# Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis

*Tracey DiSipio, Sheree Rye, Beth Newman, Sandi Hayes*

*Lancet Oncol* 2013; 14: 500–15

Published Online
March 27, 2013
http://dx.doi.org/10.1016/S1470-2045(13)70076-7

See Comment page 442

**School of Public Health and Social Work, Institute of Health and Biomedical Innovation, Queensland University of Technology, Queensland, Australia** (T DiSipio PhD, S Rye MAppSc, Prof B Newman PhD, S Hayes PhD)

Correspondence to:
Dr Tracey DiSipio, School of Public Health and Social Work, Faculty of Health, Queensland University of Technology, Victoria Park Road, Kelvin Grove, QLD 4059, Australia
**t.disipio@qut.edu.au**

## Summary

**Background** The body of evidence related to breast-cancer-related lymphoedema incidence and risk factors has substantially grown and improved in quality over the past decade. We assessed the incidence of unilateral arm lymphoedema after breast cancer and explored the evidence available for lymphoedema risk factors.

**Methods** We searched Academic Search Elite, Cumulative Index to Nursing and Allied Health, Cochrane Central Register of Controlled Trials (clinical trials), and Medline for research articles that assessed the incidence or prevalence of, or risk factors for, arm lymphoedema after breast cancer, published between Jan 1, 2000, and June 30, 2012. We extracted incidence data and calculated corresponding exact binomial 95% CIs. We used random effects models to calculate a pooled overall estimate of lymphoedema incidence, with subgroup analyses to assess the effect of different study designs, countries of study origin, diagnostic methods, time since diagnosis, and extent of axillary surgery. We assessed risk factors and collated them into four levels of evidence, depending on consistency of findings and quality and quantity of studies contributing to findings.

**Findings** 72 studies met the inclusion criteria for the assessment of lymphoedema incidence, giving a pooled estimate of 16·6% (95% CI 13·6–20·2). Our estimate was 21·4% (14·9–29·8) when restricted to data from prospective cohort studies (30 studies). The incidence of arm lymphoedema seemed to increase up to 2 years after diagnosis or surgery of breast cancer (24 studies with time since diagnosis or surgery of 12 to <24 months; 18·9%, 14·2–24·7), was highest when assessed by more than one diagnostic method (nine studies; 28·2%, 11·8–53·5), and was about four times higher in women who had an axillary-lymph-node dissection (18 studies; 19·9%, 13·5–28·2) than it was in those who had sentinel-node biopsy (18 studies; 5·6%, 6·1–7·9). 29 studies met the inclusion criteria for the assessment of risk factors. Risk factors that had a strong level of evidence were extensive surgery (ie, axillary-lymph-node dissection, greater number of lymph nodes dissected, mastectomy) and being overweight or obese.

**Interpretation** Our findings suggest that more than one in five women who survive breast cancer will develop arm lymphoedema. A clear need exists for improved understanding of contributing risk factors, as well as of prevention and management strategies to reduce the individual and public health burden of this disabling and distressing disorder.

**Funding** The National Breast Cancer Foundation, Australia.

## Introduction

Lymphoedema after breast cancer is characterised by regional swelling, typically in one or both arms, due to excess accumulation of protein-rich fluid in body tissues.[1] The adverse consequences of lymphoedema are well known, and cause much morbidity. Arm lymphoedema, and its associated symptoms, such as pain, heaviness, tightness, and decreased range of motion, impede daily function and adversely affect gross and fine motor skills, with negative ramifications for work, home, and personal care functions, as well as recreational and social relationships.[2] The appearance of a swollen and sometimes disfigured limb provides an ever-present reminder of breast cancer, which can contribute to anxiety, depression, and emotional distress in affected women.[3] Furthermore, preliminary findings show that lymphoedema might also lead to shortened survival.[4] In view of the increasing incidence of breast cancer worldwide, understanding the incidence of subsequent secondary lymphoedema and its associated risk factors is clearly of public health importance.

Individual studies report arm lymphoedema in up to 94% of patients with breast cancer,[5] with the wide variation (as low as 0%) in reported results an indication of differences in study design, diagnostic methods and criteria used, and timing of lymphoedema measurement with respect to breast cancer diagnosis and treatment.[6] Some estimates suggest that about 20% of women will develop arm lymphoedema after breast cancer—this estimation is the average incidence of studies that have been included in several systematic reviews of lymphoedema after breast cancer.[7–9] However, the average incidence of a group of studies does not take into account factors that are known to affect detection rates, such as study design or timing and method of lymphoedema assessment. How common such lymphoedema is after breast cancer is, therefore, unclear. Furthermore, our understanding of acquired and pre-existing risk factors is imperfect. Although more extensive treatment and a higher body-mass index have long been thought to be the major risk factors for the development of lymphoedema, advances in treatment over the past 10–15 years raise

questions about whether associations between the risk of lymphoedema and these characteristics, as well as other personal, treatment, and behavioural characteristics, have changed.

The body of evidence relating to the incidence of arm lymphoedema after breast cancer has grown substantially and has improved in quality during the past decade, now including findings from several prospective cohort studies. We therefore did this systematic review and meta-analysis to provide the most up-to-date estimate of the incidence of arm lymphoedema after breast cancer. Also, although the strength of treatment-related risk factors has been assessed in a 2009 meta-analysis,[10] it is important to also consider the strength and consistency of the association between lymphoedema and other non-treatment-related risk factors, as well as timely to update findings regarding treatment-related risk factors.

## Methods

### Search strategy and selection criteria

We did a systematic review to identify all studies addressing the incidence of, prevalence of, or risk factors for breast-cancer-related arm lymphoedema. We did a comprehensive search of databases including Academic Search Elite, Cumulative Index to Nursing and Allied Health, Cochrane Central Register of Controlled Trials (clinical trials), and Medline to identify studies published between Jan 1, 2000, and June 30, 2012, that included women who had undergone surgery for breast cancer. The search terms included keywords for breast cancer ("breast" and "cancer" or "onco*", or "neoplasm*"), lymphoedema ("lymphoedema" or "lymphedema"), and the outcomes of interest ("incidence", "prevalence", "risk factor", or "prognosis").

Eligibility criteria for inclusion of studies in this review and meta-analysis fell into six categories. Type of study: published research articles were included; review papers, meta-analyses, editorial or comment papers, case reports, and case series were excluded, as were randomised controlled trials that did not report lymphoedema at baseline or lymphoedema for the control group separately. Patient characteristics: studies of female patients with unilateral breast cancer were included; studies of patients with bilateral breast cancer, primary lymphoedema, or metastatic disease were excluded. Diagnosis of lymphoedema: self-reported swelling was the only symptom taken as an indication of self-reported lymphoedema; studies that reported the incidence of lymphoedema on the basis of only multiple symptoms (eg, "do you have pain, tingling, or weakness of the arm?") were excluded, because these symptoms are common irrespective of lymphoedema status,[11] and the inclusion of such symptoms might therefore lead to an overestimation of lymphoedema incidence. All objective methods of diagnosing lymphedoema were included. Outcome: incidence of, prevalence of, or risk factors for secondary lymphoedema were included—in the absence of pretreatment lymphoedema status, prevalence was thought to be a reasonable estimate of incidence because the proportion of women with lymphoedema before surgery for breast cancer has been reported to be very low.[12,13] Time period: outcome data measured within 3 months of diagnosis or surgery were excluded because arm-related changes during this timeframe were considered potentially indicative of an acute treatment-related response. Language and origin: we included studies available from all locations with reports written in English; non-English-language papers, when translations were unavailable, were excluded.

### Data extraction

One investigator (TD) selected articles that potentially met our inclusion criteria on the basis of their titles and abstracts. Full articles were then retrieved for a more detailed assessment. We developed a data abstraction sheet to collect necessary information to establish the level of evidence, study quality, and available outcome and risk factor details. From every included study, one investigator (TD) extracted data for study location (country), study design, sample size, time since breast cancer diagnosis, method of lymphoedema assessment, definition of lymphoedema, incidence or prevalence of lymphoedema, and any risk factor information. Study designs included randomised controlled trials, cross-sectional, prospective cohort, retrospective cohort, and case–control studies (case–control studies were only included for risk factor analysis). For our meta-analysis of incidence, we recorded results from randomised controlled trials assessing an exercise intervention: we included baseline data for the intervention groups and all data (including baseline date) for the control groups. Lymphoedema measurement refers to the technique used to define the presence of lymphoedema and included bioimpedance spectroscopy, arm circumferences, water displacement or perometry (optoelectronic volumeter), lymphoscintigraphy, clinician diagnosis, and patient-reported diagnosis by a clinician or self-reported swelling.

We categorised all studies that analysed the incidence of arm lymphoedema into levels of evidence, on the basis of study design, using levels of evidence (Prognosis column) defined by the Australian National Health and Medical Research Council (NHMRC).[14] Two investigators (TD, SR) independently categorised each study with disagreements resolved through discussion with a third assessor (SH) to attain consensus.

We assessed the presence of publication bias using funnel plots by precision, Egger's Test of the Intercept,[15] and Duval and Tweedie's trim and fill procedure (data not shown).[16] Funnel plots were analysed for the overall incidence and subgroup random effects models (relating to sentinel-lymph-node biopsy compared with axillary-lymph-node dissection) by plotting the event rate against the inverse of the SE. The funnel plot was symmetrical about the summary effect, with larger studies at the top