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Persistent pain in postmastectomy patients: Comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain

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Abstract

Persistent postmastectomy pain (PPMP) is a major individual and public health problem. Increasingly, psychosocial factors such as anxiety and catastrophizing are being revealed as crucial contributors to individual differences in pain processing and outcomes. Furthermore, differences in patients' responses to standardized quantitative sensory testing (QST) may aid in the discernment of who is at risk for acute and chronic pain after surgery. However, characterization of the variables that differentiate those with PPMP from those whose acute postoperative pain resolves is currently incomplete. The purpose of this study was to investigate important surgical, treatment-related, demographic, psychophysical, and psychosocial factors associated with PPMP by comparing PPMP cases with PPMP-free controls. Pain was assessed using the breast cancer pain questionnaire to determine the presence and extent of PPMP. Psychosocial and demographic information were gathered via phone interview, and women underwent a QST session. Consistent with most prior research, surgical and disease-related variables did not differ significantly between cases and controls. Furthermore, treatment with radiation, chemotherapy, or hormone therapy was also not more common among those with PPMP. In contrast, women with PPMP did show elevated levels of distress-related psychosocial factors such as anxiety, depression, catastrophizing, and somatization. Finally, QST in nonsurgical body areas revealed increased sensitivity to mechanical stimulation among PPMP cases, while thermal pain responses were not different between the groups. These findings suggest that an individual's psychophysical and psychosocial profile may be more strongly related to PPMP than their surgical treatment.

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Keywords

Mastectomy; Chronic pain/persistent pain; Quantitative sensory testing/QST; Psychosocial; Catastrophizing; Breast cancer survivors

1. Introduction

Persistent postsurgical pain is an increasingly recognized problem [3,46], negatively impacting quality of life [51] and comprising as much as 20% of new chronic pain patients [16]. The reported incidence of persistent postmastectomy pain (PPMP) ranges from 25–60% [3,13,45,53,73]. With more than 200,000 women diagnosed annually in the United States, breast cancer is the most common form of female cancer [2]. Importantly, 41% of these women undergo mastectomy [44]. Furthermore, improvements in breast cancer detection and treatment have dramatically reduced mortality, with approximately 2.5 million survivors in the United States [2]. Among breast cancer patients, PPMP is rated as the most troubling symptom [49], leading to disability and psychological distress, and is notably resistant to management [4].

The etiology of persistent pain after mastectomy is as yet unclear, although it is likely multifactorial [3,45,74] and may be partially neuropathic in nature [41]. Previous reports of PPMP have suggested a limited number of potential risk factors, which are inconsistent among studies [3]. While surgical factors, including more extensive surgery (total vs partial mastectomy), axillary lymph node dissection, and reconstruction have been postulated to serve as important risk factors for chronic pain, many studies do not support this association. Adjuvant treatment, such as radiation, chemotherapy, and hormone therapy, has also been occasionally associated with persistent pain [3,26,41,48,65]. Among demographic factors, younger age correlates with increased persistent pain incidence in some studies [26,63,65,67,74] but not others [10,38,47]. Ethnicity may also be a risk factor, with nonwhite race associated with higher incidence of PPMP [11,24]. Preexisting pain is also more frequent in those who go on to develop PPMP [48,66–68].

Increasingly, psychosocial factors such as anxiety, depression, sleep disturbance, and catastrophizing have proven to be important contributors to the development of persistent pain [69,72,77]. When measured prospectively, these predict the trajectory of *acute* pain or analgesic consumption after breast cancer surgery [55,56,81] and, in other settings, also predict the development of chronic orofacial pain [25] and widespread pain [33]. In particular, catastrophizing is strongly related to enhanced pain sensitivity in both healthy adults and patients with chronic pain [21,22,27,72,77]. Quantitative sensory testing (QST) of an individual's response to standardized pain stimuli can predict the severity of *acute* postoperative pain [5,30,36,78,79]. Similarly, several studies have used QST to predict *chronic* postsurgical pain after thoracotomy [82], shoulder surgery [34], and surgery to correct chest wall deformation [59]. Previous studies utilizing QST in mastectomy patients have focused on sensory changes at the surgical site [79], revealing both hyperalgesia and allodynia [28]. However, investigation of *nonsurgical* sites by QST may help to characterize overall pain susceptibility [31]. Previous smaller studies showed decreased pressure pain thresholds in several body areas [25], increased central sensitization [20,31,75], and decreased conditioned pain modulation in patients with PPMP [22].

In the current study, we selected 2 patient groups from a larger population (N = 611) of postmastectomy patients who had been previously characterized for pain: 100 with persistent pain and 100 without. The aim of this study was to investigate and characterize important differences in the demographic, medical, psychosocial, and psychophysical

profiles of these 2 groups by gathering their responses to QST and to psychosocial questionnaires, as well as information about their demographics, surgery, and adjuvant therapies.

2. Methods

2.1. Patient recruitment

The participants in this study represent a subset of patients in a larger study (N = 611) recruited from the Comprehensive Breast Cancer Program's pool of breast cancer patients undergoing total or partial mastectomy by a group of 12 surgeons at Magee Women's Hospital of University of Pittsburgh Medical Center. Patients' participation in this registry was initiated presurgically on a voluntary basis, with an estimated 20% of total patients accepting inclusion. University of Pittsburgh Institutional Review Board approval was obtained prior to all data collection, and all patients gave informed consent before answering questions on questionnaires. Responses to initial questionnaires were gathered via telephone interview from patients who had undergone biopsy or partial or total mastectomy. A total of 744 patients underwent telephone interviews (82% recruitment rate of those called) using standardized questionnaires, including the Breast Cancer Pain Questionnaire (BCPQ), first described by Gartner et al. [26], and 611 were found to have had total or partial mastectomy on electronic chart review. An additional 29 were excluded from analysis because the time since surgery was <6 months. Based on the presence or absence of PPMP as indicated on the BCPQ, a list of "pain" (pain rating of 3/10 or higher) or "no pain" (pain rating 0/10) subjects were created. Subjects were contacted in random order until 200 patients (goal of 100 patients with pain, 100 without pain) were recruited (70% recruitment rate) for a testing session that included further pain and psychosocial questionnaire completion and QST of pain threshold and tolerance for thermal and mechanical stimuli, as well as temporal summation of pinprick and heat pain. The mean number of days between telephone questionnaire and QST session was 103 ± 83 (range 1–404 days). Participants in the QST session were compensated for their time (\$50).

2.2. Testing session

2.2.1. Questionnaire administration—Before beginning the session, study subjects provided informed consent. Subjects first completed questionnaires over approximately 20 minutes, including 3 measures to further characterize pain: the Brief Pain Inventory (BPI) [18], Short-Form McGill Pain Questionnaire (MPQ) [54], and the BCPQ, named as such with permission of the authors who initially developed this tool to characterize breast cancer-related pain in a study of breast cancer pain in women in Denmark [26]. This tool included a detailed description of severity, frequency, and location of pain, as well as questions about the presence of pain in other body areas, and analgesic use. The Pain Catastrophizing Scale (PCS), which has been validated in pain patients and controls [71], was used to measure catastrophic thinking associated with pain [19]. Depression, Anxiety and Sleep Disturbance were assessed using short-form instruments from the National Institutes of Health roadmap initiative, Patient Reported Outcome Measurement Information System (PROMIS) [6,12,14]. The PROMIS instruments have extensive validation studies comparing with established scales, and have been calibrated on over 20,000 persons [50]. The Brief Symptom Index 18-Somatization Scale, also validated in chronic pain patients [17], was used to measure somatization. In addition, the Perceived Stress Scale (10-item version) was administered [15]. After the QST session, subjects completed 2 additional questionnaires relating to their testing experience: the Situational Pain Catastrophizing Scale (SPCS) [23] and the Gracely box scales [29], which were used to assess the unpleasantness and intensity of experimental pain stimuli during QST.

2.3. Quantitative sensory testing

2.3.1. Heart rate and blood pressure assessment—During the session, subjects were seated comfortably in a chair, with both arms on armrests. At the beginning of the testing session, the heart rate and the blood pressure were assessed, after which participants underwent the psychophysical testing procedures described below. Heart rate and blood pressure were reassessed after each segment of QST.

2.3.2. Mechanical cutaneous (pinprick) pain and temporal summation—Mechanical pinprick pain was assessed using standardized weighted pinprick applicators similar to those described by Rolke et al. [61] of 2 designated weights (260 and 360 mN), which result in a painful sensation in most subjects [32]. First, a single stimulation of the lower-weight pinprick was applied to the dorsal aspect of the index finger between the first and second interphalangeal joints of the dominant hand while resting palm down on the armrest, and then rated by the subject on a scale of 0–10. Next, after a break of at least 10 seconds, a train of 10 stimuli were applied at the same premarked spot, at a rate of 1 stimulation/second. The subject again rated pain on a scale of 0–10 after the 10th stimulus, and then rated any ongoing pain 15 and 30 seconds later. The same procedure was repeated with the higher-weight pinprick in between the first and second interphalangeal joints on the third finger of the dominant hand. Subjects underwent 3 trials at each stimulus intensity, with a break of 1 minute between trials. Since responses were nearly identical for both weights investigated, scores from all 6 trials were averaged for each individual to calculate a pain after pinprick train, or aftersensation pain score.

2.3.3. Pressure pain threshold—Mechanical pain thresholds were assessed using a digital pressure algometer (Wagner FDX, Greenwich, CT, USA) with a flat round transducer, probe area 0.785 cm². Pressure pain thresholds were determined bilaterally on the dorsal aspect of the proximal forearm over the extensor muscle compartment, between the olecranon process and the medial epicondyle. Pressure was increased at a steady rate of approximately 1 kg/s until the subject indicated that the pressure was first perceived as painful, and the pressure in kg recorded. Two trials were performed in sequence on each forearm, with a pause of 15 seconds between trials.

2.3.4. Pressure pain tolerance—Using the same algometry methods as above, mechanical force was applied over the subject's trapezius muscle at the upper back, approximately 5 cm lateral to the C8 spinous process bilaterally. Subjects indicated the pressure at which the pain was no longer tolerable. Two trials were performed sequentially over each trapezius, with a pause of 15 seconds between trials.

2.3.5. Heat threshold and tolerance—Contact heat stimuli were delivered using a 1.6 × 1.6 cm square (2.56 cm²) contact thermode (Medoc Advanced Medical Systems, Ramat Yishai, Israel). In order to measure the heat pain threshold, the thermode was applied to 4 premarked spots placed apart by 4 cm along the volar aspect (nonhairy skin) of the left forearm, from proximal to distal. In each trial, the temperature of the probe began at 32° and increased at a rate of 0.5°/s. For safety, a cut-off temperature of 50° was used. The subject clicked a mouse to indicate when they first felt the stimulus as painful (thermal pain threshold), which triggered an immediate decrease in temperature back to baseline. Next, in order to assess heat pain tolerance, the thermode was applied in a similar fashion to 4 sites along the volar aspect of the right forearm. In each trial, the subject clicked when they could no longer tolerate the pain. Time between trials was approximately 30 seconds. Blood pressure and heart rate were then reassessed.

2.3.6. Heat temporal summation (windup)—The contact thermode was again placed on the volar aspect of the left forearm, slightly lateral to the most proximal thermal threshold testing site. A train of heat stimuli over 15 seconds was applied as follows: starting temperature of 32°, with 10°C/s ramp up to baseline of 42°, followed by 10 spikes up to 47°, with frequency of 1/s. The subject indicated amount of pain (verbal rating scale 0–10) at the end of each 47° stimulation, when they felt the temperature start to go back down, for a total of 10 ratings. Fifteen seconds after this stimulus train, the subject rated any residual pain. Subjects first underwent a training trial with probe held over the palm of the hand, and then this testing paradigm was repeated twice on the forearm, with the second trial at a slightly displaced location, occurring after a pause of 2 minutes between trials. If the subject reached a rating of 10 on 2 subsequent ratings, the train was terminated by removing the probe from the arm, and values thereafter for that trial were entered as 10.

2.3.7. Cold pain threshold and tolerance—Responses to noxious cold stimulation were evaluated using a cold-pressor task, involving immersion of the right hand in an ice-water bath. This bath was prepared by filling a round plastic basin with 1-cm round ice cubes to a volume of 2 liters, then adding cold water to a total volume of 2.5 liters. This volume allowed total immersion of the hand up to the wrist within the basin. The bath was allowed to equilibrate over the course of 60 minutes, at which time the temperature was 3°C. The temperature of the bath did not change between the start and end of the test. Participants placed their right hand up to the wrist in the water and kept it still throughout the procedure. The time at which subjects first reported pain in their hand was recorded as the cold pain threshold, and the time when pain first became intolerable and the patient withdrew their hand from the water was noted as cold pain tolerance. The subject then rated the intensity of any remaining pain on a 0–10 scale immediately after withdrawal from the water.

2.4. Statistical analysis

Patients were categorized as PPMP or no PPMP according to their response during the QST session to question #1 on the BCPQ, which asked, “Do you have pain in the area of the breast, armpit, side of the body, or arm on the side where you were operated?” All statistical testing was performed using SPSS Version 20 (IBM, Armonk, NY, USA). Between-group comparisons were made using χ^2 tests (in the case of categorical variables) or *t* tests (in the case of continuous variables).

A larger ongoing study of postmastectomy patients from which this population was drawn is powered to detect genetic differences between patients. Based on significant differences seen in quantitative sensory testing in similar studies using far fewer subjects (84, *n* = 62; 23, *n* = 76), the chosen target sample size (*n* = 200) appeared to be adequate to detect differences and add sufficiently to a literature characterized by small *n* studies.

To adjust for multiple comparisons, a Bonferroni corrected *P* value was calculated and reported along with raw *P* values. Correction took into account the number of testing modalities within each domain. For demographic and psychosocial variables this included 9 modalities, and for QST this included 3 domains (QST-heat, QST-cold, and QST-mechanical). Uncorrected *P* values are presented in the Figures and Tables to give full information to the reader, and corrected significant *P* values are listed in the legends.

3. Results

3.1. Pain incidence, severity, and location in patients with PPMP

The primary determinant of pain group was based on the BCPQ [26], in which 102/200 reported persisting pain as a result of breast cancer surgery at the time of QST. There was

some discrepancy in some subjects' response on the BCPQ between the original telephone administration (BCPQ1) and the in-person administration during the visit (BCPQ2). Ten individuals who had answered "yes" to pain associated with breast cancer surgery on BCPQ1 answered "no" on BCPQ2. Similarly, 7 individuals who had answered "no" to pain associated with breast cancer surgery on BCPQ1 answered "yes" on BCPQ2. The response on BCPQ2 was used for group determination, as this represented the most current state of the subject's pain at the time of QST. Of those subjects reporting pain, the breast was the most common location ($n = 80/102$), with a mean pain severity of 4.0 ± 2.1 (Fig. 1). Pain in the axilla was also relatively common ($n = 55/102$), with reported mean severity of 3.9 ± 2.0 (Fig. 1). Less common were pain in the arm ($n = 22/102$), with severity = 4.3 ± 2.2 ; and side ($n = 15/102$), with severity 5.2 ± 1.9 (Fig. 1). Severity scores on the BCPQ correlated positively to established pain questionnaires, with significant correlations between severity scores on the MPQ ($r = 0.89$, $P < 0.001$) and the BPI ($r = 0.29$, $P < 0.001$).

The Pain Burden Index, which takes into account the number of body areas affected, as well as the severity and frequency at each body area, was calculated for each subject according to the formula: pain burden index = [frequency(1–3) * severity breast pain] + [frequency(1–3) * severity arm pain] + [frequency(1–3) * severity axillary pain] + [frequency(1–3) * severity side pain] [25]. Pain Burden Index scores ranged from 0–93 (max possible = 120 if 10/10 pain daily in all 4 body areas), with a mean of 15.1 ± 15.9 , and correlated positively with the MPQ present pain index ($r = 0.63$, $P < 0.001$), with the MPQ pain scale ($r = 0.68$, $P < 0.001$), with BPI present pain scores ($r = 0.32$, $P < 0.001$), and with the BPI average pain intensity ($r = 0.45$, $P < 0.001$). Not surprisingly, the use of analgesics was more common in the pain group ($P < 0.001$), with 19% in the pain group and 0% in the no-pain group reporting analgesic use. Similarly, it was more common for subjects in the pain group to have other body pain symptoms (71% responding "yes" to BCPQ question #16) than for those in the no-pain group (51%) ($P < 0.005$).

3.2. Surgical and treatment variables

Table 1 presents descriptive statistics for surgical and treatment variables. Importantly, time since mastectomy was not different between groups (range 6 months–8.5 years). The number of mastectomy surgeries each subject underwent ranged from 1–4, with a mean of 1.35, and was not different between groups. Subjects who had a total mastectomy (32%), including those who had modified radical or radical mastectomy (6.5%), were not more likely to report pain than those who did not. Similarly, patients who had undergone bilateral mastectomy (15%) were not more likely to have PPMP. Although 30% of patients had axillary node dissection either as part of their mastectomy or as a separate procedure, these patients were not more likely to have PPMP. Surgical complications including cellulitis (21 cases), hematoma (7 cases), seroma (30 cases), or lymphedema (15 cases) occurred in 29% of patients, but were not more common in those with PPMP. Furthermore, breast reconstruction, which was performed in 18% of patients, was not more common in those reporting pain. A larger tumor size or more advanced tumor or nodal stage was not correlated with PPMP. Adjuvant treatment with radiation therapy (77%), chemotherapy (51%), and hormone therapy (76%) was also not more common in those with PPMP.

3.3. Demographic and psychosocial variables

Table 2 presents descriptive statistics for demographic and psychosocial variables. The mean age of patients was 58.8 ± 10.3 years, and was not different between the pain and no-pain group. Body mass index was also not different between groups. Additionally, education, marital status, and exercise were not different between groups (data not shown). While 2.4% of patients in the larger study ($n = 611$) identified ethnicity as African American, all those patients who agreed to be in the current study were Caucasian. Measures

of anxiety and depression were significantly higher in those with PPMP, even after taking into account multiple comparisons. Similarly, scores on the PCS indicated that those with PPMP were more likely to catastrophize in response to pain. Somatization was also more prevalent among patients with PPMP than those without. While perceived stress was not higher in PPMP patients, those with PPMP were more likely to report sleep disturbance. Interestingly, there was no significant difference between groups on responses to the situational catastrophizing scale, which measured catastrophizing cognitions specifically during QST.

3.4. Quantitative sensory testing

Blood pressure and heart rate measured before and at points during the QST session did not differ between those with or without PPMP. In order to assess temporal summation of pain, considered a measure of central pain-facilitatory processes and an index of sensitization, subjects rated pain (scale 0–10) after a single stimulation and then after a train of 10 mechanical pinprick stimuli, as well as 15 and 30 seconds afterwards. There was no significant difference in pinprick pain intensity ratings between pain and no-pain groups for the single stimulus and 10 stimulus train ratings (Table 3). However, ratings of pain after pinprick train (aftersensation pain) were increased in PPMP patients (Fig. 2A) at 15 but not 30 seconds. There was a nonsignificant trend toward increased number of subjects reporting aftersensation pain in the pain group (Fig. 2B). Furthermore, algometric testing for pressure pain (forearm) revealed a lower pain pressure threshold in the PPMP group bilaterally (Fig. 3). However, pressure pain tolerance, measured over the trapezius, was not different between groups (Table 3). Other QST measures including pressure pain tolerance, thermal pain thresholds, tolerance, windup, and cold pain were not different between groups (Table 3). To further investigate the influence of clinical arm pain (present in 22 patients) on QST measures that involved the arm, we separately analyzed thresholds according to presence or absence of arm pain for each side. While we found trends towards lower pressure pain thresholds in those reporting left arm pain, this did not reach statistical significance. Interestingly, this trend was present independent of laterality of testing, as those reporting left arm pain were as likely to have a trend towards decreased pressure threshold on the right forearm as the left forearm.

4. Discussion

This study took a comprehensive approach to understanding PPMP by measuring demographic, surgical, treatment, disease-related, psychosocial, and psychophysical factors in one patient sample. Importantly, psychosocial processes including catastrophizing, somatization, depression, anxiety, and sleep disturbance were associated with PPMP. Additionally, several QST measures including pain pressure threshold and pain rating after pinprick mechanical temporal summation were also correlated with PPMP. Interestingly, surgical factors such as total mastectomy, axillary dissection, and reconstruction did not correlate with PPMP. Disease- and treatment-related variables including tumor size, stage, and recurrence, as well as exposure to radiation and chemotherapy, also did not correlate with PPMP. Collectively, these findings suggest that psychophysical pain sensitivity as measured by QST, as well as psychological profile as measured by psychosocial tools, strongly correlate with the development of PPMP, regardless of the type of surgical and medical treatment that patients receive for their breast cancer.

A wide variability in previously reported incidence of PPMP may arise from differences in definition, measurement tools, time since surgery, and the specific population studied. In this study we investigated patients who were at least 6 months post mastectomy. Our baseline cohort of 611 mastectomy patients had an incidence of chronic postmastectomy pain (47%) similar to previous reports [27], with a relatively smaller proportion (34%)

reporting clinically significant breast pain (pain score of 3 or more) [74]. As in previous studies, the reported location of pain was most commonly the breast, followed by the axilla, arm, and side. Both severity and burden index measurements derived from the BCPQ correlated well with more conventional pain measurement tools (McGill and BPI), adding validity to its use for studying PPMP. Importantly, we observed some crossover in the pain group between the 2 time points of BCPQ administration (telephone and in-person QST session, mean 103 ± 83 days apart). Possible contributors to this discrepancy include fluctuation in disease course, differences in telephone vs in-person questionnaire administration, or reliability of the BCPQ itself. In future, more extensive tracking of pain reporting over time in postmastectomy patients could help elucidate the natural fluctuation of this condition.

In keeping with some previous studies [10,38,47] but not others [3,26,63,65,67,74], younger age was not correlated with PPMP. Patients were exposed to various surgical approaches (ranging from lumpectomy to radical mastectomy) and adjuvant therapies (77% radiation, 76% hormone therapy, 51% chemotherapy), thus allowing an investigation of these factors' contribution to PPMP. Despite this, we did not see a strong association with surgical or treatment-related variables with PPMP. The finding that breast-conserving surgery is not protective against PPMP was expected, as prior reviews and large-scale epidemiological studies have noted a similar prevalence of PPMP following mastectomy and lumpectomy [3,26]. In contrast, previous studies have more consistently correlated axillary node dissection or upper lateral quarter tumor location to PPMP [26,35,42,53,65,73–75]. One proposed mechanism for the increased morbidity of axillary dissection is injury to the intercostobrachial nerve (ICBN) [41], but studies investigating intentional sparing of the ICBN have not found this to consistently alter the expression of PPMP [1,35,40,42,62,70]. However, the sentinel node's close proximity to the ICBN [60] may also lead to ICBN irritation, and since nearly all patients have a sentinel node dissection, this could explain the lack of increased PPMP risk with axillary dissection. Other factors associated with a larger degree of tissue disruption such as recurrence requiring reoperation [75], breast reconstruction [76], and bilateral surgery, as well as incidence of seroma, hematoma, cellulitis, or lymphedema were also not more common among patients with PPMP in this study. Radiation and hormone therapy have been more variably associated with PPMP than chemotherapy [23,26,41,48,65,74] in previous studies. In this study, however, women with PPMP were no more likely to have received these treatments than those without PPMP.

The relationship between persistent pain and psychosocial factors such as catastrophizing has been the subject of much recent study [7,26,37]. While acute pain after mastectomy is associated with anxiety, psychological distress, sleep disturbance, and mal-adaptive coping strategies (eg, catastrophizing and avoidance) [37,55,56,81], few previous studies of PPMP have included measures of psychosocial function. Anxiety and depression were positively correlated with PPMP in one study [68], but not another [20]. A recent study of postlumpectomy patients did see a strong association of catastrophizing with PPMP [20]. Similarly, in the current study, catastrophizing was the psychosocial variable most strongly related to PPMP. In contrast, a measure of situation-specific catastrophizing (SPCS) during QST did not differentiate the groups. This dissociation between catastrophizing about QST-related pain (SPCS) and recall of catastrophizing in daily life (PCS) is not unprecedented in chronic pain patients, and suggests that context-specific assessment of catastrophizing may be important in future studies [8,9,20].

The potential to use QST as a relatively more “objective” index of individual differences in pain processing has been advanced by an expansive effort to collect a database of responses of both normal controls and chronic pain patients to standardized stimuli [52,61]. Many previous studies have successfully focused on prediction of acute postoperative pain.

However, a growing collection of studies have begun to use QST in chronic postoperative pain as well [80]. While QST at the surgical site may indicate either peripheral or central sensitization of the nervous system, changes in pain sensitivity at nonsurgical body sites are likely to be more indicative of either central sensitization or of innate differences in overall pain processing. In one previous report [24], PPMP patients had decreased pressure pain thresholds at a nonsurgical site. In the present study, our findings of reduced pressure pain thresholds and elevated mechanical pain aftersensations (both observed at a site unaffected by surgery) may represent an increased tendency towards central sensitization, which has been previously reported [22,28,75]. Such facilitation of nociceptive input might function to maintain PPMP in a subset of patients or to enhance the probability of developing additional pain conditions (eg, we observe that “other body pain symptoms” are more prevalent for women with PPMP (71%) than for those in the nonpain group (51%).

4.1. Limitations

Possible methodological limitations to this study include selection bias, as enrollment in the breast cancer registry and this study was voluntary. As such, overestimation of PPMP incidence is possible, if patients are motivated to enroll by the presence of pain. However, no evidence of differential motivation for participation in pain and no-pain groups appeared in the form of differences in the measured demographics. Secondly, it is possible that the lack of significant correlation between PPMP expression and surgical, medical, and demographic variables may be due to an under-powering of the study to detect differences in some or all of these variables. However, the presence of significant psychosocial and psychophysical differences between groups at least supports the argument that psychophysical and psychosocial tests are more highly correlated with the expression of PPMP than the other variables examined. A third limitation of the study was its cross-sectional design, which, while allowing investigation of a large population of postmastectomy patients, also prevented determination of causality. It is yet unknown whether psychosocial and psychophysical differences between groups predate the surgery, or were created by the surgery and subsequent experience of persisting post-operative pain. It is possible that the presence of persistent, undertreated pain could contribute to psychological distress and catastrophizing (only 19% reported analgesic use, similar to that reported by Gartner et al (28%) [26]). However, studies of prediction of acute pain after surgery have revealed that retrospectively identified psychological variables [43] may then predict acute pain in a subsequent prospective study [39]. Furthermore, other smaller studies have successfully applied prospective QST to predict both acute pain [5,30,36,57,58,64], and chronic pain [34,59,82] after surgery. These examples of successful prospective prediction suggest that an individual's propensity to develop acute or chronic postsurgical pain may be distinguished using a set of psychosocial and psychophysical variables. In the future, prospective studies that compare QST and psychosocial factors both before and after surgical injury are needed to address this question.

4.2. Conclusions

In summary, this study investigated the relevant differences between those with and without persistent pain at an average of 4 years after mastectomy. Demographic, surgical, and treatment-related variables were relatively less associated with PPMP than were psychosocial and psychophysical variables. In particular, women with lasting pain after mastectomy were characterized by higher levels of pain-related catastrophizing and by a greater degree of mechanical pain sensitivity. Such results are important in the understanding and potential management of persistent postoperative pain, since there is relatively little overlap between the interventions that might reduce the incidence of surgery-related postoperative pain syndromes and those that might address psychosocial factors that place patients at elevated risk for enduring postsurgical pain. Overall, these findings contribute to a small but growing

body of literature documenting alterations in pain processing among women with postmastectomy or postlumpectomy pain, conducted in different countries, across different health care settings. When taken together, these studies will allow a more robust assessment of which variables are of greatest importance and utility for determining who is at risk of developing PPMP, and allow targeting of this vulnerable population for more intensive perioperative therapy, potentially allowing the prevention of pain in women after mastectomy in the future.

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Fig. 1.

Pain incidence, severity, and location in postmastectomy patients. Patients reported severity of their pain individually per body area on the Breast Cancer Pain Questionnaire (BCPQ). Pain was most common in the breast (A) and axilla (B), less common in side (C) and arm (D), but average severity scores of those reporting pain were similar across body regions.

Fig. 2.

Differences in pain after pinprick train (aftersensation pain). Subjects underwent a train of 10 pinprick stimuli on the second and third fingers of the dominant hand and rated severity of remaining pain 15 and 30 seconds afterwards. (A) Mean pain scores reported in those with remaining pain at different time points in the persistent postmastectomy pain (PPMP) and no-PPMP groups. (B) Percentage of subjects reporting remaining pain in the PPMP and no-PPMP groups. *P* values reported are uncorrected. Bonferroni correction for multiple comparisons for quantitative sensory testing (QST) testing in 3 QST domains yielded $P < 0.0167$ as significant.

Fig. 3.

Differences in pressure pain threshold. Subjects underwent testing with a handheld algometer, applied over the dorsal aspect of the proximal forearm bilaterally (threshold). No laterality effect was observed for either measure, but subjects reporting PPMP had lower pain thresholds compared to those without PPMP. *P* values shown are uncorrected. Bonferroni correction for multiple comparisons for quantitative sensory testing (QST) testing in 3 QST domains yielded $P < 0.0167$ as significant.

Table 1

Surgical, treatment, and disease-related variables.

	No PPMP group n = 98	PPMP group n = 102	P value
Time since surgery (months)	47.9 (17.4)	49.9 (31.0)	0.58
Number of mastectomies	1.3 (.49)	1.4 (.62)	0.07
Total mastectomy	31.6%	32.4%	0.91
Axillary node dissection	26.5%	31.7%	0.45
Surgical complications	27.8%	27.5%	0.95
Reconstruction	22.4%	14.7%	0.16
Tumor stage	1.3 (0.8)	1.2 (0.7)	0.56
Tumor size	1.8 (1.6)	1.7 (2.0)	0.98
Radiation tx	76.5%	76.5%	0.99
Chemotherapy	43.8%	53.9%	0.15
Hormone tx	73.5%	77.5%	0.51
Recurrence	6.1%	8.8%	0.47

PPMP, persistent postmastectomy pain.

Note: Numbers in parentheses are SDs.

Table 2

Demographic and psychosocial variables.

	No PPMP group n = 98	PPMP group n = 102	<i>P</i> value
Age	59.3 (10.2)	58.3 (10.5)	0.685
Body mass index	28.3 (5.7)	29.0 (5.8)	0.46
Anxiety	12.5 (5.2)	14.4 (6.4)	0.006
Depression	10.6 (4.1)	12.2 (6.1)	0.003
Catastrophizing	2.1 (4.0)	7.2 (8.9)	0.000
Situational catastrophizing	1.18 (1.96)	1.12 (2.05)	0.692
Somatization	8.3 (2.8)	10.4 (4.1)	0.003
Perceived stress	15.1 (5.9)	16.5 (6.1)	0.104
Sleep disturbance	20.0 (8.1)	24.2 (8.9)	0.01

PPMP, persistent postmastectomy pain.

Note: *P* values are uncorrected. Bonferroni correction for multiple comparisons for demographic and psychosocial variables yielded a $P < 0.005$ as significant. Numbers in parentheses are SDs.

Table 3

Quantitative sensory testing.

	No PPMP group <i>n</i> = 98	PPMP group <i>n</i> = 102	<i>P</i> value
Pinprick Stim 1 Score (260 mN)	.80 (.97)	1.02 (1.08)	0.135
Pinprick Stim 10 Score (260 mN)	2.57 (1.87)	2.75 (1.99)	0.494
Pinprick Stim 1 Score (360 mN)	.48 (.67)	.67 (.84)	0.072
Pinprick Stim 10 Score (360 mN)	2.24 (1.94)	2.48 (2.13)	0.419
Thermal heat pain threshold	44.7 (2.5)	44.3 (3.1)	0.341
Thermal heat pain tolerance	46.8 (2.2)	46.6 (2.6)	0.429
Thermal windup (rating 1)	3.3 (2.6)	3.5 (2.5)	0.657
Thermal windup (rating 10)	3.9 (2.7)	4.2 (2.5)	0.647
Remaining heat pain	.54 (1.6)	.73 (1.7)	0.407
Cold pain threshold	14.2 (20.0)	16.5 (24.2)	0.466
Cold pain tolerance	35.7 (34.7)	38.9 (39.2)	0.540
Remaining cold pain	3.9 (2.8)	4.5 (3.1)	0.149

PPMP, persistent postmastectomy pain.

Note: *P* values shown are uncorrected. Bonferroni correction for multiple comparisons for QST testing in 3 QST domains yielded $P < 0.0167$ as significant. Numbers in parentheses are SDs.