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What are the economic burden and treatment costs associated with breast cancer-related lymphedema? A systematic review

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Abstract (275 words)

Objectives: To provide an overview of costs associated with the treatment of breast cancer-related lymphedema (BCRL) and its possible sequelae, either borne by patients or by society.

Data sources: According to the PRISMA guideline, a systematic literature search was carried out in four electronic databases: PubMed, Web of Science, Cochrane Clinical Trials and EMBASE. Searches were performed on October, 1st 2018.

Study selection: Eligibility criteria were: 1) expenses of adults (age >18y), 2) concerning patients with BCRL, 3) overview of (in)direct costs associated with BCRL, 4) expenses in which at least 1 type of conservative treatment modality for lymphedema is included. Reviews and meta-analyses were excluded.

Data extraction: After assessing the risk of bias and level of evidence, quantitative data on direct and indirect costs for BCRL treatment during a well-mentioned timeframe were extracted.

Data synthesis: Eight studies were included. Three studies reported on patient-borne costs related to BCRL. Mean direct costs per year borne by patients ranged between \$2 306 and \$2 574. Indirect costs borne by patients ranged between \$3 325 and \$5 545 per year. Five studies estimated health care costs related to BCRL from claims data, billing prices and provider's services during 12 to 24 months. Mean direct treatment costs after 1 year of decongestive lymphatic therapy ranged between €799 (= \$902.80; €1 = \$1.13) and \$3 165. The average medical costs for BCRL, including hospital charges, were estimated between \$45 896 and \$58 088 per 2 years.

Conclusion: This systematic review reveals that BCRL imposes a substantial economic burden on patients, society and health insurances. However, there is a lack of economic analyses associated with BCRL in European countries. In future endeavor, analyses of the economic impact of decongestive lymphatic therapy in European care settings are warranted.

Key-words: Breast cancer – Breast Neoplasms – Lymphedema – Healthcare Costs – Costs and Cost Analysis

List of abbreviations

BCRL	Breast cancer-related lymphedema
DLT	Decongestive lymphatic therapy
ISL	International society of lymphology
MLD	Manual lymph drainage
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UK	United Kingdom
USA	United States of America

Introduction

Worldwide, breast cancer is accounting for 23% of all female cancer cases.⁽¹⁾ Breast cancer treatment-related lymphedema (BCRL) is internationally recognized as a feared and disabling morbidity. Since the introduction of more effective treatment modalities⁽²⁻⁵⁾ increasing the number of breast cancer survivors, the amount of patients dealing with long-term side effects, such as lymphedema, rises likewise.⁽⁶⁾ BCRL is caused by a decreased lymphatic transport capacity and/or increased lymphatic load after which fluid accumulates in the extracellular spaces of soft tissues, resulting in swelling.⁽⁷⁾ Today, pooled data reveals a BCRL incidence rate of 16.6%.⁽⁸⁾

Besides an impact on functional and psychosocial well-being⁽⁹⁾, there can be an additional deleterious effect of lymphedema on women in terms of financial costs.^(10, 11) Daily living can be affected by copayments for the increase in medical and therapeutic consultations, as well as by other direct costs for compression garments and other (in)direct therapy-related expenses.⁽¹⁰⁾ Moreover, financial burdensome can be emphasized through the impact of (advanced) lymphedema on career and employment.⁽¹¹⁾ This happens for instance when a transition from fulltime to part-time employment is required in order to spend more time on complex care.⁽¹¹⁾ Besides the lymphedema which requires appropriate treatment, complications secondary to BCRL, such as repeated infections, may arise as well.⁽¹²⁾ These episodes need early antibiotic therapy and may require hospitalization, increasing the costs of care even more.⁽¹³⁾

According to the recommendations of the International Society of Lymphology (ISL), BCRL needs to be treated with decongestive lymphatic therapy (DLT).⁽¹⁴⁾ This is a two-stage treatment programme, consisting of different conservative treatment modalities. During the first or intensive phase, lymphedema is maximally reduced. This phase consists of skin care, manual lymph drainage (MLD), multi-layer bandaging and exercise therapy. The second or maintenance phase aims to conserve and optimise the results obtained in the first phase. It consists of skin care, compression by a low-stretch compression sleeve, exercises and MLD.⁽¹⁵⁾ Although DLT is recognized as the gold standard for

conservative treatment of lymphedema^(14, 16), reimbursement for DLT has been hampered by a lack of rigorous research evidence.⁽⁷⁾ Additionally, current literature on the financial burden of BCRL treatment is extremely limited. A clear overview between patient-borne and society-borne costs within this financial burden is missing. However, this is essential to estimate the actual economic impact of BCRL for patients as for society.

Therefore, the aim of this review was to make an overview of the currently available literature on direct and indirect patient-borne as well as society-borne costs associated with the treatment of BCRL and its sequelae.

Methods

Literature search and inclusion criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline⁽¹⁷⁾ (www.prisma-statement.org), a systematic review of the literature was performed. This review has been registered on PROSPERO (<https://www.crd.york.ac.uk/PROSPERO>) with registration number CRD42018114649. In order to identify eligible studies, four electronic databases were screened on October 1st, 2018: PubMed, Web of Science, EMBASE and Cochrane Clinical Trials. A PICOS search strategy was built up, resulting in a Boolean search where following indexing terms (i.e. MeSH for Pubmed and Cochrane, Emtree for EMBASE) and keywords were combined: 'breast cancer(P)', 'lymphedema(P)', 'decongestive lymphatic therapy(I)', 'treatment(I)', 'economic analysis(O)', 'economic evaluation(O)', and 'costs(O)'. A comparison was not defined (not applicable). Equivalent searches were executed in all four databases, although modifications in keywords were included due to the differences in usage of indexing terms. When using Web of Science, an additional restriction was added to the search with the filter "document type: Article", and in EMBASE the search was limited to "Articles" or "Articles in press" and studies based on "Humans". In appendix 1, an overview of the applied search strategies for the different databases is presented.

The screening for eligible articles was two-fold and performed by two raters (T.D.V. and N.G.). A first screening upon title and abstract was achieved for all references in each database, in order to assess which articles were relevant for further scrutiny. Thereafter, a second screening on the full-texts of the selected articles was performed. Both screening steps were based upon predetermined inclusion and exclusion criteria, reported in table 1. In case of disagreement between the reviewers regarding the in- or exclusion of studies, consensus was reached during a meeting.

Data extraction

Data on study design, research question, study region, number of participants, inclusion and exclusion criteria, timespan, applied treatment for BCRL, cost- (and other) related outcome measures, and cost-related main results were extracted and summarized from the included full-texts in table 3. If studies reported both quantitative and qualitative data concerning the economic burden of BCRL, only quantitative data was extracted in the table of evidence. If studies compared treatment costs for patients with and without BCRL, or compared (so-called) standard treatment costs and an experimental/model-based treatment cost, only the BCRL treatment costs and standard treatment costs were mentioned.

Methodological quality assessment

To assess the methodological quality, the 19-item NICE checklist for (partial) economic evaluations provided by the National Institute for Health and Care Excellence (NICE)⁽¹⁸⁾ (<https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation>) was used. Selected articles were evaluated by both reviewers (T.D.V. and N.G.). As the NICE checklist initially is designed for the UK, some minor adjustments in questions were necessary in order to generalize the feasibility of the questions to all countries.⁽¹⁸⁾ An item was scored “1” if adequate information was provided and bias was unlikely. An item was scored “0” if the criterion was not met. An item was scored

“?” if the required information was lacking. Afterwards, the total methodological quality was expressed as the sum of all items receiving score “1”. In case disagreement occurred between reviewers regarding assigning a score to an item, consensus was sought during a meeting. Additionally, according to the Dutch Cochrane Centre guidelines, levels of evidence were determined for all selected studies (<http://netherlands.cochrane.org>).

Results

Study selection

At first, the search yielded 387 references, including duplicates. After a first screening upon title and abstract, 28 full-texts were retrieved for further scrutiny. After a second screening upon inclusion and exclusion criteria (table 1) and duplicates, 8 studies were included in this review: 4 cohort studies^(13, 19-21) and 4 cross-sectional studies^(11, 22-24). Figure 1 provides a detailed flowchart of the search strategy and selection procedure.

Methodological quality

An overview of the risk of bias and level of evidence of the included studies is presented in table 2. Regarding study quality, scores for the (partly) economic evaluations in both cohort and cross-sectional studies ranged between 7/11 and 8/11. A question that frequently scored negative or of which information was lacking, was the following: “Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?”, because in most cases the aim of the studies was to provide an overview of costs, rather than to make a cost-effectiveness evaluation. According to the Dutch Cochrane Centre guidelines, levels of evidence ranged between A2^(13, 19, 21) and B^(11, 20, 22-24).

Characteristics of the included studies

Altogether, costs were analyzed of 2421 patients with BCRL from 6 out of 8 included studies.^(11, 13, 19-21, 24) Two studies did not report the amount of patients upon which their cost-related outcomes were based.^(22, 23) Mean age of the included patients ranged between 49⁽¹³⁾ and 63 years⁽²¹⁾. One study did not define mean age⁽¹¹⁾, and in one study this was not mentioned since results were based on a hypothetical decision model⁽²⁴⁾. Study regions comprised the USA^(13, 20, 21, 23, 24), Australia^(11, 19), and Finland⁽²²⁾.

Costs related to BCRL

The timespan in which costs were estimated in the different studies ranged between 12 months^(19, 21, 22, 24) and 24 months^(13, 20).

Three studies^(11, 19, 21) investigated patient-borne costs related to BCRL. Of these, two studies made a clear distinction between direct (i.e. costs directly related to the treatment for BCRL such as costs for therapeutic measures, physician fees, drugs, compression therapy/garment) and indirect (productivity losses; values of lost income, unpaid help and lost unpaid work) patient-borne costs.^(19, 21) Mean direct costs per year ranged between \$2 306⁽²¹⁾ and \$2 574⁽¹⁹⁾. Indirect costs ranged between \$3 325⁽²¹⁾ and \$5 545⁽¹⁹⁾ costs per year. In the article of Boyages et al., the overall mean patient-borne costs for BCRL per year were provided, resulting in an average of A\$977 (= \$692.02; 1A\$=\$0.71) per year.⁽¹¹⁾ Hereby, no distinction between direct and indirect costs was made.

The five remaining studies^(13, 20, 22-24), discussed medical costs collected from claims data from (national) insurers^(13, 22), physician Medicare fees^(23, 24), hospitalization charges^(20, 24) and/or manufacturer's and service provider's prices⁽²²⁾. In these studies, no overview of out-of-pocket costs borne by patients was provided. One study showed that the average of non-cancer-related medical costs for BCRL was estimated on \$45 896 during 2 years.⁽¹³⁾ In Bilir et al., the total 1-year economic impact with direct and indirect costs was \$1 984 529 for standard assessment and lymphedema treatment in 627 patients (\$3 165.12 per patient).⁽²⁴⁾ Direct BCRL-related health care charges due to hospitalization (e.g. for

recurrent episodes of cellulitis and systemic infections) were estimated on \$58 088 during 2 years.⁽²⁰⁾ Direct treatment costs after 1 year of decongestive lymphatic therapy per patient were estimated on \$3 125.⁽²³⁾ In Finland, total costs per patient treated with decongestive lymphatic therapy is €799 (= \$902.80; €1 = \$1.13) per year.⁽²²⁾ An overview of the extracted data is shown in table 3.

Discussion

The purpose of this systematic review was to provide an overview of the direct and indirect patient-borne as well as society-borne costs associated with the treatment of BCRL and its sequelae.

Three out of 8 of the included studies were prospective cohort studies with sufficient sample size and follow-up. These studies were graded with a level of evidence A2.^(13, 19, 21) However, scores on methodological quality in terms of risk of bias of the included studies were relatively similar to each other.

This review reveals that BCRL imposes a substantial economic burden on patients, society and health insurances. During a 2-year post-operative period, patients with BCRL required significantly more hospitalizations and nearly 7 times higher health care charge per patient compared with patients without BCRL (\$141 388 vs. \$21 141 per patient, respectively).⁽²⁰⁾ During the first year after surgery these differences were more prominent, however, they persisted during the second year.⁽²⁰⁾ In the article of Stout et al., direct treatment costs associated with a traditional model of decongestive lymphatic therapy were compared with costs associated with a prospective surveillance model.⁽²³⁾ In the USA, the cost to manage early-stage BCRL per patient per year using a prospective surveillance model was \$636. In contrast, the costs associated with decongestive lymphatic therapy using the traditional model was \$3 125⁽²³⁾, highlighting the importance of an early treatment onset in favor of less invasive treatment expenses. This review comprises only one study that investigated the treatment cost for decongestive lymphatic therapy in a European country, whereby results showed an average cost of €799 (= \$902.80; €1 = \$1.13) per patient per year.⁽²²⁾

In this systematic review we attempted to provide an overview of the treatment costs for BCRL, given its current scarcity of recourses. However, more information is available concerning treatment costs for lower limb lymphedema in European settings. Recently, Gutknecht et al. performed in Germany an observational cross-sectional study in patients with chronic lymphedema or lipolymphedema in order to analyze all the direct and indirect costs for the patients, health insurance and society.⁽²⁵⁾ The average total cost for each patient per year was €5 784 (= \$6 533.20; €1 = \$1.13), of which €4 445 (= \$5 020.76; €1 = \$1.13) (76%) were direct costs and €1 338 (= \$1 511.31; €1 = \$1.13) (24%) were indirect costs. Out-of-pocket costs per patient were €648 (= \$731.94; €1 = \$1.13) on average per year, wherein the highest costs were for MLD therapy and disability costs (e.g. prescription fees including private costs for remedies and aids, extra payments for physician visits, hospitalisation and rehabilitation, skin care products).⁽²⁵⁾ Each year, an mean cost of €2 510 (= \$2 835.12; €1 = \$1.13) per patient is spent on manual lymphatic drainage and was considered the main cost factor for the statutory health insurances.⁽²⁵⁾ However, as this study relies on lower limbs without a separate indication of costs related to BCRL, this study was not included in our review analysis. Likewise, in another recently published study of Moffatt et al., the aim was to develop and evaluate health service and patient outcomes using an appropriate model of care within a London-based primary care trust.⁽²⁶⁾ Patients with chronic swelling of the arm(s) or leg(s), were recruited and treated for a period of 6 months, irrespective of the underlying etiology. Primary outcomes were Quality of Life, incidence of cellulitis and change in limb volumes. Additionally, costs were evaluated as well over a 6-month period. Results of this study showed the benefits of a service model for chronic edema, with clinical improvements due to a reduction in limb volume and reduced complications. Furthermore, recourses moved from the acute care setting to lower cost interventions in community: overall costs reduced from £50 171 (= \$65 403.92; £1 = \$1.30) before implementation to £27 352 (= \$35 656.62; £1 = \$1.30) within the first 6 months and subsequently £17 618 (= \$22 967.18; £1 = \$1.30) between 6 months and 1 year.⁽²⁶⁾

Several limitations of the included studies of this review need to be discussed. First and foremost, studies investigating the financial costs related to BCRL by making use of claims data^(13, 20, 24) are likely

to underestimate the real cost rates.⁽²⁷⁾ Because claims data are designed for billing purposes, they only offer information of patients who are insured. Thus, they only provide an estimation of the costs related to BCRL as they do not yield information about patients with BCRL without health insurance.⁽²⁸⁾ Furthermore, one should notice that, in case only direct costs related to hospitalizations are taken into account⁽²⁰⁾, an important underestimation of the complete (direct) costs of BCRL occurs. Evaluation of resource utilization and charges associated with outpatient care would provide a more complete assessment of the impact related to BCRL.⁽²⁰⁾

Difficulties could be experienced regarding the transferability and generalizability of some study results, especially when other than patient-borne costs are analyzed. Transferability is defined as the extent to which the results of a study hold true for a different population or setting.^(18, 29) Since different continents, even different states/countries within the same country/continent, are subjected to different health care insurance policies and reimbursement procedures, it is difficult to transfer the amount of health care costs derived in the USA^(13, 20, 21, 23, 24) or Australia^(11, 19) to European countries and vice-versa. Besides that, differences in money currencies between countries make the amount of costs derived in the different studies hard to compare. Generalizability is defined as the extent to which the results of a study can be generalized to the population from which the sample size was drawn.^(18, 29) As stated by Dean et al., even findings derived from studies conducted solely in the USA are difficult to compare over time, since some of these investigations⁽¹³⁾ conducted in the past are predate the 2010 Affordable Care Act that expanded coverage for cancer-related care.⁽²¹⁾ Another example is the following: in Shih et al., the study sample was limited to working-age women (mean age 48.8 years), therefore their findings regarding medical costs may not be generalizable to elderly with BCRL.⁽¹³⁾

These aspects make comparison, transferability and generalizability difficult. However, knowledge of costs related to BCRL not only improves the understanding of the economic burden of this morbidity, but also launches a baseline of comparison for future cost-analytic or cost-effectiveness studies.⁽¹³⁾ Therefore, further scrutiny of future longitudinal studies with long-term follow-up (≥ 12 months) where

both inpatient as well as outpatient care in European settings is being evaluated by collecting patient-borne and society-borne direct (and, if possible, indirect costs) separately, is needed in this field.

Limitations and strengths

In this review, literature searches were limited to mainly (bio)medical databases. The NHS Economic Evaluation Database (NHS EED) focuses primarily on the economic evaluation of health care interventions.⁽³⁰⁾ As a result, combining databases such as PubMed and NHS EED should have been an optimal search strategy for economic evaluations.^(30, 31) Therefore, a post-hoc search was performed on the NHS EED database on October, 19th 2018 (<https://www.crd.york.ac.uk/CRDWeb>). However, this search yielded no additional eligible records.

The present systematic review contains also several strengths. Firstly, it has a compliance with the PRISMA guideline.⁽¹⁷⁾ Furthermore, to our knowledge, this is the first overview of reported direct and indirect patient-borne as well as society-borne costs specifically associated with the treatment of BCRL, in literature. Lastly, the screening and data extraction process was performed by two blinded researchers.

Conclusion

This review reveals that BCRL imposes a substantial economic burden on patients, society and health insurances. In the USA, patient-borne direct costs related to BCRL range between \$2 306 and \$2 574 per patient per year. Patient-borne indirect costs range between \$3 325 and \$5 545 per patient per year. Mean direct treatment costs after 1 year of DLT ranged between €799 (= \$902.80; €1 = \$1.13) and \$3 165. The average medical costs for BCRL, including hospital charges, were estimated between \$45 896 and \$58 088 after 2 years. However, these conclusions are based on limited research data. Furthermore, there is a lack of economic analyses and health expenditure evaluations related to BCRL

treatment in Europe. Due to differences and changes in health policies, public insurance protocols and currencies, it is hard to transfer and extrapolate patients-borne and society-borne costs related to BCRL to other countries. In future endeavor, an analysis of the economic impact of DLT in European settings, is warranted.

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Tables and figures

Table 1. Eligibility criteria used in both screenings

PICOS	Inclusion	Exclusion
P	Adults (age > 18y)	
P	Patients with breast cancer-related lymphedema	Solely breast cancer patients without upper limb lymphedema
I	Decongestive lymphatic therapy or other conservative treatment modalities	No overview of costs regarding any type of treatment modality for BCRL
C	Not specified	/
O	Economic overview or analysis of costs related to the treatment of lymphedema and/or its sequelae	When only indirect costs are included (i.e. loss of productivity,..) without incorporation of direct costs related to any treatment modality for lymphedema
O	Outcome should be a quantitative overview of (patient-borne and/or community-based) costs during a certain timeframe	Solely qualitative results
S	Randomized controlled trial, cohort study, cross-sectional study	Review, meta-analysis
Other	Language: English, Dutch or French	Other languages
Other	Humans, Articles or Articles in press	Animal studies, unpublished material or abstracts

Figure 1. Flowchart of the Boolean search and selection procedure (PRISMA)

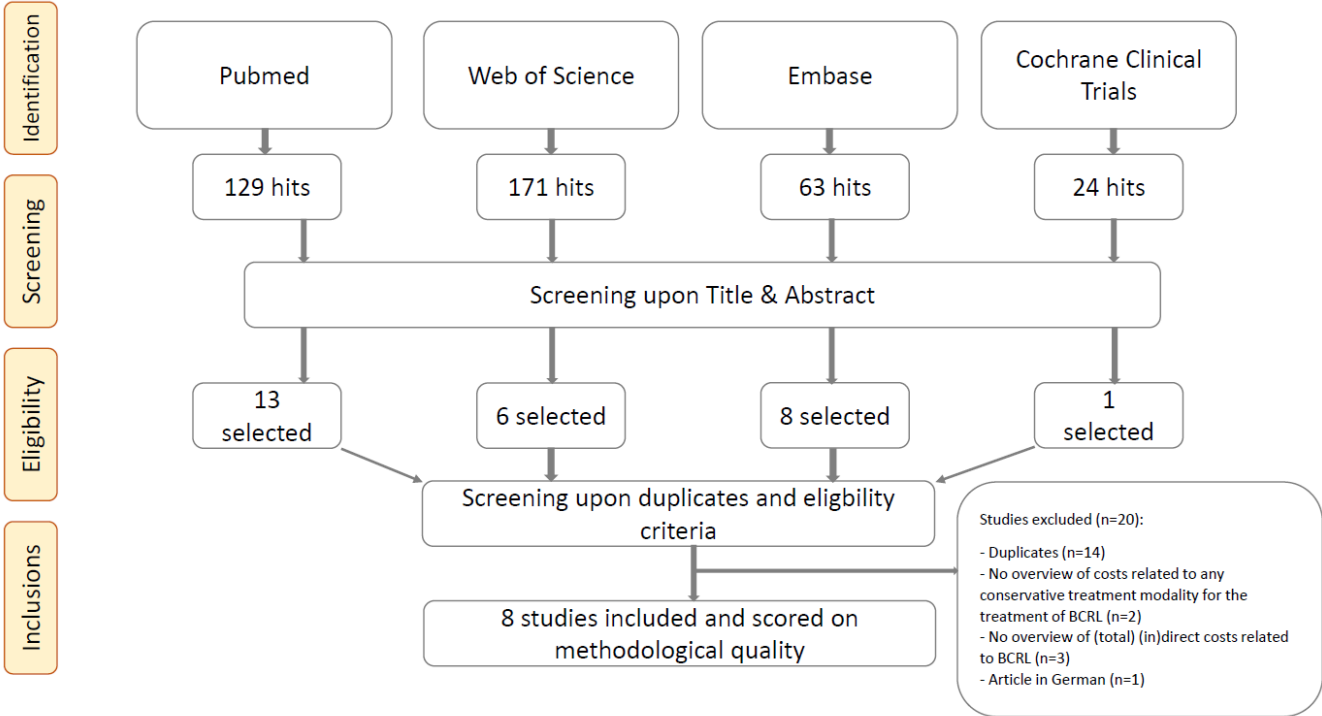


Table 2. Overview of the methodological quality of the 8 included studies (NICE checklist)

Risk of Bias									
		Shih et al., 2009	Kärki et al., 2009	Stout et al., 2012	Bilir et al., 2012	Schmitz et al., 2015	Basta et al., 2016	Boyages et al., 2016	Dean et al., 2018
Section 2: Limitations	Q1	1	1	1	1	1	1	1	1
	Q2	1	1	?	1	1	1	1	1
	Q3	1	1	1	?	1	1	1	1
	Q4	1	?	1	1	1	?	1	1
	Q5	1	1	1	?	?	1	?	?
	Q6	?	?	?	?	1	0	1	1
	Q7	1	1	1	1	1	1	1	1
	Q8	1	1	?	1	1	1	1	1
	Q9	0	0	1	1	0	0	0	0
	Q10	0	0	0	0	0	0	0	0
	Q11	1	1	1	1	1	1	1	1
Methodological Quality (Total)		8/11	7/11	7/11	7/11	8/11	7/11	8/11	8/11
Level of Evidence		A2	B	B	B	A2	B	B	A2

Table 3. Table of evidence with characteristics of the 8 included studies

Author, year	Study design	Research question	Study region	Participants			Time span	BCRL treatment	Measures and outcome		Main findings: costs
				Inclusion criteria	Exclusion criteria	Number of inclusions (n)			Cost measures and resource use	Other measures	
Shih et al., 2009	Prospective cohort study	To estimate the economic burden of BCRL among working-age women	USA	Cohort of breast cancer patients identified using a validated algorithm	Males, less than 27 months of enrollment, missing enrollee identifiers	Total n= 1877 (mean age 48.8 years) - BCRL n= 180 - no BCRL n= 1697	24 months (between 1997 and 2003)	Not enlightened	Productivity information, medical and pharmacy claims data of the Medstat MarketScan Health and Productivity Management (HPM) database	Age, comorbidities, demographic data, working status, breast cancer treatment modalities	Total not cancer-related medical cost in 24 months: -BCRL group: \$45 896 Total medical cost for PT and supplies, in 24 months: -BCRL group: \$1 083 Total medical cost for infections, in 24 months: -BCRL group: \$2 151
Kärki et al., 2009	Cross-sectional quantitative study	To explore current treatment practices and costs for BCRL	Finland	/	Patients with BCRL with reimbursed costs for LE therapy	/	12 months (between January and March 2007 for prices obtained	106 LE therapist reported treating BCRL patients. LE therapy	- Prices of CB's, CS's, gloves and 60-min sessions were obtained from service providers	Origins of referrals, use and duration of treatments, pre- and post-therapy assessments by questionnaires to	Total costs for 1 patient treated with DLT = €799 : - Ten 60-min therapy sessions: €450 EUR

							from manufacturer s/ service providers, between January and December 2004 for costs for reimbursed LE therapy sessions)	consisted of a combination of: - MLD (99%) - guidance (79%) - CS (74%) - CB (63%) - exercises (55%) Most therapist (80%) used 60-min sessions, 11 to 15 sessions	and manufactures (2007) - Data on reimbursed costs for therapy sessions were obtained from the national Social Insurance Institution (SII)	lymphoedema therapist's - Usage volumes of lymph therapy and compression bandages was collected from three hospital district and three major cities in 2005	- One compression bandage: €37.5 - Two sleeves: €155.5 - Two handkerchiefs: €156
Stout et al., 2012	Quantitative cross-sectional cost analysis	To provide an estimation of the direct costs associated with a prospective surveillance model of care compared with the direct treatment costs of a traditional model for managing BCRL	USA	/	/	/	12 months (estimated costs with a 1-year timeline)	DLT vs. Prospective Surveillance Model after breast cancer surgery	Costs for skilled therapy (direct treatment costs) and durable medical equipment (average retail costs)	/	Costs after 1 year of DLT per patient: \$3 124.92 (therapy sessions \$1 494.92, 2 sets of bandages \$230, 4 custom-made arm sleeves and hand gloves \$1 400)
Bilir et al., 2012	Payer-perspective decision model	To estimate and compare the economic outcomes associated with routine use of bio-impedance	USA	Women with breast cancer, at least 18y old	/	Cohort model begins with a hypothetical population of 1 million covered	12 months (estimated costs with a 1-year timeline)	LE treatment: current standard quarterly LE assessment and	Parameter values were obtained from the medical literature, including population characteristics,	/	For the 627 newly treated post-surgery BC patients, based upon the CTCAE v3.0 definition of lymphedema and other

		spectroscopy (BIS) vs. current standard methods following breast cancer treatment				lives. Then the cohort is stratified by disease risk characteristic ; n=627 newly treated post-surgery BC patients		treatment if required	lymphedema incidence, resource utilization, and healthcare costs were derived from publicly available fee schedules, and reflect Medicare national average reimbursement rates (costs regarding compression sleeves, pneumatic pump use, DLT, in- and outpatient physician fees, hospitalization, antibiotic therapy, depression treatment)		base-case model input values, the total 1-year budget impact, from the payer perspective, is: - \$1 984 529 for standard assessment and lymphedema treatment; - \$1 819 896 for the standard lymphedema treatments alone
Schmitz et al., 2015	Prospective cohort study	To evaluate the economic burden of adverse treatment effects from breast cancer treatment, comparing burden across women with and without these outcomes	Australia	Women who recently had undergone surgery for breast cancer, representative of the wider breast cancer population	/	Total n= 287 (mean age 55.3 years) - BCRL ^a patients with direct costs n= 75 - BCRL patients with indirect costs n= 52 - no BCRL patients with direct costs n= 111	12 months follow-up from 6 months post-surgery	Not enlightened	Patient's out-of-pocket direct, indirect and total costs between breast cancer diagnosis and 18 months post-surgery (questionnaire)	- Demographic data (e.g. age, children, occupation, private health insurance,...) - Tumor Characteristics - Type of adjuvant treatment received - Adverse treatment effect Using questionnaires	BCRL group: - Direct out-of-pocket costs for LE between 6 and 18 months post-surgery: \$2 574 - Indirect costs for LE between 6 and 18 months post-surgery: \$5 545 - Total costs for LE between 6 and 18 months post-surgery: \$6 121

						- no BCRL patients with indirect costs n= 85					
Basta et al., 2016	Retrospective cohort study	To quantify the hospital recourse utilization for LE-related sequelae	USA (Arkansas, California, Florida, Nebraska, New York)	Women, at least 18y old, who underwent lumpectomy or mastectomy with ALND	Discharges with concurrent coding for both lumpectomy and mastectomy or lumpectomy with breast reconstruction, patients with metastatic diseases, unknown discharges or death	Total n= 56 075 (mean age 60.5 years) - BCRL n= 1279 - no BCRL n= 54 796	24 months follow-up from surgery (between 1/1/2007 and 31/12/2010) Note: for California: 12 months (between 1/1/2007 and 31/12/2009)	Not enlightened	Cost claims using the Healthcare Cost and Utilization Project (HCUP) inpatient databases (= census of hospital discharges from acute care, nonfederal, community hospitals). Primary outcomes: - all-cause hospital admissions -LE-specific hospital admissions - and corresponding health care charges	- Demographic data: age, primary payer (private insurance vs. other) - Initial treatment variables: primary diagnosis - Number of chronic medical conditions - History of tobacco use Using questionnaires	Health care charges due to hospitalization: - BCRL: ± \$58 088 costs/2 years

Boyages et al., 2016	Mixed-method qualitative and cross-sectional quantitative study	To investigate the impact of lymphedema over and above breast cancer on the financial costs borne by women	Australia	Control group: female, older than 18y old, previously diagnosed with primary stage I, II or III breast cancer, completed treatment at least 1y prior to recruitment, fluent in English BCRL group: Idem + confirmed diagnosis of LE	/	Total n= 361 - BCRL n= 152 - no BCRL n=209	Cross-sectional survey (recruitment between November 2014 and March 2015)	Patients with BCRL: - 41% skin care - 53% exercises - 61% MLD - 32% CS's - 23% laser therapy - 13% Taping - 3% IPC - 1% liposuction	Electronic survey containing questions regarding impact of BCRL on employment, cost of seeing therapists, cost of CS's	LE stage, patients with breast cancer (whether or not having the diagnosis of BCRL) received questions regarding: 1) employment/career, 2) family life, 3) social/leisure, 4) self-image and 5) feeling about self	Subdivision of reported costs was made regarding LE severity. In general: - Overall mean out-of-pocket costs for BCRL/year = A\$977 - Average cost of garment/year= A\$392
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Dean et al., 2018	Prospective explanatory mixed methods design	To compare long-term out-of-pocket direct and indirect costs among women with BCRL to those without LE diagnosis	USA (New Jersey, Pennsylvania)	Women with stages I-III invasive breast cancer, active breast cancer treatment completed, >1 lymph node removed, current residents of New Jersey or Pennsylvania	Active cancer, currently pregnant or planning to become pregnant in the next 6 months	Total n= 129 (mean age 63) - BCRL n= 60 - no BCRL n= 69	12 months (started: 2015)	Not enlightened	<u>Quantitatively:</u> 1) (in)direct costs and productivity losses using a cost diary (3 months retrospectively, 6 months prospectively and estimated costs last 3 months) 2) subjective rating of economic burden using the Breast Cancer Finances Survey <u>Qualitatively:</u> semi-structured interview (n= 40 with at least n= 10 of each group)	At baseline: Demographics (self-reported), cancer history and treatment (self-reported), health conditions (self-reported) and LE (interlimb volume difference using Perometry)	Excluding productivity losses: - BCRL group: ± \$2 306 out-of-pocket costs/year Including productivity losses: - BCRL group: ± \$3 325 out-of-pocket costs/year
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Abbreviations: PT= physical therapy, MLD= manual lymphatic drainage, CB= compression bandages, CS= compression sleeves, IPC= intermittent pneumatic compression, LE= lymphedema, DLT= decongestive lymphatic therapy

Notes: ^a patients with an L-Dex score of at least 10 (BIS), or a difference in sum of arm circumferences between both arms of at least 5cm.

APPENDIX 1. Overview of the Boolean search strategies used in the different databases

<p>PubMed 1-10-2018</p> <p>("Health Care Costs"[Mesh] OR "Health Care Costs"[All Fields] OR "Costs and Cost Analysis"[Mesh] OR "health care economics"[All Fields] OR "Costs and Cost Analysis"[All Fields] OR "Cost-Benefit Analysis"[Mesh] OR "Cost-Benefit Analysis"[All Fields] OR "Cost of Illness"[Mesh] OR "Cost of Illness"[All Fields] OR "Cost-of-illness"[All Fields] OR "Hospital Costs"[Mesh] OR "Hospital Costs"[All Fields] OR "Health Expenditures"[Mesh] OR "Health Expenditures"[All Fields] OR "Cost"[All Fields] OR "cost evaluation"[All Fields] OR "economic evaluation"[All Fields] OR "cost analysis"[All Fields] OR "economic analysis"[All Fields] OR "cost effectiveness"[All Fields]) AND ("lymphedema"[MeSH Terms] OR "lymphoedema"[All Fields] OR "lymphedema"[All Fields]) AND ("breast neoplasms"[All Fields] OR "breast neoplasms"[MeSH] OR "breast cancer"[All Fields] OR "costs"[All Fields] OR "breast cancer treatment"[All Fields] OR "direct costs"[All Fields] OR "health outcomes"[All Fields] OR "upper limb"[All Fields])</p>
<p>Web of Science 1-10-2018</p> <p>(TS=(("Health Care Costs" OR ("Health" AND "Care" AND "Costs") OR "Cost Analysis" OR ("costs" AND "analysis") OR "health care economics" OR ("health" AND "care" AND "economics") OR "Cost-Benefit Analysis" OR ("cost-benefit" AND "analysis") OR "Cost of Illness" OR ("cost" AND "illness") OR "Hospital Costs" OR ("Hospital" AND "Costs") OR "Health Expenditures" OR ("Health" AND "Expenditures") OR "Cost" OR "cost evaluation" OR ("cost" AND "evaluation") OR "economic evaluation" OR ("economic" AND "evaluation") OR "direct costs" OR ("direct" AND "costs") OR "health outcomes" OR ("health" AND "outcomes") OR "economic analysis" OR ("economic" AND "analysis") OR "cost effectiveness" OR ("cost" AND "effectiveness"))) AND ("lymphedema" OR "lymphoedema") AND ("breast neoplasms" OR ("breast" AND "neoplasms") OR "breast cancer" OR ("breast" AND "cancer") OR "lymphedema treatment" OR ("lymphedema" AND "treatment") OR "upper limb" OR ("upper" AND "limb")))) AND DOCUMENT TYPES: (Article)</p>
<p>Cochrane Clinical Trials 1-10-2018</p> <p>((("Health Care Costs" OR "Costs and Cost Analysis" OR "health care economics" OR "Cost-Benefit Analysis" OR "Cost of Illness" OR "Cost-of-illness" OR "Hospital Costs" OR "Health Expenditures" OR "Cost" OR "cost evaluation" OR "economic evaluation" OR "cost analysis" OR "economic analysis" OR "cost effectiveness" OR "direct costs" OR "health outcomes") AND ("lymphedema" OR "lymphoedema") AND ("breast neoplasms" OR "breast cancer" OR "lymphedema treatment" OR "upper limb")) in Title Abstract Keyword</p>
<p>EMBASE 1-10-2018</p> <p>('health care cost'/exp OR 'health care cost' OR 'cost analysis'/exp OR 'cost analysis' OR 'costs' OR 'health care economics'/exp OR 'health care economics' OR 'cost-benefit analysis'/exp OR 'cost-benefit analysis' OR 'cost of illness'/exp OR 'cost of illness' OR 'hospital costs'/exp OR 'hospital costs' OR 'health expenditures'/exp OR 'health expenditures' OR 'cost evaluation' OR 'economic</p>

evaluation'/exp OR 'economic evaluation' OR 'direct costs' OR 'health outcomes'/exp OR 'health outcomes' OR 'economic analysis' OR 'cost effectiveness'/exp OR 'cost effectiveness') AND ('lymphedema'/exp OR 'lymphedema' OR 'lymphoedema'/exp OR 'lymphoedema') AND ('breast neoplasms'/exp OR 'breast neoplasms' OR 'breast cancer'/exp OR 'breast cancer' OR 'lymphedema treatment' OR 'upper limb'/exp OR 'upper limb') AND ([article]/lim OR [article in press]/lim) AND [humans]/lim