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# Mechanosensitivity in the upper extremity following breast cancer treatment

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ABSTRACT

*Study design:* Descriptive, cross-sectional.
*Introduction:* Breast cancer (BC) treatments place the nervous system at risk, which may contribute to upper extremity (UE) mechanosensitivity.
*Purpose of the study:* To evaluate elbow extension range of motion (EE-ROM) during upper limb neurodynamic testing (ULNT) post-BC treatment.
*Methods:* ULNT EE-ROM was measured for 145 women post-BC treatment. Women were sub-grouped by presence/absence of pain and lymphedema.
*Results:* Mean EE-ROM during ULNT1 was −22.3° (SD 11.9°) on the unaffected limb and −25.99° (SD 13.1°) on the affected limb. The women with pain and lymphedema had the greatest limitation in EE-ROM during ULNT1 testing, particularly of their affected limb (−33.8°, SD 12.9). Symptoms were reported more frequently in the affected chest, shoulder, arm, elbow, and hand. The intensity of symptoms was greater at the affected chest ($p = 0.046$), shoulder ($p = 0.033$) and arm ($p = 0.039$).
*Conclusions:* Women with lymphedema and pain after BC treatment may present with altered neural mechanosensitivity.
*Level of evidence:* 3a.



## Introduction

Many of the more than 2 million breast cancer survivors in the U.S.[1–3] have upper extremity morbidities associated with their breast cancer treatment, including pain and lymphedema. While breast surgery alone may result in physical impairments, the addition of axillary dissection, radiation, and chemotherapy are associated with increased incidence of morbidity, not only lymphedema, but neuropathy, and reductions in range of motion.[4] It is estimated that between 5 and 42% of breast cancer survivors develop lymphedema,[5–10] as many as 47% report persistent pain,[11] and up to 77% report sensory disturbance in the breast or arm.[12] These short and long term consequences have dramatic impact on physical function and quality of life in this population.[8,13,14]

For example, women who develop breast cancer-related lymphedema experience greater pain and limitation in upper extremity (UE) function, and more restrictions in activity than women without lymphedema.[4,13–15] Breast cancer-related lymphedema results from impaired lymph transport due to surgical removal of or radiation-induced damage to axillary lymph nodes and lymphatic channels,[16,17] which leads to accumulation of lymph in the UE, chest, or trunk. In addition to pain there are other symptoms associated with lymphedema that are troublesome, including heaviness, ache, or tiredness of the affected limb, jewelry or clothes feeling too tight, swelling in the limb, and difficulty writing.[8,18] Complaints of heaviness and ache often associated with lymphedema, and complaints of weakness, sensory disturbance, and pain following breast cancer treatment, may also be associated with injury to peripheral nerves.

Injury to the long thoracic, thoracodorsal, and intercostobrachial nerves has been reported with axillary dissection.[19–23] Nerve injury may be a result of positional tractioning, forceful retraction, direct laceration, or contusion of neural tissue during surgery.[19] Nerve injury can also be due to entrapment or compression related to post-operative or radiation-induced fibrosis and scarring.[19,24] Radiation-induced fibrosis is thought to occur in 3 phases.[25] The pre-fibrotic phase includes marked chronic inflammation, increased vascular permeability, edema formation, and fibroblast proliferation. During the second phase the damaged tissue is

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composed primarily of activated fibroblasts in a disorganized extracellular matrix with excessive deposition of extracellular matrix proteins and collagen. During the fibroatrophic phase, there is loss of parenchymal cells and retraction of the fibrous tissue which is dense and poorly vascularized.[26] Though relatively uncommon, radiation-induced brachial plexus neuropathy in breast cancer survivors has been described.[27,28] Damage is thought to be due to direct neuronal damage, microvascular injury and resultant ischemia, or to entrapment or compression from radiation-induced fibrotic changes in surrounding tissues.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common complication of systemic cancer treatments with chemotherapeutic agents.[29] A number of factors have been implicated in the pathophysiology of CIPN, including disruption of axoplasmic microtubule-mediated transport, axonal degeneration, and damage to the sensory nerve cell bodies in the dorsal root ganglia.[30]

Peripheral nerves may become "sensitized" when subjected to trauma and become less tolerant to the physical stresses, such as compression and stretch, imposed upon them during movement. The mechanisms responsible for development of neuropathic pain from cancer treatment (i.e. radiation-induced neuropathy, CIPN, or surgical injury) may also affect the tolerance of the nervous system to movement. For example, taxanes, commonly used in the treatment of breast cancer, are known to lead to impaired axonal transport.[31,32] Ellis et al[33] have demonstrated heightened mechanosensitivity in the sciatic nerve with a rat model of impaired axonal transport. Additionally, peripheral nerves at risk during surgery or radiation may be subjected to higher than normal physical stresses during movement due to compression or restrictions from adhesions and fibrosis.

### *Purpose*

In light of this shared theoretical etiology and overlapping symptomatic complaints, it is important to recognize the unique symptoms of altered mechanosensitivity in women following breast cancer treatment and whether this presentation is altered in the presence of lymphedema. Our hypotheses are that 1) following breast cancer treatment women will have impaired mechanosensitivity in the affected UE compared to their unaffected UE and 2) this impairment will be even greater in the women with lymphedema and pain. The results of this study will provide valuable information to clinicians who treat women with upper limb impairments following breast cancer treatment. The aims of this study were to 1) evaluate the mechanosensitivity of the UE nervous system in women following breast cancer treatment and 2) to compare mechanosensitivity between subgroups of women after breast cancer treatment (defined by presence or absence of pain and lymphedema).

## Methods

### *Participants*

Participants consisted of 145 women over the age of 18 who had completed active breast cancer treatment at least 6 months previously. Women were excluded for bilateral breast cancer, current UE infection, lymphangitis, pre-existing lymphedema, recurrence of breast cancer, or pre-existing neuromuscular or musculoskeletal conditions that would preclude UE testing. Women were recruited through the National Lymphedema Network website, San Francisco Bay area hospitals, San Francisco Bay area breast cancer or lymphedema support groups, and breast cancer conferences. The women were required to have no history of UE trauma, cervical radiculopathy, breast cancer, lymphedema, upper quadrant neurovascular entrapment, or UE peripheral nerve injury. Participants were required to be able to read, speak, and understand English. The University of California, San Francisco (UCSF) Committee on Human Research and the Clinical and Translational Science (CTSI) Clinical Research Center Advisory Committee approved both studies. Written informed consent was obtained prior to testing and the rights of participants were protected.

### *Procedures*

Participants in this cross-sectional study attended a single evaluation session at the UCSF CTSI Clinical Research Center. One investigator (BS) completed all testing.

### *Subjective measures*

Participants completed a 28-item Demographic Profile questionnaire. Information was collected regarding age, income, ethnicity, gender, menopausal status, Karnofsky Performance Status, and co-morbidities. The women completed the Norman Questionnaire, a validated self-report measure used to monitor symptoms of UE lymphedema[34] and the Lymphedema and Breast Cancer Questionnaire to collect data regarding signs and symptoms at the time of testing, during the month prior, and during the year prior.[35] Pain was evaluated using the Breast Symptoms Questionnaire (BSQ) including information on the occurrence of pain and other symptoms in the breast and UE (swelling, numbness, strange sensations, hardness). Participants rated the intensity of their average and worst pain, in the past week, using a numeric rating scale (NRS) that ranged from 0 (no pain) to 10 (worst imaginable pain). Participants were also asked to rate any symptoms in the UE using the same NRS. The NRS is a valid and reliable measure of pain intensity in adults with cancer.[36]

### *Objective measures*

A 12 inch goniometer was used to measure shoulder and elbow range of motion (ROM), following standardized procedures reported by Norkin.[37] Circumferential measurements were used to objectively document UE limb volume. A flexible tape measure was used for segmental measurement of circumference of each UE beginning at the ulnar styloid, and at 10 cm intervals proximal to this point up to a maximum of 40 cm. Volume was calculated from the circumference measurements using the following formula for volume of a truncated cone: $V = 1/12\pi \Sigma h\,(C_1^2 + C_1C_2 + C_2^2)$, where $h$ is the length of each measured segment and $C$ is the circumference at each end of that segment.[38]

Neural tolerance to movement was assessed through neurodynamic testing. The upper limb neurodynamic test 1 (ULNT1)[39] was utilized in this study as it has the highest reliability compared to other variations.[40] The ULNT1 consists of motions known to apply increased strain on the UE neural pathway from the brachial plexus to the distal peripheral nerve branches.[41–43] Measurement of the last motion during ULNT1 sequencing, elbow extension, represents a measure of the overall tolerance of the neural tissue to movement when under greater relative loading (elongation). To ensure that the limitation of elbow extension during ULNT1 was truly related to neural tissue sensitization, the findings were compared to elbow extension range of motion with the shoulder in 0 degrees of flexion, abduction, and rotation and wrist/hand in 0 degrees of flexion/extension, positions in which the neural tissue is comparatively under less loading (more slack).