Title:

Upper-body morbidity following breast cancer: incidence and evidence for evaluation,
prevention and management within a prospective surveillance model of care

Running title:

Upper-body morbidity following breast cancer

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Condensed Abstract:

Upper-body morbidity, including lymphedema, is common following breast cancer and may persist beyond the active treatment period. Integration of a prospective surveillance model into breast cancer care has the potential to optimize early diagnosis and treatment of upper-body morbidity, and in doing so will enhance women's ability to participate in daily activities and their quality of life.

Abstract:

The purpose of this paper is to review the incidence of upper-body morbidity (arm and breast symptoms, impairments and lymphedema), methods for diagnosis, and prevention and treatment strategies. It was also the purpose to highlight the evidence-base for integration of prospective surveillance for upper-body morbidity within standard clinical care of women with breast cancer. Between 10-64% of women report upper-body symptoms between 6-months to 3 years post-breast cancer and approximately 20% develop lymphedema. Symptoms remain common into longer-term survivorship and while lymphedema may be transient for some, those who present with mild lymphedema are at increased risk of developing moderate-severe lymphedema. The etiology of morbidity seems to be multifactorial, with the most consistent risk factors being those associated with extent of treatment. However, known risk factors cannot reliably distinguish between those who will and will not develop upper-body morbidity. Upper-body morbidity may be treatable with physical therapy. There is also evidence in support of integrating regular surveillance for upper-body morbidity into the routine care provided to women with breast cancer, with early diagnosis potentially contributing to more effective management and prevention of progression of these conditions.

Key words:

Breast cancer, upper-body morbidity, lymphedema, incidence, prevention, treatment

I. Overview of the epidemiology of upper-body morbidity

Upper-body morbidity following breast cancer is typically characterized by the presence of sensory or motor symptoms and impairments such as pain, weakness, tightness, poor range of motion, nerve palsies, altered movement patterns or muscle recruitment, numbness, or swelling in the shoulder, arm and/or breast of the affected side. Upper-body morbidity is typically associated with alterations in the use and function of the upper-body and adverse physical, psychosocial and social ramifications that profoundly influence all aspects of daily life and hence quality of life (QoL).[1-7] Arguably, lymphedema (swelling) is regarded as the most feared and problematic.[5] The purpose of this paper is to review upper-body morbidity incidence and risk factors, methods for diagnosis, and prevention and treatment strategies. The evidence-base for integration of prospective surveillance of upper-body morbidity within standard clinical care of women with breast cancer will also be highlighted.

II. Incidence of upper-body morbidity post-breast cancer

Upper-body symptoms and impairments

Despite advances in breast cancer treatment methods that have led to less invasive surgical techniques, such as sentinel node biopsy,[8-9] and more refined radiation techniques, such as intensity modulation,[10-11] upper-body symptoms and impairments that impact function and quality of life remain common. Incidence of individual symptoms, such as pain and weakness, as well as nerve palsies, skin fragility, soft tissue fibrosis and inflammation have been the focus of prior research studies.[12-21]

In the past 10 years, the presence of upper-body symptoms following breast cancer has been evaluated in more than 20 studies,[2, 9, 22-41] including 7 cohort studies involving population-based samples (Table 1).[22-24, 33-34, 42-43] A wide range in prevalence was reported across these studies, with higher rates generally observed in cohort studies compared with clinical trials. Symptoms (which may have included any one or more of the following: weakness, stiffness, numbness, tingling, pain, poor range of motion, swelling) was assessed in these studies via self-report methods using validated or non-validated questions. The majority of studies assessed only a subset of the known symptoms reported by women with breast cancer (e.g., weakness, stiffness and tingling were rarely assessed) and it is plausible that the entire spectrum of possible upper-body symptoms that women may experience is yet to be fully understood. The inclusion of mild symptoms as being indicative of morbidity was variable. At least 10%, but as many as 60% of women report at least one upper-body symptom at any point from 6-months to 3-years post-breast cancer surgery (Table 1). Pain (e.g., breast, axilla, myofascial pain) has possibly received the most attention of all symptoms, with its prevalence ranging from 12-51%.[13-14]

One challenge in drawing conclusions about the frequency of upper-body symptoms is that studies vary with regard to length of follow-up. There are 2 population-based studies that have assessed upper-body symptoms beyond 3 years. Results suggest similar prevalence between 4-5 years post-surgery (up to 56% of women report at least one symptom)[24, 33] to that observed during 6 months to 3 years post-surgery. Also, the presence of multiple symptoms is more common than having one symptom alone. In a population-based, prospective cohort study of Australian women, the majority of those

reporting moderate-extreme symptoms report multiple symptoms between 6-18 months post-surgery (56-68% across time points).[42] In this issue of *Cancer*, it is noted that at 6 years post-diagnosis, over 50% of breast cancer survivors from that same Australian cohort report one or more upper-body symptom (see Schmitz et al in this supplement). Taken together, these results indicate that upper-body morbidity is common following breast cancer and remains common well beyond the treatment period.

Lymphedema

Lymphedema is caused by a disruption of the lymphatic system that in the initial stages, leads to the accumulation of fluid in the interstitial tissue space (that is, increases in extracellular fluid) and eventually clinically manifests as swelling of the arm, breast, shoulder, neck or torso.[44] Later stages of lymphedema are characterized by deposition of fibrotic and adipose tissue.[45]

It is well established that the chosen diagnostic method used to assess lymphedema influences the results found in observational studies.[46-48] Bioimpedance spectroscopy assesses changes in extracellular fluid and has been shown to identify limb changes before clinical presentation of the condition and until the condition becomes non-pitting (fibrotic).[49] Methods that assess limb size (such as water displacement, perometry or circumferences), with or without conversion of measure of size to limb volume, can detect non-pitting and pitting lymphedema of sufficient magnitude, but may be insensitive to early changes in extracellular fluid. Self-report methods (such as the Norman questionnaire,[50] the Lymphedema Breast Cancer Questionnaire,[51] the Lymphoedema Quality of Life Inventory,[52] items from validated QoL-specific

questionnaires (such as FACTB+4,[53] EORTC QLQ-C30[54]) or via non-validated

questions) take into account perceived sensory and size changes, as well as presence and

intensity of related symptoms. However, as demonstrated earlier, the presence of

symptoms are common in women following breast cancer, and this is irrespective of

lymphedema status.[42] A study that used multiple measures to assess lymphedema status

in women 6-months post-breast surgery found that 40% of those with objective

lymphedema (defined by bioimpedance spectroscopy) did not self-report swelling, and

40% of those without objective lymphedema did.[48] A USA-based study similarly found

that breast cancer survivors met four different lymphedema criteria at various rates of

occurrence (43-94%), with 11% meeting all four criteria and 84% meeting at least one

criterion.[55] All clinical measures, when undertaken by trained personnel, and the

validated self-report measures have proven repeatability. However, each method's

accuracy in diagnosing cases (as well as avoiding misclassification of non-cases) is

dependent on which other diagnostic method it is being compared against.[56] As yet, there

is no agreement of which method, or combination of methods, reflects the most accurate

diagnostic tool.

Given the variation in available diagnostic methods, which ultimately assess

different attributes of lymphedema, it is not surprising that the extent of the public health

burden posed by secondary lymphedema has long been clouded by wide variations in

reported incidence. Reported rates in women following treatment for breast cancer have

varied from 6-80%.[57] Also contributing to the wide variation in incidence is timing of

measurement (2 months to 20 years post-breast cancer) and the type of cohort evaluated

(may have included only those who underwent axillary dissection and/or radiation therapy).

In the past five years, 11 prospectively-designed studies (graded as Level II prognostic studies according to the National Health and Medical Research Council, Australia)[58] have reported incidence estimates of secondary lymphedema following breast cancer (Table 2). These studies used objective diagnostic criteria and included samples generally representative of the larger breast cancer population. Median reported incidence in these 11 studies was 20% (range, 0-94%). It therefore seems plausible to suggest that from six months post-surgery, approximately one in five patients treated for breast cancer will experience secondary lymphedema. The median rate appears to increase with longer follow-up, escalating from 11% up to 12 months to 36% beyond 12 months. Findings also suggest that 45-60% of patients with long-term secondary lymphedema present with the condition by 6 months post-surgery,[59-60] while 70-80% present by 12 months post-surgery.[60-61] Consequently, it seems clear that despite advances in breast cancer treatment over the past decade, lymphedema continues to be a common concern, with new cases presenting well beyond the active treatment period.

Lymphedema is regarded as a persistent or chronic condition. However, results from 2 prospective studies, one using an objective measure[61] of lymphedema status and the other a validated self-report measure,[62] suggests this may not be the case for all women. The studies demonstrated that up to 60% of women with evidence of lymphedema had 'acute' lymphedema (lasting no more than 5 months), dissipating with or without treatment (although commencement of, or adherence to, treatment was not formally assessed). Between 30-40% had chronic and/or progressive lymphedema and

between 15-22% had fluctuating lymphedema, which may have included intermittent periods without symptoms. Therefore, lymphedema seems transitory for some, with or without treatment, and long-term for others, with or without intermittent periods of relief. This variable nature of lymphedema may further contribute to the wide range of incidence reported throughout the literature. Importantly though, those who present with mild lymphedema are at increased risk (up to 3 times increased risk) of developing moderate to severe lymphedema.[62-63]

III. Identifying known risk factors for the development or exacerbation of upper-body morbidity

The extent of upper-body morbidity following treatment for breast cancer has been a major driving force in the quest for identifying less invasive treatment strategies that could reduce morbidity without adversely influencing survival.[26] An established and growing literature base clearly demonstrates that upper-body morbidity is higher among those who undertake more invasive treatment options, such as axillary dissection versus sentinel node biopsy, mastectomy versus breast-conserving surgery, and/or radiation to the breast/chest wall and regional nodes versus radiation to the breast/chest wall only.[31, 64-68]

Injury to the intercostal brachial or thoracodorsal nerve may occur with axillary lymph node dissection and is a major cause of axillary paresthesia, muscular dysfunction (e.g., dysfunction of the serratus anterior or latissimus dorsi) and pain.[14,69] Nerve injuries may resolve over several months without therapeutic intervention; however, the

implications to muscle recruitment pattern, flow-on effect to surrounding musculature and use of the arm may be permanently altered without intervention.[70]

Research on radiation-induced upper-body morbidity has uncovered a wide range of issues, including skin fragility,[16-17] fibrosis and inflammatory changes to the soft tissue in the irradiated area,[17, 71] as well as brachial plexopathies and other neuropathic impairments that may lead to sensory and motor changes.[72-74] Radiation-induced soft tissue fibrosis is generally mild, and chronic radiation fibrosis is rare. Nonetheless, chronic fibrosis is significant and problematic and unfortunately its development and effective management is not well understood. Clinically, it is noted that fibrosis contributes to diminished joint mobility and may foster short and potentially long-term shoulder, scapulae and postural changes. Historically, due to poor shielding techniques and inadvertent exposure of the plexus to the radiation beam, radiation therapy also contributed to severe brachial plexopathies and neuropathic impairments.[72] However, modern techniques protect the brachial plexus and prevent inadvertent nerve damage. Brachial plexopathy is now considered rare, even in women for whom the supraclavicular and axillary regions are treated. Nonetheless, when it occurs, sensory and motor changes in the upper-body present, with severe cases experiencing paralysis. Results from 2 studies with over two decades of follow-up[73-74] have shown that the rate of radiation-induced soft tissue damage and neuropathies was estimated to be 1% per year, netting a cumulative incidence of near 20% by 20 years post-therapy.[73-74] While incidence estimate may no longer be representative of women treated with radiation therapy for breast cancer today, they underscore the need for long-term follow-up.

The contribution of diagnostic factors (including tumor size, positive lymph node status, stage of cancer), physiological characteristics (such as lymphatic transport, vein wall movement and venous anatomy and flow), and patient and behavioral characteristics (including body mass index, age, treatment on the dominant side, physical activity levels and socioeconomic status) with respect to development of lymphedema have also been evaluated.[57]   To date, results derived from prospective cohort studies suggest that stage of disease, node status and adjuvant therapy other than radiation therapy does not impact lymphedema risk.[57] However, as adjuvant therapies continue to evolve, their relationship with lymphedema risk will require continued exploration.

More work is also required to better understand the physiological changes associated with increased risk of lymphedema. Higher body mass index has long been considered a risk factor for lymphedema.[60, 75-80] However, when findings from more recent studies are considered the relationship is less clear, with several prospective cohort studies demonstrating no relationship between higher body mass index and lymphedema risk.[9, 61, 81] Nonetheless, higher body mass index has never been associated with reduced risk and the importance of maintaining healthy body weight in relation to other breast cancer outcomes is clear (see Demark-Wahnefried et al in this supplement). The relationship between age and risk of lymphedema is mixed, with some studies showing no relationship,[9, 60, 81] while others showing increased risk with increasing age.[61, 82-83] Race, upper-body function[61] and physical activity levels[61, 84-85] may also be associated with lymphedema risk; specifically, being African American,[86] having lower than average upper-body function and being sedentary has been associated with increased lymphedema risk.[61] Finally, those with lymphedema are more likely to report multiple

upper-body symptoms, and the presence of symptoms has been significantly associated with subsequent lymphedema development.[27]

While a number of risk factors for the development of lymphedema have been identified, at present it is not possible to accurately predict who will and will not develop this condition.[87] In one prospective, population-based study of 287 newly diagnosed breast cancer patients, 12 key treatment-related, personal and behavioural characteristics were identified as important factors with respect to lymphedema risk. However, together they explained no more than 35% of the variation between those who did and did not develop lymphedema.[42]

IV. Methods to detect upper-body morbidity

Self-report and objective methods available for detecting and monitoring lymphedema were reviewed in an earlier section (section II). When deciding which assessment method(s) are optimal, several factors must be considered, such as the sensitivity and specificity of the measure, whether the measure has been shown to detect 'subclinical' lymphedema (before patients report symptoms) and whether the measure is affordable, transportable, practical for clinic use, non-invasive and time efficient.[88] Given different methods assess different elements of lymphedema, the use of multiple assessment methods is ideal, particularly for tracking change over time.

Shoulder function can also be evaluated using any one or more of self-report or clinical methods. Validated questionnaires such as the BREAST-Q[89] and the Disability of the Arm, Shoulder and Hand questionnaire[90] provide comprehensive self-report assessment of upper-body morbidity, as well as the presence and severity of specific

symptoms. Standardized procedures exist for the assessment of active and passive shoulder range of motion in all planes using goniometry,[91] while strength and function can be assessed using isometric and isokinetic dynamometry and/or maximal or submaximal performance of set tasks/exercises using the repetition maximum method.[92] However, upper-body assessment may also involve palpation of areas, particularly in the assessment of myofascial pain[93] and tightness.[31] Visual inspection of posture of the whole body, as well as the upper-body in routine position, performance of spontaneous activities and planned tasks provides additional information regarding upper-body function.[94] Finally, it is noted that a clinical assessment involves understanding existing function in addition to revealing specific impairments.[94]

V. Evidence-based prevention and treatment strategies

Prevention strategies for minimising upper-body morbidity have focused on the use of less invasive treatment methods when clinical presentation of the disease allows and the use of shoulder exercises after breast cancer surgery to optimise function. The evidence base for prevention and treatment of upper-body morbidity is presented below.

Upper-body symptoms and impairments

Studies that have assessed the effectiveness of post-operative physical therapy contend that physical therapy is beneficial for upper-body function and does not cause any adverse effects.[95-99] These studies have been limited in sample size. In general, there is scant evidence base for the efficacy of rehabilitative (e.g. physical therapy) or exercise interventions to prevent or treat upper-body symptoms or shoulder dysfunction in breast cancer survivors beyond studies specific to lymphedema. In the absence of a strong

evidence base, the commonly used clinical approach to treating several upper-body symptoms and impairments is outlined below.

Standard physical therapy approaches to dealing with pain include gentle range of motion exercises, stretching, acupressure, myofascial stretching, as well as dry needle techniques.[93] Patient education to identify positions or activities that alleviate the symptoms is important for self-care management and a gradual, progressive mobility program is encouraged. Clinically, pain management often requires an ongoing, multidisciplinary approach to monitor changes with treatment and assess response to medication. New onset pain or increasing pain may have additional etiologies including tumor infiltration of the brachial plexus or tumor recurrence.[100]

Early assessment and intervention post-surgery, by way of education and shoulder exercises, is important to correct subtle treatment-related changes in scapulae position and stability that left untreated may lead to upper-body symptoms and impairments, and to also correct muscle recruitment imbalance.[95, 101] Ongoing assessment and education is necessary to determine if tissue changes that may occur during and beyond the adjuvant treatment period, such as shortening of the pectoralis major, perpetuate existing, or lead to the development of, upper-body morbidity.[102] Range of motion exercises play a particularly important role during and after radiation treatment to enhance tissue extensibility and promote normal movement patterns[101] and should be encouraged indefinitely to avoid tissue contracture and concomitant alterations to the joint mechanics of the shoulder. Further, manual techniques such as myofascial release have also been considered useful in improving tissue extensibility and enhancing mobility.[103]

Lymphedema

In the prevention of lymphedema, two randomized, controlled trials, one evaluating the effectiveness of a 'physiotherapy management care plan' (including education and progressive exercises)[104] and the other evaluating a physical therapy program that included manual lymph drainage, massage of scar tissue and progressive exercises),[105] have demonstrated clinically relevant benefits. Both studies showed a higher proportion of women with lymphedema in the comparison group, compared with the physical therapy intervention group. The trial that included manual lymph drainage as part of the intervention demonstrated that the risk ratio for developing lymphedema in the intervention group was 0.25 (95% CI: 1.10, 0.79) compared with the control group. Results from another randomized, controlled trial suggest that delayed (7 days post-operative) versus early (within 48 hours post-operative) commencement of shoulder exercises was more favourable with respect to lymphedema development.[106]

Notably though, the commonly available risk-reducing lymphedema guidelines are loosely based on what will minimise the production of lymph, which is directly proportional to blood flow, and what will minimise blockage to lymph transport.[107] For example, heat, infections and exercise may increase blood flow and therefore lymph production in the arm, while tight clothing may obstruct lymph flow.[107] Unfortunately, the evidence to support or refute these guidelines is scarce. There is a clear need for well-designed, population-based, prospective studies to investigate the potential causal relationship between participating in 'risky' behaviours and subsequent lymphedema development. Until this occurs, it seems reasonable for prevention strategies to be discussed with women, especially in the context of encouraging healthy behaviours, such as participation in regular exercise and maintaining healthy body weight. In fact, results

from a prospective, population-based cohort study as well as a randomized, controlled trial suggest that participating in regular exercise following breast cancer may prevent the development of lymphedema.[61, 108]

The goals of secondary lymphedema management include reduction of swelling, prevention of progression, alleviation of associated symptoms, prevention of infection and improvement in function and quality of life. Treatment options can be broadly categorised as conservative, surgical, pharmacologic or alternative. The evidence behind lymphedema treatment options has previously been reviewed.[57, 109-110] Findings from these reviews, as well as results from treatment studies published in the last 3 years are summarised below to provide an overview of the evidence for various lymphedema treatment options.

Treatment effects (limb volume reductions) for conservative treatment options are in the range of 8-66%, with several studies reporting continued reductions over 6-12 months follow up. Volume reductions achieved by manual lymph drainage or pneumatic pumps tended to be higher when therapy was combined with other conservative treatment options, such as compression and massage. However, compression alone or in combination with other treatment, led to volume reductions of 4-60% measured at 4 weeks to 6 months follow up. When reported, response rates varied between 28-66%, and characteristics of those lost to follow-up were typically not reported. Lack of reference to clinically meaningful changes, questionable representativeness of sample, potential bias caused by significant numbers lost to follow-up (likely more so for those not experiencing treatment effects), and lack of control group and/or adjustment for potential confounders severely influences the strength of these findings. Nonetheless, there is a

growing body of low-level evidence in support of these therapies, which ultimately form the primary method currently used to treat lymphedema.[111]

Low-level laser therapy (light source treatment that generates light of a single wavelength, but does not emit heat, sound or vibration) has been used as a form of lymphedema treatment since 1995 in some countries, but only received FDA approval in the USA in 2007.[112] Research in the area is limited and should be regarded as encouraging but preliminary. A randomised trial of low-level laser therapy (LTU-904 hand-held laser, RianCorp) in women with post-mastectomy lymphedema reported a trend towards reductions in arm volumes over time following two cycles of treatments, but that despite these reductions, volumes at the 3 month follow-up were not statistically different from baseline values.[113] Other studies have reported 16-79% volume reductions (using various hand-held laser devices), but compare changes to another treatment group[114] or lack a control group.[112, 115-116]

There have been several investigations evaluating the role of exercise on lymphedema status, with varying methodological qualities. Randomised, controlled trials have evaluated the role of combined exercise and relaxation therapy,[117] aqua therapy,[118] combined aerobic- and resistance-based exercise[119] and weight training.[120-121] Sample size within these studies ranged between 31-141, intervention duration ranged from 8 weeks to 12 months and lymphedema status as well as other physical and psychosocial outcomes were typically assessed. All studies demonstrated that exercise did not exacerbate existing lymphedema and had positive effects on other outcomes influencing function and quality of life. The largest of the trials, evaluating a 12-month weight-training intervention (n=141), also demonstrated significant improvements in

lymphedema-associated symptom severity, as well as reduced lymphedema exacerbations, compared with the control group.[121] The results of these trials support the use of progressive exercise, with supervision at least in the earlier part of the intervention, in optimising upper-body outcomes. Current lymphedema prevention guidelines have been labelled 'risk averse' and may therefore encourage women to avoid use of their arms and bodies. Results from exercise intervention studies involving women with lymphedema highlight the need for encouragement rather than avoidance of participation in physical activity following breast cancer.[122]

The association between body weight and lymphedema risk has led to two studies investigating the potential for weight-reduction strategies to reduce lymphedema.[123-124] While results suggest that weight-reducing strategies may be useful in the management of lymphedema, further studies utilising larger sample sizes and lymphedema assessment methods that are not sensitive to weight changes are warranted (e.g., bioelectrical impedance spectroscopy).

The use of medications to manage secondary lymphedema is of continued interest with emphasis to date being placed on benzopyrones and selenium compounds. Systematic reviews of the literature evaluating the use of these compounds in lymphedema management report that there is no evidence in support of their use.[125-126] More recently, a randomized, controlled study of 12 months treatment with pentoxifylline (which is used to improve blood flow through peripheral blood vessels) and vitamin E for the prevention of radiation-induced side effects in breast cancer patients (n=83), showed increases in arm volume in the control group but no change in the intervention group.[127]

Surgery for lymphedema includes debulking procedures to remove excess skin and subcutaneous tissue (e.g., liposuction) or the creation of new pathways for draining lymph (e.g., microsurgery, lymphatic-venous anastomosis). Surgery is typically only recommended when conservative treatment options have failed to be effective, and lymphedema is chronic and pitting. Although limited by study design (comparative studies without concurrent controls or case series) and small sample size, excellent results from studies evaluating liposuction[128-130] and lymphatic vessel-isolated vein anastomosis[131-132] have been reported, with complete resolution of excess limb volume, in addition to improvements in function and quality of life, being reported in several liposuction studies.[128-130] The potential for scarring and other complications, as well as the need for continued use of compression garments following surgery, restricts the use of this treatment to a specific subset of women with relatively severe lymphedema who experience no response to conservative treatment.

There is significant room for improvement in studies evaluating treatment for lymphedema. Weak designs continue to influence the strength of the findings reported and there is high potential for over-reporting of treatment effects. Despite the need for more research into effective lymphedema treatment strategies, a number of treatment guidelines have been developed using the available evidence (Australia: National Breast and Ovarian Cancer Centre;[133] Canada: Health Canadal;[134] Europe: European Society for Breast Cancer Specialists;[135] Sweden: Swedish Cancer Society;[136] UK: National Institute for Health and Clinical Excellence, Clinical Resources Efficiency Support Team;[137] USA: National Lymphedema Network,[138] Agency for Healthcare Research and Quality,[139] Oncology Nursing Society[140]).

VI. Overview of the potential role that prospective surveillance would play in early identification and treatment, and whether there is a need to establish baseline measures

Prospective surveillance may play an important role in the early detection and management of upper-body morbidity. Within the broader breast cancer setting, impairments detected within the hospital setting are more likely to receive intervention, and this is particularly the case for low socioeconomic and minority status groups.[141-142] This may be as a consequence of increased scrutiny in the inpatient setting, the presence of critical pathways and/or the absence of specific access barriers.

More specific to upper-body morbidity though, results from a prospective, cohort study provide preliminary findings that support the integration of formal regular surveillance.[143] In this study, lymphedema was identified in 43 of 196 women prospectively followed. When an increase in limb volume of >3%, compared with pre-operative volume (as assessed via perometry), was observed, compression garments were prescribed for 4 weeks. Limb volumes were significantly reduced following the compression garment period. Notably this was a cohort study and not a randomized, controlled treatment trial, limiting the strength of these findings. Nonetheless, even if the 3% limb volume change represented post-surgical swelling, which may spontaneously resolve, other research has reported higher risk for lymphedema at 6-9 months after surgery following post-surgical swelling.[144] Further, others have also demonstrated that those with mild lymphedema are at greater risk of developing chronic and more severe lymphedema.[62] Importantly, this prospective surveillance cohort study demonstrated that

regular assessment of upper-body morbidity (including preoperative measures) in a busy breast cancer clinic is possible, and that women were accepting of wearing compression garments for a 4-week period (although compliance with garment-wear was not tracked). This garment intervention is in contrast to many lymphedema treatment options being considered costly with respect to time, finances and lifestyle.[57] These findings are supported by another prospective breast cancer cohort study, which spanned a 10-year period (n=292).[145] Results from this study also demonstrated that the integration of regular surveillance is feasible and beneficial. Further, early diagnosis and treatment translated to more manageable lymphedema; 80% of those diagnosed with lymphedema throughout the follow-up period did not exceed 20% limb ratio volumes.

The personal costs associated with lymphedema are well known and documented, but data have only recently become available to demonstrate the potential overall financial costs. Women with lymphedema following breast cancer have between $14,887-23,167 more medical costs when compared with women without lymphedema.[146] Women with lymphedema also have more productive days lost than those without (73 versus 56 days). So while there is a clear desire for minimizing over-diagnosis of lymphedema, this must be balanced by what may be gained with early diagnosis and intervention.

The evidence presented throughout this paper provides support for the integration of regular surveillance of upper-body morbidity within standard breast cancer care, as is recommended by the prospective model published in this supplement (see Stout et al in this supplement). Pre-operative assessment of upper-body morbidity is ideal, particularly for bilateral breast cancer cases; however, pre-operative assessment is not 'true' baseline,

with the contribution of the cancer to upper-body morbidity currently unknown. Further, regular post-operative surveillance can still be successful in the absence of pre-operative measures. For unilateral breast cancer, presence and severity of upper-body symptoms, impairments and lymphedema can be compared with the contralateral limb, and for some lymphedema measures, such as bioimpedance spectroscopy, comparisons can be made with the lower-limb in the absence of an unaffected upper-limb.[147] Long-term follow-up after breast cancer has merit due to the observations that physical impairments may persist for years after treatment (see Schmitz et al in this supplement) and that some types of upper-body morbidities (e.g. radiation damage) may persist for decades after treatment.[72-73]

Comprehensive assessment of upper-body morbidity, using clinical and self-report methods is ideal, although may be impractical to administer in a busy clinic setting. A possible solution may be to ensure comprehensive assessment occurs in the first instance (pre-operative and/or first post-operative assessment), with subsequent reliance on one or select method(s) for follow-up measurements, with adverse changes in self-report symptoms or the clinical measure dictating a subsequent more comprehensive assessment. Regularity of the measurement may be variable within treating centres and scheduled among normal post-operative, adjuvant treatment or post-adjuvant treatment visits. Monthly to once every three months seems a reasonable surveillance interval, through to 12 months post-surgery, with less regular surveillance occurring beyond that period. Given that lymphedema may be transient, fluctuating or chronic, consideration may be given to increasing regularity of surveillance when clinical evidence of the condition presents or patients self-report change in symptoms, and initiation of treatment

only after a predefined threshold (volume or time) is met. Also, diagnosis of lymphedema within the first three months post-surgery or radiation is cautioned, as there is the risk of misclassifying normal post-treatment swelling. Surveillance should be supplemented with patient education on early signs and symptoms of upper-body morbidity, in particular progression of severity of concerns.[148]

VI. Summary

Upper-body morbidity is common following breast cancer and although more extensive treatment has been consistently linked with higher incidence of morbidity, morbidity remains common despite the introduction of less invasive treatment options. Upper-body symptoms, impairments and lymphedema typically present within the first 12 months following breast surgery (although cases can present years later), and as such, integration of regular surveillance into standard breast cancer care is considered appropriate and has been shown to be feasible. Participation in regular and progressive physical activity following a breast cancer diagnosis may optimize function and quality of life, as well as minimize upper-body morbidity. Upper-body morbidity seems amenable to physical therapies, with early diagnosis likely facilitating more effective treatment, as well as prevention of progression.

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Table 1: Prevalence of upper-body symptoms reported by prospective, population-based cohort studies

Study	Sample size (n) (country)	Symptoms assessed	**Months post breast cancer diagnosis/surgery (Any one symptom prevalence[a])**				
			6 (10-53%)	12 (10-61%)	18 (10-44%)	24 (21-66%)	36 (19-54%)
1. Albert et al (2006)[22]	389 (Germany)	swelling, poor ROM, pain	27%%	19%	20%	21%	19%
2. Arndt et al (2006)[23]	314 (Germany)	swelling, poor ROM, pain		24-30%			
3. Engel et al (2003)[24]	990 (Germany)	swelling, poor ROM		47%		44%	40%
4. McCredie et al (2001)[33]	809 (Australia)	stiffness, swelling, numbness, pain		16-61%		21-66%	22-54%
5. Paskett et al (2007)[34]	622 (USA)	swelling	20%	36%	44%	48%	54%
6. Hayes et al (2010)[42]	285 (Australia)	tingling, weakness, pain, poor ROM, numbness, stiffness, swelling	10-29%	10-22%	10-19%		
7. Janz et al (2007)[43]	1372 (USA)	breast, arm/shoulder pain	46-53%				

[a] studies measured at least one of the following symptoms: tingling, weakness, pain, poor range of movement (ROM), numbness, stiffness, swelling; may have included mild symptoms and used various self-report methods including items from quality of life questionnaires or unvalidated items.

Table 2: Reported incidence of secondary lymphedema (objectively measured) in prospectively-designed breast cancer cohort studies published between 2007–2011

Country and study	Sample size	Method of diagnosis	Reported incidence post-surgery (%)		
			6-month PS	12-month PS	18-month+ PS
Australia					
Hayes et al (2008)[56]	211	BIS, >3SD than normative data, circ, >5cm difference[b]	11%	8-11%	12-15%
Belgium					
Devoogdt et al (2011)[149]	49	circ, >10% difference[b]			18%
Canada					
Helyer et al (2009)[150]	137	per, >200cc difference[b]			12%
Thomas-MacLean et al (2008)[38]	347	circ, 3 definitions of difference[b]		9-16%	
England					
Bennett Britton et al (2007)[151]	50	circ, >10% difference[b]		11%	28%
Korea					
Yang et al (2010)[41]	191	circ, >1cm difference[b]	9%	12.0%	
Norway					
Nesvold et al (2008)[152]	263	circ $\geq$2cm change[a] or $\geq$10% difference[b]			RM=20% BCT=8%
Sweden					
Celebioglu et al (2007)[153]	60	per, >10% difference[b]			SNB=0% ALND=20%
United States of America					
Armer et al (2010)[154]	213	circ, $\geq$2cm change[a], per $\geq$200mL or $\geq$10% change[a]	11-44%	22-66%	29-94%[c]
McLaughlin et al (2008)[155]	936	circ, >2cm change[a]			SLNB=5% ALND=16%

| Wernicke et al (2011)[156] | 223 | circ, 1cm difference[b] | SLNB=5% |
| | | | ALND=35% |

Abbreviations: PS, post-surgery; circ, circumferences; per, perometry; BIS, bioimpedance spectroscopy; RM, radical mastectomy; BCT, breast conserving treatment; [a] change from baseline, [b] difference between limbs, [c] range of occurrence rates of lymphedema measured at 18, 24, 30, 36, 48, or 60 months (using 3 definitions).