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Original article

Risk factors for lymphoedema in women with breast cancer: A large prospective cohort☆

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ABSTRACT

A prospective study was conducted to identify women at increased risk for lymphoedema (LE) based on axillary surgery. Assessment occurred prior to surgery, within 4 weeks, and at 6, 12 and 18 months following surgery. Following post-surgery assessment, women were asked to complete weekly diaries regarding events that occurred in the previous week. Risk factors were grouped into demographic, lifestyle, breast cancer treatment-related, arm swelling-related, and post-surgical activities. Bio-impedance spectroscopy thresholds were used to determine presence of LE. At 18-months, 241 women with <5 nodes removed and 209 women with ≥5 nodes removed were assessed. For those with <5 nodes removed, LE was present in 3.3% compared with 18.2% for those with ≥5 nodes removed. There were insufficient events to identify risk factors for those with <5 nodes removed; for those with >5 nodes removed, independent risk factors included presence of arm swelling at 12-months (Odds Ratio (OR): 13.5, 95% CI 4.8, 38.1; $P < 0.01$), at 6-months (5.6 (2.0, 16.9); $P < 0.01$), and radiotherapy to the axilla (2.6 (0.7, 8.9); $P = 0.14$). Arm swelling at 6 and 12 months was associated with taxane-based chemotherapy, high body weight at diagnosis and arm swelling within 4 weeks post-surgery. Of the post-surgical events assessed in a sub-group of women with >5 nodes removed and who maintained weekly diaries, only blood drawn from the 'at-risk' arm was identified as a potential risk (OR 2.0; 0.8, 5.2). For women with ≥5 nodes removed, arm swelling in the first year poses a very strong risk for presence of LE at 18-months.

Introduction

Lymphoedema (LE) is common following treatment for breast cancer [1,2]; however, its risk factors for development are still not clearly understood due to methodological confounders within the reported literature. One confounder is related to the inclusion criteria for analysis. Despite axillary lymph node dissection (ALND) being a significant factor for LE [1,2], some studies analyse those who have undergone a sentinel lymph node biopsy (SLNB) together with those who have undergone an ALND [3–7]. This is further confounded by what constitutes a SLNB and ALND. For some, SNLB may include removal of more than a few lymph nodes [e.g. 8,9]. If the premise is that risk of LE is dependent on removal of lymph nodes, dichotomising on the label rather than the number of nodes removed may mask risk factors.

A second confounder has been the timing of LE diagnosis. Particularly in the first year, many women experience transient swelling in the arm on the side of surgery [10–14]. Arm swelling may be related to surgery or to factors such as taxane-based chemotherapy, known to give rise to swelling [15]. Classification of all swelling that appears within the first year as LE, even though it may subsequently resolve, may mask risk factors.

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A third potential confounder relates to the variable criteria for LE diagnosis; some studies use self-report of swelling whereas others base the diagnosis of LE on physical measures [1,2]. The advantage of subjective reports is that they can reflect the perception of swelling over a period of time [16–18], in contrast to physical measures which reflect the status of the limb at a single time point. However, given the discrepancies between self-report and physical measures of LE, it raises concern as to whether the subjective report is of LE [16,18–20]. While physical measures of LE provide an objective evaluation of limb differences, there are possible confounders related to the diagnostic thresholds used. Many studies do not adequately account for limb dominance [e.g. 7,21,22], location along the limb where an interlimb difference is noted or consider the change relative to the unaffected limb [e.g. 23–28]. However, this will impact on whether inter-limb differences are within normal variance [29]. Bioimpedance spectroscopy (BIS) takes into account limb dominance, quantifies the whole limb [30], and uses thresholds based on normative population. BIS is recognised as having greater capability than other tools to detect the small changes in extracellular fluid volume associated with developing LE [31].

Finally, evidence for other factors thought to increase the risk of LE, such as needle punctures, has returned conflicting findings [32–34]. Investigations into post-surgical events thought to increase risk of LE require further study. The current study was therefore designed to identify the risk factors for LE at 18-months, while addressing methodological confounders.

Methods

Study design

A prospective cohort study was conducted between 2009 and 2013 in which women diagnosed with breast cancer were recruited from six cancer centres prior to treatment, and followed for 18 months following surgery. Women were assessed prior to surgery, within 4 weeks post-surgery (POST), and at 6, 12 and 18-months following surgery. At the POST assessment, women were educated about completion of weekly diaries until the 18-months assessment. The diaries recorded events that occurred in the previous week, related to risk factors which women may be cautioned against, e.g. medical procedures to the 'at-risk' arm. Ethics approval was obtained from the research institution as well as recruiting hospital sites and all participants provided written informed consent.

Participants

Women diagnosed with breast cancer, who understood English, and were available for assessments were recruited prior to surgery from seven cancer centres; only women with Stage I–III were followed post-surgically. Women were excluded if they had a pacemaker.

Data collection

Risk factors

Risk factors were recorded at the time of assessments, extracted from medical records, or determined from post-surgical events extracted from weekly diaries. Demographic factors included age, weight, body mass index (BMI) at baseline, hand dominance, level of education, whether or not they were currently living with a partner, number of comorbidities, and medications. Lifestyle factors at the time of surgery included smoking, alcohol consumption, and volume of physical activity, using questions from the '45-and-up' study [35]. Breast cancer treatment-related variables included: side of surgery; oestrogen receptor status; HER2 status; type of breast surgery; number of nodes removed and involved; radiotherapy treatment (chest and supraclavicular regions) and specifically radiotherapy including the axilla; use of chemotherapy and chemotherapy regimen; and use of hormone therapy. Arm swelling-related variables included the extent to which women were protective of the 'at risk' arm using a visual analogue scale ranging from '0' not at all to '10' extremely protective, and whether in the first year, swelling was identified in the 'at-risk arm' at any assessment.

Variables related to post-surgical events were extracted from weekly diaries. Women completed the diary through an on-line survey (60%), over the phone at a specified day and time of their choosing (13%), or using a paper diary (27%). Participants were instructed if they missed one week to reflect over the period from the last diary; if they missed submitting two consecutive digital diaries, a research assistant contacted the participant by phone to discuss using a different strategy, e.g., weekly phone call. The following areas were explored: travel or environmental; physical activity; injuries and/or trauma to the arm on the side of surgery; and procedures to the arm or chest on the side of surgery (Table 3).

Diagnosis of LE

BIS was used to quantify extracellular fluid, of which lymph is the major component, and has been validated against changes of limb volume and is highly reliable [19]. Each limb was measured separately using a standardised protocol and the inter-limb impedance ratio determined to account for non-LE related changes in limb volume [19]. Women were categorised as having LE either if their impedance ratios exceeded the normative-based, dominance-controlled thresholds, or increased by at least 0.1 from baseline [36].

Limb swelling

Limb circumferences of both arms were measured at 10 cm intervals to 40 cm, commencing at the ulnar styloid, following a standardised reliable procedure [19]; limb volumes were calculated and expressed as a ratio, side-of-surgery to non-surgery side.

Data analysis

To address the issue of homogeneity, participants with <5 and ≥ 5 nodes removed, indicative of SNB and ALND [8,9,37] respectively, were analysed separately to identify the risk factors for LE at 18-months, excluding data from the diaries, using a multivariable logistic regression model. As we aimed to provide a parsimonious model that could be used by clinicians to identify patients at most risk rather than a model of causal factors and confounders in an epidemiological sense, we used a forward sequential approach to identify which significant univariate predictors were independent predictors [38]. For factors that comprised continuous data (e.g., age), a receiver operator characteristics (ROC) curve was used to identify the optimal predictor cut-off point that indicated whether or not LE was present. Variables were considered for inclusion in the model if the OR was ≥ 2.0 or $P < 0.1$. A sequential method was used to build the model; at each step, changes to the model were examined to assess multicollinearity and instability in the model [39]. Independent variables were retained in the final model if the OR was ≥ 2.0 or $P < 0.1$.

The process described above was also used to identify: i) the risk factors for LE at 18-months, derived specifically from the variables recorded in the diaries; and ii) through secondary analysis, the risk factors for swelling at POST and after 6 and 12 months following surgery. To ensure data from the diaries reflected events over the