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Risk factors for the initiation and aggravation of lymphoedema after axillary lymph node dissection for breast cancer

Key Messages

1. Previous inflammation or infection of the breast, chest or arm is a major risk factor associated with the initiation and aggravation of lymphoedema in patients who have received axillary lymph node dissection for breast cancer.
2. Surgery on the side of the dominant hand, obesity and ageing are other risk factors associated with aggravation of lymphoedema.
3. Patients who are at risk of developing lymphoedema should be educated about the importance of monitoring and preventing infection-inflammation, and seek medical advice immediately when signs of inflammation are noted.
4. Exercise regimens should target weight control and lymphatic drainage.
5. A threshold of 5 to 10% difference in arm circumference is significant as a means of predicting severe arm symptoms.

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Introduction

Lymphoedema is relatively common following axillary dissection for breast cancer. Several causes are well known, including the extent of axillary surgery and the use of radiation therapy to the axilla after surgery. Many of the potentially modifiable factors, such as participation in weight-bearing exercise and airline travel have been inadequately studied. Women are advised to avoid physical activities, constrictive pressure on their affected arm, and other activities that could lead to arm injury or infection, but it is not known whether these activities actually contribute to lymphoedema.

Methods

Study design

A matched case-control study was conducted in one Hospital Authority hospital from May 2004 to December 2005.

Sample

The sample was recruited from those who had undergone unilateral axillary dissection for breast cancer and were followed up in the oncology unit. Participants assigned as 'cases' were those who had been diagnosed with lymphoedema for no more than 5 years. Controls had no lymphoedema and were matched to cases according to their surgery date (<2 months), whether they had radiation to the axilla or not, and their stage of cancer.

Main outcome measures

Two questionnaires were used to collect information about risk factors, arm morbidity and quality of life by either interview or self-completion. The outcome measure was the degree of lymphoedema. While patients with lymphoedema were designated as cases and those with no lymphoedema were controls, within the case group, those with moderate-to-severe degrees of lymphoedema were designated as cases and while those with none-to-mild lymphoedema were controls. Arm circumference measurement was performed for cases and controls. A difference between the two arm circumferences of 3 cm or above was classified as moderate lymphoedema and more than 5 cm as severe. Anything less than 3 cm was considered mild lymphoedema. Arm morbidity included arm swelling, pain, numbness/tingling, limitations of movement and infections; and their interference with life activities. The risk factors included diabetes, high blood pressure, cigarette smoking, shoulder injury, flexibility exercises, strength training exercises, recreational activities requiring walking, medical procedures, arm/hand injury, airline travel, height, weight, and occupation.

Statistical analysis

Multivariate logistic regression analyses were used to assess the association between potential risk factors and lymphoedema, as well as the presence of moderate-to-severe lymphoedema, with adjustment for possible confounders. Stepwise procedures were used to identify statistically significant predictors ($P<0.05$) for the model.

Table 1. Patient and clinical factors related to different status of lymphoedema*

Patient and clinical factors	Initiation of lymphoedema		Aggravation of lymphoedema	
	Controls (n=101)	Cases (n=101)	None to mild (n=128)	Moderate to severe (n=74)
Age at recruitment (years)	50.3±7.7	53.0±9.6	50.5±7.7	53.7±10.02
Body mass index at recruitment (kg/m^2)	22.4±3.3	23.5±4.0	22.4±3.4	23.9±4.1
Age at axillary dissection (years)	46.5±7.9	49.6±9.8	46.9±8.0	50.1±10.1
Body mass index at axillary dissection (kg/m^2)	17.2±2.5	18.1±2.8	17.2±2.6	18.3±2.8
Surgical wound healing time (days)	12.1±7.8	15.6±11.7	13.0±8.6	15.3±12.2
Diabetes mellitus				
No	92 (91.1)	94 (93.1)	116 (90.6)	70 (94.6)
Yes	9 (8.9)	7 (6.9)	12 (9.4)	4 (5.4)
Hypertension				
No	88 (87.1)	76 (75.3)	110 (85.9)	54 (72.9)
Yes	13 (12.9)	25 (24.8)	18 (14.1)	20 (27.0)
Co-morbid disease				
No	69 (68.3)	54 (53.5)	84 (65.6)	39 (52.7)
Yes	32 (31.7)	47 (46.5)	44 (34.4)	35 (47.3)
Recurrence/metastasis of breast cancer				
No	92 (91.1)	90 (89.1)	116 (90.6)	66 (89.2)
Yes	9 (8.9)	11 (10.9)	12 (9.4)	8 (10.8)
History of infection-inflammation				
No	87 (86.1)	64 (63.4)	108 (84.4)	43 (58.1)
Yes	14 (13.9)	37 (36.6)	20 (15.6)	31 (41.9)
Drainage tube left in place after surgery				
Yes	9 (8.9)	11 (10.9)	11 (8.6)	9 (12.2)
No	92 (91.1)	90 (89.1)	117 (91.4)	65 (87.8)
Needle aspiration after surgery				
No	89 (89.9)	91 (91.9)	115 (91.3)	65 (90.3)
Yes	10 (10.1)	8 (8.1)	11 (8.7)	7 (9.7)
Any medical conditions which limited arm or shoulder movement prior to surgery				
No	92 (91.1)	95 (94.1)	115 (89.8)	72 (97.3)
Yes	9 (8.9)	6 (5.9)	13 (10.2)	2 (2.7)
Flexibility exercises				
No	21 (20.8)	24 (23.8)	26 (20.3)	19 (25.7)
Yes	80 (79.2)	77 (76.2)	102 (79.7)	55 (74.3)
Strength training exercises				
No	90 (89.1)	95 (94.1)	116 (90.6)	69 (93.2)
Yes	11 (10.9)	6 (5.9)	12 (9.4)	5 (6.8)
Leisure activities requiring walking				
No	20 (19.8)	27 (26.7)	25 (19.5)	22 (29.7)
Yes	81 (80.2)	74 (73.3)	103 (80.5)	52 (70.3)
Medical procedures (blood drawn, blood pressure) on hand/arm on side of cancer				
No	70 (69.3)	80 (79.2)	89 (69.5)	61 (82.4)
Yes	31 (30.7)	21 (20.8)	39 (30.5)	13 (17.6)
Injury to hand/arm on side of cancer				
No	85 (84.2)	92 (91.1)	108 (84.4)	69 (93.2)
Yes	16 (15.8)	9 (8.9)	20 (15.6)	5 (6.8)
Travel on airplane				
No	45 (44.6)	53 (52.5)	55 (43)	43 (58.1)
Yes	56 (55.5)	48 (47.5)	73 (57.0)	31 (41.9)
Axillary dissection on side of hand dominance				
No	41 (40.6)	39 (38.6)	59 (46.1)	21 (28.4)
Yes	60 (59.4)	62 (61.4)	69 (53.9)	53 (71.6)

* Data are shown as mean±standard deviation, or No. (%)

Results

The sample consisted of 202 women who underwent a unilateral axillary dissection for breast cancer: 101 cases with lymphoedema and 101 matched controls. Among the cases, 74 were graded as having moderate-to-severe lymphoedema and 27 had mild lymphoedema; 101 controls without lymphoedema were pooled together.

There were no demographic differences between cases and controls including marital status, education, occupation, employment status, lifting activities as part of work and average lifting of weight per time. There were also no disease-related differences in terms of histology subtypes of cancer, tumour location, and stage of cancer. Nor were the following treatments different: surgery type, breast reconstruction, number of removed lymph nodes, number of positive nodes, institution in which surgery was performed, adjuvant radiation to axilla, dose of axillary radiation, hormonal therapy, chemotherapy and details of chemotherapy ie anthracycline-based chemotherapy, taxane and number of chemotherapy courses. The above factors

Table 2. Odds ratios (OR) and 95% confidence interval (CI) for patient and clinical factors for initiation and aggravation of lymphoedema

Patient and clinical factors	Lymphoedema		Moderate-to-severe lymphoedema	
	OR (95% CI)	P value	OR (95% CI)	P value
Older age at recruitment	1.04 (1.01-1.07)	0.03	1.04 (1.01-1.08)	0.01
Higher body mass index at recruitment	1.09 (1.01-1.18)	0.03	1.11 (1.03-1.21)	0.007
Older age at axillary dissection	1.04 (1.01-1.07)	0.02	1.04 (1.01-1.08)	0.01
Higher body mass index at axillary dissection	1.10 (1.01-1.19)	0.03	1.13 (1.04-1.23)	0.006
Prolonged surgical wound healing time	1.04 (1.01-1.09)	0.03	1.02 (0.99-1.05)	0.14
Diabetes mellitus				
No	1	-	1	-
Yes	0.76 (0.27-2.13)	0.60	0.55 (0.17-1.78)	0.32
Hypertension				
No	1	-	1	-
Yes	2.23 (1.07-4.65)	0.03	2.26 (1.11-4.63)	0.03
Smoker				
No	1	-	1	-
Yes	3.06 (0.31-2.99)	0.34	0.57 (0.06-5.59)	0.63
Co-morbid disease				
No	1	-	1	-
Yes	1.88 (1.06-3.33)	0.03	1.71 (0.96- 3.07)	0.07
Recurrence/metastasis of breast cancer				
No	1	-	1	-
Yes	1.25 (0.49-3.16)	0.64	1.17 (0.46-3.01)	0.74
History of infection-inflammation				
No	1	-	1	-
Yes	3.59 (1.79-7.2)	0.0003	3.89 (2.0-7.56)	<0.0001
Drainage tube left in place after surgery				
Yes	1	-	1	-
No	0.80 (0.32-2.02)	0.64	0.68 (0.27-1.72)	0.42
Needle aspiration after surgery				
No	1	-	1	-
Yes	0.78 (0.3-2.07)	0.62	1.13 (0.42-3.05)	0.82
Any medical conditions which limited arm or shoulder movement prior to surgery				
No	1	-	1	-
Yes	0.65 (0.22-1.89)	0.42	0.25 (0.05-1.12)	0.07
Flexibility exercises				
No	1	-	1	-
Yes	0.89 (0.46-1.74)	0.73	0.74 (0.38-1.45)	0.38
Strength training exercises				
No	1	-	1	-
Yes	0.52 (0.18-1.46)	0.21	0.70 (0.24-2.07)	0.52
Leisure activities requiring walking				
No	1	-	1	-
Yes	0.68 (0.35-1.31)	0.25	0.57 (0.3-1.11)	0.10
Medical procedures (blood drawn, blood pressure) on hand/arm on side of cancer				
No	1	-	1	-
Yes	0.59 (0.31-1.12)	0.11	0.49 (0.24-0.99)	0.046
Injury to hand/arm on side of cancer				
No	1	-	1	-
Yes	0.52 (0.22-1.24)	0.14	0.39 (0.14-1.09)	0.07
Travel on airplane				
No	1	-	1	-
Yes	0.73 (0.42-1.27)	0.26	0.54 (0.30-0.97)	0.04
Axillary dissection on side of dominant hand				
No	1	-	1	-
Yes	1.09 (0.62-1.91)	0.77	2.16 (1.17-3.99)	0.01

were also similar between the none-to-mild lymphoedema controls and moderate-to-severe lymphoedema cases, except that more subjects with moderate-to-severe lymphoedema had their surgery performed in public hospitals and adjuvant radiation to the axilla.

Table 1 summarises the factors focusing on patient and clinical variables between controls (no lymphoedema) and cases (with lymphoedema), and between none-to-mild lymphoedema controls and moderate-to-severe lymphoedema cases. Table 2 shows that older age and higher body mass index (BMI) at axillary dissection were associated with lymphoedema and moderate-to-severe lymphoedema. The other significant risk factors were hypertension and a previous history of infection-inflammation. Prolonged surgical wound healing time and co-morbid diseases such as cardiac disease, deep vein thrombosis, arterial disease in the affected limb, asthma, drug allergies, immunological disorders were also associated with lymphoedema. Surgery on the side of hand dominance was associated with

Table 3. Adjusted odds ratios (OR) and 95% confidence interval (CI) for main risk factors associated with lymphoedema*

Risk factors	Adjusted OR (95% CI)	P value
Previous infection-inflammation event	3.80 (1.84-7.87)	0.0003
Older age at axillary dissection	1.06 (1.02-1.10)	0.007

* Forced entry model: factors included in the model but OR not shown are body mass index at recruitment, marital status, education level, occupation, lifting activities as part of work

Table 4. Adjusted odds ratios (OR) and 95% confidence interval (CI) for main risk factors associated with moderate-to-severe lymphoedema*

Risk factors	Adjusted OR (95% CI)	P value
Previous infection-inflammation event	4.49 (2.16-9.30)	<0.0001
Axillary dissection on the side of hand dominance	2.97 (1.46-6.03)	0.003
Higher body mass index at recruitment	1.11 (1.01-1.21)	0.02
Older age at recruitment	1.05 (1.01-1.10)	0.016

* Forced entry model: factors included in the model but OR not shown are marital status, education level, occupation, lifting activities as part of work

moderate-to-severe lymphoedema. No relationship with either lymphoedema or moderate-to-severe lymphoedema was found for diabetes, recurrence/metastasis of breast cancer, drainage tube left in place after surgery and needle aspiration after surgery, and patient's life activities. It should be noted that data about smoking were not reported as there were too few smokers.

A stepwise logistic regression was carried out by entering the demographic, breast cancer disease–related, treatment-related, and patient and clinical variables into the model. This was done separately for lymphoedema and moderate-to-severe lymphoedema. The significant predictors selected were a history of infection-inflammation and older age at axillary dissection for lymphoedema; and a history of infection-inflammation, axillary dissection on the side of hand dominance, higher BMI and older age at recruitment for moderate-to-severe lymphoedema

Because of the possibility that demographic variables not entered into the final model may have small confounding effects, the odds ratios (OR) for the significant factors were adjusted for potential confounders. The adjusted OR for lymphoedema development in subjects with previous infection-inflammation was 3.80 (95% confidence interval (CI), 1.84-7.87); if there was an increase by 1 year of age at axillary dissection, the adjusted OR was 1.06 (1.02-1.10) [Table 3]. The adjusted OR for the development of moderate-to-severe lymphoedema, if there was previous infection-inflammation was 4.49 (2.16-9.30) [Table 4] which was markedly higher than that observed for lymphoedema development. The adjusted ORs for moderate-to-severe lymphoedema, if axillary dissection was on the side of hand dominance was 2.97 (1.46-6.03); if there was an increase in 1 kg/m^2 BMI at recruitment, it was 1.11 (1.01-1.21); and if there was an increase in 1 year of age at recruitment, it was 1.05 (1.01-1.10).

Discussion

This study highlights, for the first time in the scientific literature, the effect of patient and life activity–related factors on the development of lymphoedema after axillary dissection in patients with breast cancer. There was a very strong relationship between having a history of infection-inflammation in the breast, chest or arm and the development and severity of lymphoedema. The lymphoedematous tissues are extremely sensitive to infection, and any simple burns and puncture wounds can develop into generalised erysipelas, which may produce further lymphatic destruction and blockage.[1]

Increasing age at axillary dissection is a risk factor for developing lymphoedema. This may be attributed to the formation of lymphovenous anastomoses in younger patients.[2] Autopsy results have shown that these lymphovenous anastomoses are much less common in older patients, because of the ageing process.[3] Older age at recruitment rather than that at axillary dissection was a risk factor for lymphoedema progression. The normal process of progressing to a more severe degree of lymphoedema may be age dependent.

It is not clear whether higher BMI (obesity) is a direct risk factor for developing lymphoedema. It is certainly a risk factor for infection and poor wound healing.[2] Prolonged surgical wound healing time was highly significant in the univariate but not in the multivariate analyses in this study. This support the theory that obese patients have delayed wound healing secondary to a cycle of fat necrosis leading to secondary infection, regional lymphangitis, and lymphatic obstruction.[4]

Despite the finding of an association between surgery on the side of the dominant hand and development of moderate-to-severe lymphoedema, it is difficult to determine whether this is an independent risk factor, because this may be linked to the degree of activity and muscular use of the limb involved.

Patient life activities that have not been specifically analysed in other studies are of substantial interest in our study. When analysing the data on frequency of leisure activities requiring walking, protective effects were observed when these were performed at a frequency of once a week to twice a week, after adjusting for other risk factors. The adjusted ORs were 0.23 (0.08-0.66) and 0.19 (0.05-0.69) for lymphoedema appearance and exacerbation respectively, when compared with never or occasionally participating in leisure activities requiring walking. Although not significant there was an increased OR of 1.06 (0.53-2.12) when the activities were performed three times or more per week. This could not indicate a threshold for

the level of activities, but may imply a possible relationship between lymphoedema and excessive use of the limb, especially surgery on the dominant arm has been identified as a risk factor in the present study. There is concern that excessive exercise may increase blood flow into the limb, possibly exacerbating the problem.[5]

Conclusion

This study found that previous infection-inflammation and older age at axillary dissection are risk factors associated with the initiation of lymphoedema. Previous infection-inflammation, surgery on the side of the dominant hand, higher BMI (obesity) and older age at time of recruitment are also associated with the severity of the lymphoedema. Infection may be an initiating factor and is more likely to aggravate existing lymphoedema. Hypertension is not an independent risk factor. No association between lymphoedema and air travel and chemotherapy is found. Although our results suggest leisure activities requiring walking have a protective effect on the initiation of lymphoedema, further prospective studies are needed to confirm these findings.

As lymphoedema is a multi-factorial condition that cannot be cured at present, it requires comprehensive preventive and supportive programmes, including evidence-based health education and exercise regimens specifically tailored for the Chinese population.

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References

1. Aitken DR, Minton JP. Complications associated with mastectomy. Surg Clin North Am 1983;63:1331-52.
2. Marcks P. Lymphedema. Pathogenesis, prevention, and treatment. Cancer Pract 1997;5:32-8.
3. Pezner RD, Patterson MP, Hill LR, et al. Arm lymphedema in patients treated conservatively for breast cancer: relationship to patient age and axillary node dissection technique. Int J Radiat Oncol Biol Phys 1986;12:2079-83.
4. Getz DH. The primary, secondary, and tertiary nursing interventions of lymphedema. Cancer Nurs 1985;8:177-84.
5. Pain SJ, Purushotham AD. Lymphoedema following surgery for breast cancer. Br J Surg 2000;87:1128-41.