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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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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

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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

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