Research on Risk Assessment for Secondary Lymphedema following Breast Cancer Treatment

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Research studies report a wide range (3-87%) of lymphedema occurrence among breast cancer survivors. Past discrepancies in occurrence rates are due to difficulties in measurement methods, variance in diagnostic criteria, and diverse length of follow-up, as well as varying sample characteristics. Even following the conservative surgical approach of sentinel lymph node biopsy, estimates of lymphedema occurrence range from 0% (1, 2) to 23% (3), with an average of 6% across 15 studies with 4,241 patients (4, 5). More than 2.5 million breast cancer survivors living in the United States are at risk of developing lymphedema after treatment (6). If the estimate of lymphedema incidence is conservatively set at 20%, more than 500,000 breast cancer survivors will be affected. Based on even the lowest estimates in the United States, lymphedema following breast cancer treatment affects hundreds of thousands of women over their lifetimes and represents a major societal problem. Worldwide, it is an even greater concern (7, 8). Lymphedema has a major societal effect on health, quality of life, functional status, family, and finances.

Among measurement and design issues to be considered in assessment of lymphedema incidence, prevalence, and estimated severity are the variety of approaches and criteria for assessment, from circumferences, self-reported symptoms, volume change (via water displacement or perometry), to bioelectrical impedance spectroscopy. Designs may be retrospective or prospective, with varying periods of follow-up, from as little as 3 months to 20 years, and may be planned with or without a baseline value (9). The more rigorous studies are planned with a pre-intervention baseline, over a longer follow-up time, with rigorous (validated and reliable) measurements.

A constellation of factors related to individual predisposition and treatment factors affect risk of lymphedema development and progression (Fig. 1). The effect of interactive factors and the extent of the effect identified to date are not yet fully understood and are the subject of current studies, with the goal of early identification of risk factors that can be mediated to prevent, reduce, or delay emergence of lymphedema.

Identification of these factors and their relative effect and interaction are key to reducing lymphedema occurrence and effect. Early detection and intervention hold the greatest promise of reducing this widespread condition (10, 11). Identification of epidemiologic and clinical factors associated with risk, incidence, and progression will provide the necessary foundation for preventive intervention. Personal and historical (including treatment) characteristics such as age, weight, infection, radiation therapy, body mass index, and axillary dissection are generally believed to affect women’s risk for lymphedema onset (12-14). Research has found that patient compliance is the most important factor in treating lymphedema (11, 15). Interventions to increase self-care for risk reduction and management of existing lymphedema are essential, as are surveillance programs for at-risk individuals recommended to detect early-onset lymphedema, and assess and monitor risk factors. Surveillance is needed to capture the true significance of this distressing condition (16).

To move this field forward, we need more well-designed studies, with precise measurements, larger well-defined study cohorts, followed over longer time periods, with stand-alone and bundled interventions, incorporating standard of care versus optimal care guidelines (17). Together, these will lead to more definitive evidence-based recommendations for the optimal management of secondary lymphedema.

The research report by Norman et al. in this issue is a prospective, population-based study of a random sample of 631 women diagnosed with breast cancer between 1999 and 2001. Risk factors were assessed by questionnaire and medical record review. Hazard ratios were used to estimate relative incidence rates of lymphedema, and Cox proportional hazards models were used to examine clinically plausible treatment interactions.

This study takes the first step in what is needed in drawing a large sample of participants at risk of lymphedema. However, there are also limitations in the study design and methods of this article that may prove insightful for other researchers and clinicians.

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The assessment of lymphedema diagnosis and stage by self-report using a tool validated only by the authors when medical records were also available is regrettable. This may be an example of misplaced precision, in that the most central outcome measure (lymphedema occurrence and severity) may be the least rigorous measure in the study. It is implied the referent for "you are the only person who would notice this" in the interview is the patient (not the interviewer).

It is unclear how treatment data sources were prioritized where multiple sources existed (patient report and medical records). With medical records available, number of radiation treatments and total dosage of radiation (beyond the fields) would seem retrievable. These data might provide sufficient information for stratification by radiation dosage. Opportunity for a more rigorous examination of the available data is lost in the categorization of available continuous data such as lymphedema self-report and radiation.

In examining clinical factors that potentially affect lymphedema risk and progression, it is important to consider the theoretical and chronological relationships among the variables of interest. For example, stage of disease influences treatment decisions related to surgery, radiation, and chemotherapy. Entering into a hierarchical equation stage of disease or considering it as a covariate are reasonable steps in that the biological factors associated with the disease state effect (in fact, delineate) the treatment factors, which may in turn affect the risk for lymphedema. Conceptually, simply put, the hierarchy would be disease stage, number of positive nodes, followed by treatment protocol. It is unclear that this hierarchical analytic approach was considered. Looking prematurely at the end point of selected treatment without considering disease stage may lead to findings that are difficult to interpret and may lend themselves to conclusions that are not validated for application to clinical practice. A study with preliminary findings without solid theoretical

### Predisposing factors
- Family or personal history of lymphedema
- Genomic variation
- Pre-morbid conditions
- Medications causing fluid retention/imbalance
- Body mass index
- Type of surgery and node dissection
- Re-excision of tumor for clear margins
- Breast radiation
- Axillary radiation
- Chemotherapy
- Post-op trauma and infection(s)
- Weight gain during/after treatment
- Prior injury, trauma, surgery to affected side

### Limb volume change and symptoms
- Problem solving
- Protective mechanisms
  - Social support
- Psychosocial adjustment
- Breast cancer post-treatment outcomes
  - Overall quality of life
  - Functional health status
- Coping effectiveness and symptom management

**Figure 1.** BioPsychoSocial model of secondary lymphedema including predisposing factors, protective mechanisms, limb volume change and symptoms, coping effectiveness and symptom management, and breast cancer posttreatment outcomes.
underpinnings must be followed up with increasingly rigorously designed studies with solid conceptual frameworks.

- When available, additional information about tumor size, histology, estrogen receptor status, grade, and endocrine therapy are pertinent factors associated with choice of treatments, eventually affecting risk for lymphedema. Further, it is important to note how women undergoing no chemotherapy differ from those who undergo chemotherapy; in those with “no chemo,” either physicians or patients made a decision about the value of systemic chemotherapy and additional information would ensure that this was not biased toward other biological factors. The authors in this study found that women who received sentinel lymph node biopsy and radiation had increased risk of lymphedema when anthracycline-based chemotherapy (the predominant chemotherapy used) was given. Interestingly, if patients receive axillary lymph node dissection, then the effects of chemotherapy are not evident. This important finding needs further discussion.

- Findings displayed in Table 4 suggest that the treatment scenarios resulted in a significant increase in the risk of lymphedema when compared with no treatment. Any comparison beyond that would face the issue of having hazard ratios with confidence intervals that overlapped. Caution must be taken in interpreting results for clinical application without further validation.

No one study can answer all the relevant research questions in a given field. Researchers build on prior work and recommend next steps in examining the issues under investigation. The current article lays the groundwork for further research while eliciting a note of caution in readily applying these preliminary findings to clinical decision-making in cancer survivorship.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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