood pressure measurement, subcutaneous and intramuscular injection, and other clinically occurring non-accidental skin puncture procedures wherever possible in medical practice.

However, contradictory to this evidence, there was an absence of reports between 1966 and 2004 in the PubMed literature, correlating venepuncture to cellulitis in the lymphoedematous limb (Greene et al, 1995). It has also been shown that suction-assisted lipectomy, using up to 30 incision sites, did not result in cellulitis, which is believed to be one of the precursors for lymphoedema (Miller et al, 1999). Furthermore, it has been determined that if appropriate protocol guidelines are followed during intravenous procedures, there is a low risk of complications (Winge et al, 2010).

Conclusion

Historically, lists of lymphoedema precautions have been developed to educate breast cancer survivors about strategies to reduce their risks of lymphoedema. There is some concern that, although logical, these precautions are not based on any research findings (Herd-Smith et al, 2001). There has also been little systematic research in the area of preventive strategies for lymphoedema. The relative efficacy of different preventive measures has not been evaluated, nor has it been shown that preventive strategies are of any benefit.

In the authors' opinion, randomised controlled trials or cohort studies are clearly needed to evaluate the efficacy of preventive interventions specifically designed to prevent lymphoedema after breast cancer treatment, and the efficacy of one mode of prevention over another must be assessed. Larger, methodologically rigorous studies are required to provide an evidence base for healthcare professionals to properly advise breast cancer survivors. JL

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Key points

- Lymphoedema cannot be cured; therefore, it is essential to prevent or minimise this condition through increased awareness, promotion of self-care activities and preventative techniques.
- Sentinel lymph node biopsy has improved upper limb morbidity and reduced lymphoedema prevalence.
- Further research trials are required to elucidate what factors play a role in the initiation or aggravation of lymphoedema, as the literature is inconsistent and precautions vary between organisations.
- Although lymphoedema may not be initiated by medical procedures, such as venepuncture or blood pressure measurements, already established severe lymphoedema can be made significantly worse.