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PERSISTENT BREAST PAIN FOLLOWING BREAST CANCER SURGERY IS ASSOCIATED WITH PERSISTENT SENSORY CHANGES, PAIN INTERFERENCE, AND FUNCTIONAL IMPAIRMENTS

Dale J. Langford[1], **Steven M. Paul**[1], **Claudia West**[1], **Jon D. Levine**[2], **Deborah Hamolsky**[1], **Charles Elboim**[3], **Brian L. Schmidt**[4], **Bruce A. Cooper**[1], **Gary Abrams**[2], **Bradley E. Aouizerat**[1,5], and **Christine Miaskowski**[1]

[1]School of Nursing, University of California, San Francisco, California

[2]School of Medicine, University of California, San Francisco, California

[3]Redwood Regional Oncology Group, Santa Rosa, California

[4]College of Dentistry, New York University, New York, New York

[5]Institute for Human Genetics, University of California, San Francisco, California

Abstract

Inter-individual variability exists in persistent breast pain following breast cancer surgery. Recently, we used growth mixture modeling to identify three subgroups of women (n=398) with distinct persistent breast pain trajectories over six months following surgery (i.e., Mild, Moderate, Severe). Purposes of this study were to identify demographic and clinical characteristics that differed among the breast pain classes and, using linear mixed effects modeling, determine how changes over time, in sensitivity in the breast scar area, pain qualities, pain interference, and hand and arm function differed among these classes. Several demographic and clinical characteristics differentiated the breast pain classes. Of note, 60% to 80% of breast scar sites tested were much less sensitive than the unaffected breast. Significant group effects were observed for pain qualities and interference scores, such that, on average, women in the Severe Pain class reported higher scores than women in the Moderate Pain class. In addition, women in the Moderate Pain class reported higher scores than women in the Mild Pain class. Compared to the Mild Pain class, women in the Severe Pain class had significantly impaired grip strength and women in the Moderate and Severe Pain classes had impaired flexion and abduction.

Address correspondence to: Christine Miaskowski, RN, PhD, FAAN, Professor and Associate Dean for Academic Affairs, Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, 415-476-9407 (phone), 415-476-8899 (fax), chris.miaskowski@nursing.ucsf.edu.

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Keywords

breast pain; breast cancer surgery; pain qualities; pain interference; range of motion; grip strength; sensory changes; persistent pain; chronic pain

INTRODUCTION

The majority of women diagnosed with breast cancer will undergo either breast conserving surgery or mastectomy. Unfortunately, a common sequela of either procedure is persistent post-surgical pain,[11] defined as pain that persists for longer than 3 months. In fact, this pain may persist for several years[5,20] and has detrimental effects on patients' functional status and quality of life.[4,28]

Considerable inter-individual variability exists in the experience of persistent pain after breast cancer surgery and prevalence estimates vary widely between 25% and 60%.[11] Most of the studies that evaluated persistent pain were retrospective and used a dichotomous pain outcome, with varying definitions of persistent "post-mastectomy" pain.[2] However, a detailed phenotypic characterization of this pain, including changes in sensitivity; pain qualities; as well as its impact on daily functioning, muscle strength, and shoulder mobility, is lacking.

Recently, in a large prospective study (n=398), we evaluated the prevalence and severity of breast symptoms following breast cancer surgery. In order to account for inter-individual variability and better characterize persistent pain phenotypes, we used growth mixture modeling (GMM) to identify subgroups (i.e., latent classes) of women with distinct trajectories of breast pain over six months following surgery.[21] In addition to women who reported no pain at all six monthly assessments (32% No Pain), three latent classes with distinct breast pain trajectories were identified: 43% with Mild Pain, 13% with Moderate Pain, and 12% with Severe Pain.[21]

The use of GMM allows for the identification of patient subgroups, as well as the identification of potential risk factors for persistent pain. We identified a number of demographic, pre-, intra-, and postoperative characteristics that differed among the four GMM pain classes.[21] However, this analysis did not include an evaluation of differences in demographic and clinical characteristics among only the three pain classes. In addition, a detailed description of the persistent pain experience and how pain-related characteristics (e.g., pain qualities, pain interference) changed over time within and among the persistent pain classes were not evaluated. A clearer understanding of how these persistent pain classes differ might inform our understanding of the mechanisms that underlie the development of persistent breast pain, as well as guide the development of tailored interventions and ongoing assessments of physical functioning in these patients.

Therefore, the purposes of this study were to: identify demographic and clinical characteristics that differed among the three breast pain classes (i.e., Mild, Moderate, Severe) and determine how changes over time, in sensitivity in the breast scar area, in

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ratings of pain qualities and pain interference, as well as in hand and arm functions (i.e., grip strength, shoulder mobility) differed among the three persistent breast pain classes.

MATERIALS AND METHODS

Patients and Settings

The methods are described in detail elsewhere.[21] In this paper, the methods are abbreviated and focus on specific measures and procedures used in this analysis. This prospective, longitudinal study is part of a larger study that evaluated neuropathic pain and lymphedema in women undergoing breast cancer surgery.[19,21,22] Patients were recruited from seven breast care centers including a Comprehensive Cancer Center, two public hospitals, and four community practices.

Women were eligible to participate if they: were ≥18 years; were scheduled to undergo unilateral breast cancer surgery; were able to read, write, and understand English; agreed to participate; and gave written informed consent. Patients were excluded if they were having breast cancer surgery on both breasts and/or had distant metastasis.

A total of 516 patients met these criteria and were approached to participate, 410 were enrolled (response rate 80%), and 398 completed the study. Common reasons for refusal were: too busy, overwhelmed with the cancer diagnosis, or insufficient time available to do the baseline assessment prior to surgery.

Subjective Measures

The demographic questionnaire obtained information on age, marital status, education, ethnicity, employment status, living situation, and financial status. Patients completed the Karnofsky Performance Status (KPS) scale, which is widely used to evaluate functional status in patients with cancer and has well established validity and reliability.[15,16] Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).

The Self-Administered Comorbidity Questionnaire (SCQ) is a short and easily understood instrument that was developed to measure comorbidity in clinical and health service research settings.[31] The questionnaire consists of 13 common medical conditions. Patients were asked to indicate if they had the condition; if they received treatment for it; and whether the condition limited their activities. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions.[3,31]

Breast pain was evaluated using the Breast Symptoms Questionnaire (BSQ). The BSQ consists of 2 parts. Part 1 obtained information on the occurrence of pain and the occurrence of other symptoms in the breast scar area (i.e., swelling, numbness, strange sensations, hardness). These additional symptoms were identified in studies by Tasmuth and colleagues.[38,39] In Part 2, patients were asked to rate 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). The NRS is a valid and reliable measure of pain intensity.[12]

In addition, patients rated the level of interference caused by breast pain with sixteen activities using a 0 (does not interfere) to 10 (completely interferes) NRS. This interference scale is an adaptation of the interference scale from the Wisconsin Brief Pain Inventory (BPI).[7] The interference scale is a valid and reliable measure that was used to evaluate the extent to which a person's pain interferes with their ability to function.[6,32] In addition to the original eight items on the BPI interference scale (i.e., general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life, sexual activity), the eight additional activities that were evaluated were those assessed in studies by Tasmuth and colleagues (i.e., ability to sleep on the operated side, touch, ability to reach out, ability to carry things, ability to get up from bed, ability to do handicrafts, ability to drive a car, ability to write).[38,39] Patients completed the BSQ prior to surgery and monthly for 6 months after surgery.

Postsurgical pain was evaluated using the Postsurgical Pain Questionnaire. Patients were asked to rate average and worst pain intensity, using a 0 to 10 NRS, in the first 24 to 48 hours after surgery. This questionnaire was completed during the month 1 study visit.

The 20-item Pain Qualities Assessment Scale (PQAS)[13,40] is an adaptation of the Neuropathic Pain Scale developed by Galer and Jensen.[10] Sixteen items evaluate the magnitude of the different pain quality descriptors (e.g., sharp, hot, aching, cold) measured with NRSs. Four items evaluate global and spatial qualities of pain. Three subscale scores were calculated (i.e., paroxysmal pain [shooting, sharp, electric, hot, radiating], surface pain [itchy, cold, numb, sensitive, tingling], deep pain [aching, heavy, dull, cramping, throbbing, tender]).[40] The PQAS has well-established validity and reliability.[13,40]

Objective Measures

Sensitivity in the breast scar area was tested at 4 to 8 sites around the length of the scar, using a 5.07 gram monofilament and compared to the corresponding area on the unaffected side. For each site tested, the patient reported whether it was "much less sensitive than the opposite side," "same as the opposite side," or "much more sensitive than the opposite side." The percentage of the total number of sites on the affected side classified as "much less," "same," and "much more" were calculated.

Grip strength in kilograms (kg), in both hands, was measured using a Jamar hydraulic hand dynamometer (Patterson Medical, Bolingbrook, IL). This measure was used to evaluate for changes in muscle strength in women following breast cancer surgery[39] and other forms of breast cancer treatment.[27] The measurement was performed with women in a standing position with the arm held in a comfortable position according to the procedures described by Spijkerman and colleagues.[33] Grip strength was measured 3 times in each hand. If a variance of more than 20% occurred among the 3 readings on a hand, the test was repeated. The 3 readings from each hand were averaged.

Shoulder mobility was assessed using goniometric measurements of range of motion (ROM). While the patient was lying supine, ROM was measured, in degrees, twice on each side in 4 positions (i.e., flexion, abduction, internal rotation, external rotation). For each position, the two measurements were averaged.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Boards at each of the study sites. During the patient's preoperative visit, a clinician explained the study to the patient and determined her willingness to participate. For those women who were willing to participate, the clinician introduced the patient to the research nurse. The research nurse met with the women, determined eligibility, and obtained written informed consent prior to surgery. After obtaining written informed consent, patients completed the enrollment questionnaires (Assessment 0). Following the completion of these questionnaires, the research nurse performed the following objective measures: height, weight, grip strength, and shoulder mobility.

The research nurse met with the patient either in their home or in the Clinical Research Center at 1, 2, 3, 4, 5, and 6 months after surgery. During each of the study visits, the women completed the study questionnaires, provided information on new and ongoing treatments, and had the objective measures done by the research nurse. Over the course of the study, patients' medical records were reviewed for disease and treatment information. Inter-rater reliability among the research nurses, for each of the objective measures, was evaluated every 6 months and exceeded 0.80.

Characterization of the persistent breast pain classes

A description of the GMM analysis that was used to characterize the persistent breast pain classes was reported previously.[21] In brief, at each assessment, patients were asked, "Are you experiencing pain in your affected breast?". If the patient reported pain, she was asked to rate her worst breast pain in the previous week using a 0 (no pain) to 10 (worst pain) NRS. Prior to conducting the GMM analysis, patients who reported no pain in their affected breast for all seven assessments (i.e., prior to surgery and 1, 2, 3, 4, 5, and 6 months) were identified (n=126; 32%) and were not included in the GMM analysis. For the remaining 272 women, six ratings of worst breast pain (i.e., prior to surgery, and 2, 3, 4, 5, and 6 months) were used in the GMM analysis to assign each patient into a latent class. Pain ratings obtained at the 1-month assessment were excluded from the model because of the high prevalence of pain and reduced variability in pain ratings. The GMM analysis was done using Mplus 6.1.[24] Because patients in the No Pain class did not complete the remaining pain measures (i.e., BPI, PQAS), their data could not be modeled. Therefore, only data from the three breast pain classes (i.e., Mild, Moderate, Severe) were evaluated in this study.

Statistical Analyses

Data were analyzed using SPSS version 21. Descriptive statistics and frequency distributions were calculated for patients' demographic and clinical characteristics. One-way analyses of variance, Kruskal-Wallis or Chi-square tests with Bonferroni corrected post hoc comparisons were performed to evaluate for differences in demographic and clinical characteristics among the three breast pain classes.

Linear mixed effects models fit by restricted maximum likelihood estimation (REML) were evaluated to determine if any differences existed over time among the breast pain classes in:

sensitivity in the breast scar area (i.e., percentage of sites in the breast scar area that were more, the same, or less sensitive than the unaffected breast); PQAS subscale scores (i.e., Paroxysmal, Surface,, Deep); individual pain interference items; grip strength; and shoulder mobility (i.e., abduction, flexion, internal rotation, external rotation). The tests of Group x Time interactions determined whether changes over time in any of these outcomes were significantly different among the breast pain classes. In addition, group effects (differences among the classes) and time effects (changes over time across the classes) were evaluated for significance using mixed-model tests of main effects. Post hoc pairwise comparisons with Bonferroni correction were used to identify differences among the classes. Time effects were described based on an evaluation of estimated marginal means and respective plots, and supplemented with post hoc pairwise comparisons between the monthly timepoints.

As was done with the GMM analysis of persistent breast pain,[21] data from the postsurgical assessment (i.e., Month 1) were excluded from the linear mixed effects models. The linear mixed effects model approach does not require that each patient have complete data at all six assessments. It allows patients to contribute as many assessment measurements as they completed. For the evaluation of differences among the classes in demographic and clinical characteristics, all calculations used actual values. Adjustments were not made for missing data. Therefore, the cohort for each of these analyses was dependent on the largest set of complete data across groups. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Differences in Demographic and Clinical Characteristics among the Breast Pain Classes

A comprehensive description of differences in demographic and clinical characteristics among all four latent classes is provided elsewhere.[21] Differences in select demographic and clinical characteristics among the three breast pain classes are listed in Table 1. Significant differences were found in years of education, Karnofsky Performance Status (KPS) and comorbidity scores, body mass index (BMI), annual household income, and occurrence of high blood pressure and rheumatoid arthritis. Post hoc pairwise comparisons revealed that women in the Severe Pain class had significantly fewer years of education than women in the Mild and Moderate Pain classes. Women in the Moderate and Severe Pain classes had significantly lower KPS scores than women in the Mild Pain class. Women in the Severe Pain class had significantly higher comorbidity scores, higher BMI, and lower annual household incomes than those in the Mild Pain class. A higher proportion of women in the Moderate Pain class had radiation therapy during the six months of the study compared to the other pain classes. Finally, a higher proportion of women in the Severe Pain class had high blood pressure and rheumatoid arthritis than women in the Mild Pain class.

Differences in Preoperative Breast Symptoms and Postoperative Pain among the Breast Pain Classes

The pain classes differed with respect to preoperative breast symptoms and postoperative pain intensity ratings. As shown in Figure 1A, a significantly larger proportion of women in the Severe Pain class, compared to the Mild Pain class, reported swelling and numbness in the breast prior to surgery. As shown in Figure 1B, women in the Severe Pain class reported significantly higher average and worst postoperative pain intensity scores than women in the Mild and Moderate Pain classes. Women in the Moderate Pain class reported higher worst pain intensity scores than women in the Mild Pain class.

Changes over Time in Sensitivity in the Breast Scar Area among the Breast Pain Classes

Figure 2 illustrates changes over time, among the breast pain classes, in the percentage of breast scar sites that were reported as less, the same, or more sensitive than the unaffected breast. Across the three breast pain classes, a higher percentage of sites on the affected side were reported to be much less sensitive than on the unaffected side (between 60% and 80% of sites). Fewer than 10% of the breast scar sites were more sensitive than on the unaffected side.

In terms of differences among the breast pain classes, in sensitivity in the breast scar area, no significant group or interaction effects were observed. However, a significant main effect of time was found for the percentage of sites classified as less sensitive ($P = .02$) and the “same” ($P = .001$) as the unaffected breast. As depicted in Figure 2, regardless of pain class, the percentage of breast scar sites classified as less sensitive showed a decrease over time, whereas the percentage of breast scar sites classified as the “same” increased over time. For the percentage of breast scar sites classified as more sensitive, no main effect of time was found.

Changes over Time in Pain Qualities among the Breast Pain Classes

Figure 3 illustrates changes over time among the breast pain classes in the PQAS Paroxysmal, Surface, and Deep subscale scores. Significant group effects were found for all of the PQAS subscale scores (all $P < .001$). Post hoc pairwise comparisons with Bonferroni correction revealed that for all subscales, women in the Severe Pain class had higher scores than women in the Mild and Moderate Pain classes, and women in the Moderate Pain class had higher scores than women in the Mild pain class (i.e., Mild < Moderate < Severe; all $P < .01$). In addition, a significant time effect was found for the Surface subscale ($P < .001$). As depicted in Figure 3B, on average, Surface pain qualities showed a quadratic pattern, such that scores increased from Month 0 to Month 2, plateaued, and decreased slightly by Month 6. No significant Group x Time interactions were found for any of the PQAS subscales.

Changes over Time in Pain Interference among the Breast Pain Classes

Figure 4 illustrates changes over time among the breast pain classes in pain interference scores. Each of the panels displays an exemplar plot for the pain interference items that demonstrated: only a group effect (A); a group effect and a time effect (B); a group effect and a Group x Time interaction (C); and a group effect, a time effect, and a Group x Time interaction (D).

Pain interference items that demonstrated only a group effect (A) included sleep on the affected side, sleep (general), ability to touch the affected site, and normal work (all $P < .001$). Post hoc pairwise comparisons with Bonferroni correction revealed that women in the Severe Pain class reported higher interference scores than women in the Mild and Moderate

Pain classes. Women in the Moderate Pain class reported higher interference scores than women in the Mild Pain class (all pairwise comparisons $P < .01$).

Pain interference items that demonstrated a group (all $P < .001$) and a time effect (all $P < .05$) (B) included enjoyment of life; walking ability; ability to carry things, do handicrafts, drive a car, and reach above the head; as well as general activity; relations with others; and the total interference score (i.e., the mean of all interference items). For all of these items, except ability to drive a car, group effects followed the expected pattern of Severe > Moderate > Mild (pairwise comparisons for all items $P < .05$). For ability to drive a car, women in the Severe Pain class had higher interference scores than women in the Mild and Moderate Pain classes ($P < .05$). In general, interference scores for these items demonstrated a quadratic pattern over time. Aside from enjoyment of life, walking ability, and relations with others, which demonstrated a slight decrease in pain interference scores over time, pain interference scores for the other items generally demonstrated an increase in scores from Month 0 to Month 2, which plateaued, then decreased slightly over time.

The two pain interference items that demonstrated both a group effect (both $P < .01$) and a Group x Time interaction (both $P < .05$) (C) were the ability to reach in front and sexual activity. For the ability to reach in front, group effects were in the expected direction (Mild < Moderate < Severe; all pairwise comparisons $P < .05$). For sexual activity, women in the Moderate and Severe Pain classes reported greater interference than women in the Mild Pain classes ($P < .05$). Interaction effects for both items appeared to demonstrate an increase in interference scores over time for the Moderate Pain, but not for the Mild or Severe Pain classes.

Finally, pain interference items that demonstrated a group effect (all $P < .001$), a time effect (all $P < .01$), and a Group x Time interaction (all $P < .05$) (D) included mood, the ability to get up from bed, and the ability to write. Group effects for mood and the ability to get up from bed were in the expected direction (Mild < Moderate < Severe; all pairwise comparisons $P < .05$). For the ability to write, women in the Moderate and Severe Pain classes reported higher interference scores than women in the Mild Pain class ($P < .05$). In terms of interaction effects, for mood, pain interference scores showed a decrease over time for women in the Mild and Severe Pain classes, but showed a slight increase over time for women in the Moderate Pain class. For the ability to get up from bed, all classes demonstrated a sharp increase in interference scores from month 0 to month 2. However, while scores for the Severe Pain class returned to preoperative levels, scores for the Mild and Moderate Pain classes remained higher than preoperative levels. For the ability to write, pain interference scores were very low across the three pain classes (i.e., < 1.5 for the Mild and Moderate classes), which hindered valid interpretation of this interaction effect.

Changes over Time in Grip Strength and Shoulder Mobility among the Breast Pain Classes

Figure 5 illustrates changes over time among the breast pain classes in grip strength and shoulder mobility (i.e., flexion, abduction, internal rotation, external rotation). For grip strength, only a significant group effect ($P = .023$) was found. Post hoc pairwise comparisons with Bonferroni correction revealed that women in the Severe Pain class had weaker grip strength than women in the Mild Pain class ($P < .05$). For flexion and abduction, significant group (both $P < .001$) and time (both $P < .001$) effects were found. Women in the Moderate and Severe Pain class had decreased flexion and abduction angles compared to women in the Mild Pain class (both $P < .05$). Only a time effect was observed for external rotation ($P = .001$). As depicted in Figures 5B and 5E, both flexion and external rotation appeared to exhibit a quadratic pattern, such that these measures decreased from Month 0 to Month 2, then increased slightly from Month 2, yet remained lower than Month 0. A significant Group x Time interaction was found for abduction ($P = .029$). Abduction appeared to improve from Month 2 to Month 6 for women in the Severe Pain class, but stayed relatively consistent for the Mild and Moderate Pain classes (Figure 5C). No significant group, time, or Group x Time effects were observed for internal rotation (Figure 5D).

DISCUSSION

This study extends our previous work that identified subgroups of women with distinct breast pain trajectories following breast cancer surgery.[21] In this analysis, in order to evaluate the impact of pain severity, differences among the Mild, Moderate, and Severe breast pain classes in a number of pain characteristics and functional outcomes were identified.

In terms of preoperative characteristics, compared to the Mild Pain class, nearly three times the number of women in the Severe Pain class reported presurgical swelling and numbness in the affected breast. These symptoms may reflect differences in the tumor microenvironment. For example, tumor-associated macrophages contribute to breast carcinogenesis[37] and inflammation[1] which can lead to sensory disturbances. Alternatively, these symptoms may reflect increased somatic awareness, which is associated with the development of a number of persistent pain conditions.[8]

Consistent with research that demonstrated an association between postoperative pain severity and persistent pain,[35,38] women in the Severe Pain class reported higher levels of average and worst postoperative pain compared to women in the Mild and Moderate Pain classes. These findings may reflect inherent inter-individual variability in pain perception[9,42] or analgesic responses.[34] In addition, these findings suggest that effective postoperative pain management is needed to reduce the occurrence of persistent pain.

In terms of localized changes in sensitivity in the breast scar area, no statistically significant differences were found among the latent classes in ratings of increased, similar, or decreased sensitivity. Of note, regardless of pain class membership, when compared to the unaffected breast, a higher percentage of breast scar sites (i.e., 60% to 80%) were perceived as much less sensitive than much more sensitive (i.e., <10%). Postoperative sensory loss[17] and descriptors such as “numb”[36] were reported previously, as well as by over 50% of the current sample. This finding of prevalent and persistent sensory loss in the breast scar area might be secondary to surgical disruption of primary afferent neurons innervating the epithelium at the site of the scar.

In contrast to the sensory findings, compared to the other latent classes, women in the Severe Pain class reported consistently higher scores on all of the PQAS subscales (i.e., paroxysmal, deep, surface). The increasing trend in Surface scores from prior to surgery to 2 to 3 months after surgery may reflect changes in pain qualities in the postoperative period while healing occurs. Otherwise, all PQAS subscale scores are relatively stable over time.

Persistent pain following breast cancer surgery is described predominantly as a neuropathic pain condition.[14] However, other mechanisms, including a persistent inflammatory response,[41] may contribute to this persistent pain condition. In addition, awareness of the complexity of this persistent pain problem is increasing.[2] Interestingly, the pattern of PQAS subscale scores for the Severe Pain class are more consistent with scores reported by patients with non-neuropathic pain conditions.[40] For example, patients with low back pain and osteoarthritis (non-neuropathic pain) reported similar severity scores for the Paroxysmal and Deep subscales, but lower scores for the Surface subscale.[40] Taken together, the findings from the sensory examination (i.e., majority of sites less sensitive regardless of pain class) and the self-report measure of pain qualities (i.e., differences in severity ratings among the pain classes and previous patterns observed in several non-neuropathic pain conditions) suggest that the mechanisms that underlie persistent breast pain are multifactorial. Certainly, the traumatic injury itself, as well as postoperative complications (e.g., hematomas, seromas, infections), which were extremely low in this sample,[21] could contribute to the development of persistent pain. A more detailed evaluation of changes in sensations in the breast scar area in patients with persistent pain, using quantitative sensory testing,[30] may provide insights into the complex mechanisms that underlie this persistent pain condition.

In general, pain interference scores differed among the latent classes in the expected direction (i.e., Severe > Moderate > Mild Pain). Interference scores were in the mild range (i.e., < 4) across all items for the Mild and Moderate Pain classes. However scores were in the moderate range (i.e., 4 to 7) for the Severe Pain class for: ability to touch the site; carry things; sleep on operative side; reach above the head; mood; enjoyment of life; and sleep (general). Of note, several items, primarily concerned with interference with physical function, showed an average increase over time (i.e., ability to carry things, do handicrafts, drive a car, reach above the head, reach in front, get up from bed, general activity, overall interference score). While this increase in pain interference may be due in part to the large increase in pain in the initial months after surgery, it is important to note that this increase persisted for six months. These findings, which are consistent with a previous report,[5] suggest the need for clinical evaluation and interventions long after the surgical incision has healed.

Group by time interactions were observed for five of the pain interference items (i.e., ability to reach in front, get up from bed, write, sexual activity, mood). With the exception of the ability to write, the remaining four items exhibited the same general pattern. While women in the Mild Pain class had low, stable scores over time, women in the Moderate Pain class had scores that increased slightly over time. Women in the Severe Pain class had scores that decreased over time. Of note, the increases observed for the Moderate Pain class are consistent with the trajectory of worst breast pain ratings that increased over time.[21] These findings may be partially explained by the higher proportion of women in the Moderate Pain class who underwent radiation therapy.[21] In contrast, the trajectory of worst breast pain ratings for the Severe Pain class was stable across time.[21] It is unclear why pain interference scores do not mirror the pain intensity trajectory. It is possible that these women underwent a response shift that resulted in reevaluation of interference based on changes in internal standards[29] or that they developed strategies to better manage pain interference over time.

Group effects were less pervasive for grip strength and shoulder mobility. Women in the Mild Pain class had higher grip strength than women in the Severe Pain class and greater degrees of flexion and abduction than women in the Moderate and Severe Pain classes. However, degrees of internal and external rotation did not differ among the latent classes. Medium to large effect sizes were found for the differences in grip strength (d=0.44), flexion (d=0.87), and abduction (d=0.71) between the Mild and Severe Pain classes. Differences among the classes did not meet published standards for clinically meaningful differences in grip strength of 6 kg[25] and flexion/abduction of 20°.[18] However, these "standards" are based on cross-sectional studies. Persistent changes of lesser magnitude may be clinically meaningful. Moreover, the observed effect sizes, coupled with the significant group effects for several pain interference items associated with various aspects of physical function, suggest that clinically meaningful differences in functional status exist among the breast pain classes.

Grip strength and internal rotation remained stable over time, while flexion, abduction, and external rotation showed decreases from preoperative levels to 2 to 3 months after surgery, with measurements recovering slightly in the 3 months of the study. Of note, the decreases over time in external rotation are not clinically meaningful. The statistically significant reductions in flexion and abduction are driven by the differences between measurements taken prior to surgery and two months following surgery. However, it is important to note that patients did not return to preoperative levels of arm function at the six-month assessment. These findings correlate with the patterns of change in several of the pain interference items, particularly those items related to physical functioning, and emphasize the need for continued clinical evaluation. However, a longer evaluation period (e.g., 12 months) may be needed to determine if full resolution of shoulder mobility occurs.[26]

Limitations of this study need to be acknowledged. With a larger sample size, additional differences and interaction effects may be identified. In addition, because this cohort of women was relatively homogenous (predominantly white, middle-aged women), findings may not generalize to other populations. Patients were asked to recall the severity of their postoperative pain at the Month 1 assessment. Future studies need to assess postoperative pain and its management prospectively. Finally, these findings are specific to persistent breast pain. In fact, an independent GMM analysis identified only two latent classes of patients with persistent pain in the ipsilateral arm/shoulder over six months following breast cancer surgery (i.e., 40% Mild Arm Pain, 60% Moderate Arm Pain).[23] In our companion paper, we describe how sensations in the upper arm and axilla, pain qualities, interference, and hand and arm function differ between these two arm pain latent classes. In addition, we compare the findings for persistent arm pain to the current findings for persistent breast pain.

In conclusion, the three persistent breast pain classes differed primarily with respect to severity in terms of pain qualities, interference, and hand and arm function. As such, these three breast pain phenotypes may be mechanistically similar, but differ only in the severity of the pain problem. Therefore, although higher doses of a specific intervention may be warranted for those patients with severe pain, differentially targeted interventions for patients with mild, moderate, or severe pain may not be necessary. However, a number of different mechanisms may play a role in the development and maintenance of persistent breast pain and contribute to variations in pain severity. Therefore, parallel efforts are underway to identify molecular markers associated with latent class membership. In addition, this persistent breast pain condition is associated with persistent interference with function, as well as decrements in shoulder mobility and sustained sensory loss, which suggest the need for ongoing assessments and interventions (e.g., physical therapy) beyond the healing of the surgical wounds.

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Perspective

Subgroups of women with persistent postsurgical breast pain differed primarily with respect to the severity rather than the nature or underlying mechanisms of breast pain. Pervasive sensory loss and the association between persistent breast pain and sustained interference with function suggest the need for long term clinical follow-up.

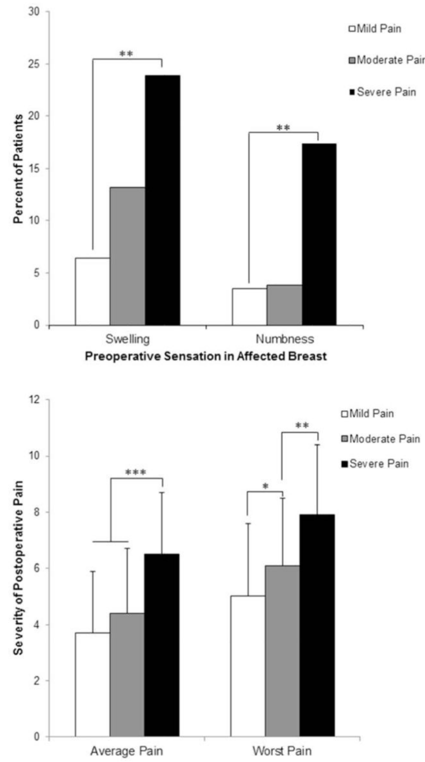

Figure 1.

(A) Percentage of women in each of the latent classes who reported swelling or numbness in the breast prior to surgery. (B) Average and worst postoperative pain ratings (on 11-point numeric rating scale) for 24 to 48 hours following breast cancer surgery for each of the pain classes. Values are plotted as means and standard deviations. Note: $P < .001$ for the difference in worst postoperative pain ratings between Mild and Severe Breast Pain classes. *$P < .05$; **$P < .01$; ***$P < .001$

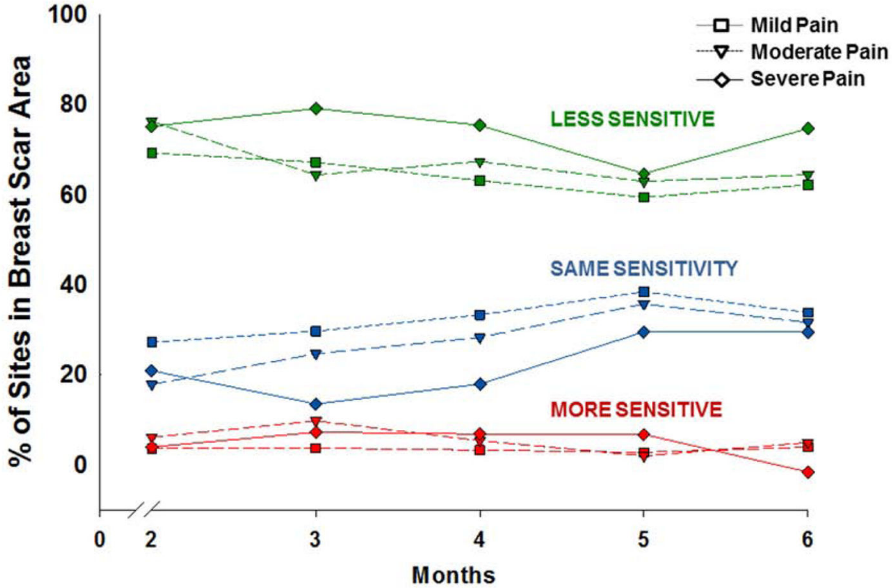

Figure 2.

Plots of the estimated marginal means over time among the breast pain classes for the mixed effects model for the percentage of breast scar sites reported as less sensitive (green), the same (blue), and more sensitive (red) than the unaffected breast. Statistically significant findings: Percentage less sensitive – time effect: $P = .02$; Percentage the same – time effect: $P = .001$.

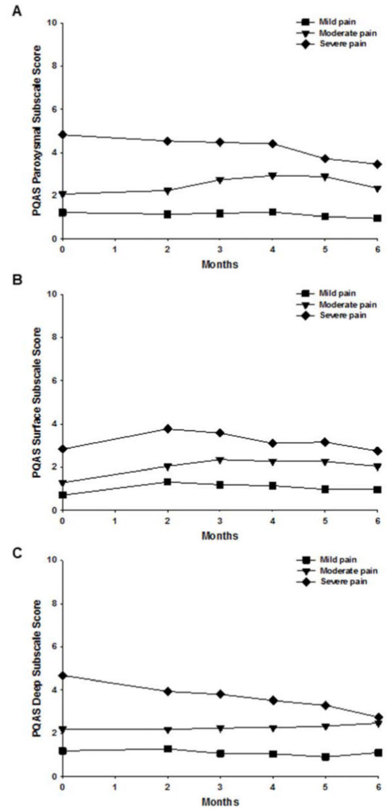

Figure 3.

Plots of the estimated marginal means over time among the breast pain classes for the mixed effects models for the Pain Qualities Assessment Scale (PQAS) Paroxysmal (A); Surface (B); and Deep (C) subscale scores among the pain classes. Statistically significant findings: Paroxysmal group effect: $P < .001$; Surface group effect: $P < .001$ and time effect: $P < .001$; and Deep group effect: $P < .001$.

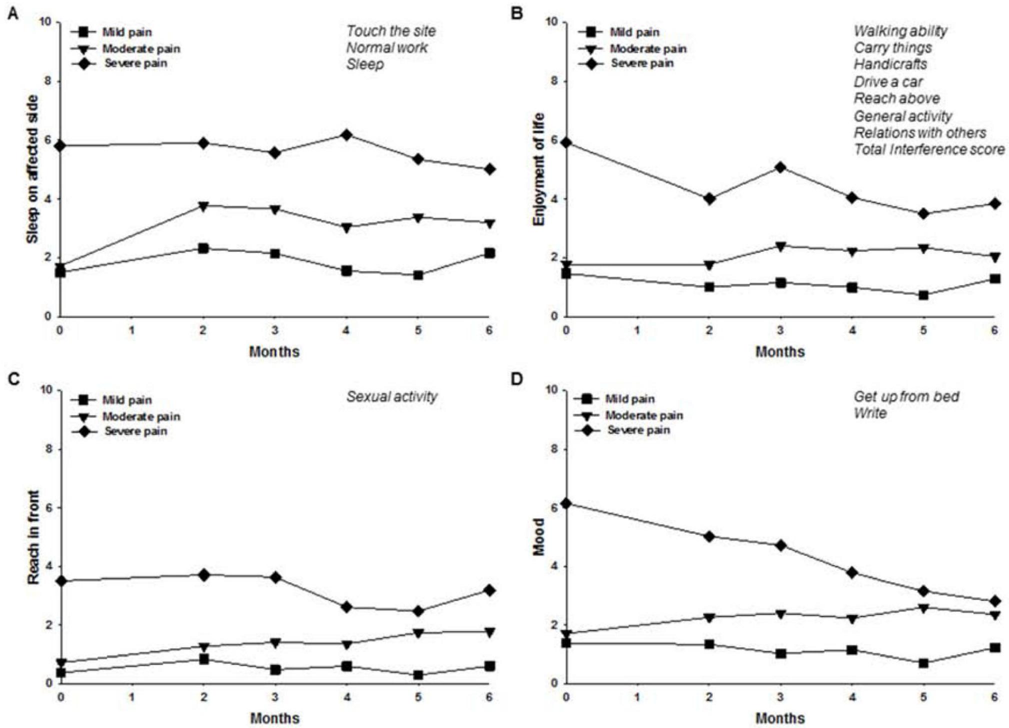

Figure 4.

Plots of the estimated marginal means over time among the breast pain classes for the mixed effects models for pain interference scores. For each pattern of effects, an exemplar plot is displayed. Inset italicized items denote items with the same pattern of effects as the exemplar. Panels display items with statistically significant: group effects only (A); group and time effects (B); group and Group x Time interaction effects (C); and group, time, and Group x Time interaction effects (D).

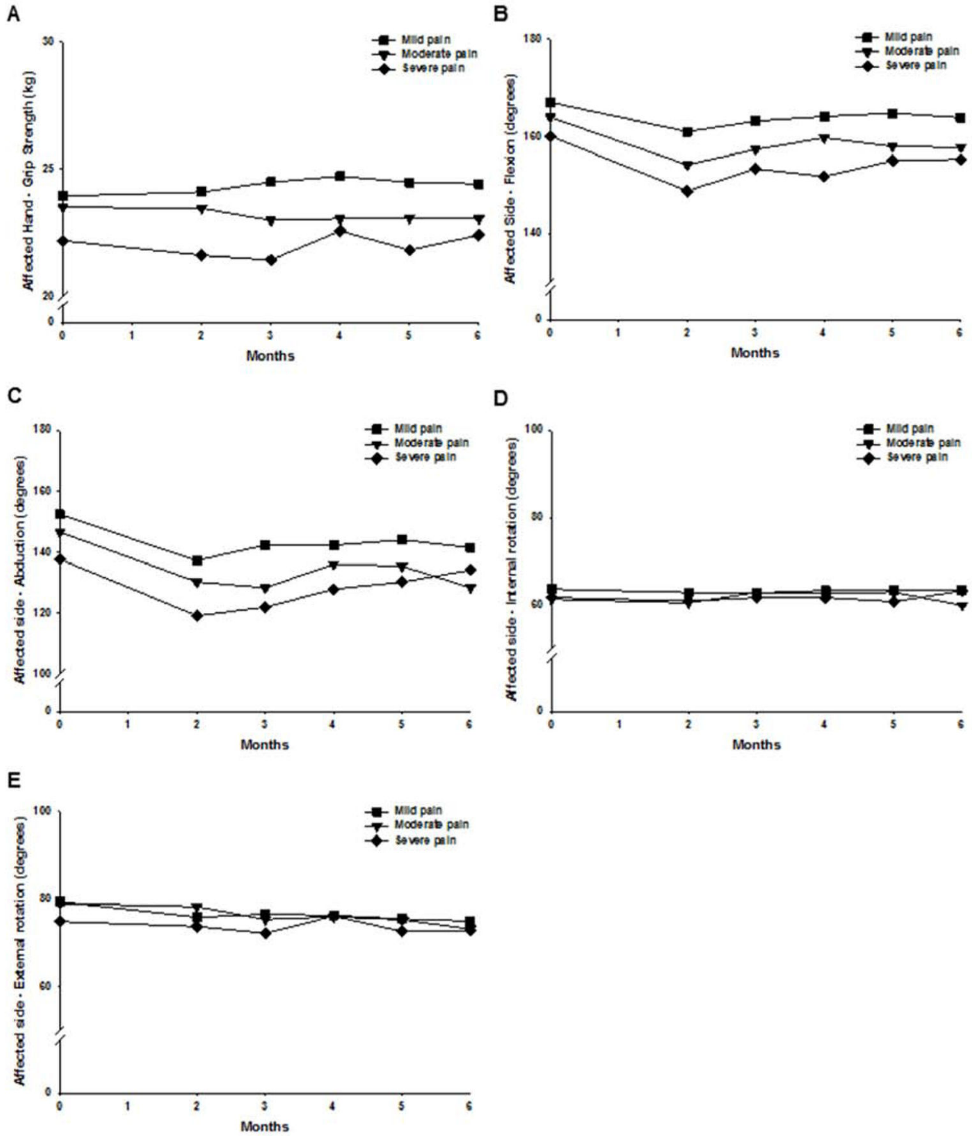

Figure 5.

Plots of the estimated marginal means over time among the pain classes for the mixed effects model for grip strength (A), flexion (B), abduction (C), internal rotation (D), and external rotation (E). Statistically significant findings: Grip strength - group effect: $P = .02$; Flexion - group effect: $P < .001$; time effect: $P < .001$; Abduction - group effect: $P < .001$; time effect: $P < .001$; Group x Time interaction: $P = .03$; External rotation - time effect: $P = .001$.

Table 1

Differences in Demographic and Clinical Characteristics among the Three Breast Pain Classes

Characteristic	Mild Pain (1) n=173 (63.6%)	Moderate Pain (2) n=53 (19.5%)	Severe Pain (3) n=46 (16.9%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	53.4 (11.5)	53.4 (12.1)	52.4 (9.3)	F=1.73, *P*=.850
Education (years)	16.0 (2.6)	15.6 (2.2)	14.3 (2.9)	F=7.97, *P*<.001 1 and 2 > 3
Karnofsky Performance Status score	93.6 (9.3)	89.6 (9.3)	87.6 (14.9)	F=7.52, *P*<.001 1 < 2 and 3
Self-Administered Comorbidity Scale score	4.0 (3.0)	4.7 (2.9)	5.6 (3.2)	F=5.06, *P*=.007 1 < 3
Body mass index (kg/m^2)	25.9 (5.3)	27.6 (6.3)	28.6 (6.3)	F=5.03, *P*=.007 1 < 3
	% (N)	% (N)	% (N)	
Ethnicity				X^2=11.72, *P*=.068
White	63.7 (109)	66.0 (35)	41.3 (19)	
Black	8.8 (15)	11.3 (6)	21.7 (10)	
Asian/Pacific Islander	12.9 (22)	9.4 (5)	21.7 (10)	
Hispanic/Mixed ethnic background/Other	14.6 (25)	13.2 (7)	15.2 (7)	
Lives alone				X^2=0.47, *P*=.791
Yes	24.6 (42)	26.4 (14)	29.5 (13)	
No	75.4 (129)	73.6 (39)	70.5 (31)	
Marital status				X^2=5.41, *P*=.067
Married/Partnered	39.5 (68)	37.7 (20)	58.1 (25)	
Single, separated, widowed, divorced	60.5 (104)	62.3 (33)	41.9 (18)	
Currently working for pay				X^2=4.84, *P*=.089
Yes	50.9 (87)	39.6 (21)	34.8 (16)	

Characteristic	Mild Pain (1) n=173 (63.6%)	Moderate Pain (2) n=53 (19.5%)	Severe Pain (3) n=46 (16.9%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
No	49.1 (84)	60.4 (32)	65.2 (30)	
Total annual household income				
<$10,000 to $29,999	17.8 (26)	33.3 (13)	44.7 (17)	KW, P=0.001
$30,000 to $99,999	40.4 (59)	35.9 (14)	39.5 (15)	1 > 3
≥$100,000	41.8 (61)	30.8 (12)	15.8 (6)	
Occurrence of comorbid conditions				
High blood pressure	24.3 (42)	30.2 (16)	45.7 (21)	X^2=8.10, P=.017 1 < 3
Diabetes	5.8 (10)	7.5 (4)	17.4 (8)	X^2=6.62, P=.037 pw comparisons ns
Rheumatoid Arthritis	2.9 (5)	1.9 (1)	13.0 (6)	X^2=9.88, P=.007 1 < 3
Type of surgery				
Breast conserving	77.5 (134)	75.5 (40)	82.6 (38)	X^2=0.79, P=.672
Mastectomy	22.5 (39)	24.5 (13)	17.4 (8)	
Sentinel lymph node biopsy				
Yes	82.7 (143)	86.8 (46)	71.7 (33)	X^2=4.06, P=.131
No	17.3 (30)	13.2 (7)	28.3 (13)	
Axillary lymph node dissection				
Yes	38.4 (66)	41.5 (22)	52.2 (24)	X^2=2.85, P=.240
No	61.6 (106)	58.5 (31)	47.8 (22)	
Received hormonal therapy during the 6 months				
Yes	41.6 (72)	47.2 (25)	30.4 (14)	X^2=2.98, P=.225
No	58.4 (101)	52.8 (28)	69.6 (32)	
Received radiation therapy during the 6 months				
Yes	54.3 (94)	75.5 (40)	41.3 (19)	X^2=12.39, P=.002

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Characteristic	Mild Pain (1) n=173 (63.6%)	Moderate Pain (2) n=53 (19.5%)	Severe Pain (3) n=46 (16.9%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
No	45.7 (79)	24.5 (13)	58.7 (27)	2 > 1 and 3
Received adjuvant chemotherapy during the 6 months				
Yes	34.7 (60)	28.3 (15)	39.1 (18)	X^2=1.33, *P*=.513
No	65.3 (113)	71.7 (38)	60.9 (28)	
Occurrence of lymphedema	18.0 (31)	20.8 (11)	32.6 (15)	X^2=4.65, *P*=.098

Abbreviations: kg/m^2 = kilograms per meter squared; KW = Kruskal-Wallis; ns = not significant; pw = pairwise; SD = standard deviation