

# IMPERATIVES FOR RESEARCH TO MOVE THE FIELD FORWARD

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Worldwide, more than a million women are newly diagnosed with breast cancer every year, accounting for one-tenth of all new cancers and nearly one-quarter (23%) of all female cancer cases (American Cancer Society [ACS], 2007).

All breast cancer survivors are at lifetime risk for developing lymphoedema, limb, breast or truncal swelling following treatment (ACS, 2007; Casley-Smith, 1992). Depending on diagnostic criteria applied, estimates of post-breast cancer lymphoedema vary. Although typically less than half of breast cancer survivors may develop lymphoedema, even using conservative estimates, the number of survivors affected and potentially affected by secondary lymphoedema is staggering.

## Extent of the problem

Perhaps in part because of difficulties in limb measurement and lymphoedema diagnosis, the reported incidence of lymphoedema varies greatly among women treated with surgery and radiation for breast cancer.

There is a common misconception that lymphoedema is not a problem of the present or future due to modern procedures such as sentinel lymph node biopsy (SLNB), and breast conservation surgical approaches such as lumpectomy. However, recent published data has revealed lymphoedema occurrence to be at a significant level of concern in spite of these improved techniques (Wilke et al, 2006). Clinicians and researchers have reported modest estimates of

lymphoedema following breast cancer surgery even for SLNB-only patients (Petrek et al, 1998; Kattlove et al, 2003; Armer et al, 2004; Jacobs, 2004; Wilke, 2006). The recent American College of Surgeons Oncology Group (ACOSOG) data reveals lymphoedema incidence of 7% after SLNB-only at a short follow-up to six months (Wilke, 2006). Because this SLNB-only group with node-negative disease represents the group at lesser risk for lymphoedema, and because this lymphoedema occurrence is commonly reported by clinical observation rather than objective limb measurement, there is a high probability that the condition is under-represented. Further, current protocols require more extensive nodal dissection for node-positive disease, creating a group at higher lymphoedema risk than those receiving SLNB-only (Kett et al, 2002; Clark et al, 2005; ACS, 2006; ACS and National Comprehensive Cancer Network, 2007). Based on even the lowest estimates in the US, lymphoedema affects hundreds of thousands of women over their lifetimes and represents a major societal problem. Worldwide, it is an even greater concern (Wilke et al, 2006; National Cancer Institute, 2004).

In a three-year follow-up study in Britain of breast cancer patients (N=188 retained of 251 enrolled), 20.7% developed lymphoedema, with risk factors identified as hospital skin puncture, mastectomy, and body mass index (BMI; >26) (Clark et al, 2005). Of the 39 with lymphoedema, 20 (51.3%) were diagnosed prior to the three-year follow-up. These 20 included nine (45%) diagnosed by six months, and 16 (80%) by 12 months. Beyond these 20 who were diagnosed prior to the three-year follow-up, 19 more (48.7%) were found to have lymphoedema at the three-year

follow-up (Clark et al, 2005). This finding suggests a bimodal distribution of early- and late-onset lymphoedema, which should be further explored in additional studies with rigorous measurement at diagnosis and long-term follow-up.

## Reducing lymphoedema occurrence

Early detection and intervention hold the greatest promise of reducing this widespread condition (Rockson, 1998; Petrek et al, 2000). Identification of epidemiological and clinical factors associated with risk and incidence will provide the necessary foundation for preventive intervention. Although personal and historical characteristics such as age, weight, infection, radiation therapy, BMI and axillary dissection are generally believed to affect women's risk for lymphoedema onset (Deutsch and Flickinger, 2003; Kattlove et al, 2003; Clark et al, 2005), research has found that patient compliance is the most important factor in treating lymphoedema (Rose et al, 1991; Petrek et al, 2000).

Little is known about factors influencing patient compliance and effective self-management strategies for lymphoedema symptoms. For example, many of the most promising lymphoedema management techniques are time-consuming, difficult to accomplish by patients themselves, and may be vulnerable to incomplete patient compliance without strong support and practical assistance from family or friends (Cheville et al, 2003; Radina and Armer, 2004). Such support and practical assistance may diminish over time (Manne et al, 2003). Unfortunately, support groups and training in practical problem-solving seem to be infrequently available to patients, as documented by the

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limited number of lymphoedema support groups in the US listed by the National Lymphedema Network (NLN) (167 in 2003; 75 in 2008; source [www.lymphnet.org](http://www.lymphnet.org)), and certified lymphoedema therapists (441 in 2003; 907 listed as trained or Lymphology Association of North America [LANA] members in 2008) in all 50 US states.

As limited as are the proven-effective physiological interventions in lymphoedema management (Johansson et al, 1999), testing of psychosocial interventions has been even more limited. Our preliminary data analysis from an ongoing study suggest that the lack of social support and avoidant coping are related to psychosocial and functional morbidity in lymphoedema patients. As survivors age, avoidant coping may be more prevalent, leading to long-term problems. In one study, women who had poor social support, pain, and/or passive and avoidant coping styles reported the highest levels of disabilities (Passik et al, 1995). In addition, a recent qualitative study by Heppner et al (in press), revealed that helpful coping strategies included approach-coping actions rather than avoidant actions, and that social support was a significant component of coping (Heppner et al, 2002). Thus, Heppner concluded that psychosocial factors such as social support and applied problem-solving capacity may serve as personal and environmental resources. If available, these resources may allow women to successfully manage their chronic condition and its emotional and psychological impact; while a lack of these resources may exacerbate the functional impact of lymphoedema. Further study is needed to better understand psychosocial factors, especially applied problem-solving capacity and social support, in relationship to the progression of lymphoedema over an extended time period.

### Research prerequisites and imperatives

To further develop intervention research directed at lymphoedema risk reduction, early detection, treatment, and symptom management, it is crucial that researchers first conduct

investigations with increased precision in lymphoedema measurement to establish its current incidence and prevalence among breast cancer survivors and identify protective mechanisms over an extended time period.

Studies are needed to provide valuable new information about women struggling with early- and late-onset lymphoedema over extended time periods. Such studies must examine associations between limb volume changes (LVC) and other symptoms, in relation to perceived coping effectiveness and ways of managing the symptoms in the long term.

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### Measurement issues

Studies in progress or just completed (Ridner et al, 2007; Piller, 2008) compare all or most accepted lymphoedema clinical assessment measures, such as circumferences (Callaway, 1988), water displacement (Swedborg, 1977), perometry (Tiernay et al, 1996; Armer and Stewart, 2005), electrical impedance (Ridner et al, 2007), and tonometry (Moseley and Piller, 2008). Consensus panels have been convened in Great Britain, Australia and the United States to move the field to uniformity in measurement standards. This fundamental work will help establish a measurement standard that is both rigorous and clinically feasible, a key development that will help the fields of lymphology and lymphoedema move forward substantially and efficiently.

### Psychosocial factors influencing adaptation to breast cancer lymphoedema

Beyond the physical symptoms and risks, challenges associated with lymphoedema may also lead to post-treatment psychosocial distress. Tobin et al (1993)

were among the first researchers to examine the psychological morbidity of lymphoedema. The examination of psychosocial adjustment related to lymphoedema is in its infancy (Passik and McDonald, 1998). As is often the case, the initial studies investigating a particular problem are not theory-driven, but descriptive (Armer et al, 2002). Although descriptive studies can be informative, the lack of theory-driven research can inhibit more complete understanding of an area. After reviewing the lymphoedema literature, Petrek and Heelan (1998) noted that the scanty evaluation of lymphoedema may be attributed to several factors, including a history of relative neglect of women's health problems and, perhaps most importantly, the traditional view that quality of life is less important than the eradication of cancer and detection of recurrence. Unfortunately, neglect of lymphoedema has not only meant that many women go undiagnosed and fail to receive basic preventive information (Ridner, 2006), but has also inhibited the development of effective psychosocial interventions.

Treatment of lymphoedema has been, and continues to be, a major challenge for healthcare professionals (Petrek et al, 2000). By incorporating rigorous anthropometric and psychosocial data collection based on sound conceptual models in prospective longitudinal research designs, researchers can do much to combat the shortcomings of the field of lymphoedema studies. Since a substantial amount of lymphoedema develops more than three years after breast cancer diagnosis (Petrek et al, 2001; Lasinski, 2005), because causes of delayed-onset differ (Armer and Stewart, 2005), and because long-term physical and psychosocial ramifications of living with lymphoedema are unknown, further research in long-term survivorship is imperative.

### Future work in lymphoedema research

The author and her colleagues' examination of lymphoedema at the University of Missouri (Armer et al, 2002) takes as its guide a biobehavioral model of cancer, stress and disease

progression proposed by Anderson et al (1994), as well as emerging models of stress and coping (Holahan, 1996). Research clearly indicates that both minor and major stressors can substantially affect a person's psychological and physiological well-being (Lazarus and Folkman, 1984). Moreover, in the last 15 years, growing empirical evidence has suggested that psychosocial factors, such as problem-solving and social support, play key roles in adaptive responses to stress (Zeidner and Endler, 1996).

Specific known and potential predisposing personal, historical, and treatment-related factors which may contribute to lymphoedema development after breast cancer treatment should also be considered. These include: pre-morbid conditions such as diabetes; medications causing fluid retention/imbalance; body mass index (BMI); type of surgery and extent of nodal dissection; re-excision of tumour for clear margins; breast radiation; axillary radiation; chemotherapy; post-operative trauma and infection(s); weight gain during or after treatment; family or personal history of lymphoedema; prior injury, trauma, or surgery to the affected side; and genetic predisposition to lymphoedema. As these potential factors are examined for their association with secondary lymphoedema with rigorous research approaches, researchers can move forward in identifying potentially modifiable predisposing factors and target those persons at higher risk for focused risk-reduction and self-management interventions.

In the author's current seven-year study, because both effective problem-solving and high social support have been implicated as protective mechanisms in the progression of lymphoedema (Passik et al, 1995), and because social support and problem-solving capacity may be critical personal and environmental resources in coping with and managing the disease course (Meyer and Mark, 1995; Heppner and Baker, 1997), the instruments used are designed to provide a fine-grained assessment of problem-solving and six different types of

social support to assess these variables. In addition, since patient compliance has been suggested as an important variable in lymphoedema progression over the long term (Rose et al, 1991), this study is examining the association of lymphoedema coping efficacy and symptom management in predicting LVC, lymphoedema-associated symptoms, and outcomes of psychosocial adjustment and functional health status.

Preliminary analysis of 12-month data from the original research project reveals that the identified psychosocial variables account for considerable variance in long-term psychosocial adjustment following cancer treatment (unpublished data). By tracking changes in these variables over time, along with changes in functional health status and psychosocial adjustment, researchers will be able to investigate Time 1 (predisposing) psychosocial variables (e.g. problem-solving ability, social support), and Time 2 (post-treatment) coping effectiveness and symptom management as predictors of LVC, psychosocial adjustment outcomes, and functional health status over time. The goal of this study is to identify variables that influence lymphoedema risk reduction, disease progression, and psychosocial adjustment and functional health over an extended period of time, which can inform subsequent interventions and provide a foundation for a future focus on both patient compliance and overall quality of life.

### Summary

Of two million women with breast cancer in the US and 10 million breast cancer survivors around the world, at least one in four is likely to have lymphoedema within 11 years (Petrek and Heelan, 1998), and experience a wide range of potentially debilitating outcomes as a result (Armer, 2002). At this point, much remains unknown about lymphoedema measurement, incidence, and correlates, including effective and ineffective self-management strategies. There is a dearth of evidence about how psychosocial factors such as problem-solving and social support might reduce lymphoedema severity and progression. Very little is known about the full impact of early- and late-onset lymphoedema

on psychosocial health and functional health. Lack of research on these topics inhibits understanding of lymphoedema, its impact, and the development of effective intervention strategies to reduce the debilitating outcomes that make it a major health risk. Perhaps more distressing, among the most fundamental issues in lymphoedema research there continues the 'critical weakness' in previous incidence research: lack of knowledge about the total pool of participants who may develop lymphoedema during their lifetimes (Petrek and Heelan, 1998). Rigorous extended follow-up from pre-operative baseline measurements will increase our understanding of factors related to late-onset and long-term management of both early- and late-onset lymphoedema.

A fundamental step that is imperative in lymphoedema research examining outcomes related to cancer treatment is that of establishing standard measurements. Thorough training of measurers in techniques, along with regular assessment of inter-rater reliability, will make anthropometric methods more credible, a necessary development for consistent and reliable measurements. Although orchestrating pre-operative baseline measurements is a complicated and complex undertaking requiring collaboration at many levels, it is possible, as evidenced by the more-than-350 Missouri participants enrolled and followed since 2001 (Armer and Stewart, 2005; Armer et al, 2002), and the number of funded and non-funded studies identified at the 2007 International Society of Lymphology, the 2008 biennial National Lymphedema Network, and other recent professional lymphology meetings.

Additionally, further attention must be paid to the psychosocial components associated with the risk of development of post-breast cancer lymphoedema, and the factors that influence ability to learn and maintain necessary self-care for both risk-reduction and health maintenance. The lessons learned will benefit the great number of breast cancer survivors at risk for lymphoedema and eventually other persons experiencing primary and secondary lymphoedema. JL

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