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Incidence and risk of arm oedema following treatment for breast cancer: a three-year follow-up study

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Summary

Background: Breast-cancer-related lymphoedema is a chronic condition with estimates of incidence ranging from 6 to 83%. Lymphoedema has been associated with a variety of risk factors. However, this evidence has suffered from methodological weaknesses, and so has had little impact upon clinical practice.

Aim: To examine incidence and risk factors [hospital skin puncture, surgical procedure, Body Mass Index (BMI), age, axillary node status, number of axillary nodes removed, radiotherapy and surgery on dominant side] for breast cancer-related arm lymphoedema.

Design: Prospective observational study, with measurement of limbs pre-operatively and at regular intervals post-operatively.

Methods: We recruited 251 women who had surgical treatment for breast cancer that involved sampling, excision or biopsy of axillary nodes, aged $\geqslant 18$ years, and free of advanced disease and psychological co-morbidities. Of these, 188 (74.9%) were available for 3-year follow-up.

Results: At follow-up, 39 (20.7%) had developed lymphoedema. Hospital skin puncture (vs. none) (RR 2.44, 95%CI 1.33–4.47), mastectomy (vs. wide local excision or lumpectomy) (RR 2.04, 95%CI 1.18–3.54), and BMI $\geqslant 26$ (vs. BMI 19–26) (RR 2.02, 95%CI 1.11–3.68) were the only significant risk factors.

Discussion: Lymphoedema remains a significant clinical problem, with 1:5 women in this sample developing the condition following treatment for breast cancer. Risk factors are identified in the development of lymphoedema that should be taken into account in clinical practice.

Introduction

Lymphoedema is a chronic condition caused by the abnormal accumulation of protein-rich fluid in the interstitial space due to inadequate lymphatic drainage.[1] Clinical manifestations include swelling, fibrosis and hardening of affected tissues, leading to decreased joint mobility, pain and discomfort. The static protein-rich environment promotes bacteria, increasing the risk of infection.[2]

Estimates of the incidence of breast-cancer-related lymphoedema range from 6% to 83%.[3–11] Oedema may arise immediately or many years after treatment, and has been associated with a range of factors, primarily those causing trauma to the lymphatic system: axillary dissection and radiotherapy;[4–7,10,12–18] soft tissue infection;[9,11,12,15,16] weight gain after treatment;[9,10,12,15,17] venepuncture in the ipsilateral arm;[17,19–21] axillary node status;[5] number of axillary nodes removed;[4] surgical procedure;[6,7] and age.[17]

However, the credibility of this evidence base is undermined by widespread methodological flaws. Other than one prospective study,[6] studies

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used either a cross-sectional or retrospective design (thereby excluding the possibility of pre-operative assessment of lymphoedema), with other limitations, including analyses based upon patients' self-diagnosis of lymphoedema,[6,7] or upon patients' measurements of their own arms,[9] or using self-selected samples of patients' who identified an association between a risk factor and onset of lymphoedema.[20]

We aimed to examine incidence and risk factors for breast-cancer-related arm lymphoedema using a robust, prospective design, with accurate measurement of limbs pre-operatively and at regular intervals post-operatively.

Methods

Participants

From June 1999 to December 2000, 370 women aged $\geqslant$18 years were admitted to Worthing Hospital, West Sussex, UK, for surgery related to breast cancer. At baseline, we excluded 75 women with: acute psychological distress, as determined by a specialist breast care nurse ($n=30$); previous breast cancer treatment ($n=17$); pre-existing physical condition that might be associated with limb swelling (e.g. recent thrombosis) ($n=11$); bilateral cancer ($n=2$); advanced cancer ($n=3$); or a combination of these factors ($n=12$). Of the remaining 295, six declined to participate and 38 were not invited (due to lack of researcher's time for recruitment and consent). Thus of 295 eligible women, 251 (85.1%) were recruited and formed the study sample. One hundred and eighty-eight (74.9%) of the sample participated in the 3-year follow-up; of the remaining 63: 19 (7.5%) were deceased; 18 (7.1%) were lost to follow-up; 18 (7.1%) declined further participation; and 8 (3.2%) were unable to participate due to illness.

Data collection

Data were collected during surgical pre-assessment, surgery and post-surgical in-patient stay by a researcher (WH), a physiotherapist, and theatre and ward nursing staff. Arm volumes were calculated using the formula for a cylinder from circumference measurements taken with a nylon tape measure at 4-cm intervals from wrist to axilla. Baseline arm measurements were taken during surgical pre-assessment, and follow-up measurements at 6 months (by WH), and 3 years post-surgery (by BC).[22] Researchers were trained in measurement technique by a Lymphoedema Nurse Specialist with over 10 years clinical experience. Body mass index (BMI) was calculated using weight and height measurements taken in the surgical pre-assessment clinic. Patients were asked by the researcher to identify their dominant arm. 'Skin puncture' was defined as any intentional puncture by a health professional or patient of the patient's skin in the hand or arm on the ipsilateral side with a needle for any purpose, including finger prick glucose testing. These data were collected by clinical staff within each relevant department using proformas prepared by the research team. Data for age, axillary node status, number of axillary nodes removed, type of surgery and radiotherapy were extracted from routinely collected clinical information.

Calculation of change in limb volume

Peripheral oedema conventionally is quantified by the difference in volume between the affected (ipsilateral) and unaffected (contralateral) limb, expressed as a percentage of the contralateral limb volume:

$$\mathrm{PVD}_j = \frac{\mathrm{I}_j - \mathrm{C}_j}{\mathrm{C}_j} \times 100 \qquad (1)$$

where I_j is the volume of the ipsilateral arm at time j, C_j is the volume of the contralateral arm at time j, and PVD_j is Percentage Volume Difference at time j.

The sole outcome measure in this study was change in PVD from baseline to 3 years post treatment, calculated using the formula:

$$\mathrm{PVD}_{\mathrm{change}} = a\mathrm{PVD}_f - \mathrm{PVFD}_b \qquad (2)$$

where PVD_b is PVD at baseline and $a\mathrm{PVD}_f$ is PVD at follow-up. adjusted for volume change in the contralateral limb, so:

$$a\mathrm{I}_f = \mathrm{I}_f - (\mathrm{C}_f - \mathrm{C}_b) \qquad (3)$$

and:

$$a\mathrm{PVD}_f = \frac{a\mathrm{I}_f - \mathrm{C}_b}{\mathrm{C}_b} \times 100 \qquad (4)$$

where I_f is the ipsilateral volume at follow-up, C_b and C_f are contralateral volumes at baseline and follow-up, respectively, and $a\mathrm{I}_f$ is the affected volume post-treatment adjusted for any change in the unaffected limb.

Definition of lymphoedema

Participants in this study were categorized as having lymphoedema when any of the following occurred: (a) a clinical diagnosis of lymphoedema was made by a qualified health care professional,

such as the participant's General Practitioner or a Lymphoedema Clinical Nurse Specialist; (b) upon measurement, PVD was found to be 20% or more; (c) upon measurement, $a\text{PVD}_{\text{change}}$ was found to be 5% or more.

Risk factors

We classified participants into dichotomous variables according to the following risk factors: hospital skin puncture (yes, no); BMI (<26, $\geqslant 26$); axillary node status (positive, negative); radiotherapy (any, none); surgical procedure (mastectomy, wide local excision (WLE)/lumpectomy) (all patients also had level II axillary clearance); dominant arm (ipsilateral, contralateral); age (<60, $\geqslant 60$). The number of axillary nodes removed was analysed separately.

Statistical analysis

We calculated relative risks of lymphoedema at three years post-surgery with 95% confidence intervals. The Mann-Whitney U test was used to see if there was any association between the number of axillary nodes removed, and whether participants had developed lymphoedema or not.

Results

Thirty-nine women (20.7%) had lymphoedema at 3 years post surgery. Of these, 20 were diagnosed before the 3-year follow-up, and a further 19 were found to have $a\text{PVD}_{\text{change}}$ of 5% or more at 3-year follow-up. Of the 20 women who were diagnosed before 3-year follow up, 9 (45%) had developed oedema by 6 months post-operatively and 16 (80%) by 12 months (Figure 1).

At 3-year follow-up, we measured 168 women. $a\text{PVD}_{\text{change}}$ ranged from -16.1% to $+13.5\%$: 133 (79.2%) had $a\text{PVD}_{\text{change}}$ between -5% and $+5\%$; 19 (11.3%) had $a\text{PVD}_{\text{change}} > 5\%$; and 16 (9.5%) $a\text{PVD}_{\text{change}} < -5\%$.

Table 1 presents lymphoedema outcome at 3 years in relation to each risk factor. A statistically significant result was found for three factors: skin puncture while in hospital; mastectomy; and BMI $\geqslant 26$. The Mann Whitney U test for the number of axillary nodes removed was non-significant ($U = 0.117$).

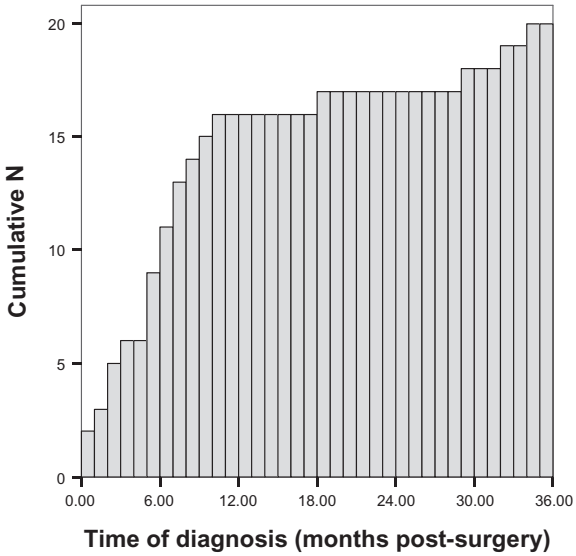

Figure 1. Cumulative frequency chart showing range of development times for lymphoedema up to 3 years post-surgery.

Discussion

Principal findings

In this sample of 188 women, 39 (20.7%) had developed lymphoedema at 3 years after surgery. Of those women diagnosed with lymphoedema before reaching 3-year follow up, 80% had developed lymphoedema by 1 year post surgery. Skin puncture, mastectomy, and BMI $\geqslant 26$ significantly increase the risk of lymphoedema. Other features previously postulated as risk factors (surgery on dominant side, age, axillary node status, number of axillary nodes removed, radiotherapy) were not associated with lymphoedema in this study.

Strength and weaknesses of this research

This was a prospective study in which aspects of patients' pre-assessment and hospital treatment for breast cancer were systematically observed and documented at the time they happened, and in which patients' lymphoedema status was monitored at regular intervals by means of a standardized assessment of arm volume. The prospective design (including baseline measurement of arms pre-surgery), the close observation in hospital and the use of an adjusted volume measure for lymphoedema are major strengths compared to previous research in this topic. In addition, patients repeatedly expressed their appreciation of being monitored for the onset of lymphoedema, stating that lymphoedema was of great concern to them.

Sixty-three (25.1%) of the original sample of 251 women were lost to follow-up, of whom 27 were either deceased or unable to participate due to illness. While we feel this is an acceptable attrition rate in this sample of mostly older women who had received treatment for breast cancer, loss to follow-up might have introduced bias, in that had

Table 1 Risk factors for lymphoedema at 3 years

Risk factor	Baseline *n* (%)	Lymphoedema at 3 years *n* (%)	No lymphoedema at 3 years *n* (%)	RR (95%CI)
Hospital skin puncture				
No puncture	170 (90.4)	31 (18.2)	139 (81.8)	1
Any puncture	18 (9.6)	8 (44.4)	10 (55.6)	2.44 (1.33–4.47)
Continuous infusion via cannula	9	3 (33.3)	6 (66.7)	
Venepuncture for blood test	6	2 (33.3)	4 (66.7)	
Repeated finger prick test (blood glucose)	3	3 (100)		
Surgical procedure				
Mastectomy + level II clearance	65 (34.6)	21 (32.3)	44 (67.7)	2.20 (1.39–3.51)
Any other procedure	123 (65.4)	18 (14.6)	105 (85.4)	1
Wide Local Excision + level II clearance	97 (78.9)	15 (15.5)	82 (84.5)	
Lumpectomy + level II clearance	26 (21.1)	3 (11.5)	23 (88.5)	
*BMI**				
⩾26 (overweight, obese, very obese)	92 (49.7)	26 (28.3)	66 (71.7)	2.02 (1.11–3.68)
19–26 (healthy)	93 (50.3)	13 (14.0)	80 (86.0)	1
Age (years)				
Mean (SD)	–	62.7 (11.6)	61.8 (11.5)	
⩾60	103 (54.8)	25 (24.3)	78 (75.7)	1.47 (0.82–2.65)
<60	85 (45.2)	14 (16.5)	71 (83.5)	1
Axillary node status				
Positive	65 (34.6)	17 (26.2)	48 (73.8)	1.46 (0.84–2.55)
Negative	123 (65.4)	22 (17.9)	101 (82.1)	1
Radiotherapy				
No radiotherapy	62 (33.0)	15 (24.2)	47 (75.8)	1
Radiotherapy	126 (67.0)	24 (19.0)	102 (81.0)	0.79 (0.45–1.39)
Breast only	103 (81.7)	18 (17.5)	85 (82.5)	
Chest wall only	12 (9.5)	2 (16.7)	10 (83.3)	
Axilla + supraclavicular fossa + breast	6 (4.8)	2 (33.3)	4 (66.7)	
Supraclavicular fossa + chest wall	5 (4)	2 (40)	3 (60)	
*Surgery on dominant side***				
Yes	93 (49.7)	16 (17.2)	77 (82.8)	0.74 (0.41–1.31)
No	94 (50.3)	22 (23.4)	72 (76.6)	1

Values are numbers (percentages within group) unless otherwise stated. *Three women with BMI < 19 were excluded from the analysis. **One ambidextrous woman was excluded from the analysis

lymphoedema developed, the participant might well have re-presented for treatment. The main weakness of this study is that it used a relatively small sample from a single site, and so its generalizability may be questioned. These limitations were applied for pragmatic purposes, due to the fact that the study had only a low level of funding. In addition, participation in the study inevitably raised the participants' awareness of lymphoedema and its prevention; for example, women were provided with advice and information by the researcher at follow-up visits.[23] Incidence of lymphoedema in the study population might therefore be higher than the 20.7% found in this sample. Finally, we acknowledge that tape measurement may be less accurate than water displacement or optoelectronic plethysmographic devices in estimating lymphoedema volumes; however, the fact that all measurements were taken by only two operators should have kept error to a minimum. Despite these weaknesses, we feel this study makes a considerable contribution to the evidence base.

Implications for policy and clinical practice

In this sample, 1:5 women developed arm oedema following surgical treatment for breast cancer. Given that lymphoedema is a lifelong condition, this frequency represents a considerable clinical burden upon the NHS. Our results suggest that the condition can be associated with some risk factors, and so attention needs to be paid to reducing risks whenever possible. Specifically, health care staff

should avoid puncturing the skin in the ipsilateral extremity, while patients should be advised to avoid both accidental and non-accidental skin puncture (e.g. finger-prick glucose testing), and those who are overweight or obese should be encouraged to lose weight. The increased risk associated with mastectomy should also be borne in mind when making treatment decisions.

Of the 39 women with lymphoedema, only 50% had had their condition recognized and treated prior to 3-year follow-up. Anecdotally, in most of these cases, the swelling was first noticed by the patient herself, who actively sought advice from a health care professional. The remainder, found to have lymphoedema only through the study follow-up, seemed unaware of their condition. Clearly, the importance of patients monitoring their arm condition needs to be repeatedly emphasized by healthcare staff post surgery.

Future research

A large, multi-centre, long-term prospective study would be of great value. A sample of thousands, rather than hundreds, would provide a better estimate of incidence; moreover, it is important to replicate this work with a sample that includes a variety of levels of axillary intervention, including sentinel axillary node biopsy. A repeat examination of other major risk factors is also needed. In particular, our findings contrast with previous results regarding the risk associated with radiotherapy. Due to our sample size and the wide variety of radiotherapy administered, we could examine this factor only in broad terms. Further research that considers whether risk varies with different radiotherapy sites, techniques, and doses would be timely.

There are a whole host of other posited factors that patients have associated with the onset of lymphoedema, and which some might argue should be examined, such as air travel, general cuts and scrapes, insect stings, sports injuries, sunburn, the carrying of heavy loads, and other various causes of tissue trauma or 'strain'.[24] The problem with this list is that it is endless, as potentially it includes any act that causes damage to arm tissue; it would seem preferable to concentrate on enhancing our understanding of the biological basis of lymphatic dysfunction rather than conduct numerous studies examining unusual risk factors.

Conclusions

Lymphoedema remains a significant clinical problem, with an incidence of 1:5 women developing the condition following treatment for breast cancer. Risk factors have been identified in the development of lymphoedema that should be taken into account in clinical practice.

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