

A REVIEW OF THE EPIDEMIOLOGY OF BCRL

Peter Franks, Anne Williams, Christine Moffatt

Problems exist in all studies in relation to the epidemiology of breast cancer-related lymphoedema (BCRL). However, the evidence suggests that lymphoedema occurs in approximately one-quarter to one-third of patients who have undergone surgery for breast cancer. Factors which appear to predispose patients include: use of irradiation; extent of axillary node dissection; combined axillary surgery and irradiation; obesity; surgical wound infection; tumour stage and extent of surgery. There is some evidence that improved surgical technique may result in a reduced risk of BCRL, but this may be confounded by methodological differences.

Key Words

Breast cancer
Lymphoedema
Epidemiology
Prevalence and incidence
Risk factors

Lymphoedema of the upper arm and related trunkal areas is a recognised consequence of treatment for breast cancer. Despite this, the evidence on the epidemiology of this secondary cause of lymphoedema remains poor. This article will review the evidence as it stands, and the prevalence/incidence and factors that predispose patients to develop lymphoedema following treatment for breast cancer.

Defining prevalence and incidence

Prevalence is defined as the proportion of an 'at-risk' population who are suffering from a condition at any one time. The units of measurement will depend on the frequency of cases

Peter Franks is Professor of Health Sciences, Christine Moffatt is Professor of Nursing, Centre for Research and Implementation of Clinical Practice (CRICP), Thames Valley University, London, and Anne Williams is Cancer Nursing Research Fellow, School of Acute and Continuing Care Nursing, Napier University, Edinburgh

(with disease) in relation to the total population. Thus, for different diseases and studies, prevalence rates may be quoted as percentages, or rates per 1,000 or per million population, depending on the disease frequency.

The incidence of disease is given by the number of new cases in an 'at-risk' population that develop the condition over a specified time interval. This time interval will again vary according to the type of disease process (per day for many infectious diseases), but is likely to be quoted on an annual basis for most chronic diseases such as lymphoedema. It is important that in incidence studies, cases with pre-existing disease must be excluded before the study, otherwise this will have the effect of artificially inflating the incidence figures for the condition. Because of difficulties in determining the precise nature of studies undertaken, the authors have chosen to use the terms 'rate' and 'risk' rather than the precise terms 'prevalence' and 'incidence', as these may not be true representations of the results presented.

Defining cases of lymphoedema

In evaluating the epidemiology of a condition, it is essential to describe precisely how the disease is defined. A repeatable, valid and accepted definition will allow for comparisons between, and within, 'at-risk'

populations, to evaluate temporal and geographical differences and give some indication of the nature of the disease. While definitions are essential to determine the consistency of measurement, lymphoedema is rarely defined in precise terms. In a previous review, Logan (1995) highlighted some of the problems inherent in ascertaining rates in lymphoedema. Among various studies (Stanton et al, 2000) there are inconsistencies in methods used to determine the presence of swelling, quantify the degree of swelling, and assess skin and tissue changes.

Using measurements to define lymphoedema

Various methods exist for the measurement and calculation of the degree of swelling. Limb circumference measurements are commonly quoted, though water displacement and electric volumetry are alternatives. Each method may be subject to variations in the methodology adopted. For example, limb circumferences may be taken at a wide range of sites. In the UK, the most common technique consists of measuring circumferences every 4cm extending distally to proximally, which are used to calculate the volume of the limb as a cylinder. A number of studies have explored the validity and reliability of limb volume measured by these different methods, and most conclude that while these methods are highly

correlated and reliable, they are not interchangeable and cannot be mixed or substituted (Stanton et al, 2000; Megens et al, 2001; Sander et al, 2002; Karges et al, 2003).

In their review, Stanton et al (2000) highlight a volume of > 200 ml as measured by water displacement as a sensitive indicator of lymphoedema, and this definition is used in many studies. Clearly, reducing this cut-off figure to > 100 ml may appear to increase the prevalence of lymphoedema, but it may also be argued that this enables identification of mild oedema (Berlin et al, 1999). Stanton et al (2000), however, suggest that percentage differences are more universally applicable, allowing for easier comparison and, as such, a difference of 10% in volume may be an appropriate cut-off point. The potential accuracy of the volumes also depends on equations used in the calculations and the standardisation of measurement technique (Sitzia, 1995).

Circumferential measurements alone are widely used. However, many patients with lymphoedema do not have uniform swelling throughout the limb, and it is common for swelling to be localised to the hand or upper arm. The use of one or two circumferential measurements is likely to be an inadequate and less sensitive method than water displacement, or calculation of volume from multiple circumference measurements.

The length of time to lymphoedema development is also an important consideration. Most patients experience an acute post-operative oedema and this leads to temporary swelling of the limb. Persistent oedema of longer than three months duration is more likely to be lymphoedema, and oedema before this point should not be considered as true lymphoedema. Additionally, studies need to be undertaken over an adequate time period as lymphoedema may develop at any stage post-treatment. Edwards (2000) showed that the onset of lymphoedema generally occurred in the first 18 months post-surgery, while others report a 39-month median time interval for lymphoedema

to develop (Coen et al, 2003). This suggests that studies require a longer follow-up to ensure that later occurring lymphoedema is recognised.

Literature search

To evaluate the literature in a systematic way, a search was undertaken of PubMed, Medline (for articles dating from 1966), CINAHL (from 1982) and the Cochrane Database of Systematic Reviews. The terms lymphoedema, chronic oedema, prevalence, incidence and epidemiology were used. Only those articles that related to BCRL were accessed for this review.

Magnitude of the problem of breast cancer-related lymphoedema

In 1921, Halstead recognised the problems of arm-swelling following breast surgery, and assumed this 'surgical elephantiasis' was due to streptococcal infection. One of the largest early studies of breast cancer which reported on 950 women treated between 1889 and 1931 did not discuss the problem of lymphoedema (Lewis and Reinhoff, 1932). Despite this, there is evidence in the literature of an ongoing interest in lymphoedema throughout the early and mid-part of the last century.

In 1954, Fitts et al cited studies from the 1940s showing rates of BCRL lymphoedema ranging from 8–95%. These authors presented their own study of 130 patients following radical mastectomy for breast cancer treatment, in which 49% of patients developed lymphoedema. In 1962, Britton and Nelson also reported lymphoedema rates of 6.7–62.5%, from 14 studies with different patient numbers undertaken between 1908 and 1949. Their paper described five further papers written from 1950 to 1960, in which they identify similar rates (13–57.5%) despite improvements in surgical technique and the introduction of antibiotics (to prevent infections which may lead to worsening of lymphoedema). An extensive review of studies between 1944 and 1960 produced rates ranging from 41% to 80% (Hughes and Patel, 1966). In 1998, Petrek and Heelan highlighted a

wide variation in rates (6–30%), and concluded that the definitive study on incidence of BCRL had yet to be done.

Factors associated with the development of breast cancer-related lymphoedema

Most studies have considered aetiological factors for lymphoedema, examining rates in specific patient groups rather than providing data on larger populations. Treves (1957) provided a comprehensive review of 'literature on causation' and analysed aetiological factors in 1,007 women following mastectomy. This study established that 41% of women suffered from BCRL and highlighted obesity and radiotherapy as risk factors. In the 1980s, much of the literature was concerned with lymphoedema rates in relation to different breast cancer treatment protocols (Markowski et al, 198; Kissen et al, 1986; Pezner et al, 1986; Rytto et al, 1988; Aitken et al, 1989). Aitken et al (1989) compared arm morbidity in those who had mastectomy with axillary sampling with those who had mastectomy and axillary clearance, or radiotherapy for nodal metastases (n = 40). Persistent oedema was noted in 32% of those who were node positive and had axillary irradiation, as compared with 8% in those who were node negative and had only axillary sampling. Schunemann and Willich (1997) also reported on 5,868 women treated between 1972 and 1995, highlighting a rate of lymphoedema in 22.3% of patients after radical mastectomy, increasing to 44.4% when radiotherapy was included. These findings are similar to those from a study undertaken in the UK (Mortimer et al, 1996) that used questionnaires to survey 1,249 women within one health district. This demonstrated an overall rate of 28% that increased to 38% in those who received axillary surgery combined with axillary radiotherapy, and reduced to 20% in those who received axillary surgery only.

More recently, Hojris et al (2000) undertook a retrospective study of 84 patients in Denmark showing 14% with lymphoedema following surgery and radiotherapy, compared with 3% lymphoedema in those who had surgery

alone. Similar results were found in other studies with lymphoedema developing in approximately 15–18% of those patients who received radiotherapy, and in 3.6–10% of those who did not (Tengrup et al, 2000; Meric et al, 2002). A further study followed up 1,278 patients operated on by the same surgeon between 1989–1997 and identified 15.9% with lymphoedema, correlating the risk of lymphoedema with post-operative radiotherapy and removal of > 30 lymph nodes (Herd-Smith et al, 2001).

The impact of specific interventions was examined by Box et al (2002), who studied a group of 65 women in Australia two years post-treatment and reported lymphoedema in 21%, defined by an increase of > 200ml in volume. This study had randomised the patients post-operatively to a treatment group who received specific information on lymphoedema risk minimisation and early management, and a control group. Lymphoedema in the treatment group occurred in 11% of patients, compared with 30% in the control group, suggesting that specific interventions can be used to reduce the lymphoedema risk.

Various other aetiological factors have been associated with swelling. Petrek et al (2001) studied a cohort of 923 women treated for breast cancer with mastectomy and axillary clearance in the USA. They show that the presence of lymphoedema had a statistically significant association with post-treatment weight gain and with arm infection or injury. Of the 263 women followed up at 20 years, 49% reported a sensation of swelling with 13% found to have severe swelling, defined as > 2 inch increase in arm circumference at one or more of two sites above and below the elbow, as measured by the patients themselves. Of those developing lymphoedema, 77% did so within three years following breast cancer treatment. Querci della Rovere et al (2003) studied 201 patients following a level I/level II axillary node dissection, showing an overall prevalence of lymphoedema in 32.8%. They measured the limb circumference at the hand and at two sites above and below the elbow,

suggesting that lymphoedema was present if there was a > 5% increase in circumference. Patients also reported their subjective assessment. This group identified risk factors for lymphoedema as positive nodal status, dominant limb and right-sided treatment, and excluded radiotherapy, the extent of breast surgery and infection as aetiological factors, but did suggest that a longer-term follow up was required.

Subjective assessment by patients and self-reporting of swelling is used

Various other aetiological factors have been associated with swelling. Petrek et al (2001) studied a cohort of 923 women treated for breast cancer with mastectomy and axillary clearance in the USA. They show that the presence of lymphoedema had a statistically significant association with post-treatment weight gain and with arm infection or injury.

in several studies and raises various issues. Kissane et al (1998) studied psychological disturbance in patients following breast cancer treatment and reported a subjective description of swelling in 4.3% of the group. Kornblith et al (2003) studied long-term survivors of breast cancer at 20 years post-chemotherapy. The results are based on telephone interviews with 153 patients using standardised measures, and suggest that 39% of respondents experienced lymphoedema at some point following breast cancer treatment. Clearly, patient reporting may be subjective and depends on accurate retrospective recall. Mortimer et al (1996) tested and validated their questionnaire before the study. Fifty patients with a history of arm swelling in their notes and 50 patients without were asked about the presence of swelling in their arm. All the 43 returned from the 'lymphoedema group' responded positively, and from a total of 46 responders in the 'non-lymphoedema group', six who responded positively were found, on examination by the clinician, to have lymphoedema.

Edwards (2000) explored lymphoedema prevalence in 201 patients who had undergone breast cancer treatment in Australia from 1994 to 1996. A subjective assessment where patients reported on any swelling noticed over a three-month period before the date of assessment was used with volumetric water displacement technique. Lymphoedema was identified as a swelling of > 10% on volumetric measurements. The authors identified a subjective rate of swelling in 23.4%, reducing to an overall rate of 11% once volumetric measurements were taken. They surmised that this inconsistency was related to daily variation in swelling, although it is also possible that the patients detected changed sensations in their arm, or limitations that were not objectively identified due to the 10% cut-off point. Interestingly, when this was lowered to 5% volume difference between arms, the rates of swelling increased to 30%. In this study, no significant relationship between lymphoedema and the extent of axillary treatment was found.

Kwan et al (2002) studied patients treated in British Columbia from 1993 to 1997. A screening questionnaire was mailed to 744 patients who were at least two years post-diagnosis. Those classified as symptomatic using the questionnaire underwent interview and clinical assessment. Arm volume was measured using water displacement and lymphoedema diagnosed if limb volume was > 200 ml, as compared with the unaffected arm. Arm circumferences were also taken at the hand, wrist, and above and below the elbow. From the questionnaire, 49.9% suffered from arm symptoms and 12.5% had lymphoedema. Lymphoedema occurred in 30% of those who had axillary surgery and radiotherapy, and 5% of those who had axillary surgery alone, reflecting the findings from previous studies (Kissen et al, 1986). In another study (Querci della Rovere et al, 2003), only 50% of those patients who reported swelling were found to have an actual increase in circumference, while 31% had an increased circumference but did not report this subjectively. This

suggests that subjective reporting of lymphoedema may be open to inaccuracies.

Some recent studies indicate an apparent reduction in lymphoedema rates, most likely due to improved surgical techniques, particularly in terms of managing the axilla (Hojris et al, 2000; Meric et al, 2002; Coen et al, 2003). Coen et al (2003) found a 10.7% risk of lymphoedema in those who had breast conservation surgery and radiotherapy to the breast and three axillary nodal levels, as compared with a 1% risk in those who had surgery and breast irradiation (to include the lower axillary lymph nodes) (n = 727). The authors cite an overall rate of 4.1% and suggest the extent of axillary surgery to be insignificant, although the findings are questionable as lymphoedema was defined by an increase in arm circumference at only one site on the forearm.

Another recent study reports a 6.2% rate of lymphoedema (Rampaul et al, 2003). The authors describe the breast cancer treatment protocol undertaken in the preceding 10 years as mastectomy, or wide local excision and axillary node sampling with a four-node sample. Node positive patients then received radiotherapy, or occasionally surgical clearance to the axilla unless their tumours were grade one. In part one, 1,242 patients attending the follow-up breast cancer clinic were asked about symptoms of arm swelling and were examined by a clinician. Of these, 0.4% reported problematic symptoms affecting quality of life. Part two took place over a 13-week period, and 677 patients completed a questionnaire that combined the FACT B4, EQ-50 and the Spielberger quality-of-life questionnaires. 'A lot' of arm swelling was reported by 6.2% of patients.

This study indicates that the rate of severe lymphoedema in breast cancer patients may be low when standard surgery includes a four-node sampling of the low axilla and axillary irradiation, or clearance in less than 20% of patients. There are,

however, some limitations with this study. Arm volumes or circumference measurements were not taken, and part one relies on the subjective reports of patients and doctors. However, swelling is often localised, may not affect the whole limb and may vary in severity and, therefore, may not always be easily recognised. It has already been noted that subjective self-reporting may lead to inaccuracies and inconsistencies. Furthermore, it is not clear from the questionnaire results how many patients had some degree of swelling that did not fall into the category of 'a lot'. Mild to moderate swelling has the potential to increase and become complicated by recurrent infection, if not identified and treated. The authors' assertion that a lymphoedema service may be a 'waste of time' fails to recognise the potential for preventive interventions in apparently mild lymphoedema.

The introduction of mammographic screening, leading to early detection of breast cancer, may also have played a part in the changing nature of BCRL (Suneson et al, 1996).

The role of sentinel node biopsy in informing axillary treatment decisions and, therefore, influencing the risk of lymphoedema development, has been the focus of a number of recent studies. Sener et al (2001) reported a 3% rate of lymphoedema in 120 patients who underwent sentinel lymphadenectomy, and 17% in those who underwent sentinel lymphadenectomy and axillary dissection. Tumours located in the upper outer quadrant and post-operative trauma were both identified as risk factors for lymphoedema. Golshan et al (2003) compared patients who underwent sentinel lymph node biopsy with those who had level I and level II axillary node dissection. From a total of 125 patients, arm measurements at two sites above and below the elbow showed an increase in size by > 3 cm in 27% of those who underwent axillary lymph node

dissection, compared with 2.6% in those who had sentinel node biopsy and axillary sampling.

It appears that breast conservation surgery and minimal axillary intervention are important factors in reducing the risk of lymphoedema (Ridings and Bucknall, 1998). The introduction of mammographic screening, leading to early detection of breast cancer, may also have played a part in the changing nature of BCRL (Suneson et al, 1996). This has recently been confirmed in two clinical trials comparing sentinel node biopsy with standard axillary clearance (Chetty et al, 2000; Mansel et al, 2006). In the first trial, arm volume increased by an average of 4.1% in those randomised to axillary clearance (Chetty et al, 2000), while Mansel et al (2006) showed that patients who underwent sentinel node biopsy (n = 515) had a reduced rate of lymphoedema development than for the 516 randomised to standard axillary clearance (5% vs 13%).

A study by Clark et al (2005) identified 188 patients three years post-surgery. At follow up, 20.7% of the patients had developed lymphoedema. Hospital skin puncture, mastectomy and increased body mass index (BMI) were all significantly associated with its presence. While surgical technique is clearly important in the development of lymphoedema, other factors must be considered, such as obesity and skin puncture leading to infection.

Conclusion

This review highlights limitations in the current literature, both in terms of quality of studies and lack of sound incidence and prevalence data. Critical reviews of methods used raises awareness and insight into how subsequent research might be conducted, and where the possible pitfalls lie. There is also a need to consider other problems not highlighted in previous studies, such as breast oedema. Sound incidence data on particular high-risk groups should be produced, as these will contribute to the pool of new patients.

Despite the limitations of studies, there is some evidence on factors that may give rise to higher risk of lymphoedema development. Factors which appear to predispose patients to BCRL include: use of irradiation; extent of axillary node dissection; combined axillary surgery and irradiation; obesity; surgical wound infection; tumour stage; and extent of surgery. Despite improvements in surgical technique, it is difficult to see an overall reduction in the risk of lymphoedema, with more recent studies still exhibiting high rates of BCRL development in women. However, this may also be a consequence of detecting more mild cases.

Using the data from recent studies, we have estimated the prevalence of BCRL in the UK population (Moffatt et al, 2003). It has been estimated that there are 200,000 women with a history of breast cancer alive today. On this basis, that between one quarter and one third of these women may suffer from lymphoedema post-treatment, it is predicted that there are 50,000–67,000 women suffering from BCRL in the UK alone.

In addition to surgical technique and peri-operative care, prevention strategies and early detection may help to minimise the impact of BCRL on the patient, and prevent the development of other co-morbidities such as acute inflammatory episodes. These strategies may reduce the impact that lymphoedema has on the quality of life of these patients. **JL**

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Key Points

- ▶▶ Lymphoedema is a common morbidity following treatment for breast cancer in women.
- ▶▶ Methodological problems exist in relation to definition of lymphoedema, patient selection and duration of follow up.
- ▶▶ A number of risk factors for BCRL have been identified that relate to disease severity, surgical technique, including axillary node dissection, use of radiation and obesity.
- ▶▶ There is little evidence that the rate of BCRL is reducing, though this may be confounded by methodological differences.

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