NATIONAL BREAST
AND OVARIAN
CANCER CENTRE

REVIEW OF RESEARCH EVIDENCE ON SECONDARY LYMPHOEDEMA: INCIDENCE, PREVENTION, RISK FACTORS AND TREATMENT

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Evidence Review Working Group

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EXECUTIVE SUMMARY

National Breast Cancer Centre (NBCC)* commissioned an evidence review in August 2007 to inform the development of evidence-based education and information programs about secondary lymphoedema for health professionals and consumers.

The objectives of the review were to:

- describe the prevalence, incidence and nature of secondary lymphoedema following treatment for cancer
- identify risk factors associated with the development of secondary lymphoedema following treatment for cancer
- provide an overview of the evidence pertaining to strategies for prevention of secondary lymphoedema
- describe the evidence surrounding treatment strategies for secondary lymphoedema.

The evidence review has summarised the best available evidence published between 2005 and September 2007 (the date of completion of the review) and built on a number of existing reviews including:

- *Review of current practices and future directions in the diagnosis, prevention and treatment of lymphoedema in Australia* published by the Department of Health and Ageing in 2006.[1]
- *Review of research evidence on secondary lymphoedema: 2003-June 2006*, commissioned by the National Breast Cancer Centre and undertaken by Professor Kate White and colleagues at the University of Sydney.[2]

A total of 39 eligible studies were included in this evidence review and the findings are summarised below.

The incidence of secondary lymphoedema following treatment for cancer in Australia is unknown and it is likely that its prevalence is underestimated.[3] Incidence estimates for various cancers range between 5% and 66%. 70-80% of those who have lymphoedema after breast cancer present within the first 12 months. The incidence of lower-limb secondary lymphoedema following inguinal node surgery seems to be at least as common as upper-limb secondary lymphoedema following axillary node surgery. Lower-limb secondary lymphoedema also seems to be more common following treatment for particular cancers (e.g. cancer of the vulva, as compared with ovary). Taken together, conservative estimates suggest that 20% of breast, genitourinary, gynaecological, or melanoma survivors will experience secondary lymphoedema. This equates to more than 8000 new cases per year in Australia, highlighting the potential public health burden of cancer-related secondary lymphoedema.

* In February 2008, National Breast Cancer Centre (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

The aetiology of secondary lymphoedema seems to be multifactorial, with acquired abnormalities as well as pre-existing conditions being contributory factors.[4] Many patient, treatment and behavioural characteristics bear inconsistent relationships to secondary lymphoedema risk, and the few that are consistently associated with risk do not alone accurately distinguish the at-risk population.[5] Stage of disease, nodal status and addition of adjuvant treatments (other than radiation treatment) do not adversely influence risk. Minimally aggressive/invasive surgical and radiation treatment are recommended to reduce risk of subsequent secondary lymphoedema. The relationships between patient and behavioural risk factors, such as age, body mass index, treatment on the dominant side, socioeconomic status, social support, participation in physical activity and healthy eating patterns are currently unclear.

At this time the evidence base for prevention recommendations is limited. There is a clear need for well-designed, population-based prospective studies to investigate the causal relationship between suggested risk factors and subsequent development of secondary lymphoedema. In the meantime, it is reasonable for health professionals to discuss preventive strategies with patients to encourage healthy lifestyle behaviours.[6]

Secondary lymphoedema is associated with adverse physical and psychosocial effects and may have a profound impact on daily life. Lack of treatment may also lead to progression of secondary lymphoedema. Available treatment options are varied and often based on little or no evidence of benefit. However, conservative lymphoedema treatment, including complex physical therapy, manual lymph drainage, compression, bandaging, elevation and massage, is associated with volume reductions and improvements in quality of life. The role of exercise in secondary lymphoedema treatment remains uncertain, but to date there have been no reports of secondary lymphoedema being initiated or worsened as a consequence of exercise. Surgical treatment for secondary lymphoedema should only be considered for a small subset of sufferers who have failed to obtain relief from less invasive measures. Available evidence does not support the use of specific pharmacological intervention. There are not adequate studies investigating any one specific complementary or alternative treatment, to comment on their effectiveness.

Adverse effects, such as financial, time and lifestyle burden, have also been associated with treatment for secondary lymphoedema. Therefore, consideration of the acceptability of treatment strategies to patients may be as important as monitoring compliance or treatment success (as defined by reductions in swelling, which was the criteria used for defining treatment success in this evidence review).

CONCLUSION

It is important that patients at risk of secondary lymphoedema and health professionals working with these patients are provided with evidence-based information regarding how best to identify, prevent and treat the disorder. The key conclusions drawn from this review of evidence include:

- lymphoedema is prevalent following treatment for breast cancer, affecting about 20% of survivors; more attention is required to better understand lymphoedema prevalence following other cancers such as melanoma, bladder, gynaecological, prostate and head and neck cancers
- standard diagnostic criteria are needed to advance knowledge regarding prevention and treatment of cancer-related secondary lymphoedema
- current prevention and treatment guidelines are frequently derived from theoretical speculation and/or anecdotal experience
- future research must focus on building the evidence upon which to base effective prevention and treatment activities, taking into account potential adverse physical and psychosocial sequelae.

RECOMMENDATIONS

- Health professionals should acknowledge secondary lymphoedema as an adverse side effect of cancer treatment, and act to minimise the physical, psychological and social impacts of the condition.
- Conservative surgical and radiation treatment for cancer should be used to reduce the risk of secondary lymphoedema.
- Health professionals should be alert to signs and symptoms of secondary lymphoedema, as early diagnosis and treatment of the condition appears to be an important factor in the success of treatment.
- In discussing prevention strategies for secondary lymphoedema with patients, health professionals should describe the lack of empirical evidence and consider the potential impact of recommendations on the patient's (or partner's) health or quality of life.
- While there is no clear relationship between high body mass index and development of secondary lymphoedema following treatment for cancer, maintenance of a healthy body weight in cancer survivors should be encouraged because of the other associated health benefits.
- Health professionals should be familiar with evidence about the range of treatment options for secondary lymphoedema and able to describe these options to patients, recognising that lack of treatment may lead to worsening of symptoms:
    - complex physical therapy, manual lymph drainage, compression and massage therapy are associated with volume reductions
    - use of pharmacological interventions, such as use of benzopyrones and selenium compounds, is not supported by evidence
    - surgical techniques may be useful for a small subset of secondary lymphoedema sufferers who have failed to obtain relief from less invasive measures
    - too few studies investigating any one specific complementary or alternative treatment are available to comment on their effectiveness.

NATURE AND BURDEN OF SECONDARY LYMPHOEDEMA FOLLOWING CANCER

Lymphoedema is a condition characterised initially by regional swelling due to excess accumulation of protein-rich fluid in body tissues. It occurs when the demand for lymphatic drainage exceeds the capacity of the lymphatic circulation.[7] Lymphoedema usually affects the limb(s), although it may also involve the trunk, head or genital area.[8,9] It may be primary or secondary in origin. Primary lymphoedema or 'lymphoedema of unknown aetiology' may be associated with congenital abnormalities, while secondary lymphoedema is 'acquired' following an event such as physical trauma or treatment for cancer.[10]

In Australia, secondary lymphoedema occurs most commonly following treatment for cancer,[11] in particular breast, genitourinary and gynaecological cancers and melanoma. Variations in definition and approaches to diagnosis mean that the true incidence of the condition is unknown. However, given that more than 38,000 Australians are diagnosed with these cancers each year, the population at risk of developing the condition is not insignificant.[12] It is also reasonable to assume that the incidence of secondary lymphoedema may increase with increasing cancer incidence.

Survival exceeds 80% for most of these cancers[12] and quality of life is an important issue for survivors. Secondary lymphoedema has the potential to influence quality of life adversely, with some people experiencing profound effects on daily life. A number of physical, psychological and social impacts of secondary lymphoedema have been described.[13] Gross (e.g. walking) and fine (e.g. writing) motor skills can be affected,[7] impacting work, home and personal care functions, as well as recreational activities and social relationships.[14] Other physical symptoms may include feelings of discomfort, heaviness, pain, tenderness and aching, and reports of multiple associated symptoms are common.[9] Changes to the skin, including hardening, fibrosis, dryness and flakiness, can occur in chronic conditions.[8,15] In addition to physical symptoms, changes in body image and self-image have been reported, with dressing concerns reflecting one practical issue faced.[16] Other psychosocial impacts may include increased psychological distress, depression and anxiety.[17,18]

Given increasing cancer incidence and survival rates, the incidence of secondary lymphoedema is expected to increase. The physical, psychological and social impacts of the condition are considerable. The evidence base available to inform current policy and practice in this area is weak. It is important that guidelines about detection, treatment and support are informed by best available evidence, and that further research is undertaken to improve our understanding about how to prevent its development, where possible, and to improve the quality of life for those with the condition.

OBJECTIVES OF THE REVIEW

National Breast Cancer Centre (NBCC)* was awarded a grant by the Australian Government Department of Health and Ageing in June 2007 to undertake a 12-month program to improve the knowledge and management of secondary lymphoedema in Australia. This program of work was funded in recognition of the fact that:

- inconsistent information and advice is often provided to patients at potential risk of secondary lymphoedema
- evidence about effective treatments for secondary lymphoedema is limited
- research about secondary lymphoedema has been undertaken predominately in women following a diagnosis of breast cancer, with few studies in other cancer populations.

NBCC commissioned this evidence review in August 2007. The outcomes of the review will be used to inform the development of evidence-based education and information programs about secondary lymphoedema for health professionals and consumers.

As a first step, NBCC established a Secondary Lymphoedema Evidence Review Working Group (see Appendix A for details of membership). The role of this Group was to:

- comment on the scope and validity of existing evidence reviews as they relate to this initiative
- inform the development of a brief that could be used to commission an evidence review on secondary lymphoedema
- provide expert comment on the review
- develop and provide evidence-based recommendations from the findings of the review to inform the development of education and information material for health professionals and consumers.

The Secondary Lymphoedema Evidence Review Working Group developed a framework outlining the objectives, scope and content of the evidence review. The Group agreed that the evidence review should build on existing reviews and summarise the best available evidence published between 2005 and September 2007 (the date of completion of the review).

The objectives of the review were to:

- describe the prevalence, incidence and nature of secondary lymphoedema following treatment for cancer
- identify risk factors associated with the development of secondary lymphoedema following treatment for cancer
- provide an overview of the evidence pertaining to strategies for prevention of secondary lymphoedema
- describe the evidence surrounding treatment strategies for secondary lymphoedema.

* In February 2008, National Breast Cancer Centre (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

METHODS

LITERATURE REVIEW

In undertaking this review, two previous reviews were considered, specifically:

1. *Review of current practices and future directions in the diagnosis, prevention and treatment of lymphoedema in Australia:*[1] this review, published by the Department of Health and Ageing in 2006 (referred to in this report as the 'DOHA review'), summarised the literature published between January 1966 and August 2003
2. *Review of the Research Evidence on Secondary Lymphoedema: 2003–2006:*[2] this review, commissioned by the National Breast Cancer Centre and undertaken by Professor Kate White and colleagues at the University of Sydney (referred to as the 'White review') summarised the best available evidence published between January 2003 and June 2006.

The scope and content of the current review was determined by the Secondary Lymphoedema Evidence Review Working Group. The Group agreed that the review should incorporate and build on the findings of the DOHA and White reviews by presenting a summary of the conclusions reached by these reviews together with additional findings published between January 2005 and September 2007. While a systematic review of the papers included in the DOHA and White reviews was not undertaken, relevant studies were retrieved and assessed to determine agreement with summaries presented in each review.

SEARCH STRATEGIES

Electronic databases listed in Table 1 were searched using the search strategy presented in Table 2. This search strategy specifically reflects that used under the EBSCOhost platform to search Medline and CINAHL, and formed the basis for searching the other databases listed. In addition, key national and international researchers identified by the Secondary Lymphoedema Evidence Review Working Group were contacted in an attempt to ascertain research findings that may not have been captured by the searches, for example findings recently accepted for publication or unpublished results (list of contacts can be retrieved on request). The authors were interested in capturing unpublished results to determine the likelihood of publication bias (that is, studies reporting no relationship presumably being more difficult to publish).

Table 3 outlines the eligibility criteria for inclusion of studies in this review. Of particular note are the eligibility criteria relating to the method by which secondary lymphoedema was diagnosed. Currently no standard diagnostic criteria exist and the presence of secondary lymphoedema is defined according to a variety of objective, physical or subjective techniques. For the purposes of this review, only studies based on clinical diagnosis or physical measurements suggesting secondary lymphoedema were included;

secondary lymphoedema based on patient self-report of arm swelling alone was not considered sufficient for inclusion. Further detail regarding the rationale for this decision is provided in the next section.

Table 1 Electronic databases used for the literature search

Database – Period covered includes January 2005 – September 2007
Medline
Pubmed (includes pre-Medline)
CINAHL
Databases of Abstracts of Reviews of Effectiveness
Cochrane Controlled Trials Register
Cochrane Database of Systematic Reviews

Table 2 Medline search strategy using the EBSCOhost platform for studies investigating secondary lymphoedema

#	**Query**	**Limiters/Expanders**
S1	cancer or onco* or neoplasm*	
S2	LE or lymphoedema	
S3	(S2 and S1)	
S4	(S2 and S1)	Date of Publication from: 200501-200712
S5	sensitiv* or specific*	Date of Publication from: 200501-200712
S6	diagnos*	Date of Publication from: 200501-200712
S7	(S6 or S5) and S4	Date of Publication from: 200501-200712
S8	treatment and S4	Date of Publication from: 200501-200712
S9	prevention and S4	Date of Publication from: 200501-200712

Table 3 Eligibility criteria for the selection of studies

		Inclusion criteria	Exclusion criteria
1	Type of study	• Published manuscripts • Systematic reviews	• Animal, laboratory or scientific studies • Case reports and case series • Non-systematic review papers • Editorial papers • Papers that report no clinical results • Unpublished research
2	Patient group	• Patients at risk of developing lymphoedema following cancer treatment • Patients diagnosed with secondary lymphoedema associated with cancer treatment	• Patients with primary lymphoedema • Patients with secondary lymphoedema that is not associated with cancer treatment
3	Outcome	• Secondary lymphoedema following treatment for cancer, where treatment was completed **at least 6 months prior** and as defined by the authors, when assessment used **objective** techniques • Secondary lymphoedema following treatment for cancer, as **diagnosed** by a health professional but where specifics of the diagnostic criteria used is lacking	• Secondary lymphoedema defined by self-report of patient
4	Language	• Studies available in English or non-English studies translated	• Non-English text where the translations were not available[a]

[a] Time restraints meant translation of non-English text was not possible.

DIAGNOSTIC CRITERIA FOR SECONDARY LYMPHOEDEMA

Studies included in this review were those that implemented an objective method to diagnose secondary lymphoedema. It will be helpful to understand the advantages and disadvantages of each of the available objective techniques when reviewing the results of this review. Objective techniques currently used to assess secondary lymphoedema include circumferences, perometry, tonometry, ultrasound, water displacement,

lymphoscintigraphy, lymphangiography and bioimpedance spectroscopy (details of each method are provided in Appendix B). Each of these methods has limitations.[19]

- Simple volumetric measures, such as water displacement and circumference, assess size change but cannot relate changes causally to secondary lymphoedema. The size of a limb or body segment may change for reasons other than fluid accumulation, and density of secondary lymphoedema can be variable. In practical terms, these measures are also time-consuming. Reports of the reliability of these methods are mixed; some studies report poor repeatability with unacceptable bias and limits of agreement (water displacement, –4 ± 6.3% and circumference, 12 ± 19%),[20] while others suggest the methods are highly correlated and reliable, although not interchangeable.[21–23]
- Methods such as tonometry and ultrasound are insensitive to low-grade clinically assessed secondary lymphoedema.[19]
- Lymphoscintigraphy and lymphangiography may provide a more accurate picture of lymphoedema but are invasive and costly procedures.[24,25]
- Bioimpedance spectroscopy shows promise as a direct, accurate and reliable measure of extracellular fluid (and therefore secondary lymphoedema)[19] that appears to be more sensitive to change than other objective measures;[26] however, its application in secondary lymphoedema research has only recently emerged.

Even within individual objective measurement techniques, there is little agreement on specific methodology and appropriate criteria for diagnosis. For example, criteria applied in the context of diagnosing secondary lymphoedema following breast cancer treatment include:

- differences between treated and untreated limbs of 10% or 200 ml in volume[27]
- greater than 5 cm difference in the sum of arm circumferences[28]
- greater than 2 cm difference in circumference at any site.[29]

It is also important to recognise that all techniques require adequate training of the person undertaking the measurement (with some methods being particularly prone to intra- and inter-observer error) and are somewhat limited in the absence of pre-treatment measures. This is particularly the case for diagnosing secondary lymphoedema in patients receiving treatment for bilateral breast cancer or those who have undergone treatment(s) that could cause swelling in both limbs (upper or lower) and/or the trunk (e.g. treatment for gynaecological cancers).

Self-report and/or symptoms such as limb discomfort, heaviness or tightness have been used when defining secondary lymphoedema status. However, presence of symptoms is not an accurate indicator of swelling.[30] A study investigating the characteristics of breast cancer patients screened for participation in a randomised trial on secondary lymphoedema found that only 28% of those presenting for secondary lymphoedema treatment were eligible for the trial on the basis of sufficient excess volume (>15% difference between treated sides). Furthermore, some patients presented with arm

symptoms that may not have been related to secondary lymphoedema.[31] In another Level IV study of breast cancer patients, presence of treatment-related symptoms, such as heaviness, tightness, aching, stiffness and limited range on the treated side, were common among those with (24–64%) and without (15–62%) secondary lymphoedema.[32] Thus, use of self-report alone as a diagnostic method could lead to overestimation of incidence. However, its potential benefit over objective measures is the ability to capture secondary lymphoedema status over an extended period of time. In order to avoid overstating the incidence of secondary lymphoedema or exaggerating the effect of prevention or treatment modalities, studies using self-report alone to diagnose secondary lymphoedema were excluded from this review.

SEARCH RESULTS

The abstract or, when insufficient information was presented in the abstract, the entire manuscript was used to identify eligible studies for inclusion in the current review. A summary of the search results is provided in Figure 1. A total of 231 manuscripts were identified, 151 of which were excluded following abstract review. Full manuscripts were sourced for the remaining 80 publications relating to incidence, risk factors, prevention strategies or treatment modalities of secondary lymphoedema following cancer treatment. A further 41 publications were excluded during the process of data extraction (see Appendix C and D for details), with the remaining 39 publications meeting the inclusion criteria. These studies focused on:

- incidence and risk factors (n=21; see Appendix E for details)
- prevention strategies (n=3; see Appendix F for details)
- treatment modalities (n=17; see Appendix G for details).

(Note: two studies covered multiple focus areas)

The evidence presented in this report was classified using the levels of evidence defined by the National Health and Medical Research Council (NHMRC) in *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Pilot program 2005–2007* (Table 4).[64] A summary of the evidence arising on different topics between January 2005 and September 2007 was graded, using the body of evidence assessment matrix, according to NHMRC guidelines (see Appendix H for details).

Figure 1 Summary of search results

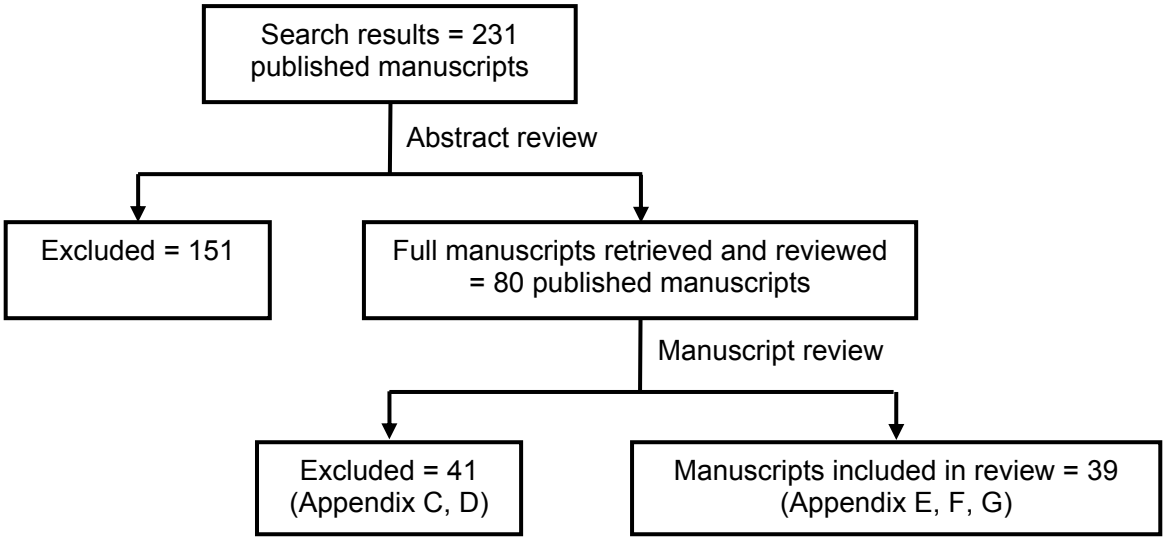

Table 4 Designation of levels of evidence according to type of research question[a]

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A study of test accuracy[b]	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial	A study of test accuracy[b]	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: non-randomised, experimental trial; cohort study; case-control study; or interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for level II or III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: non-randomised, experimental trial; cohort study; or case-control study
III-3	A comparative study without concurrent controls: historical control study; two or more single-arm studies; or interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: historical control study or two or more single-arm studies
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

[a] Table represents a reduced form of that presented in *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Pilot program 2005-2007*;[64]

[b] A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation

INCIDENCE OF SECONDARY LYMPHOEDEMA

The extent of the public health burden posed by secondary lymphoedema has long been clouded by wide variations in reported incidence. Much of this variation can be explained by differences in study definitions of secondary lymphoedema and sampling procedures for recruitment of study participants. Nonetheless, due to increasing incidence for some cancers and improved survival for most cancers, secondary lymphoedema is a significant and potentially growing public health issue.

INCIDENCE FOLLOWING BREAST CANCER

KEY POINTS

- Breast cancer surgery appears to be the most common cause of upper-limb secondary lymphoedema in Australia.
- Wide variations in incidence of secondary lymphoedema in breast cancer survivors have been reported.
- According to current data, on average one in five people treated for breast cancer may develop lymphoedema following treatment.
- Incidence appears to increase with time from surgery, with 70–80% of patients with long-term lymphoedema presenting by 12 months post-surgery.
- Further prospective studies with large cohorts are warranted to clarify the incidence of lymphoedema following breast cancer treatment.

Cancer populations at highest risk of secondary lymphoedema are those requiring surgery to regional lymph nodes. Available evidence suggests that the most common cause of upper-limb secondary lymphoedema in Australia is surgical treatment for breast cancer. The reported incidence of breast cancer-related secondary lymphoedema was 6–80% in the DOHA review and 0–48% in the White review. Reported rates varied depending on the extent of axillary surgery, addition of radiation therapy and timing of measurement. The quality of the studies included in these reviews was variable. Some studies used a retrospective design and included small patient numbers with a wide range of time since diagnosis (2 months to 20 years). In addition, studies usually included patients from a single institution, and/or reported an imprecise denominator.

Since publication of these two reviews, nine prospectively designed studies (graded as Level II prognostic studies) have reported incidence estimates of secondary lymphoedema following breast cancer (Table 5). These studies used objective diagnostic criteria for secondary lymphoedema and included patient populations generally representative of the larger breast cancer population. Reported incidence of secondary lymphoedema in these nine studies was 7–70% from 6 months post-surgery,

with time of measurement and measurement technique the most likely reasons for the variation.

Taking all reported incidence rates into consideration, it seems plausible to suggest that from 6 months post-surgery, approximately one in five patients treated for breast cancer will experience secondary lymphoedema (mean rate 22%; median rate 17%). The rate appears to increase with longer follow-up (median rate up to and including 6 months = 11%; median rate beyond 6 months = 19%). Reported findings suggest that 45–60% of patients with long-term secondary lymphoedema present with the condition by 6 months post-surgery,[33,34] while 70–80% present by 12 months post-surgery.[34]

Appendix B includes a summary of papers published between January 2005 and September 2007 that reported secondary lymphoedema incidence and associated risk factors. In addition to the nine studies presented in Table 5, breast cancer-related secondary lymphoedema incidence was reported in a further nine studies. Although these studies used a poorer quality design and/or have limited generalisability, the incidence rates reported are similar to those presented in Table 5. When all rates from all studies, irrespective of grade, are taken into consideration, the median incidence rate of lymphoedema following breast cancer surgery is 20%.

In summary, additional prospective studies using standard diagnostic criteria and large cohorts are warranted to provide a clearer picture of the incidence of lymphoedema following treatment for breast cancer. In the meantime, the body of evidence supporting the current findings is considered 'good', with data derived from several Level II studies of representative samples and reported findings being relatively consistent and having substantial clinical impact.

Table 5 Reported incidence of secondary lymphoedema in prospectively designed breast cancer cohort studies (2005–2007)

Country and study	Method of diagnosis	Reported incidence (%)		
		6 month PS	12 month PS	18 month+ PS
USA				
Armer *et al.* (2005)[33]	circ, per, 4 definitions	8–46%	42–70%	
Francis *et al.* (2006)[35]	circ, >5% change*		SNB = 17% ALND = 47%	
Lucci *et al.* (2007)[36]	circ, ≥2 cm change*		SNB = 6% ALND = 11%	
Wilke *et al.* (2006)[37]	circ, >10% difference**	7%		

England				
Bennett Britton *et al.* (2007)[38]	circ, >10% difference**		11%	28%
Clark *et al.* (2005)[34]	HP diagnosis, circ – 20% difference** or 10% change*			21%
Pain *et al.* (2005)[39]	circ, >10% difference**		10%	
Australia				
Hayes *et al.* (2007)[28]	BIS, circ, 2 definitions	11–20%		
Finland				
Ronka *et al.* (2005)[40]	circ, >5% difference**		17%	

PS: post-surgery; USA: United States of America; circ: circumferences; per: perometry; BIS: bioimpedance spectroscopy; SNB: sentinel node biopsy; ALND: axillary lymph node dissection; HP: health professional; * change from baseline; **difference between limbs

INCIDENCE FOLLOWING OTHER CANCERS

KEY POINTS

- Surgical treatment of axillary or inguinal lymph nodes for cancers other than breast cancer (e.g. gynaecological, prostate and bladder cancers and melanoma) is a risk factor for secondary lymphoedema. Lymphoedema is likely to be a risk factor following lymph node treatment for other cancers such as head and neck cancer; however, as yet, no data are available.
- Good quality data regarding the incidence of secondary lymphoedema following treatment for cancers other than breast cancer are lacking.
- Incidence of secondary lymphoedema following axillary or inguinal surgery for cancers other than breast cancer appears to be influenced by type of cancer.
- Incidence of lower-limb secondary lymphoedema following surgery to inguinal nodes appears to be at least as common as upper-limb lymphoedema following surgery to axillary nodes for breast cancer.

Patients with cancers other than breast cancer requiring surgical treatment of axillary or inguinal lymph nodes are also at risk of developing secondary lymphoedema. Good estimates of the incidence of secondary lymphoedema following treatment for cancers other than breast cancer are lacking. Only four publications relating to lymphoedema following treatment for cancer other than breast cancer were summarised in the DOHA review and six were included in the White review. Incidence of lymphoedema following cancer other than breast was reported in five papers published between January 2005 and September 2007. Three of these studies assessed secondary lymphoedema with objective measures and therefore met the inclusion criteria of this review (Appendix D)[41–43]. The two remaining studies reported the incidence of secondary lymphoedema

following treatment for gynaecological cancer (specifically vulvar[44] and cervical cancer[45]); however, the manner by which secondary lymphoedema status was assessed was not clearly outlined and therefore the papers were excluded from the current review. These studies were, however, included in the White review, which had broader inclusion criteria.

A brief summary of the findings from the studies included in the DOHA, White and current review is provided below.

- The reported incidence of secondary lymphoedema following treatment for **gynaecological cancers** was 18% in the DOHA review (7–47%: lowest ovarian cancer; highest vulvar cancer). However, these rates were derived from a retrospective study utilising patients from a single institution with a response rate of 66%. The White review reported a similar incidence range of 7–40% following treatment for gynaecological cancers. In the current review, one cross-sectional population-based survey of Queensland gynaecological cancer survivors was published. The reported average (median) incidence, based on a clinical diagnosis of lower-limb secondary lymphoedema, was 10% up to 5 years post-diagnosis (range 8–36%: lowest ovarian cancer; highest vulvar cancer).
- The reported incidence of secondary lymphoedema following treatment for **prostate cancer** was 25–66% in the DOHA review (25–30% following lymph node biopsy and radiation treatment; 66% following pelvic dissection and radiation treatment). No prostate cancer studies were reported in the White review or the current review.
- The reported incidence of secondary lymphoedema following treatment for **bladder cancer** was 13–20% in the DOHA review. No bladder cancer studies were reported in the White review or the current review.
- The reported incidence of secondary lymphoedema following treatment for **melanoma** was 6–29% in the DOHA review (6% following axillary surgery; 29% following inguinal surgery). The White review reported a broader incidence range of 6–58%, with rates influenced by type of surgery, diagnostic criteria and timing of measurement. The current review identified two papers reporting secondary lymphoedema incidence following treatment for melanoma involving axillary[42] or inguinal[43] surgery. These rates were obtained from a prospectively designed trial using limb circumferences to determine secondary lymphoedema status. Reported incidence of secondary lymphoedema was higher following inguinal surgery (18%) compared with surgery involving axillary lymph nodes (9%) at 51–59 months post-surgery.

It should be noted that the studies contributing to the rates reported in the DOHA review for prostate and bladder cancer and for melanoma were not summarised, and consequently the generalisability of these findings is unknown. It is also noteworthy that across the three reviews, only one study was found assessing secondary lymphoedema following prostate cancer. Given that the annual incidence of prostate

cancer now exceeds that of breast cancer (Table 6), more recent investigations are clearly warranted. Furthermore, no publications involving head and neck cancer patients could be identified.

In summary, the body of evidence regarding incidence of lymphoedema secondary to cancer other than that of the breast is poor. Relevant studies are predominantly graded as Level III or IV, with too few focused on any one cancer to determine consistency of evidence. Nonetheless, existing data suggest that incidence of lower-limb secondary lymphoedema is more common following treatment for particular cancers (e.g. vulvar cancer compared with ovarian cancer) and that lower-limb secondary lymphoedema following surgery to inguinal nodes is as least as common as upper-limb secondary lymphoedema following surgery to axillary nodes for breast cancer.

CONCLUSION

The incidence of secondary lymphoedema reported throughout the literature is variable[46,47] and its intermittent nature is anecdotally discussed by clinicians and patients. However, the natural course of the disease lacks documentation. Objective measures are likely to under-diagnose the condition, and thus it is plausible that the incidence data presented above are conservative estimates. Further prospective studies with objective measures of secondary lymphoedema status at regular intervals following surgical treatment for breast cancer and other cancers are required. Results from such studies would build the evidence base regarding secondary lymphoedema incidence as well as providing a clearer picture of the variable nature of the disease.

Table 6 presents a summary of annual incidence data relating to lymphoedema secondary to cancer, alongside the most recent annual incidence rates for related cancers and their respective 5-year survival rates. Australian males have a one-in-three lifetime risk of developing cancer, with prostate cancer the most common male cancer.[12] Lifetime risk of cancer for females is one in four, with breast cancer the most common female cancer.[12] Survival rates following cancers associated with secondary lymphoedema are currently as high as 92%. Based on the available evidence to date, conservative estimates suggest that at least 20% of survivors of breast, gynaecological and prostate cancers or melanoma will experience secondary lymphoedema. This equates to more than 8000 Australians per year, highlighting the potential public health burden of lymphoedema following cancer.

Table 6 Australian annual incidence of cancers and international incidence of lymphoedema associated with these cancers

Primary cancer	Annual incidence[a]	5-yr survival rates	LE incidence (2005–2007)[b]	LE incidence (≤2005)[c]
Breast	11889	84%	20%[d]	
Prostate	13526	83%		25-66%
Uterus	1613	81%	8%[e]	18%
Ovary	1084	42%	5%[e]	7%
Cervix	725	75%	24%[e]	18%
Vulva	220		36%[e]	11–47%
Bladder	2229	65%		13–20%
Melanoma	9524	92%	9% (axillary surgery) 18% (inguinal surgery)[f]	6% (axillary surgery) 29% (inguinal surgery)

LE: lymphoedema; [a]AIHW data representing 2003 incidence data;[12] [b]Estimates of secondary lymphoedema incidence from studies included within this review (median incidence reported); [c]Estimates of secondary lymphoedema incidence based on excluded studies and data presented in previous reviews;[1,2] [d]Incidence taken from conclusion based on information presented in Table 5; [e]Beesley *et al*. (2007);[41] [f]De Vries *et al*. (2005 and 2006)[42,43]

RISK FACTORS ASSOCIATED WITH SECONDARY LYMPHOEDEMA

Secondary lymphoedema appears to have a number of associated risk factors, with acquired abnormalities and pre-existing conditions playing a contributory role.[4] Some of these risk factors are modifiable, while others are not. Table 7 lists those risk factors for secondary lymphoedema that have been investigated, presented under the broad categories of disease- and treatment-related characteristics; physiological characteristics; and patient and behavioural characteristics. This section provides an overview of the evidence under each of these broad categories, including results from the DOHA and White reviews and from the current review.

Table 7 Potential risk factors for secondary lymphoedema

Potential risk factors
Disease- and treatment-related characteristics
Cancer site
Stage of cancer
Extent of surgery
Extent of lymph node surgery
Radiotherapy – extent and combination with lymph node surgery
Chemotherapy
Hormone therapy
Positive lymph node status
Tumour size
Experience of surgeon
Hospital skin puncture
Physiological characteristics
Lymphatic transport
Vein wall movement
Venous anatomy and flow
Protein uptake into local blood
Proteolysis
Patient and behavioural characteristics
Body mass index
Age
Treatment on dominant side (in relation to breast cancer)
Physical activity

Marital status/support
Socio-economic status
Ethnicity
Gender
Co-morbidities
Other (e.g. trauma or injury to the treated side, flight travel, blood pressure monitoring on treated side, etc)

DISEASE- AND TREATMENT-RELATED RISK FACTORS

KEY POINTS

- Current evidence supports conservative surgical and radiation treatment to reduce risk of secondary lymphoedema.
- Current evidence suggests that stage of disease, nodal status and adjuvant treatments other than radiotherapy do not impact risk of secondary lymphoedema.
- One study, based on unadjusted analysis, suggests that hospital skin puncture may be associated with increased risk of secondary lymphoedema; however, further research is needed to confirm this finding.

SURGERY AND RADIATION

Development of secondary lymphoedema following treatment for cancer is caused by disruptions to lymphatic drainage patterns following surgery or radiation treatment. However, it is not possible to identify which individuals will develop lymphoedema following treatment.

It is generally accepted in the literature that more extensive treatment increases the risk of secondary lymphoedema, in particular surgery,[30,48–50] lymph node removal[14,48,50–52] and radiation treatment,[30,49,50,52–57] especially when combined with axillary node dissection.[30,56,58,59] Studies summarised in the DOHA and White reviews support the notion that surgical and radiotherapy protocols that are less harmful to lymphatic drainage pathways are associated with reduced risk of secondary lymphoedema. Although epidemiological studies and some randomised controlled trials contribute to this evidence base, findings have been derived commonly from studies of breast cancer patients from single medical facilities and lack adjustment for potential confounding factors. Added to these limitations is the issue of variations in the type and timing of secondary lymphoedema assessment utilised in the studies.

Findings from recent studies included in the current review involving patients treated for breast cancer,[28,34–36,38,40,60] gynaecological cancer[41] and melanoma[42,43] confuse rather than clarify these relationships.

- Three studies, two of which used adjusted results[28,41] and two of which were Level II studies,[28,35] found no association between more extensive breast surgery and risk of secondary lymphoedema. In contrast, another Level II study concluded that more extensive surgery did increase the risk of secondary lymphoedema.[34]
- Seven studies supported the notion that more extensive lymph node dissection increases risk of secondary lymphoedema,[35,36,40–43,60] while two other studies found no effect of more extensive lymph node dissection on secondary lymphoedema risk.[28,34]
- Radiation treatment (irradiated area not usually described) was found to have no effect on secondary lymphoedema risk in four studies,[28,34,35,38] but showed an adverse association with risk of secondary lymphoedema in two others.[41,61]

Despite improvements in study design compared with studies published prior to 2005, most of the results in the current review reflect unadjusted findings.[34,36,38,40,42,43,60] Therefore, the potential for results to be confounded by treatment or other related characteristics is unknown.

In summary, in studies conducted to date, more extensive surgery and radiation therapy either had no effect or increased secondary lymphoedema risk. Current evidence therefore supports conservative surgical and radiation treatment to reduce risk of secondary lymphoedema. Nonetheless, while conservative treatment may reduce risk, it does not guarantee protection from secondary lymphoedema. It is also important to note that the results of conservative procedures (e.g. sentinel node biopsy) may dictate progression to more extensive treatment (e.g. full axillary nodal clearance).

OTHER DISEASE- AND TREATMENT-RELATED RISK FACTORS

The White review presented unadjusted findings from four retrospective Level III or IV studies regarding the relationship between positive node status[62,63] or stage of disease[56,65] and risk of secondary lymphoedema. Two studies found that positive node status was associated with increased secondary lymphoedema risk following breast cancer treatment.[62,63] Recent studies included within the current review report no association between stage of cancer[35,41,61] or positive node status[34,61] and risk of secondary lymphoedema. These more recent findings take into account potential confounding factors[41,61] or are derived from Level II studies.[34,35]

The effect of other adjuvant therapies, such as hormonal therapy or chemotherapy, on risk of secondary lymphoedema has been considered only recently. After adjustment for other potential characteristics of interest, the inclusion of such adjuvant therapies was found to have no effect on secondary lymphoedema risk following treatment for breast cancer[28,61] or gynaecological cancer.[41]

Results from a Level II study of the effect of hospital skin puncture on risk of secondary lymphoedema in patients with breast cancer were published recently.[34] The study

concluded that hospital skin puncture was related to increased risk of secondary lymphoedema; however these are unadjusted findings.

In summary, although worthy of future investigation, evidence is emerging to suggest that stage of disease, node status and addition of adjuvant treatments other than radiotherapy does not impact secondary lymphoedema risk. Further research is required to identify the relationship between hospital skin puncture, and other treatment-related factors, and risk of secondary lymphoedema.

PHYSIOLOGICAL RISK FACTORS

KEY POINTS

- There is currently insufficient evidence to determine the physiological changes associated with increased risk of secondary lymphoedema.

Few studies have examined the relationship between physiological risk factors of secondary lymphoedema. Szuba and colleagues[11] investigated the presence of functional axillary lymph nodes and lymph drainage in women with and without breast cancer-related lymphoedema. Although all patients received axillary surgery, functional axillary lymph nodes were present in women with and without mild secondary lymphoedema. However, there was no evidence of functional axillary lymph nodes in those with severe secondary lymphoedema. All patients, irrespective of secondary lymphoedema status, had reduced lymphatic transport on the treated side compared with the untreated side. The authors concluded that the presence of functional axillary lymph nodes after surgery may protect against development of secondary lymphoedema. However, this study was limited by its design (Level III-3), and the approach to defining secondary lymphoedema and severity of the condition was questionable.

Pain and colleagues[39,66] attempted to describe the specific physiological abnormalities or changes that result from breast cancer treatment and may be associated with secondary lymphoedema risk. The authors concluded that:

- uptake of protein into local blood and/or proteolysis increased following surgery, which may serve to protect against secondary lymphoedema development
- alterations to venous flow patterns were associated with breast cancer-related lymphoedema
- vein wall movement was reduced following surgery for all breast cancer patients, and venous stenosis with impaired flow was observed in the absence of breast cancer-related lymphoedema.

Although derived from Level II studies, one study involved only 16 subjects[66] and the results should be considered preliminary at this stage with further research required to confirm findings and determine their clinical implications.

In summary, there is currently insufficient evidence to identify the physiological changes associated with risk of secondary lymphoedema following treatment for cancer.

PATIENT AND BEHAVIOURAL RISK FACTORS

KEY POINTS

- While a definitive relationship between higher body mass index (BMI) and increased risk of lymphoedema has not been demonstrated, maintenance of a healthy BMI in cancer survivors is supported due to other associated health benefits.
- Current evidence suggests that secondary lymphoedema risk may be associated with older age.
- There is insufficient evidence to determine whether there is a relationship between other patient and behavioural characteristics and risk of secondary lymphoedema.

BODY MASS INDEX

Higher BMI has long been considered a risk factor for secondary lymphoedema.[48,53,55] This was not considered in the DOHA review, but the White review provides details of five studies in patients with breast cancer[34,57,63,65,67] published between 2003 and June 2006 that support this relationship. Only one study published during this period[68] reported no association between elevated body mass index and secondary lymphoedema risk. However, this study was cross-sectional in nature, used self-report to determine secondary lymphoedema status and the generalisability of the findings were questionable given the low participation rate of 55%.

The relationship between BMI and secondary lymphoedema risk is less clear when findings from more recent studies are considered. Two Level II studies[35,36] and one Level IV study with adjusted findings[61] demonstrated no relationship. Three other studies,[34,37,41] including one Level II study with adjusted findings,[37] found that higher BMI increased secondary lymphoedema risk. The majority of these studies were conducted in women with breast cancer with only one study using a population-based gynaecological cohort.[41]

In summary, the relationship between BMI and risk of secondary lymphoedema risk has become less clear, with improvements in study design and data analysis. However, higher BMI has never been associated with reduced risk of secondary lymphoedema and maintenance of a healthy BMI brings with it other health-related benefits. Therefore, maintaining a healthy BMI is supported following treatment for cancer.

AGE

Two studies[57,68] investigating the relationship between age and secondary lymphoedema risk were included in the White review. Only one study[57] used an objective method to diagnose secondary lymphoedema and found no relationship between age and risk. Since 2005, age has been the most studied patient-related characteristic, with mixed results reported. One Level IV study with unadjusted findings found that older age was associated with a reduced risk.[32] Five studies reported no relationship,[28,34–36,41] while two others[37,61] presented positive associations between older age and secondary lymphoedema risk. The studies showing either no relationship or positive relationships with increasing age are stronger in design, with Level II studies included and results that have been clinically and statistically adjusted.

In summary, current evidence suggests that risk of secondary lymphoedema may be lower among younger cancer survivors.

TREATMENT OF THE DOMINANT LIMB (IN RELATION TO BREAST CANCER TREATMENT)

The relationship between treatment of limbs on the patient's dominant side and risk of secondary lymphoedema was not examined in the DOHA review. However, two studies published prior to 2003 reported no association between treatment on the dominant side and secondary lymphoedema risk.[30,48] One study used self-report and the other used self-report and circumferences to define secondary lymphoedema status.

Mixed findings were summarised in the White review, with results from three studies showing no risk,[69] low risk[63] or high risk[62] of secondary lymphoedema when treatment was on the patient's dominant side. Self-report or circumferences were used to define secondary lymphoedema status in these studies. It is noteworthy that the study that reported an association between treatment on the dominant side and increased secondary lymphoedema risk used circumferences as the diagnostic tool.

The current review identified two published studies that investigated this relationship, both using circumferences to diagnose lymphoedema. Both studies found no association between treatment on the dominant side and secondary lymphoedema risk.[34,61]

There is a natural tendency for the dominant limb to be larger than the non-dominant limb. Unless pre-treatment size differences are taken into account when using circumferences as a diagnostic measure, there is a likelihood that secondary lymphoedema will be over diagnosed. A recent population-based breast cancer study in which lymphoedema was diagnosed using circumferences demonstrated that the odds of a diagnosis of secondary lymphoedema was 1.9 times higher among those treated on the dominant side compared with those treated on the non-dominant side.[28] However, when bioimpedance spectroscopy was used as the diagnostic measure, the odds of a lymphoedema diagnosis for those treated on the dominant side was significantly reduced (odds ratio = 0.2).

In summary, more research utilising population-based cancer cohorts and objective diagnostic methods other than size-sensitive measures is required before the relationship between secondary lymphoedema risk and side of dominance in relation to the treated side can be determined.

OTHER PATIENT AND BEHAVIOURAL RISK FACTORS

The White review reported mixed findings for the presence of comorbidities, such as diabetes,[57] hypertension[57,68] and renal failure,[65] and risk of secondary lymphoedema, with reduced, no risk or increased risk being reported, dependent on the condition(s) being assessed. Recent novel findings relating to other personal characteristics identified that lower socio-economic status (as defined by education) was associated with a significantly increased risk of secondary lymphoedema,[28] while marital status[28] and gender[42,43] had no impact on risk of the condition. These represent findings from single studies addressing particular patient characteristics and, as such, replication of results is required to confirm findings. Other behavioural characteristics, such as participation in physical activity, flight travel and injury, will be dealt with in the 'Prevention' section of this review.

SUMMARY

A particularly problematic aspect of secondary lymphoedema is the difficulty in determining an individual's predisposition to heightened risk.[24] Current evidence demonstrates inconsistent relationships between many patient, treatment and behavioural characteristics and risk of secondary lymphoedema (BMI, age, treatment on the dominant side). The few characteristics that are consistently associated with increased risk, such as more extensive surgery or radiation treatment, cannot alone distinguish between those who will and will not develop the condition.[5]

The body of evidence surrounding secondary lymphoedema risk factors ranges from poor to good, depending on the specific risk factor being discussed. In general, current evidence provides some support for recommendations but care should be taken in its application (Grade C). Undoubtedly, research has improved in recent years, but more work utilising well-designed prospective cohorts, including cohorts other than breast cancer patients, is required to further our understanding.

PREVENTION STRATEGIES FOR SECONDARY LYMPHOEDEMA

The known physical and psychosocial consequences of secondary lymphoedema, and the resulting question of 'How can I reduce my personal risk?' has led to the development of a range of secondary lymphoedema prevention guidelines. These guidelines have been developed by various sources, including lymphoedema associations, cancer associations and treatment centres/hospitals. As outlined by Petrek *et al*.,[70] common risk-reduction guidelines include:

- avoid vaccinations, injections, blood drawing, blood pressure readings and intravenous treatment administration to the treated side
- avoid puncturing or injuring the skin
- use meticulous skin and nail/cuticle care
- pay immediate attention to and use standard first-aid care on all (minor-to-significant) injuries
- avoid constrictive clothing (e.g. socks, undergarments) or jewellery and wear a padded bra strap to avoid constriction and pressure
- avoid heat, including sunburns or tanning, hot baths and saunas
- avoid violent exercise and strenuous exertion; consider vigorous exercise only when the limb is supported by compression garments.

Other common recommendations include:

- avoid flight travel or long-distance car travel
- use compression garments during long-distance travel
- wear gloves/long pants/closed shoes while participating in activities that may cause skin injury (e.g. working with tools, gardening, using chemicals such as detergents)
- seek immediate medical advice if a rash, itching, increased pain, redness or increased temperature occurs
- use an electric rather than a manual razor when shaving
- take care when playing with pets
- moisturise skin daily with an unscented moisturiser or oil
- avoid overworking the limb and rest the limb
- avoid sitting in one position for more than 30 minutes
- for women following breast surgery, avoid carrying a handbag on the treated side.

These common risk-reducing behaviours are loosely based on two principles: minimising the production of lymph, which is directly proportional to blood flow, and minimising blockage to lymph transport.[70] For example, heat, infections and vigorous

arm exercise increase blood flow and thus lymph production in the arm, while tight clothing may result in obstruction to lymph flow.[70] However, evidence supporting or refuting these guidelines is scarce, and the evidence that does exist is derived solely from studies utilising breast cancer patients.

KEY POINTS

- Evidence supporting specific strategies to prevent secondary lymphoedema following treatment for cancer is scarce.
- Well-designed, population-based, prospective studies investigating the causal relationship between participating in 'risky' behaviours and secondary lymphoedema risk are required.
- In discussing prevention strategies with patients, health professionals should describe the lack of empirical evidence and should consider the potential impact of recommendations on the patient's health or quality of life.

BLOOD PRESSURE AND INJECTIONS

Two studies[47,49] published during the review period of the DOHA review, which demonstrated a similar incidence of secondary lymphoedema in patients receiving treatment for bilateral breast cancer compared with those treated for unilateral disease, raise questions about the impact of having blood tests, injections or blood pressure readings taken on the treated side.

The White review identified studies in which an association was reported between blood pressure measurement,[28] trauma[63] and hospital skin puncture[34] and increased risk of secondary lymphoedema. However, despite two of these studies being prospective in design,[28,34] the causal relationship could not be determined adequately.

USE OF COMPRESSION GARMENTS AND AVOIDANCE OF TIGHT CLOTHING

Evidence to support or refute other common guidelines, such as use of garments during flight travel, avoidance of tight clothing etc is lacking (i.e. studies addressing these issues could not be identified).

EXERCISE AND LYMPHOEDEMA RISK

There is no evidence to support avoidance of strenuous activity as a strategy to prevent secondary lymphoedema. A 'satisfactory' level of evidence presented in the White review demonstrates that secondary lymphoedema is neither initiated nor exacerbated as a consequence of exercise.[71–74] Results from more recent studies identified in the current review support these findings[75,76] and are presented in the 'Treatment' section of this report. These are particularly important findings given the association between regular activity following cancer treatment and improved quality of life,[77,78] and more recently reduced risk of cancer recurrence and improved survival.[79–81]

A question of clinical importance is whether use of compression garments should be encouraged during exercise. Only one study was found that investigated this issue.[76] Ten women with breast cancer-related lymphoedema participated in a specifically designed arm exercise program, with or without compression garments on different days and in a randomised order. Secondary lymphoedema status was assessed before, directly after and 24 hours after the exercise session using two objective measures (water displacement and bioimpedance spectroscopy). Irrespective of garment use, arm volume increased immediately after the session, but by the 24-hour follow-up period, volume had returned to baseline levels (with a tendency towards reduced levels compared to baseline). These are preliminary findings requiring replication. Therefore, given the lack of evidence surrounding the topic, other factors, such as impairment of heat transfer mechanisms, reduced range of motion and discomfort associated with wearing garments, need to be considered by health professionals advising garment use during exercise for patients.

PHYSIOTHERAPY

Of research interest is the potential role of standard physiotherapy treatment in preventing secondary lymphoedema. The DOHA review summarised results from a randomised controlled trial of 65 women following breast cancer treatment, in which the effect of a specific physiotherapy plan, including education, a graduated exercise program and early intervention with a self-management program, on secondary lymphoedema was investigated.[82] Referral for complex physical therapy treatment was made if the swelling did not respond to the self-management program. The incidence of secondary lymphoedema was lower in the treatment group compared with the control group at 24 months follow-up (11% vs 30%).[83]

In contrast, results from two recent prospectively designed studies[84,85] showed no difference in secondary lymphoedema incidence between the physiotherapy-based intervention and control groups (details presented in Appendix E). In one study, the intervention group received standard physiotherapy (not further defined)[85] and in the other, patients followed an exercise program from a pamphlet as well as a pectoral muscle stretching program.[84] Both studies included a pseudo-control group that received an exercise program from a pamphlet plus visits from a physiotherapist. Interpretation of the results from these studies is limited by the lack of a 'true' control group, small sample sizes (n=30[85]; n=64[84]) and questionable representativeness of the larger breast cancer cohort.

STANDARD LYMPHOEDEMA TREATMENT

The potential preventive role of standard secondary lymphoedema treatments, such as use of manual lymph drainage immediately after treatment, is of clinical interest. However, only one Level III-2 study (published within the period of the current review) has been identified examining this option. The study investigated the effect of manual lymph drainage, peristaltic lymph drainage and compression therapy over a 6-month period in reducing lymphoedema incidence following treatment for breast cancer.[86] This was a comparative study of 50 women in two groups matched for age, pathology and treatment and followed for 5 years. By 5 years of follow-up, nine women in the control group had developed secondary lymphoedema compared with two women in the treatment group. The two women who developed secondary lymphoedema in the treatment group subsequently underwent microsurgery, which resulted in complete long-term resolution of secondary lymphoedema. The authors concluded that the preventive regime reduced the incidence of secondary lymphoedema. However, this was a non-randomised comparative study and information about adherence with the preventive program by those in the treatment group is lacking. Furthermore, it is unknown whether the women in the control group who developed secondary lymphoedema received treatment and, if so, whether treatment led to secondary lymphoedema dissipation. Consequently, the clinical implications of these results, in particular the worth of partaking in 6 months of extensive treatment to prevent secondary lymphoedema, is questionable.

SUMMARY

Much remains to be learnt before evidence-based recommendations about how to reduce the risk of secondary lymphoedema are available to patients. There is a clear need for well-designed, population-based, prospective studies investigating the causal relationship between participating in 'risky' behaviours and secondary lymphoedema risk. In the meantime, it is reasonable for health professionals to discuss prevention strategies with patients, especially when encouraging healthy lifestyle behaviours such as participation in regular exercise.[6] In doing so, discussion of the physiological rationale behind prevention strategies and lack of empirical studies in the area is relevant. Importantly, in the absence of evidence, it is pertinent that adherence to currently available prevention recommendations does not lead to other adverse health consequences or reduced quality of life.

TREATMENT STRATEGIES FOR SECONDARY LYMPHOEDEMA

The goals of secondary lymphoedema management are prevention of progression, reduction and maintenance of swelling, alleviation of associated symptoms, prevention of infection, and improvement of function and quality of life.[87] However, choosing treatment is confusing for patients as there are a number of methods, some with questionable effectiveness, administered by a range of practitioners, including physiotherapists, occupational therapists, nurses and remedial massage therapists.[70]

CONSERVATIVE TREATMENT OPTIONS

KEY POINTS

- The body of evidence supporting conservative treatment options provides some support for recommendation(s), but care must be taken in its application.
- Volume reductions have been demonstrated following complex physical therapy, manual lymph drainage, compression and massage therapy in patients with breast cancer. However, the level of evidence is low and results are open to bias.
- Despite early results from two studies suggesting low-level laser therapy may be useful for treating secondary lymphoedema, further work is required to validate treatment doses and regimes that can then be tested in a randomised controlled trial.
- The role of exercise in secondary lymphoedema treatment remains uncertain, but to date there have been no reports of secondary lymphoedema being initiated or worsened as a consequence of exercise.
- Preliminary studies of the impact of diet in the treatment of secondary lymphoedema suggest that weight loss may be beneficial; however, these studies require replication before definitive conclusions can be drawn.

Conservative treatment options include complex physical therapy, manual lymphatic massage, pneumatic pumps, oral pharmaceuticals, low-level laser therapy, compression bandaging, compression garments, limb exercises and limb elevation.[88] Generic details regarding specific treatment options have been summarised in a recent review by Mosely *et al*:[88]

- **complex physical therapy**: involves 2–4 weeks of manual lymph drainage (described below), followed by compression bandaging, skin care and prescribed limb exercises undertaken by the patient
- **manual lymph drainage**: uses various light massage techniques that start at areas distant or adjacent to the affected limb before moving to the limb root, distal section of the limb and back to the limb root

- **massage**: involves a simplified version of manual lymph drainage using 'sweeping' strokes applied by the patient or another individual
- **pneumatic pumps**: uses single- or multiple-chambered pumps that engulf the limb, inflating and deflating at different cycles and pressures
- **low-level laser therapy**: uses low-intensity wavelengths of 650–1000 nm in a scanning or spot laser device
- **compression bandaging**: consists of a gauze sleeve, soft cotton wrap or high-density foam and two-to-three layers of short-stretch bandaging
- **compression garments**: provide greatest compression at the distal end of the limb and the least at the proximal end.

COMPLEX PHYSICAL THERAPY, MANUAL LYMPH DRAINAGE, COMPRESSION, MASSAGE AND PUMPS

Evidence presented in the DOHA review supported the following statements in relation to conservative treatment for secondary lymphoedema:

- long-term use of compression (low-stretch garments or compression bandaging) is effective in reducing and/or controlling limb swelling and may be an essential component of combination physical therapies
- favourable outcomes have been described following complex physical therapy; however, some of the evidence is inconsistent and further trial evidence is required to define an optimal strategy.

Results from six studies published during the period covered by the White review supported the notion that conservative treatment leads to significant reductions in limb volume.[89–94] One study investigated lower limb lymphoedema[94] with the remainder investigating breast cancer-related lymphoedema.

During the current review period, nine articles investigating the effect of conservative treatment options, excluding exercise, were published.[88,91,95–101] Of these, one was a systematic review conducted by Mosely *et al*.,[88] which included findings from studies published prior to 2005. While this review should, theoretically, have included the same investigations summarised in the DOHA and White reviews, it included different work, but of a similar quality. A summary of the results of the Mosely review follows.[88]

- Treatment effects (limb volume reductions) for **conservative treatment options** were in the range of 8–66%, with three studies reporting continued reductions over 6–12 months follow-up.
- Volume reductions of 104–156 ml were achieved by **manual lymph drainage** alone with larger reductions achieved when combined with compression therapy (47–260 ml).
- Similar findings were reported for studies of the effectiveness of **pneumatic pumps**. Volume reductions were achieved by pump therapy alone, but better volume reductions were observed when pump therapy was combined with other

therapies, including manual lymph drainage, compression garments and massage.

- Use of **compression garments** alone or in combination with other therapies also demonstrated volume reductions[88,102–107], with one out of six studies included in the systematic review involving patients with upper and lower limb lymphoedema.[102] Compression alone or in combination with other forms of treatment, including bandaging, limb exercises or self massage, exercise and skin care, led to volume reductions of 4–60% measured at 4 weeks to 6 months follow-up, with sample sizes of 22–38.
- Also summarised in the Mosely review was an investigation of **limb elevation** as a treatment for secondary lymphoedema.[108] Following arm elevation for a 5-hour period, a 'significant' 3% reduction in arm volume was observed in 33 women with breast cancer-related lymphoedema. However, this study lacked follow-up measurements and therefore the sustainability of these reductions could not be determined. Furthermore, the clinical significance of these findings (i.e. 3% reduction) in light of the effort to achieve these reductions is questionable.

The remaining eight studies investigating conservative treatment options published during the period of the current review, were categorised as Level III-1 or weaker. One study investigated manual lymph drainage alone[91] (also included in the White review), one investigated the effectiveness of a specific pneumatic pump[101] and the remainder investigated complex physical therapy. Patient numbers ranged from 4 to 357 and all patients had developed lymphoedema following breast cancer. Of the studies that presented sufficient data, response rates ranged from 28%[97] to 66%.[100] Characteristics of those lost to follow-up were not reported. Secondary lymphoedema status was assessed using various objective measures, most commonly circumferences, with perometry, tonometry and water displacement also used. Mean reductions of 10–404 ml were reported, representing reductions of 24–56%. Assessments were made at varying time points, including immediately following treatment (which included 2–4 weeks of 'intensive' complex physical therapy and/or manual lymph drainage) through to 12 months post-treatment. Volume increases were observed during the maintenance period for one study, although levels remained lower at 12 months follow-up compared with initial volumes.[100] All eight studies have limitations, including no reference to clinically meaningful changes, questionable representativeness of samples, potential bias caused by significant numbers lost to follow-up (possibly more so for those not experiencing treatment effects) and lack of documentation or measurement of changes in other personal, treatment or behavioural characteristics that may have influenced findings.

Only one of the eight studies attempted to assess the relevant contribution of particular components of the treatment to changes in limb swelling.[98] This study suggested the individual contribution to volume declines of complex physical therapy, manual lymph drainage and home programs was 56%, 41% and 24%, respectively, at 12 months

follow-up.[98] However, the participants were not randomised to treatment groups and there was no control group, making causal inferences from these findings difficult.

In summary, research on the effects of complex physical therapy, manual lymph drainage, compression and massage as options for the management of secondary lymphoedema has produced consistent results, with volume reductions demonstrated. However, the low level evidence (Level III-1 or lower studies) and the focus on only breast cancer patients, limits the generalisability of these findings. There is also the potential for over-reporting of positive treatment effects given that the characteristics of those lost to follow-up were not presented.

LOW-LEVEL LASER THERAPY

Use of low-level laser therapy is considered a form of conservative treatment. Research in this area is limited,[109–111] with results summarised in the DOHA and White reviews and in the systematic review by Moseley *et al*.[88] suggesting it may have benefits in volume reduction.

A randomised trial of low-level laser therapy in women with post-mastectomy lymphoedema reported clinically relevant reductions in arm volume at 3 months following two cycles of nine treatments (31% of treated women had volume reductions compared to 4% in the control group). However, mean arm volume in the treatment group was not significantly different to that measured at baseline.[109] In another study, volume reductions of 19.3% were observed after 10 weeks of a different laser and treatment regime, with further reductions observed at 6 months (40%) and 36 months (29%) of follow-up.[110,111] However, this study lacked a control group, making it impossible to distinguish treatment effects from regression to the mean. Both studies of low-level laser therapy were based on small sample sizes.

In summary, the results of studies investigating the use of low-level laser therapy as a treatment for secondary lymphoedema should be regarded as preliminary with further work required to validate treatment doses and treatment regimes that can then be tested in a randomised controlled trial.

EXERCISE

No studies were included in the DOHA review that examined the relationship between exercise and lymphoedema. The three studies[72–74] presented in the White review were dealt with in the context of prevention, rather than treatment, of lymphoedema, and only one had pre-existing lymphoedema defined as an eligibility criterion. Nonetheless, the evidence suggested that secondary lymphoedema is neither initiated nor exacerbated as a consequence of exercise.

Three studies published during the current review period examined the effect of various exercise programs on secondary lymphoedema status.[75,76,112]

- One study assessed the role of 'gentle' arm exercises combined with deep breathing, and observed an average reduction in arm volume of 100 ml (9%) at 1 month follow-up.[112] The authors concluded that participation in gentle arm exercises and deep breathing led to significant reductions in arm volume. However, the study lacked a control group and the clinical significance of the observed change was neither predefined nor discussed.
- A Level III-3 study involving 18 women with breast cancer-related lymphoedema reported no short-term change in arm volume 24 hours after a session of weight-bearing exercise.[76] While pre- and immediately post-exercise changes are of interest, the clinical implications of these findings are limited.
- A randomised controlled trial investigating the effect of participation by women with breast cancer-related lymphoedema of varying duration in a 3 month, supervised weight-training program reported no changes in secondary lymphoedema status among those in the intervention group, following completion of the program or at 6 months follow-up.[75]

In summary, these results support the notion that, at worst, exercise (in this case resistance exercise) neither initiates nor exacerbates secondary lymphoedema. The evidence levels of these studies, including those in the current review and other earlier studies[71,72] (one of which was described in the White review),[72] are variable and those rated as Level II involved relatively small samples. Further studies of exercise interventions using larger sample sizes are warranted to further our understanding of the potential role exercise may play in secondary lymphoedema management.

DIET

Weight-reducing strategies have recently been tested for their potential in the management of secondary lymphoedema. This is in part due to the perceived association between higher body weight and increased risk of secondary lymphoedema (see 'Risk factor' section). A randomised controlled trial involving 64 women with breast cancer-related lymphoedema compared the effect of participation in a reduced energy intake diet or low-fat diet with a control diet of habitual intake.[113] Body weight was reduced significantly in the dietary intervention groups (3–4 kg by 24 weeks follow-up). Arm volumes were also reduced, but the reductions were not statistically significant (14–15% excess arm volume change in the intervention groups compared with a 12% excess volume change in the control group). The authors concluded that weight loss through reduced energy intake or low-fat diet appears to be helpful in the treatment of breast cancer-related lymphoedema. However, study limitations, including use of a secondary lymphoedema status assessment method that is sensitive to weight changes and lack of data demonstrating the potential to sustain these benefits following return to 'habitual' eating patterns, make it difficult to justify these claims.

In summary, while results suggest that weight-reducing strategies may be useful in the management of secondary lymphoedema, further studies using lymphoedema assessment methods that are not sensitive to weight changes are warranted before definitive conclusions can be drawn.

SURGERY

KEY POINTS

- No surgical method for secondary lymphoedema treatment has received universal acceptance and surgical techniques are considered useful for only a small subset of secondary lymphoedema sufferers who have failed to obtain relief from less invasive measures.

Surgery is generally only recommended as a treatment for secondary lymphoedema when conservative treatment options have not been effective.[87] The two main surgical approaches for secondary lymphoedema treatment are:[114]

- debulking procedures to remove excess skin and subcutaneous tissue (e.g. liposuction)
- surgery to create new pathways for draining lymph (e.g. microsurgery, lymphatic-venous anastomosis).

The DOHA review concluded that surgery for secondary lymphoedema had not yet been evaluated in large, well-designed, clinical trials and was regarded cautiously by many clinicians.

A series of four studies published prior to 2005 reported findings related to liposuction for treating breast cancer-related lymphoedema followed by continued use of compression garments.[115–118] Results from all studies showed mean volume reductions at 12 months follow-up of 66–179%. However, at 12 months, within 1 week of removal of compression garments in a small cohort of patients (n=6), arm volume had increased by an average of 370 ml (reversed by reinstating garments). The authors concluded that, despite significant reductions in arm volume, surgery should only be used as a last resort, especially since ongoing compression was needed to sustain improvements.

Two other small studies reported the effect of anastomosis on secondary lymphoedema in patients treated for breast cancer (n=7[119] and n=18[120]). Although positive changes were reported using subjective measures[119] and circumference,[120] compression garments were needed to sustain benefits.

Excellent results have been reported from recent studies (predominantly Level III or IV) using liposuction[121–123] and microscopic lymphatic vessel-isolated vein anastomosis[124] to treat secondary lymphoedema. The three studies investigating the effect of liposuction on breast cancer-related lymphoedema reported complete resolution of excess limb volume.[121–123] One of these studies[122] compared the effect of controlled compression treatment with liposuction and concluded that, while compression reduced arm volume by half, liposuction had a significant impact on secondary lymphoedema status, completely removing swelling. These studies included women with an average duration of secondary lymphoedema of 8 years.

The small study of microscopic lymphatic vessel-isolated vein anastomosis reported beneficial results in the treatment of unilateral and bilateral lower limb secondary lymphoedema,[124] with eight limbs (72%) having 'good' to 'excellent' results following the procedure.

In summary, the body of evidence supporting surgery as a treatment option is limited (Grade C–D). While positive results have been obtained by some studies, no surgical method for secondary lymphoedema treatment has received universal acceptance. Furthermore, the potential for scarring and other complications, as well as the need for continued use of compression garments, means that surgery is considered useful for only a small subset of people with secondary lymphoedema.

PHARMACOLOGICAL INTERVENTIONS

KEY POINTS

- Available evidence does not support the use of pharmacological interventions, such as benzopyrones and selenium compounds, in the management of secondary lymphoedema.

The use of medications to manage secondary lymphoedema is under constant investigation, with particular emphasis placed on benzopyrones.[87] These medications increase proteolysis, resulting in the removal of protein and reductions in oedema. However, according to results from a systematic review by Badger *et al*.[125] (presented in the White review), there is no conclusive evidence that benzopyrones are effective in secondary lymphoedema treatment. Fifteen trials were included in the Badger review, six of which included only patients with secondary lymphoedema following breast cancer treatment; the remaining studies included patients with cancer- and non-cancer-related lymphoedema. The authors of the review commented that in many cases, insufficient data were provided in the trials to calculate per cent reduction, or increase, in baseline excess limb volume. Furthermore, important statistical information, such as standard deviations or confidence intervals and the number in the groups at various stages of the trial, was also missing. Thus, while patients may report improvements in symptoms on an individual basis, the routine use of benzopyrones in the management of secondary lymphoedema is not supported by current evidence.

Biological response modifiers, such as selenium compounds, have also received attention, as they act as toxicity antagonists for prevention of chemotherapy- and radiotherapy-associated side effects. A systematic review of the literature by Dennert *et al*.[126] identified only one randomised controlled trial that investigated the effects of supplementary selenium on secondary lymphoedema.[127] The authors concluded that, at present, there is insufficient evidence to suggest a treatment effect and that potential hazards of supplementing a trace mineral should be kept in mind when considering their use.

OTHER POTENTIAL TREATMENT APPROACHES INCLUDING COMPLEMENTARY AND ALTERNATIVE THERAPIES

KEY POINTS

- There is a paucity of evidence regarding the use of treatments such as ultrasound, hyperbaric oxygen, vitamin E supplementation, microwave therapy, acupuncture and other complementary therapies in the treatment of secondary lymphoedema.

Other potential treatment options proposed and investigated include the use of ultrasound therapy,[128] hyperbaric oxygen therapy,[129] vitamin E supplementation,[130] microwave therapy,[131] acupuncture and moxibustion (a heating therapy that uses specific Chinese herb sticks to heat acupoints),[132] mulberry leaf,[133] aromatherapy oils,[134] and magnetic fields, vibration and hyperthermia.[135] These findings were published prior to 2005, and only some have been summarised in previous reviews.[128,131,132] A paucity of data exists relating to these treatment options, and for some even the physiological mechanisms behind their potential for treatment is unclear.[135] Moreover, some have not been tested on patients with secondary lymphoedema[133] and most are of Level IV design.

FACTORS INFLUENCING SEVERITY OF LYMPHOEDEMA AND TREATMENT SUCCESS

KEY POINTS

- Patient factors, such as BMI, history of cellulitis, time between treatment for cancer and onset of secondary lymphoedema, extent of surgery and duration of secondary lymphoedema, can lead to higher lymphoedema volumes and reduce the potential for effective treatment.
- Early diagnosis and treatment of lymphoedema may be an important factor in the success of treatment.
- Patient compliance may affect the success of treatment for lymphoedema.

PATIENT FACTORS

A number of patient factors have been associated with higher secondary lymphoedema volumes, including higher BMI,[99,136] past history of cellulitis,[136] longer period between cancer to secondary lymphoedema onset,[136] more extensive chest surgery (mastectomy)[136] and longer duration of secondary lymphoedema.[99,136] Higher secondary lymphoedema volumes adversely influence the potential treatment effect.[137] These are important findings, indicating that such characteristics should be measured and considered when designing and interpreting findings of secondary lymphoedema treatment studies.

The findings also highlight the importance of early diagnosis and treatment for secondary lymphoedema.[137] Early diagnosis is dependent on awareness of the condition by patients treated for cancer and health professionals, as well as access to health professionals experienced in secondary lymphoedema diagnosis and management. Educating patients and health professionals about signs of pre-secondary lymphoedema would make early diagnosis easier. However, while associations exist between symptoms such as heaviness, pain, tingling, weakness, poor range of motion and stiffness and secondary lymphoedema, it is currently not possible to use these as indicators of secondary lymphoedema because they are frequently reported by patients who do not develop the condition.[24]

Compliance issues may also influence treatment success. Compliance may be affected by ease of access to treatment (due to geography or lack of knowledge), cost of treatment (and lack of cover by private health insurance in Australia) and the time involved in undergoing treatment.[1] Emotional reasons, such as dislike of treatment, tolerance of the condition or the necessity for ongoing treatment, have been reported as reasons for non-compliance to treatment.[139] Consideration of the acceptability of treatment strategies to patients may be as important as monitoring of compliance, particularly when treatment success depends on compliance. These are important treatment considerations and may be used to guide the development of less onerous treatment. For multimodal interventions, such as complex physical therapy, research into the relative effects of components on symptoms and psychosocial factors will help guide the development of interventions that are effective as well as acceptable to patients.

CLINICIAN FACTORS

Of clinical interest is the potential impact of therapist experience in the management of secondary lymphoedema treatment. While attempts have been made to establish minimum criteria to certify therapists as having adequate competency in the treatment of secondary lymphoedema, standardised training methods do not currently exist.[138] However, given the current lack of evidence confirming the efficacy of some treatment options, it is perhaps too early to examine the potential role that therapist experience may play in secondary lymphoedema management.

CAN TREATMENT CAUSE HARM?

An important clinical question is whether treatment of secondary lymphoedema can cause harm. As reported in the DOHA review, clinical practice guidelines from Canada state that ultrasound is contraindicated over areas of active or potential cancer metastases. This recommendation was based on trial evidence derived from a study in mice in which high-intensity, and to a lesser extent low-intensity, ultrasound was associated with increased tumour growth.[29] Anecdotal reports that manual lymph drainage has the potential to exacerbate or contribute to disease progression have also emerged,[140] leading to widespread prohibition of manual lymph drainage in patients with recurrent or metastatic disease.

Metastasis, for the most part, implies an inability to effectively treat the disease, but does not imply an inability to treat symptoms such as secondary lymphoedema. Godette states "*Research confirms that an 'optimal microenvironment' is necessary for metastasis"* and that *"it was recognised 110 years ago that metastasis is not simply a function of cancer cells' ability to get to various parts of the body but also to grow when they get there. This fact, once recognised by us and taught to our patients, will facilitate the appropriate treatment, even in the presence of incurable disease*".[140] In addition to the lack of evidence to describe how secondary lymphoedema treatment could cause metastasis, there is also no known documentation of this event occurring.

Harm caused by treatment might also refer to initiation or progression of secondary lymphoedema, or to other adverse changes to quality of life. Using the broad search terms of the current review, no publication was found that reported worsening of secondary lymphoedema as a consequence of treatment. However, literature does exist highlighting the financial, time and lifestyle burden caused by treatment for secondary lymphoedema[141] and the consequent adverse effect on quality of life.[91] Integration of a quality of life measure into treatment investigations will assist in understanding the psychosocial as well as physical ramifications of such treatments.

SUMMARY

The DOHA and White reviews concluded that there is a lack of high-quality evidence available to guide clinical practice in the management of secondary lymphoedema. Only studies of pharmacological interventions utilised double-blinded, randomised, controlled designs. Conservative and surgical interventions were investigated predominantly in retrospectively designed or pre–post intervention studies and used breast cancer cohorts exclusively.

Results published between 2005 and 2007 demonstrate some consistency in outcomes, with the bulk of evidence demonstrating volume reductions following secondary lymphoedema treatment, particularly when conservative treatment options are used. Research suggests that lack of treatment is related to secondary lymphoedema progression, although this requires further confirmation. Again, all

studies were conducted in breast cancer patients and therefore the generalisability of outcomes to patients with other cancers is unknown.

The vast majority of evidence relating to treatment options for secondary lymphoedema is derived from Level III-1 or lower studies. Only two out of 17 treatment-related publications included in the current review were of Level II design and neither assessed the more common physiotherapy-based forms of secondary lymphoedema treatment (one assessed exercise,[75] the other diet[113]).

The potential for over-reporting of treatment effects also exists. It is possible that patients who experience negative results or no change in status following treatment for secondary lymphoedema are more likely to be lost to follow-up and therefore positive results may be overstated. There is also a tendency for positive findings to be published more readily than studies showing no effect. As part of this review, key national and international researchers were contacted to ascertain the extent to which publication bias has influenced the evidence base. No additional investigations were identified by this method, suggesting that an inability to publish is unlikely to be an important factor.

The bulk of evidence pertaining to secondary lymphoedema treatment is graded as poor to satisfactory, and recommendations based on the evidence must be applied with caution. Nonetheless, treatment guidelines do exist. In 1998, Rockson proposed that treatment is largely influenced by clinical experience rather than a conclusive body of evidence.[5] Nearly 10 years on, the results of this review support this view. Clinical experience should not be underestimated, and without treatment secondary lymphoedema may worsen. However, the results of this review demonstrate the importance of continued, but improved, investigations on the treatment of secondary lymphoedema, taking into account the effect of treatment on quality of life as well as symptom management.

LIMITATIONS

A number of limitations should be taken into account when considering the results of this and previous reviews. Differences in secondary lymphoedema measurement techniques and definitions contribute to inconsistencies in the scientific literature and consequently to confusion surrounding clinical practice in the prevention and management of this condition. The vast majority of secondary lymphoedema research uses indirect objective or self-report methods to assess secondary lymphoedema status, despite the availability of more direct measures of extracellular fluid.[142] The timing of secondary lymphoedema assessment also has implications for research findings. If assessed too early, for example, within 3 months of surgery, 'normal' and temporary post-operative swelling could be misclassified as evidence of secondary lymphoedema.[143] Moreover, secondary lymphoedema may develop at any stage post-treatment, and therefore only studies with long-term follow-up or retrospective designs will identify late-onset of the condition.[143]

The majority of findings presented in this and previous reviews are derived from research investigating secondary lymphoedema among women following treatment for breast cancer. While more research involving breast cancer patients is needed, significantly more work is required involving other cancer populations at risk of secondary lymphoedema, in particular, patients treated for genitourinary cancer, head and neck cancer, gynaecological cancer or melanoma. Until such time as results from such studies become available, the generalisability of available evidence to populations other than breast cancer patients is unknown.

Researchers must pay particular attention to the design quality of future studies. This includes recruitment of population-based cohorts rather than patients from single institutions, and studying cohorts prospectively with longer term follow-up. The quality of study design in studies investigating incidence and risk factors of secondary lymphoedema has improved markedly over the years, but further research is needed in order to confirm more recent findings. The design quality of studies conducted to date to investigate the effect of secondary lymphoedema treatment options has been poor. In order to advance our knowledge, treatment research must use experimental, in particular randomised controlled trials, rather than observational study designs. Furthermore, adequate description of the characteristics of the group/s studied, including those lost to follow-up, is required in order to determine the generalisability of findings.

Finally, the manner by which data are presented is often inadequate and/or inappropriate, further limiting interpretation of findings. Many studies report 'mean' results, when the 'median' would be a more accurate representation of the group average. Significant knowledge would be gained by presentation of the proportion of participants experiencing improved, worsening or no change in secondary lymphoedema status throughout the study period. In addition, the majority of studies

have published ‘unadjusted’ relationships between secondary lymphoedema and other characteristics. Consequently, any associations presented may in fact be flawed by the presence of ‘potential confounders’. The importance of defining predetermined statistical as well as clinical significance must be given greater attention in the future to ensure that the clinical impact of ‘significant’ findings is understood.

SECONDARY LYMPHOEDEMA: IMPLICATIONS AND PRIORITIES FOR FUTURE RESEARCH

As cancer incidence, as well as survival rates following cancer treatment, continue to rise, so too does the public health burden and awareness of treatment-related side effects. Consequently, there is a need not only to produce evidence-based guidelines for patients and health professionals, but to understand when best to integrate this advice into the care plan of cancer patients. In a recent study, breast cancer survivors reported inadequate information about secondary lymphoedema, maintaining that they were not told about their risk before cancer treatment.[144] However, people with secondary lymphoedema were less likely to recall pre-treatment education than those without the condition, suggesting either that education reduces risk or that development of secondary lymphoedema diminishes information recall.[144] If the latter is true, information dissemination should utilise a variety of approaches to education. Timing of dissemination of information is another consideration given that concerns about distant, potential side effects such as secondary lymphoedema may not be heard while making treatment-related decisions that are focused on preserving life.

The paucity of methodologically sound research on secondary lymphoedema makes it difficult to develop evidence-based recommendations regarding prevention, management or reduction. However, the research field in this area is evolving. There is global recognition of the need for an agreed 'gold standard' in secondary lymphoedema measurement, although it is unlikely that one measure of choice will be agreed by all researchers in the field. There is also widespread recognition of the need for better designed, larger cohort investigations utilising multicentre or population-based recruitment approaches. It is prudent to present what is currently known in light of limitations, while results from more rigorous studies are awaited. This review provides a summary of current knowledge together with the level of evidence upon which this knowledge is based. Clearly, there is still much to be learned. However, we know enough to raise awareness of a condition whose prevalence is likely to be underestimated; to educate patients on potential risk factors and prevention strategies, allowing for informed decisions regarding treatments and behaviours; and to appreciate that treatment for secondary lymphoedema is likely to lead to volume reductions and that lack of treatment may lead to progression of the condition.

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APPENDIX A

MEMBERSHIP OF THE NBOCC SECONDARY LYMPHOEDEMA EVIDENCE REVIEW WORKING GROUP

Chair	
Dr Julie Thompson	General Practitioner, Division of General Practice Victoria and Primary Care Manager, NBOCC
Members	
Dr Sandi Hayes	National Breast Cancer Foundation Research Fellow, School of Public Health, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD
Ms Emma Tavender	Coordinator, Cochrane EPOC Satellite, National Institute of Clinical Studies, Melbourne, VIC
Professor Kate White	Director (Research), Faculty of Nursing and Midwifery, College of Health Sciences, University of Sydney, NSW
Ms Louise Koelmeyer	Occupational Therapist, NSW Breast Cancer Institute, Sydney, NSW
Secretariat	
Ms Elizabeth Metelovski	Program Manager, NBOCC
Ms Janice Peterson	Project Officer, NBOCC

APPENDIX B

TESTS FOR THE DIAGNOSIS AND QUANTIFICATION OF LYMPHOEDEMA

Parameter	Test
Limb circumference	Tape measure (circumference) Perometry
Limb volume	Tape measure with truncated cone volumes Perometer Plethysmography (water displacement)
Imaging lymphatic circumlation	Lymphoscintigraphy Fluorescence microlymphangiography Indirect lymphography
Assessment of soft tissues	Tonometry Ultrasound Computed tomography Magnetic resonance imaging Positron emission tomography
Intra- and extracellular fluid	Bioimpedance spectroscopy

APPENDIX C

SUMMARY OF EXCLUDED PAPERS RELATING TO INCIDENCE, RISK FACTORS AND PREVENTION OF SECONDARY LYMPHOEDEMA AND REASONS FOR EXCLUSION

Reference	Reasons for exclusion
Abu-Rustum *et al*. (2006)[145]	LE defined by patient or health professional, documented at least 6-weeks PS following R_x for uterine corpus cancer. Inc=1.2% at median FU=3 years, risk factor = 10 or more lymph nodes removed during surgery (Inc=3.4%). Age, weight, type of hysterectomy and type of adjuvant therapy not associated with LE. Level IV
Arrault *et al.* (2006)[146]	Non-English. Results presented in abstract state that type of surgery, axillary LND, radiation, overweight at time of cancer, weight gain after surgery, skin puncture and reduction in physical activity increase LE risk.
Ballo *et al.* (2006)[147]	Retrospective cohort study with patients with nodal metastases from melanoma, n=466. LE measure not specifically stated. Inc=9%, 9% and 11% at 3-, 5- and 10-year PS. 5-year LE rates based on site of LND disease were 0%, 1%, 20% and 27% for epitrochlear, cervical, axillary or groin LN disease. Level IV.
Bani *et al.* (2007)[148]	LE defined by self-report. Retrospective BC cohort study involving 742/1123 women. Inc=31.7% at 4.3 year FU. Unadjusted analysis showed no association with tumour size, nodal status, chemotherapy, antihormonal therapy, type of surgery and menopausal status. Radiotherapy was associated with increased LE risk. Uptake of LE R_x based on PS provision of information is assessed, but causal relationship is questioned. Level IV.
Bellati *et al.* (2005)[149]	Prospective vulvar cancer cohort study (n=14). LE outcome not defined. Inc=21% at median FU of 57.5 months. Level II.
Bergmark *et al.* (2006)[150]	Case (cervical cancer, n=332)-control cross-sectional study. 77% response rate, 25% of cases reported (self) LE. Level III-3.
Campisi *et al*. (2006)[86]	Prospective BC cohort study (n=50), allocated to either control or prevention of LE R_x (6 months of MLD and compression) group; FU=1-, 3-, 6-months, and 1-, 3- and 5- years using lymphoscintigraphy and water displacement. LE defined as volume difference between sides of 150 ml, unknown how lymphoscintigraphy was used to diagnose cases. Inc=22% (water displacement method) but this figure likely included PS swelling (within the first 3 month) and nor was information provided regarding nature (i.e. did those with swelling in first 3 months continue to have swelling at later FU). Prevention R_x group showed lymphatic alterations in 22/25 patients (4 had alterations pre-surgery). Level II.
Ceballos *et al.* (2006)[45]	A retrospective evaluation of lymph node metastases and outcome, including complications (such as LE, but not defined) in patients with FIGO 1A1 and 1A2 adenocarcinomas of the cervix. Inc=7% at mean FU=54 months. Level III-3.

Dardarian *et al.* (2006)[44]	Retrospective evaluation of patients with carcinoma of the vulva undertaking inguinal lymphadenectromy. LE measures not defined. Short-term LE (<6 months) was 67% and 72% in the vein-ligated and vein-spared groups, respectively, while long term LE persisted in 38% of the vein ligated group compared to 11% in the vein-spared group. Level III-3.
Eversley *et al.* (2005)[151]	Retrospective study using self-report of LE symptoms. African Americans, Latinos and other women were more likely to report swelling than Caucasians ($p < 0.05$). Level IV.
Grabsch *et al*. (2006)[152]	RCT of supportive-expressive group therapy in women with BC. LE was a secondary outcome and method of assessment not adequately defined. Inc=11.5%. Level II.
Haines *et al.* (2007)[153]	Retrospective audit of swelling at 6-weeks post-surgery. Level III-3
Hershko *et al*. (2007)[154]	Retrospective study of 25/27 women undergoing hand surgery following ALND for BC. Median FU not specified, nor was the measure to assess LE. Four patients had pre-existing LE, two had temporary worsening of the condition following hand surgery, no new LE cases. Level III-3.
Hidaka *et al*. (2006)[155]	Retrospective study of 128 patients who had total abdominal hysterectomy and bilateral salpingo-oopherectomy with (n=68) or without (n=60) lymphadenectomy. LE measure not adequately defined (defined as >2 NCI-CTC version 2 – which is moderate LE requiring compression). Incidence in the lymphadenectomy group was significantly (no effect size given) higher than those without lymphadenectomy. Level III-3.
Indelicato *et al.* (2006)[156]	Retrospective investigation assessing Inc of delayed breast cellulitis. Median FU was 6.4 years. LE measure not defined. Level III-2.
Karki *et al.* (2005)[157]	Prospective survey assessing arm morbidity (including self-report LE) at 6- and 12 months PS. Inc of axilla oedema and upper limb oedema at 6 months was 38% and 23% respectively, and was 27% and 26% at 12 months PS. Rates were higher in the modified radical mastectomy group versus breast conserving surgery for axilla oedema at 6 months and for axilla and upper limb at 12 months. Level II.
Lane *et al*. (2007)[158]	Comparison of lymphatic function in BC patients with (n=10) and without (n=10) and controls at rest and during exercise. Lymphatic function did not differ between groups at rest. Lymphatic function in the affected arm was similar between controls and BC subjects, while BCLE subjects had a significantly lower axillary uptake and significantly greater forearm activity. Level IV.
Langer *et al*. (2005)[159]	Prospective study on 55 women undergoing endoscopic ALND. LE diagnosis included arm morbidity symptoms. Inc=6% at median FU of 72 months. Level II.
Lock-Anderson *et al*. (2006)[160]	Prospective study of patients undergoing SNB for primary cutaneous malignant melanoma. LE measure not defined. 1/198 patients had developed LE by median FU of 24 months PS. Level II.
Mansel *et al*. (2006)[161]	RCT of BC patients (ALMANAC trial); 954/991 patients investigated. LE defined by self assessment and measured using volume via circumferences. While volume of treated arm was compared with pre-treatment volumes and the change was expressed as a ratio, LE was not defined in this manner (therefore excluded from inclusion within the review). Based on self assessment, Inc=5% for SNB, 13% for ALND, at 1

	year FU. Authors stated that analyses of circumferential measurements indicated that patients in the ALND group had more arm swelling than SNB group (backed by statistical significance at 1, 3, and 6 months PS but not 12 months PS). More extensive axillary clearance considered a risk factor. Level II.
Milathianakis *et al.* (2005)[162]	Retrospective analysis of morbidity following prophylactic inguinal lymphadenectomy with saphenous vein preservation for squamous cell penile cancer (n=7). LE measure not defined. Temporary LE (resolved within 3–6 months) developed in three patients. Level III-3.
Purushotham *et al*. (2005)[163] and (2007)[164]	Prospective BC cohort study investigating morbidity after SNB. LE objectively measured but specific diagnosis criteria not defined and subjective diagnosis was used in the analysis involving odds of LE. Level II.
Ridner (2006)[6]	Commentary.
Roaten *et al*. (2005)[165]	Retrospective study of 339 patients treated with SNB or regional LND for melamona. LE measure not defined. Inc=1% in SNB at median 9 month FU, 8% in regional LND at 16-month FU. Level III-2.
Rockson (2006)[24]	Unsystematic review/overview of LE.
Sabel *et al*. (2007)[166]	Retrospective review on patients who underwent an inguinal LND for melanoma. LE defined by self report. Inc=30% at median FU of 2 years. Level III-3.
Senkus-Konefka *et al*. (2006)[167]	Non-systematic review.
Sultana *et al*. (2007)[168]	Prospective cohort study comparing outcomes of two surgical incisions for radical vulvectomry. LE measure not defined. Inc=9% in butterfly incision group, no cases with triple incision, difference between groups not statistically significant, FU at 5-year PS. Level II.
Tanaka *et al*. (2007)[169]	Retrospective cohort study investigating the effect of leaving the peritoneum open on the incidence of LE of the legs following pelvic lymphadenectomy for gynaecological malignancies. Inc=25.3% versus 50.5% for the non-closure group compared with the closure group at 3-year PS. Having radiation significantly increased incidence especially in the non-closure group (without radiation, Inc=15.8%, with radiation, Inc=44.4%). Level III-2.
Van Doorn *et al*. (2007)[170]	Systematic review to determine whether the combined R_x strategy using chemoradation therapy followed by surgery is effective and safe in vulvar cancer patients. LE was an outcome of interest but manner by which studies included in the review defined LE, not clarified. Complicated wound healing, lymphoedema, lymphorrhea and lymphoceles reported in 18–71%. Level I.
Williams (2005)[143]	Non-systematic review.

Zhang *et al*. (2007)[171]	Prospective cohort study investigating comparing sparing of saphenous vein to saphenous vein ligated surgery while treated with inguinal lymphadectomy for vulval malignancies. LE measure not defined, but those in the sparing group experienced less LE. Inc=25% for sparing group and 49% for excision group; FU point unclear (likely 5 years). Level II.

LE: lymphoedema; R_x: treatment; Inc: incidence; FU: follow-up; LND: lymph node dissection; LN: lymph node; BC: breast cancer; PS: post-surgery; FIGO: International Federation of Gynecology and Obstetrics; ALND: axillary lymph node dissection; NCI-CTC: National Cancer Institute – Common Toxicity Criteria; SNB: sentinel node biopsy; RCT: randomised controlled trial; BCLE: lymphoedema following breast cancer

APPENDIX D

SUMMARY OF EXCLUDED PAPERS RELATING TO TREATMENT OF SECONDARY LYMPHOEDEMA AND REASONS FOR EXCLUSION

Reference	Reasons for exclusion
Becker *et al*. (2006)[172]	Level III-3 intervention study on microsurgical lymph node transplantation, 24 women with BCLE, mean age=58 years. LE assessed by 'measurements' but not defined any further. Arm volume returned to normal in 10 cases, decreased in 12 cases and remained unchanged in two.
Dennert *et al*. (2006)[126]	Level I systematic review of studies assessing the effect of selenium supplementation on adverse effects (including LE) following cancer treatment. Only one study had LE as an outcome and the manner by which they assessed LE not reported. This study was an RCT using selenium supplementation in treatment group, placebo in control, but both groups had physical therapy. Episodes of erysipelas was primary outcome and while authors of paper concluded episodes decreased in treatment group, review author stated study quality and reporting made conclusions questionable.
Loprinzi *et al*. (2007)[173]	Non-systematic review. The paper provides an update of clinical trial outcomes related to cancer treatment (including LE), and emphasises the importance of publishing positive and negative study results to separate what works and what does not. Reported only one trial regarding LE: trial evaluated the use of coumarin to alleviate LE and did not show any benefit.
Mayrovitz *et al*. (2005)[93]	Level IV study investigating transcutaneous oxygen tension (TcPO2) before and after LE treatment. Despite significant amounts of LE (n=15), TcPO2 was not initially less in affected arms nor was it changed by therapy that improved both LE and fibrosis.
Modolin *et al*. (2006)[174]	Level IV study investigating surgical effect (modified Charles procedure, consisting of excision of the affected skin followed by scrotoplasty and midline suture simulating the scrotal raphe) on LE (included secondary LE from various causes). Subjective evaluation of LE. Outcome: clear improvement of the aspect of the genitalia and subsequent improvement of ambulation, hygiene and ability to void in the standing position.
Salgado *et al*. (2007)[175]	Level IV study investigating the surgical effect (perforator flap surgery) on lower limb LE. Cases included secondary LE following cervical cancer for 10, following ovarian for one and unknown cause for four. Lymphoscintigraphy used to measure LE status. Conclusions: surgery led to effective, long-lasting and cosmetically appealing results.

Strauss-Blasche *et al*. (2005)[176]	Level IV study investigating the changes of QoL, mood, and the tumour marker CA 15-3 associated with a 3-week in-patient breast cancer rehabilitation program incorporating spa therapy (n=149), participating in the study 3–72 months PS. 71% of sample defined as having 'small, medium or large' severity of LE but specifics for classifying LE were not stated. Conclusions: patients with a greater LE showed slightly greater improvements but results presented do not allow assessment of this conclusion.
Thomas *et al*. (2007)[177]	Level IV study investigating whether having radiation and more extensive lymph node removal influenced success of complex decongestive therapy in a BCLE [b] cohort (n=53). No statistically significant difference in treatment results between those who had and had not had radiation and no correlation was observed between number of nodes sampled and number of sessions to plateau.

LE: lymphoedema; BCLE: lymphoedema following breast cancer; RCT: randomised controlled trial; QoL: quality of life; PS: post surgery

APPENDIX E

SUMMARY OF PAPERS REPORTING LYMPHOEDEMA INCIDENCE FOLLOWING CANCER TREATMENT AND ASSOCIATED RISK FACTORS

Author/s and dates	Details	Sample size	Incidence	Measurement method	LE definition	Risk factors	Level of evidence and comments*
Breast cancer-related studies							
Armer *et a*l. (2005)[32]	Retrospective BC cohort study	100	30.6–41.2% at 28 months PS	Circumferences	>2 cm difference between sides at any site	Age	Level IV, unadjusted results
Armer *et al*. (2005)[33]	Prospective BC cohort study including pre- to 12 month PS measures	118	8–46% at 6 months PS 42–70% at 12 months PS	Circumferences and perometry	4 methods (2 involving between limb comparisons, 2 involving change from baseline)	None assessed	Level II
Bennett Britton *et al*. (2007)[38]	Prospective BC cohort	50/70	28% at 39–48 months PS	Circumferences	% volume difference between arms of >10% or 200 ml	More extensive LND	Level II study, however, do not report on characteristics of those lost to FU, assumed unadjusted analysis with no effect size presented
Celebioglu *et al*. (2007)[60]	Prospective BC SNB and ALND cohort with pre, 1-, 2-, 3-year PS measures	30 with SNB, 30 with ALND	0% in SNB group, 20% in ALND group at 2–3 year FU	Arm volume	>10% difference between limbs	More extensive LND	Level III/2, groups appear comparable at baseline, results were unadjusted for other characteristics related to LE

Author/s and dates	Details	Sample size	Incidence	Measurement method	LE definition	Risk factors	Level of evidence and comments*
Clark *et al.* (2005)[34]	Prospective BC cohort study with pre- to 3-years PS measures	251	20.7% at 3-year PS	Health professional diagnosis or arm volumes (circumferences)	20% difference between limbs, 5% change from baseline	Skin puncture while in hospital, mastectomy and BMI>26	Level II, 25% lost to FU, unadjusted risk factor analysis.
Francis *et al*. (2006)[35]	Prospective BC cohort study	152/209	67.7%; 17% after SNB and 47% after ALND	Arm volume using circumferences	>5% change from baseline	More extensive LND	Level II study, however, group incidence seems high and figures presented don't add up. Variability in adjusted and unadjusted results
Graham *et al*. (2006)[61]	Cross-sectional study of women with BC	89/197	42–45% at 1–8 years post-radiation, 8–15% following radiation to the SCF, 27–33% with wide SCF and 55–59% with axillary boost	Arm volume using circumferences	>200 ml difference between limbs, >2 cm difference between sides at any site	Axillary irradiation and older age	Level IV, baseline differences exist in treatment groups, multivariate analyses used in identifying characteristics associated with risk
Hayes *et al*. (2005)[28]	Prospective BC cohort study	176/294	11–20% at 6 months PS	Circumferences and BIS	>3 SD above reference scores for BIS, >5 cm difference in total circumferences between limbs	Treatment on the non-dominant side and lower levels of education	Level II

Author/s and dates	Details	Sample size	Incidence	Measurement method	LE definition	Risk factors	Level of evidence and comments*
Jeffs (2006)[97]	Retrospective cohort study of women with BC related LE	263	59% developed swelling within 12 months PS, 35% within 3 months PS	Perometry	Mild = volume difference <20%, moderate = >20% difference between limbs	None assessed	Level IV
Kao *et al*. (2005)[178]	Prospective cohort study of women undergoing radiation treatment and chemotherapy for unresectable locally advanced BC	16	7 (43%) at median of 44 months FU	Circumferences	>2.5 cm difference between limbs	None assessed	Level II, unclear whether definition is based on difference at one site or sum
Kingsmore *et al*. (2005)[179]	Retrospective BC cohort study	212	5–14% dependent on treatment regime; axillary sampling, clearance and radiation alone = 5%, 6%, 4%, respectively combined radiation with sampling = 11%, combined radiation with clearance = 14%	Clinician diagnosis	Persistent swelling at least 1 year after completion of axillary treatment, requiring treatment	Combined radiation and axillary procedure	Level III-3 study, time at FU not defined but study included women being treated between 1986 and 1991
Lee *et al*. (2007)[84]	Prospective cohort study of women with BC undertaking radiation treatment	64	22% at 7 month post-radiation	Circumferences	≥ 2 cm change from baseline at any site		Level II, don't report on characteristics of those lost to FU

Author/s and dates	Details	Sample size	Incidence	Measurement method	LE definition	Risk factors	Level of evidence and comments*
Lucci *et al*. (2007)[36]	RCT/Prospective BC cohort (Z0011 trial – ACOSOG)	821/891	11% for SNB + ALND at 1-year PS; 6% for SNB alone at 1-year FU	Circumferences	≥2 cm change from baseline when compared with other limb	More extensive axillary clearance	Level II
Pain *et al*. (2005)[39]	Prospective BC cohort study	70/103	10% at 12 months PS	Circumferences	>10% or 200 ml volume difference between limbs	Lower venous pulsatility uptake	Level II, preliminary results
Pain *et al*. (2005)[66]	Prospective BC cohort study	16	25% at 3-year FU	Circumferences	>10% volume difference between limbs between allowing for preoperative difference	Reduced uptake of protein into local blood and/or proteolysis	Level II, small n, preliminary results
Ronka *et al*. (2005)[40]	Prospective BC cohort study	83/109	17% at 1-year FU, incidence calculated from data presented	Circumferences	>5% volume difference between limbs, allowing for preoperative difference	More extensive ALND	Level II; Authors objectively measured but did not specifically define LE diagnosis
Szuba *et al*. (2007)[11]	Case-control study of BC with (mild and severe) and without LE	6 without LE, 6 mild LE, 7 severe LE		Circumferences	<2 cm difference at any site = intermittent/ mild, ≥2 cm difference = severe	Functional axillary nodes present in axilla of those with and without mild LE; lymphatic transport lower on treated side compared with untreated side for all women	Level III-3 study, questionable objective evidence of LE in those included in the mild LE group, questionable severity of those in the severe group, baseline differences exist between the groups that could influence conclusions made

Author/s and dates	Details	Sample size	Incidence	Measurement method	LE definition	Risk factors	Level of evidence and comments*
Wilke *et al*. (2006)[37]	Prospective BC cohort study (Z0010 trial)	4069/ 5327	7% at 6 month PS	Circumferences	≥2 cm difference from baseline when compared with contralateral limb	BMI>30, older age	Level II, adjusted results but unclear as to all variables in model
Cancer other than breast							
Beesley *et al*. (2007)[41]	Cross-sectional population-based survey of gynaecological cancer survivors	802/1420	10% (3 months–5 years post-diagnosis) cervical cancer = 24%, uterine = 8%, ovarian = 5%, vulvar = 36%, other = 9%	Health professional	Clinical diagnosis	Cervical cancer: radiotherapy, LND; uterine and ovarian cancer, LND and being overweight	Level IV, older women slightly under-represented, women with undiagnosed but symptomatic LE were included in the multivariate analysis of correlates
De Vries *et al*. (2006)[43]	Retrospective cutaneous melanoma cohort study	66/127	Inc=18% at 51 months FU; 6% who had inguinal SNB and 64% who had had inguinal SNB plus groin dissection	Leg volume	>6.5% difference between limbs	More extensive LND	Level IV, unadjusted analysis for risk factors
De Vries *et al*. (2005)[42]	Retrospective cutaneous melanoma cohort study	58/119	Inc=9% at 59 months FU; 11% who had SNB and 7% who had SNB plus axillary dissection	Arm volume	>10% difference between limbs	More extensive LND	Level IV, unadjusted analysis for risk factors

* Studies presented in tables may have been classified as 'prognosis' or 'aetiology' and the levels of evidence reflects the appropriate category BC: breast cancer; PS: post surgery; LND: lymph node dissection; FU: follow-up; LE: lymphoedema; SNB: sentinel node biopsy; ALND: axillary lymph node dissection; BIS: bioimpedance spectroscopy; SD: standard deviation; RCT: randomised controlled trial; BMI: body mass index; SCF: supraclavicular fossa

APPENDIX F

SUMMARY OF PAPERS REPORTING PREVENTIVE SECONDARY LYMPHOEDEMA STRATEGIES

Author & date	Study type and evidence level	Patient group	Patient characteristics	Intervention	Comparison	Length of FU	Outcome measure	Outcome and conclusions
Beurskens *et al*. (2007)[85]	Level III-1, pseudo-randomised controlled trial	30	Women undergoing BC treatment including ALND	PT treatment	FIyer with advice and exercises for the weeks following surgery, no further PT contact	Baseline (PS), 3- and 6 months PS	Volume via water displacement	Volume of the related arm showed no significant improvement between both groups at baseline and FU. Randomisation successful, assessment of LE prevention secondary objective and therefore did not specifically report number of LE cases at any of the testing phases
Campisi *et al*. (2006)[86]	Level III-2, comparative study with concurrent controls	50 BC patients	Not specified, but groups comparable for age, pathology and treatment	MLD, peristaltic lymph drainage and compression regime over 6 months	Unknown whether those with LE in control group sought treatment	Up to 5-years PS	Volume via water displacement	25 women (22/25 with lymphatic alterations) underwent prevention protocol, at FU only 2 had evidence of LE and these not responsive enough to MLD + underwent microsurgery which brought about complete long term LE. AC: the diagnostic and therapeutic preventive procedures allowed us to reduce the LE incidence. However, LE progression and treatment undertaken by control group unclear, representativeness of sample unclear.
Lee *et al*. (2007)[84]	Level III-1, pseudo-randomised controlled trial	61/64	Post- BC surgery, pre-RT, mean age = 53 years, more women in the control group had axillary surgery	6 weeks duration, usual care plus pectoral muscle stretching program**, stretching	Control group to follow usual care*	Pre-, post- and 7 month FU	Circumference measures and a >2 cm difference at any site between limbs	4 new cases in control group at 7 month FU (total = 6), 1 new case in study group (total = 5). No differences between groups for all outcomes measured at 7 month FU. Generalisability limited since this cohort all were receiving radiation, majority in study group were compliant during

			compared with the study group	encouraged to continue until 7 month FU.			used to identify LE	treatment but none continued regular use of exercise to the 7 month FU. AC: pectoral stretching for women undergoing RT unnecessary.

FU: follow-up; BC: breast cancer; ALND: axillary lymph node dissection; PT: physiotherapy treatment guidelines with advice and exercise for arm/shoulder, posture correction, coordination exercises, exercises for muscular strength and improvement of general physical condition, exercises to prevent lymphoedema, instruction for soft tissue massage of the surgical scar, 9 session, once or twice weekly, thereafter once a fortnight or less, all within 3 months. Patients also asked to perform home exercises for 10 minutes/day; PS: post-surgery; LE: secondary lymphoedema; MLD: manual lymph drainage; RT: radiation therapy; AC: Author's conclusion.

*involved following independently an exercise program on a pamphlet given after BS and were seen on a weekly basis by the physical therapist (for skin care and LE info)

** low load, passive stretches,

APPENDIX G

SUMMARY OF PAPERS REPORTING EFFECT OF TREATMENT MODALITIES FOR SECONDARY LYMPHOEDEMA

Author & date	Study type and evidence level	Number and type of patients	Patient characteristics	Intervention	Comparison	Length of FU	Outcome measure	Effect size	Additional comments and source of funding if relevant
Complex physical therapy, manual lymph drainage, massage, compression									
Didem *et al.* (2005)[95]	Level III-1, RCT	53 with LE presenting for average of 3 years, 60% mod LE, 40% mild LE	Women with BCLE	4 weeks duration of CDP + HP	Standard physiotherapy plus HP*	Pre- and post-test	Circumferences and water displacement	Both groups experienced reductions in LE with mean changes being 56% in treatment group and 37% in UC group.	AC: LE can be decreased by the use CDP. Limitations: data are lacking to show differences in group reductions, clinical importance of reductions (at least observed in those with mild LE) and whether reductions were sustained longer term. Errors throughout paper.
Hamner *et al*. (2007)[96]	Level IV, pre/post test design	135	Women with BCLE	CDT	None	Pre- and post-induction phase	Water displacement	Average volume and % reduction was 236ml and 42%, respectively.	AC: A program of LE therapy can reduce the volume of oedema and reduce pain. Limitations: average decrease provided with no evidence of spread, no longer-term FU and therefore unsure whether changes are sustained.

Author & date	Study type and evidence level	Number and type of patients	Patient characteristics	Intervention	Comparison	Length of FU	Outcome measure	Effect size	Additional comments and source of funding if relevant
Howell *et al*. (2005)[91]	Level IV, pre/post test design	4 with LE presenting 3-weeks to 4-years PS	Women with BCLE	MLD – not further defined	None	Pre-, 4-weeks and post-treatment (this time point varied according to number of treatments)	Circumferences	Volume decreased for all women by 83-518ml	AC: Arm volume reduced but QoL worsened as women realised the condition requires life-long treatment. LE programs must recognise the multidimensional impact of condition. Limitations: small sample, varying treatment, 3/4 women experienced less than 100 ml declines (clinical significance?), no long-term FU.
Jeffs (2006)[97]	Level IV	74/263 patients with BCLE	At baseline: Unclear percentage who presented with breast, mild, moderate or severe arm swelling and the majority presented with more than one complication	Self-care, MLD, multi-layer bandaging, exercise, depending on severity of swelling at presentation	None	12-month FU	Perometry, mild <20% difference, moderate 20–40% difference, severe >40% difference, between limbs	Mean reduction in excess limb volume = 10–40 ml, excess limb volume at baseline was 8–30% and at 12 month FU was 5–18%, depending on initial LE and site	Limitations: 95 patients excluded from analysis as did not receive treatment from the clinic, only 74 of remaining had 12 month FU data, difficult to follow numbers, clinical significance of results not discussed, generalisability questionable, no reasons behind who and why did people not present for FU. Funding source: Smith's charity

Author & date	Study type and evidence level	Number and type of patients	Patient characteristics	Intervention	Comparison	Length of FU	Outcome measure	Effect size	Additional comments and source of funding if relevant
Koul *et al*. (2007)[98]	Level III-3, cohort comparative study without concurrent controls,	138/250 BCLE	Typical BC cohort, unclear severity of swelling at baseline, mean age = 54 years	55% had CDT, 32% MLD, home program 13%, treatment given dependent of therapist discretion, LE severity and patient compliance	None	12 month FU	Circumferences	Volume reduction of 166 ml (47%), Volume difference of treated side based on CDT, MLD and home program was 223 ml (56%), 164 ml (41%) and 98 ml (24%).	81 excluded from analysis as FU data not available (26 due to non-compliance), non-randomisation to treatment group, data not presented to allow for baseline comparison between treatment groups, AC: CDT and MLD with exercise were associated with a reduction in LE volume. Age, type of surgery and body mass index related to LE severity. Limitations: conclusion limited by lack of control group, also unable to comment on the contribution of each component of CDT for LE. Funding source: HSC Medical Staff 2004 fellowship funds.

Author & date	Study type and evidence level	Number and type of patients	Patient characteristics	Intervention	Comparison	Length of FU	Outcome measure	Effect size	Additional comments and source of funding if relevant
Moseley *et al*. (2007)[88]	Systematic review including studies of Level II-III-3 studies		Women with BCLE	CPT, MLD, self massage, pneumatic pumps, oral pharmaceuticals, low-level laser, compression bandaging, compression garments, limb exercises, limb elevation		Varied	Varied	Formal diagnosis of BCLE – no other definition provided	Treatments predominantly implemented by health professionals yielded greatest reductions.
Vignes *et al*. (2007)[100]	Level IV pre/post cohort	356/537	Women with BCLE	CDT		Pre and 12-month FU	Circumferences	LE decreased following CDT (mean 407 ml)	Slight volume increase (84 ml) during 1-year maintenance period, but remained lower than initial volumes, AC: Compliance to elastic sleeve use and low stretch bandage required to stabilise LE. Limitations: 67% at 12-month FU; potential bias towards compliant patients.
Vignes *et al*. (2006)[99]	Level IV pre/post cohort	357	Women with BCLE	CDT		Pre- and immediately post- CDT	Circumferences	Mean volume reduction 404 ml	AC: BMI and duration of LE were predictors of absolute volume reduction. Higher BMI and longer LE duration associated with higher initial

									volumes.
Author & date	**Study type and evidence level**	**Number and type of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of FU**	**Outcome measure**	**Effect size**	**Additional comments and source of funding if relevant**
Wilburn *et al*. (2006)[101]	Level III-3, crossover study of 2 treatment regimes	10	Women with BCLE, mean age = 54 years and time since treatment = 36–288 months	1-hour Flexitouch** treatment for 14 days, then crossover; 1-week washout with garment only preceded each treatment phase	Self administered massage for 1 hour	Pre- and post treatment	Circumferences	Flexitouch** led to volume reductions (mean 200 ml), but self-administered massage did not (50 ml)	AC: device may provide better maintenance oedema control than self-administered massage. Limitations: sustained benefit unknown. Funding: Tactile Systems inc, manufacturer of Flexitouch**, however, author's state no financial ties to company.
Exercise and Diet									
Ahmed *et al*. (2006)[75]	Level II, RCT of weight training	45	BC surgery, 8 with objective LE, were 4–36 months PS, mean age = 62 years	Upper- and lower-body weight training, 3 months supervised (twice/week) followed by 3 months unsupervised	Control group, no intervention	Baseline and 6-month FU	Circumferences	Circumference measures of the treatment group did not increase overtime	AC: resistance exercise did not increase risk or exacerbate symptoms of LE. Limitations: small number of cases in both groups.
Johansson *et al*. (2007)[76]	Level III-3, intervention study on weight bearing exercise	18	Women with BCLE	Weight-bearing exercise	None	Pre-, 30 minutes, 24 hours post-exercise	Water displacement and BIS	No change in volume by 24 hour FU	AC: controlled short-duration exercise program using weights does not increase LE. Limitations: shows acute effect only, lack of control

									group.

Author & date	Study type and evidence level	Number and type of patients	Patient characteristics	Intervention	Comparison	Length of FU	Outcome measure	Effect size	Additional comments and source of funding if relevant
Moseley *et al*. (2005)[112]	Level IV, pre/post test design	38	Women with BCLE	Gentle arm exercise and deep breathing (daily for 1 month but 24 continued to do treatment regime for another month)	None	1-hour, 24-hour, 1-week and 1-month FU	Volume	Reductions in arm volume at all FU measures (50-100ml)	Reductions also seen in arm symptoms. AC: gentle arm exercise and deep breathing is easy to perform and implement and significantly reduces arm volume and symptoms. Limitations – design, sample size, unsure how many n make up 1month FU (did it include those who did not continue exercises and deep breathing for the month?), sustained benefit unknown
Shaw *et al*. (2007)[113]	Level II, RCT	64	Women with BCLE	(1) Reduced energy intake, (2) Low-fat diet with no change in energy intake	Habitual intake	Pre- and 24-weeks FU	Perometry and circumferences, >20% difference in limbs required for entry into study	Volume decreased but not significantly in dietary groups.	Significant reduction in weight and BMI in group 1 and 2 at FU. Weight and volume reductions associated. AC: weight loss appears to be helpful in reducing LE. Limitations: measure of LE status sensitive to weight change, sustained benefit unknown

Author & date	Study type and evidence level	Number and type of patients	Patient characteristics	Intervention	Comparison	Length of FU	Outcome measure	Effect size	Additional comments and source of funding if relevant
Surgery									
Bagheri *et al*. (2005)[121]	Level III-3 intervention study	20	All had non-pitting BCLE, mean age = 50 years, had previous LE treatment with only 1 considering that treatment successful	Liposuction	None	Pre-surgery, 1-, 3, 6- and 12 month FU	Tonometry and volume (method not defined)	Treated arm was smaller than normal arm at 1 year FU, 109% reduction by 12 months FU	Significant reductions observed 2-weeks PS and continued to decline over time. AC: tonometer could register PS changes in tissue tonicity. Funding source: Foundation Against Cancer.
Brorson *et al*. (2006)[123]	Level III-3 intervention study	11	Nonpitting BCLE	Liposuction	None	6 month FU	Plethysmography	Treated arm smaller than normal by FU (109% reduction)	AC: Complete reduction of LE, excess amount of fat of 81% in the volume aspirated. Funding source: several organisations with no competing interests
Brorson *et al*. (2006)[122]	Level III-2, non-randomised intervention study	49	Women with BCLE, mean age = 54 years, mean duration of LE = 8 years	Liposuction + CCT	CCT alone	Pre-, 6 month and 12 month FU	Water displacement	Complete reduction of oedema in treatment group, halving in CCT alone group	Conclusion: Liposuction + CCT removed oedema completely and improves QoL. CCT was beneficial too, but to a lesser extent. Funding source: several organisations with no competing interests
Matsubara *et al*. (2006)[124]	Level IV, pre/post test design	9	Women with uni or bilateral LE following	Microscopic lymphatic vessel-isolated		21–87 months	circumferences	'Excellent' through to 'poor' reductions	'Excellent' reductions observed in 6 limbs (>5 cm), 'good' reductions (2–5 cm) observed in

			radical hysterectomy with radiation therapy for uterine cancer, average duration of LE = 11.4 years	vein anastomosis					2 limbs and 'poor' reduction (<2 cm) in 3 limbs. Frequency of cellulitis also decreased. AC: results show that microscopic lymphatic vessel-isolated vein anastomosis is a minimally invasive operation with good long-term FU, making it the treatment of choice for intractable secondary LE of the lower limb. Limitations: sample and sample size

FU: follow-up; RCT: randomised controlled trial; LE: secondary lymphoedema; BCLE: breast cancer-related lymphoedema; CDP: complex physical therapy (complete decongestive physiotherapy including lymph drainage, multi layer compression bandage, elevation, remedial exercises and skin care); HP: home program (compression bandage, exercises, skin care and walking); AC: author's conclusions; CDT: manual lymph drainage, compression garments, skin care and range of motion exercises, induction phase (twice weekly for 8 weeks), followed by maintenance phase individualised to needs, PS: post-surgery; MLD: manual lymph drainage; QoL: quality of life; BC: breast cancer; CPT: complex physical therapy; BIS: bioimpedance spectroscopy; CCT: controlled compression therapy using a garment that gave compression in the range of 32-40mmHg and was adjusted as arm size changed, garment worn permanently, and treatment was interrupted only briefly when showering and possibly for social occasions

* bandage, elevation, head-neck and shoulder exercises and skin care
**Flexitouch mechanically stimulates manual lymph drainage

APPENDIX H

Body of evidence assessment matrix[a]

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Volume of evidence	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population*	Population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

[a] Table replicated from NHMRC document: *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Pilot program 2005-2007,*[64] * e.g. results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patient with another cancer

Definitions for grades of recommendation[a]

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

[a] Table replicated from NHMRC document: *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Pilot program 2005-2007*[64]