Secondary lymphoedema trajectories among breast cancer survivors

Elizabeth Quinlan, Roanne Thomas, Thomas Hack, Winkle Kwan, Sue Tatemichi, Anna Towers, Andrea Tilley, Baukje Miedema

Key words

Arm dominance, Breast cancer, Longitudinal analysis, Lymphoedema

Elizabeth Quinlan, University of Saskatchewan; Roanne Thomas, University of Ottawa; Thomas Hack, University of Manitoba; Winkle Kwan, Fraser Valley Cancer Centre; Sue Tatemichi, Dalhousie University; Anna Towers, McGill University Health Centre; Andrea Tilley, Atlantic Health Sciences; Baukje Miedema, Dalhousie University, Canada

Declaration of interest: None.

Abstract

Background: Breast cancer surgery is the most common cause of secondary lymphoedema, yet there is little understanding about the changes in lymphoedema over time in breast cancer survivors. Further, the role of arm dominance in the development and persistence of lymphoedema has not been adequately explored. **Aim:** This study aimed to determine the rate of change of secondary lymphoedema over the 2-year post-surgery period in a cohort of breast cancer survivors. Additionally the authors compare the rate of change of lymphoedema in those whose dominant arm is cancer-affected to those whose non-dominant arm is affected. **Methods:** Latent growth curve modelling methods were used. The analysed data were drawn from a large Canadian longitudinal study of arm disability in over 700 breast cancer survivors. **Results:** The study's key results are that lymphoedema did not improve for the average survivor, but rather increased with time. There are significant differences in the trajectories of the two groups of survivors, those whose dominant arm was affected by cancer and those whose dominant arm was unaffected. **Conclusion:** The confounding effect of arm dominance demonstrates that the pre-operative measurement of both arms is important and should be incorporated in post-surgery measurements. The implications for cancer survivors are that such measurements should be requested of their healthcare providers prior to surgery.

Over 23 000 Canadian women are newly diagnosed with breast cancer each year (Canadian Cancer Society, 2014). Increased screening and more effective treatments have led to improved survival rates. However, treatment often brings arm morbidity, including lymphoedema.

Despite the advent of sentinel lymph node biopsy, numerous researchers show that lymphoedema remains a significant concern (Miedema et al, 2001; Tilley et al, 2009; Hack et al, 2010; Thomas-MacLean et al, 2010). Breast cancer treatment is recognised as the most common cause of secondary lymphadenoma (Armer, 2005). Of all the complications from the treatment of breast cancer, lymphoedema is the most debilitating (McLaughlin et al, 2008).

The condition involves swelling and associated abnormal accumulation of observable and palpable protein-rich fluid (Armer, 2005). Petrek and Heelan (1998) argued that except for a recurrence of cancer, no event is more 'dreaded' than the development of lymphoedema. Preliminary findings from the authors' ethnodrama study corroborate Petrek and Heelan's further claim that pain caused by clinicians trivialising the non-lethal nature of lymphoedema compounds the physical symptoms of lymphoedema (Quinlan et al, 2014).

There is little consensus among healthcare providers regarding the treatment of lymphoedema among breast cancer survivors, and new treatment protocols continue to emerge (Brennan and Miller, 1998; Chau and Harris, 2002; Radina et al, 2004; Lymphoedema Framework, 2006; Moseley et al, 2007).

However, standard treatment techniques for lymphoedema are exercise, compression, and specialised massage. Patients are advised to avoid carrying heavy objects, wet shaving the armpit, receiving injections or having blood pressure measurements taken on the affected arm (Lymphoedema Framework, 2006; Harmer, 2009).

Rates and risk factors

Reported rates of incidence and prevalence of lymphoedema are divergent. Researchers have found that, on average, the onset of lymphoedema starts 6.9 months after surgery (Stout Gergich et al, 2008). Petrek and Heelan (1998) found the incidence of breast-cancer related lymphoedema to range from 6% to 30%. Harmer (2009) argued that one-in-five breast cancer survivors will experience secondary lymphoedema and the number of patients increases with time after surgery.

Twenty years following surgery, 50% of a sample of 263 breast cancer survivors reported some level of lymphoedema and 13% reported severe lymphoedema (Petrek et al, 2001). In their systematic review, Cormier et al (2010) found the reported incidence of lymphoedema was higher in those studies in which the patient follow-up was longer. Armer and Stewart (2005) demonstrated that cases of lymphoedema continue to emerge up to 60 months following breast cancer surgery.

Taken together, the recent findings point to higher rates of incidence and prevalence of lymphoedema than previously understood. However, such an assertion is difficult to

confirm since accurate, replicated studies require standardised research procedures, definitions and measures. As it stands, there is much variation in completeness rates of patient follow-up and intervals between surgical treatment and follow-up data collection.

Perhaps more important sources of variation are the measurement protocols and definitions of lymphoedema. From their comparative analysis of 118 women 12 months post-surgery, Armer and Stewart (2005) showed that the a difference of 10% between left and right limb volume is the most conservative definition and the 2 cm circumferential difference is the most liberal definition of lymphoedema.

Risk factors

Studies regarding risk factors for lymphoedema have also produced varying findings. McLaughlin et al (2008) found greater baseline weight and current weight, higher body mass index, and infection and injury in the affected arm are statistically significant risk factors. Harmer (2009) corroborated these findings regarding infection and obesity and adds age as a risk factor.

The combination of axillary dissection and radiotherapy may lead to arm lymphoedema and limited shoulder mobility and higher pain as compared to radiotherapy after lumpectomy (Deutsch and Flickinger, 2001).

Although the axillary lymph node dissection and/or mastectomy is considered by many to be a major risk factor, Cormier et al (2010) found in their systematic review that lymphoedema from surgery occurs in the range of 7%, even after sentinel lymph node biopsy.

Some studies find age, current marital status, time since diagnosis, stage of disease, and level of education are negative predictors of quality of life (QoL) among breast cancer survivors, while others find these to be positive predictors of QoL, and still others find they are not significant as either positive or negative predictors (Mols et al, 2005).

When pain and range of motion restrictions are considered in addition to lymphoedema, the impact on QoL becomes more complex.

Survivors often experience difficulties engaging in recreational activities and have to limit their previously enjoyed hobbies and leisure pursuits (Miedema et al, 2011; Thomas et al, 2014).

The economic burden of breast cancer-related lymphoedema (BCRL) has been estimated in a matched cohort analysis involving breast cancer survivors 2 years post-surgery (Shih et al, 2009). The findings from the US study show that the 10% of survivors with lymphoedema had significantly higher medical costs, in particular outpatient care costs for mental health services, diagnostic imaging, and physician visits. Cormier et al (2009) found that survivors with severe lymphoedema (i.e. >15% arm volume change) are five times more likely to have low QoL scores than their counterparts without lymphoedema.

Measuring lymphoedema

There are discrepant results obtained from objective measures compared to those based on subjective measures. In their systematic review of the literature on cancer-related secondary lymphoedema, Cormier et al (2009) found that patients enrolled in studies using objective measurement methods of water displacement and circumferential measures were twice as likely (OR=1.91) to be identified with lymphoedema compared with studies that used subjective scales of patient self-reports and clinicians' observations.

When both objective and subjective definitions are used in the same study, these discrepancies can be explored in detail. In a comparison of the two types of results, McLaughlin et al (2008) reported two discordances in the results among 936 women 5 years post-surgery: some symptomatic cases did not have measured lymphoedema, and some objectively measured cases were asymptomatic. However, there were many more cases of the first type of discordance: only 41% of the women reporting arm swelling had measured lymphoedema; whereas 5% of those reporting no swelling had measured lymphoedema.

The complications associated with measuring secondary lymphoedema were identified by Armer (2005). One concern is the reliability of instruments. For instance, consistent circumferential measures require a uniform tightness of a tape applied around a subject's limb; this determination is time-consuming and requires considerable experience to obtain (Cormier et al, 2009). Therefore they are subject to intra- and inter-measurer variation. Most studies rely on clinical research associates to measure limb size, with the exception of Petrek et al (2001), who took the novel approach of asking the participating women to measure themselves following a handout of instructions.

The water displacement measurement of limb volume has greater reliability than circumferential measures, although correlations between the displacement and the manual circumferential measurements have been found to be as high as 0.98 (Armer, 2005). Because of its greater reliability, the water displacement method was considered the gold standard as recently as 2005. However, it is unwieldy and messy; consequently, it is not often used.

Bio-impedance spectroscopy is an alternative to both circumferential and water displacement techniques and has been used in lymphoedema assessment for almost 20 years (Ward et al, 1992; Rockson, 2007). The advantage of the bio-impedance spectroscopy is its capacity is distinguish volume changes due to muscle from those related to changes in fluid.

However, its application to research is limited by its need for baseline measurements on the affected limbs or both affected and unaffected limb measurements (Ward et al, 2011). Its application to clinical practice is limited by its cost, especially for general practitioners. Thus, in family medicine and nursing, circumferential measures are the most feasible method for the near future, despite concerns about accuracy.

The second concern is the matter of timing of the measurements. Ideally, baseline measurements, used to compare to follow-up measurements, should be taken before surgery or other known trigger events (Petrek et al, 2001). However, this is an expensive research design that requires a good deal of planning and lead time. Further, the timing of follow-up measurements is not standard since it is based on researchers' understanding of the time period during which lymphoedema is likely to present in subjects.

The third issue associated with the measurement and definition of lymphoedema is the assumptions about limb shape underlying the measurements taken and calculated. For instance, most studies assume a basic symmetry of limbs

and that symmetry is constant over time and across subjects. When differences between affected and control limbs over time are taken as the measure of lymphoedema, we miss the inherent asymmetries in bodies and the dynamic changes in the limb shape.

Petrek and Heelan's 1998 review of literature on breast carcinoma-related lymphoedema found several different thresholds in circumferences of affected versus non-affected limbs are being used to indicate lymphoedema: some studies use 2 cm, others 3 cm, 4–8 cm, and even 10 cm. Armer (2005) found that most commonly lymphoedema is defined if there is >2 cm difference in circumference or if there is a 200 mL volume difference between affected and non-affected limbs.

More recently, studies have moved away from defining lymphoedema with a dichotomous variable indicating simply the presence or absence of lymphoedema and instead using degrees of severity of lymphoedema (Cormier et al, 2009). For instance, a circumferential difference between affected and non-affected of less than 1.25 cm is considered mild lymphoedema, up to 5 cm is moderate lymphoedema, and greater than 5 cm is severe lymphoedema.

While the redefinition of lymphoedema from a dichotomous to a categorical variable marks an important development in lymphoedema research, it is not sufficient to resolve all issues.

First, there are natural differences in limb size across subjects. How do we account for these differences if we use standard thresholds and definitions of lymphoedema? The same measure cannot be applied to those with naturally thin limbs and those with naturally thick limbs. Furthermore, limb volume can change over time for many individuals. Unless a longitudinal cohort research design is used, these differences within subjects are not taken into account. Moreover, for the results of studies to be truly comparable, the circumference measurement must be taken at the same points on the limb. For instance, an added 2 cm at the wrist signals substantially more swelling than 2 cm at the upper arm.

Finally, similar to the thresholds of a dichotomous definition of lymphoedema, the cut points of the categorical lymphoedema variables are seemingly arbitrary. A continuous variable defining lymphoedema overcomes the arbitrariness in the definition of lymphoedema. Continuous variables will become more common as the use of bioelectric impedance increases (Rockson, 2007; McLaughlin et al, 2008).

Because this approach to measuring lymphoedema, in which electrical current determines the amount of inter-cellular fluid in the limbs, is relatively new, the cost of the equipment can be prohibitive for most clinicians and researchers. However, there are no studies to the authors' knowledge that use a continuous variable, based on circumferential or volume calculations, to indicate the presence of some lymphoedema although Armer (2005) promotes its use.

Aims

The study reported in this paper demonstrates the value of using a continuous variable to analyse lymphoedema to investigate the changes in lymphoedema over time in breast cancer survivors, and the role of arm dominance in the development and persistence of lymphoedema, aspects that have been under-researched. This study aims to answer the following two questions: What is the rate of change of secondary lymphoedema over the 2-year post-surgery period in a cohort of breast cancer survivors? How does the rate of change of lymphoedema in those survivors whose dominant arm is cancer-affected compare to those whose non-dominant arm is affected by cancer?

Data

The data used in this paper are collected in the context of a larger study of arm disability in breast cancer survivors. The parent study is currently being carried out by an interdisciplinary research team with members representing oncology, family medicine, psychology, physiotherapy and sociology and had over 30 collaborators with clinical/research experience in arm disability. Beginning in 2005, data are being collected from four Canadian locations – Surrey, British Columbia; Winnipeg; Montreal; and Fredericton, New Brunswick. Over 700 women are enrolled in the study.

Patients are recruited into the study within a window of 6 to 12 months following surgery. Breast cancer patients at the four sites who met the inclusion criteria are introduced to the study by various clinical personnel (e.g. a receptionist, nurse or physician).

If potential participants are interested in the study, research associates then explain the study to the patients and obtain informed consent. Patient demographic and disease information are then recorded, followed by the clinical assessment. Additional information is obtained from the patient's medical record.

In the clinical assessment, seven circumferential arm measurements are taken on both arms of each subject: metacarpophalangeal joints (MCP), thumb base, wrist crease, and wrist crease +10, 20, 30, and 40 cm. Other variables used in the analysis include urban/rural residence, presence of other illnesses, presence of pre-existing shoulder and/or arm problems, swelling in armpit, chest wall, or breast, time lapse between surgery and first assessment dates, pain (using the McGill 15-item Pain Index), and range of motion restrictions (external rotation in degrees, shoulder abduction, and self-reports).

To minimise intra- and inter-measurer variation noted above (Cormier et al, 2010), the study's clinical research associates, hired to conduct the clinical examinations and arm measurements, received two days of training from a certified physiotherapist at the beginning the study. The training included a comprehensive manual with illustrative photographs, video and live modelling, trainer observation, video-recorded practice, and trainer feedback.

There has been very little turnover in research associates and midway through the first phase of the study, the research associates received further training in the form of a refresher course on clinical data collection techniques and are scheduled for another at the midpoint of the study's second phase.

The inclusion criteria for the study's participants are women 18 years of age and older, English or French speaking, able to provide informed consent, with unilateral Stage I–III breast cancer. Women with bilateral breast disease are excluded because they are few in number and comparative assessment of the contralateral and ipsilateral arms is precluded. The study protocol was approved by the review committee for human research ethics at each participating institution.

Data used in this study are collected at

three different time points: 6–12 months, 18–24 months and 30–36 months post-surgery. Because the study is still underway and data continues to be collected, there is less data in the later time points.

At 6–12 months post-surgery, or Time1, there are 740 cases; at 18–24 months (Time2) *n*=626; at 30–36 months (Time3) *n*=366. All cases with data at Time2 have Time1 data and all but six cases with Time3 data have Time2 data. Because the method used to analyse the data makes use of all cases, as described in the next section, the analysis in the study is based on 1732 data points (740 for Time1, 626 for Time2, and 366 for Time3). By contrast, if the analysis was done using repeated measures ANOVA, only 1098 data points (366 for each of the three time points) could be used. Both objective and subjective data concerning lymphoedema were collected, however, the focus of the analysis presented in this paper is on the objective data.

Method

The study uses latent growth curve modelling (LGCM), a form of longitudinal analysis that allows researchers to investigate change in conditions, such as lymphoedema among breast cancer survivors. LGCM is an application of structural equation modelling (SEM), a multi-variate statistical technique, which combines path analysis and factor analysis (Bollen, 1989; Byrne, 1994; Tabachnick and Fidell; 1996). SEM is used to explore the underlying structures between latent constructs (also known as factors), which are concepts that cannot be observed or measured directly, e.g., discrimination, intelligence, social class. In the LGCM application of SEM, the latent constructs are the intercept and slope of the linear trajectory model. Measurement of latent constructs is achieved by using observable data to indicate the constructs.

In SEM and its LGCM application, predictive models are comprised of parameter estimates akin to regression coefficients in regression models. Using the standard inferential statistical approach, these parameter estimates are tested for statistical significance as part of the model output.

Model fit indices are used to assess how well the predicted model matches the sample data. Fit indices that do not meet the commonly accepted threshold values indicate an unacceptable level of chance of reaching false conclusions (Hoyle, 1995; McDonald and Ho, 2002). While there is general agreement on the limitations of fit indices, consensus concerning the best fit index has not yet been reached. Prevailing practice followed by SEM researchers on the use of fit indices seems to adhere to the recommendations put forward by Hu and Bentler (1999).

The exhaustive testing carried out by these authors reveals the performance of various fit indices under a variety of conditions, including sample size, model mis-specification and estimation method. On the basis of their results, Hu and Bentler (1999) recommended the use of two indices: the Standardized Root Mean Square Residuals index (SRMR), and one other of the following: the Root Mean Square Error of Approximation (RMSEA), the Tucker-Lewis Index, Bollen's Fit Index, the Relative Noncentrality Index, Gamma Hat, McDonald's Centrality Index, the Normed Fit Index, the Goodness-of-fit Index, and the Comparative Fit Index (CFI).

This study follows that recommendation and uses the CFI and RMSEA indices with the following thresholds: CFI ≥0.95; and RMSEA ≤0.06. A perfect fit would be indicated by CFI=1.0 and RMSEA=0.0. Few models achieve a perfect fit.

The precision of model fit is increased with greater number of time points of data. The models presented in this paper use the three time points. However, because the study is currently collecting five waves of clinical data, we can look forward to more precise models in the future when we add the additional two time points into the analysis.

Further advantages will be provided with five waves of data – we can adjust the models to allow for potential non-linearity in the rate of change in arm morbidity since LGCM permits the use of use of polynomial functions and/or piecewise functions. For instance with five waves of data, the trajectory could be comprised of up to four separate linear functions each with different slopes.

The one limitation of LGCM is that it cannot handle randomly assigned temporal spacing between data points; however, this is not a problem for this study since all our participants are sampled at each of the time points.

Repeated measures ANOVA is the most commonly used technique in research contexts such as this. But, repeated measures can only determine if a condition changes over time. It cannot determine at what rate the change occurs and even the predictors of that rate of change, questions that LGCM can answer. Another advantage of LGCM is that it uses all cases for which there are data for the first time point and calculates the most likely value for each missing data point in the subsequent time points. In comparison to the more conventional methods of handling missing data used by repeated measures, LGCM makes more efficient use of the data (Allison, 2005; Bollen and Curran, 2006). Because LGCM uses more of the available values, it provides a truer picture of the trajectories.

The study's analysis was conducted in two steps. SPSS, version 18 was used for the first stage of the analysis, in which univariate and bi-variate analyses were done. Frequencies, T-tests for continuous variables, and chi-squared tests for categorical variables, were performed on all the variables. In the second step of the analysis, MPLUS, version 6, was used to test the LGCM model (Muthén and Muthén, 2007).

Results

The lymphoedema variable (excess volume per cent) was derived by calculating the volume difference in the affected arm compared to the unaffected arm, expressed as a percentage and based on the calculated arm volume using the truncated cone formula (Brown, 2004). Lymphoedema is defined when the result of the calculation, the excess volume, is a positive value.

A concordance variable was derived on the basis of whether the dominant side is affected by breast cancer. The variable was derived for the purpose of investigating the negative values of lymphoedema uncovered in the first stage of the analysis (*Figure 2*).

The sample was divided into two sub-groups based on the concordance variable – dominant is breast cancer affected (DBC) and dominant is not breast cancer affected (DNBC) in order to compare separate LGCM models. Sample size for SEM studies need to be at least 10 cases for each of the estimated parameters (Bollen, 1989). The model discussed here has eight parameters, so with well over 80 cases for each of the time points, it more than adequately satisfied the sample size requirements.

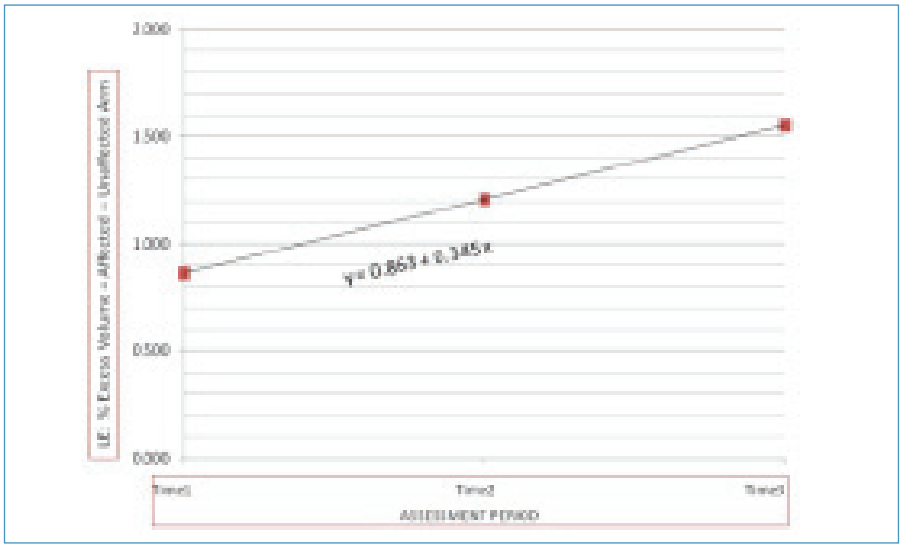

Figure 1. The generalised trajectory of lymphoedema from 6–12 months to 30–36 months post-surgery, defined by y = 0.863 + 0.345x.

As preliminary analysis to the modelling, the derived lymphoedema variable was tested for associations with range of motion restrictions and pain. The results indicate that lymphoedema at 6–12 months post-surgery is significantly correlated with the reported sensation of heavy pain at this first time point (0.101, $P<0.01$). It also correlates significantly with shoulder abductor (–0.319, $P<0.01$) and external rotator restrictions (–0.307, $P<0.01$).

T-tests reveal that the mean lymphoedema levels for those women with self-reported range of motion restrictions is significantly different from the mean lymphoedema for those women with no restrictions (1.31 vs 0.29, t=-2.498, P=0.013).

At 18–24 months post-surgery, significant correlations were found between lymphoedema and many more of the pain sensations: throbbing (0.083, $P<0.01$), hot burning (0.115, $P<0.01$), heaviness (0.206, $P<0.01$), splitting (0.101, $P<0.01$), tiring (0.154, $P<0.01$) and overall pain (0.094, $P<0.01$).

At 30–36 months post-surgery, lymphoedema correlates with shoulder abductor and external rotator restrictions (–0.384, $P<0.01$ and –0.375, $P<0.01$ respectively) and two types of pain sensations: heaviness (0.201, $P<0.01$) and tiring (0.169, $P<0.01$).

The LGCM model or trajectory (*Figure 1*) illustrates the average starting level of lymphoedema and its average rate of change over time from 6–12 months to 30–36 months post-surgery. Expressed algebraically as y = 0.863 + 0.345x, it indicates that the average woman has 0.863% volume difference ($P<0.01$) between her two arms 6–12 months post-surgery and that difference increases with time at the rate of 0.345% each year ($P<0.01$). The positive slope indicates that lymphoedema increases with time. That is, lymphoedema is getting worse for the average woman.

We tested for a correlation between the starting level of lymphoedema and its rate of change, we find the two are not associated (r=0.129, P=0.46). So, the rate of change is not influenced by the extent of initial lymphoedema. However, the relationship between initial lymphoedema and its rate of change might become significant when we have more data and more time points. Soon the study will have more data for additional time points and up to 300 more women for the 30–36 months post-surgery time point.

The fit statistics for the model in *Figure 1* are CFI = 1.0; RMSEA = 0.007. The CFI indicates a perfect correspondence between the data and the model and the RMSEA an almost-perfect fit (Hoyle, 1995). The small degree of incongruency between the model and the data, exhibited by the RMSEA index, is due to the fact that the model does not apply to every individual in the sample. Instead, it represents the average woman.

To illustrate the variation in the sample, several selected individual women's trajectories are shown in *Figure 2*. These individuals were selectively chosen to best illustrate the degree of variation within the sample. For some women, lymphoedema gets worse over time (e.g. case M017). For others, it improves, only to get worse (e.g. W084). For some, it gets worse with time, but not as rapidly (e.g. F001). It must be noted that F027 has only data for only Time1 and Time2. As LGCM uses all cases, this case and others like it are included in the analysis. Note that all the women in this small sub-sample have less that 5% lymphoedema at the first time point.

The negative percent differences in volume (e.g. F027 and F001 at Time1 in

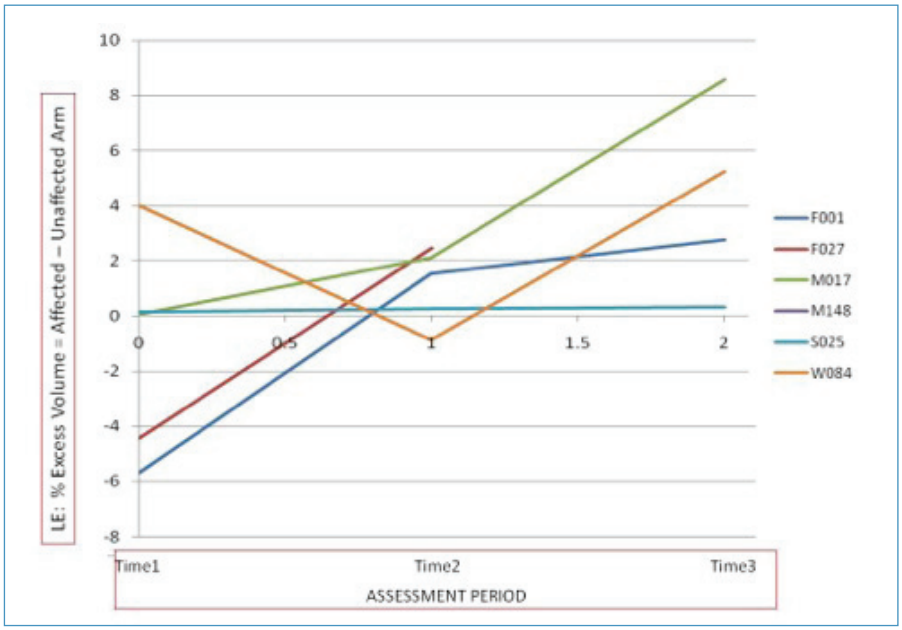

Figure 2. Individual trajectories of lymphoedema from 6–12 months to 30–36 months post-surgery.

Table 1. Frequencies of the study sub-groups.

	Frequency	Per cent	Valid per cent	Cumulative per cent
Affected breast matches dominant arm (DBC)	353	47.7	47.7	51.8
Affected breast does not match dominant arm (DNBC)	357	48.2	48.2	100.0
Unknown	30	4.1	4.1	4.1
Total	**740**	**100.0**	**100.0**	

Figure 2) were surprising. They indicate that the arm affected by cancer has less volume than the unaffected arm, a result that runs counter to the usual understanding of lymphoedema as a larger affected arm. In the entire sample of 740 women, 329 (44%) had negative per cent differences in volume at Time1. Of 626 cases for which there are data at Time2, 271 (43%) had negative differences in volume; and of the 466 cases for which there are data at Time3, 157 (34%) had negative differences in volume.

We investigated the phenomenon of negative volume difference further by exploring the role of arm dominance. The investigation proceeded by testing the hypothesis that a negative difference in volume would be more likely in those women whose dominant arm is unaffected by breast cancer. The hypothesis rests on the commonly held assumption that the dominant arm is usually larger than the non-dominant arm in all populations.

The resulting univariate analysis revealed that, not unlike the general population, 92% of the 740 women are right-handed, 7% are left-handed, and 1% are ambidextrous. The eight ambidextrous women were re-classified as left-handed to reduce skewing in the derived variable. Frequencies on these two groups (*Table 1*) shows that 353 women (47.7%) have dominant arms affected by cancer and 357 (48.2%) of women have non-dominant arms affected by cancer.

A bivariate analysis confirms that dominance is not associated with whether the affected breast is right or left (χ^2=1.184, degrees of freedom [df] = 1, *P*=0.277). Subsequent t-tests and chi-squared tests on differences between the DBC and DNBC groups reveal no significant difference in the two groups on the following four variables:

- Presence of other illnesses (χ^2=0.024, df=1, *P*= 0.877).
- Swelling in armpit, chest wall, or breast (chi-sq=0.004, df = 1, *P*=0.947).
- Urban/rural residence (χ^2=0.028, df=1, *P*=0.866).
- The time lapse between their surgery dates and first assessment dates (*t*= 0.684, df=662, *P*=0.494).

However, a statistically significant difference was found between the two groups on the following variables:

- The presence of pre-existing shoulder and/or arm problems (χ^2=10.136, df=4, *P*=0.038) with mean external rotation of 74.07˚ in the DBC group versus 77.33˚ in the DNBC group.
- The mean initial lymphoedema (*t*=–7.916, df=708, *P*=0.000), with 2.43% for the DBC group and –0.67% for the DNBC group.

Thus, membership in the DBC or DNBC group influences initial lymphoedema values.

Separate LGCM models were created for the DBC and DNBC groups (*Figure 3*). The results confirm our hypothesis that the average DBC survivor has a positive initial lymphoedema value whereas the average DNBC survivor has a negative initial lymphoedema value.

Figure 3 shows different trajectories for the average survivor in the each group. Both groups have positive slopes indicating that lymphoedema increases over time; however, because the DNBC women's affected arms are initially smaller than their non-affected arms, even as late at 30–36 months post-surgery, lymphoedema is still less than 1% for the average woman in this group.

The model fit statistics for the DBC group are CFI=1.0 and RMSEA=0.000, indicating a perfect correspondence between the data and the model. The fit statistics for the DNBC group are CFI=0.986 and RMSEA=0.092, a near perfect fit of model to data.

In both groups, the initial lymphoedema is not correlated with its rate of change (*r*=0.329, *P*=0.333 for DBC and *r*=–0.126, *P*=0.463 for DNBC). However, as stated above, the association between the degree of initial lymphoedema and the rate at which it changes might be found significant when more data are added.

Figure 3 illustrates the confounding effect of dominance. The average DNBC woman has an affected arm smaller than her non-affected arm until 30–36 months post-surgery.

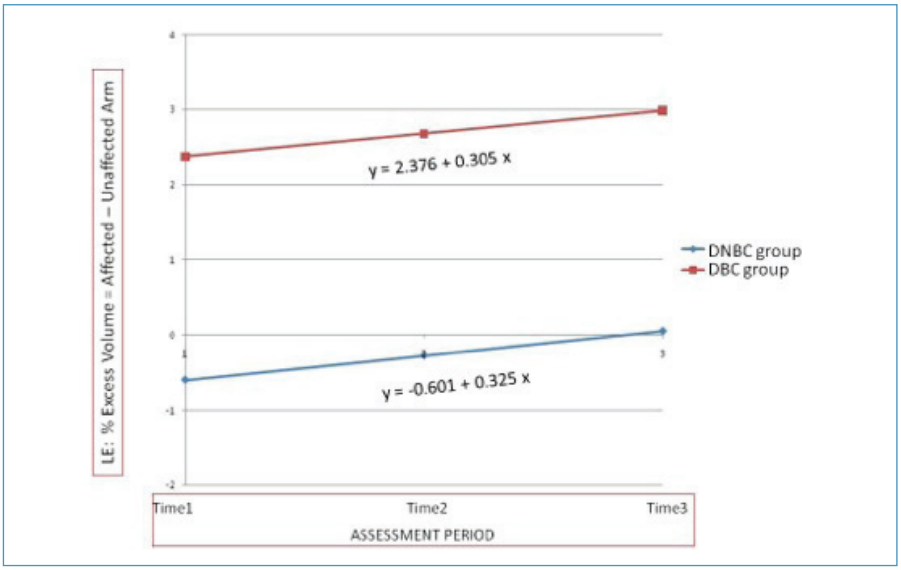

Figure 3. Generalised trajectories of lymphoedema from 6–12 months to 30–36 months post-surgery for the two sub-groups.

Discussion

Our results of the trajectories of lymphoedema in breast cancer survivors indicate that for the average survivor, lymphoedema gets worse with time. The analysis of individual trajectories demonstrates important diversities within the overall general pattern of increased lymphoedema over time. For some survivors, lymphoedema gets worse over time more rapidly than it does for others. For other survivors, lymphoedema improves in the first year or two following surgery only to then become markedly worse.

The study's finding of increased lymphoedema over time is consistent with other studies. The percentage of Cormier et al's (2009) sample each with mild, moderate, and severe lymphoedema increased over 30 months post-surgery. *Figure 1* indicates that at 18–24 months post-surgery, the average woman has 1.208% volume difference between arms, and at 30–36 months she has 1.553% difference.

The modelling results produced statistically significant values for both the initial lymphoedema and its rate of change although the absolute values are low. A volume difference of less than 2% might not be noticeable. However, the correlations with symptoms such as range of motion and types of pain demonstrate that these minimal values of lymphoedema have some clinical implications.

The study finds that the starting level of lymphoedema is not associated with its rate of change, suggesting that the extent to which there is lymphoedema shortly after surgery does not influence the rate at which it changes over time. However, the relationship between initial lymphoedema and its rate of change might become significant when we have more data and more time points. Soon the study will have more data for additional time points and up to 300 more women for the 30–36 months post-surgery time point.

Initial levels of lymphoedema are dependent on the interaction of arm dominance and the cancer-affected side. The results confirm our hypothesis that the average survivor whose dominant side is the same as the cancer-affected side has a positive initial lymphoedema value whereas the average survivor whose dominant side is different from the cancer-affected side has no initial lymphoedema. Although lymphoedema in both groups of survivors increases over time, because in the latter group the cancer-affected arms are smaller than their non-affected arms, even as late at 30–36 months post-surgery, lymphoedema is still minimal for the average woman in this group.

The authors' results can be compared to McLaughlin et al (2007), one of the few studies that incorporated analysis of dominance. McLaughlin et al found arm dominance did not significantly influence the number of precautionary behaviours practised – avoiding IVs, playing racquet sports, lifting weight over 6.8 kg (15 lb), gardening, housework, and wearing gloves when gardening and compression sleeves when flying. So it does not matter if the cancer-affected arm is dominant or non-dominant, women's practices are the same. However, these authors also found that arm dominance was significant in predicting perceptions of lymphoedema.

Women in this study with perceived lymphoedema were more likely to have a dominant arm that was affected by cancer. These authors speculate that their findings could be accounted for because perceptions of changes in one's dominant arm are generally more acute than changes in non-dominant arms. As the lymphoedema is occurring in the dominant arm, the DBC group is more likely to perceive the swelling.

While the analysis reported in this paper does not rely on subjective data, the findings suggest that if it did, the difference in trajectories between the DBC and DNBC survivors would be even greater. The DBC group would be likely to have higher levels of initial lymphoedema and perhaps would have higher rates of increased lymphoedema over time.

The study's findings on the relationship to arm dominance point to the importance of considering arm dominance when diagnosing lymphoedema in breast cancer survivors.

Measuring arms before surgery establishes a baseline measurement that reflects natural differences due to dominance. The baseline measure can then be used in comparison with post-surgery measurements taken at prescribed intervals. The baseline should be incorporated in post-surgery measurements for lymphoedema diagnoses.

Conclusion

The literature on lymphoedema in general, and in breast cancer survivors in particular, continues to expand. There is considerable variation in the findings in the studies on incidence, prevalence, and risk factors. The differing, indeed even contradictory results are in part because of different measurement protocols and definitions of lymphoedema.

Upon review of these various protocols and definitions, the paper argues for the use of continuous variables to represent lymphoedema as a way of eliminating the variation and arbitrariness of the threshold values.

By way of example, this paper promotes, in concert with Cormier et al (2009), the use of continuous variables to represent lymphoedema. The study reported in this paper uses percent differences in arm volume as a continuous variable for lymphoedema in a cohort of over 700 breast cancer survivors. Latent growth curve modelling, an application of structural equation modelling to the longitudinal context, is used to examine the average trajectory of lymphoedema over time first among the entire sample and then among two sub-groups.

This study finds that lymphoedema does not improve, but rather increases with time, for the average survivor, which corroborate findings by other lymphoedema researchers, particularly Cormier et al (2009). Although the initial lymphoedema and the rate of change are small percentages (less than 3%), the correlations between initial lymphoedema with symptoms such as pain and range of motion restrictions demonstrate their clinical relevance.

For many women in the sample, the cancer-affected arm had less volume than the unaffected arm. This is a result that runs counter to the usual understanding.

To investigate the peculiar result, we explored the role of arm dominance by testing the hypothesis that a negative initial volume difference would be more likely in those women whose dominant side is not affected by cancer.

Confirming the hypothesis, the study finds significant differences in the trajectories of two groups of survivors. First, women whose dominant side is affected by cancer (DBC) have initial lymphoedema, whereas women whose dominant arm is not cancer-affected (DNBC) do not have lymphoedema.

Second, although in both groups, the volume of affected arms increases over time relative to non-affected arms, the DNBC women's affected arms remain smaller than their non-affected arms up until 30–36 months post-surgery.

The confounding effect of dominance demonstrates the importance of pre-operative measurements of both arms to isolate the circumferential or volume differences due to dominance, which can then be incorporated in post-surgery measurements.

The limitation of this study is the lack of these very measurements: the study's first time period is not pre-operative, but rather 6–12 months post-surgery.

A pre-operative measure would allow the authors to incorporate the difference between dominant and non-dominant arms independent of the effects of cancer. Another refinement to further study on the impact of arm dominance would be to use bio-impedance spectroscopy to distinguish changes in muscle from fluid.

As the study is currently under way, it will be possible to test the models with more data for the second and third time periods and, ultimately, fourth and fifth time points. In addition, further work will see the authors capitalise on the capacity offered by the LGCM to test predictors of the initial lymphoedema and its rate of change.

Based on the results from this study, other literature, and the team's clinical experience, these predictors will include match of dominance to affected arm, surgery type, weight, and age as predictors of the intercept and age, weight, infection, and treatment for the rate of change.

Such a study will contribute to the clarification of contradictory literature on risk factors.

Based on this study's results of different trajectories of the DBC and DNBC women, future research will also explore potential differences in the predictors for the two groups of survivors. The combined results of the future programme of work will further clinical practice and the development of rehabilitation policy for breast cancer survivors.

Acknowledgements

The authors received financial support for the research from the Canadian Institutes of Health Research.

References

Allison PD (2005) Missing data techniques for structural equation modeling. *J Abnorm Psychol* 112(4): 545–57

Armer JM (2005) The problem of post-breast cancer lymphedema: impact and measurement issues. *Cancer Invest* 23(1): 76–83

Armer JM, Stewart BR (2005) A comparison of four diagnostic criteria for lymphedema in a post-cancer population. *Lymphat Res Biol* 3(4): 208–17

Bollen KA (1989) *Structural Equations with Latent Variables*. Wiley & Sons, New York

Bollen KA, Curran PJ (2006) *Latent Curve Models: A Structural Equation Perspective*. Wiley & Sons, New York

Brennan MJ, Miller LT (1998) Overview of treatment options and review of the current role and use of compression garments, intermittent pumps, and exercise in the management of lymphedema. *Cancer* 83(Suppl 12): 2821–7

Brown J (2004) A clinically useful method for evaluating lymphedema. *Clin J Oncol Nurs* 8(1): 35–8

Byrne BM (1994) *Structural Equation Modelling with EQS and EQS/Windows*. Sage Publications, London

Canadian Cancer Society (2014) Breast cancer statistics. Available at: www.cancer.ca (accessed 01.05.2014)

Chau N, Harris SR (2002) Practices and opinions of physiotherapists treating patients with breast cancer-related lymphedema. *Physiotherapy Canada* 54(3): 156–63

Cormier JN, Xing Y, Zaniletti I (2009) Minimal limb volume change has a significant impact on breast cancer survivors. *Lymphology* 42(4): 161–75

Cormier JN, Askew RL, Mungovan KS (2010) Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer* 116(22): 5138–49

Deutsch M, Flickinger JC (2001) Shoulder and arm problems after radiotherapy for primary breast cancer. *Am J Clin Oncol* 24(2): 172–6

Hack TF, Kwan WB, Thomas-MacLean RL et al (2010) Predictors of arm morbidity following breast cancer surgery. *Psychooncology* 19(11): 1205–12

Harmer V (2009) Breast cancer-related lymphoedema: Risk factors and treatment. *Br J Nurs* 18(3): 166–72

Hoyle R (1995) *Structural Equation Modeling: Concepts, Issues and Applications*. Sage Publications, London

Hu L, Bentler PM (1999) Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Structural Equation Modeling* 6(1): 1–55

Lymphoedema Framework (2006) *Best Practice for the Management of Lymphoedema: International Consensus*. MEP, London

McDonald RP, Ho MH (2002) Principles and practice in reporting structural equation analyses. *Psychol Methods* 7(1): 64–82

McLaughlin SA, Wright MJ, Morris KT et al (2008) Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymphedema node biopsy or axillary dissections: patient perceptions and precautionary behaviours. *J Clin Oncol* 26(32):5220–6

Mols F, Vingerhoets AJ, Coebergh JW, van de Poll-Franse LV (2005) Quality of life among long-term breast cancer survivors: a systematic review. *Eur J Cancer* 41(17): 2613–9

Miedema B, Hamilton R, Tatemichi S et al (2011) Do breast cancer survivors' post-surgery difficulties with recreational activities persist over time? *J Cancer Surviv* 5(4): 405–12

Moseley AL, Esplin M, Piller NB, Douglass J (2007) Endermologie (with and without compression bandaging) – a new treatment option for secondary arm lymphedema. *Lymphology* 40(3): 129–37

Muthén LK, Muthén BO (2007) *Mplus User's Guide*. 5th ed. Muthén & Muthén, Los Angeles

Petrek JA, Heelan MC (1998) Incidence of breast carcinoma-related lymphedema. *Cancer* 83(12 Suppl American) 2776–81

Petrek JA, Senie RT, Peters M, Rosen PP (2001) Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer* 92(6): 1368–77

Quinlan E, Thomas R, Ahmed S, Fichtner P (2014) The Aesthetic Rationality of the Popular Expressive Arts: Lifeworld Communication Among Breast Cancer Survivors Living with Lymphedema. *Social Theory and Health* (in press)

Radina ME, Armer JM, Culbertson SD, Dusold JM (2004) Post-breast cancer lymphedema: understanding women's knowledge of their condition. *Oncol Nurs Forum* 31(1): 97–104

Rockson S (2007) Bioimpedance analysis in the assessment of lymphedema diagnosis and management. *Journal of Lymphoedema* 2(1): 44–8

Shih YC, Xu, Y, Cormier JN et al (2009) Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. *J Clin Oncol* 27(12): 2007–14

Stout Gergich NL, Pfalzer LA, McGarvey C et al(2008) Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer* 112(12): 2809–19

Thomas R, Hack T, Quinlan E et al (2014) At arm's length: Impact of arm morbidity on leisure activities following breast cancer. *Canadian Journal of Nursing Oncology* (under review)

Thomas-MacLean R, Spriggs P, Quinlan E et al (2010) Arm morbidity and disability: reporting the current status from Canada. *Journal of Lymphoedema* 5(2): 33–8

Tabachnick BG, Fidell LS (1996) *Using Multivariate Statistics*. 3rd ed. HarperCollins, London

Tilley A, Thomas-MacLean R, Kwan W (2009) Lymphatic cording or axillary web syndrome after breast cancer surgery. *Can J Surg* 52(4): E105–6

Ward LC, Bunce IH, Cornish BH (1992) Multifrequency bioelectrical impedance augments the diagnosis and management of lymphedema in post-mastectomy patients. *Eur J Clin Invest* 22(11): 751–4

Ward LC, Winall A, Isenring E (2011) Assessment of bilateral limb lymphedema by bioelectrical impedance spectroscopy. *Int J Gynecol Cancer* 21(2): 409–18