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IDENTIFICATION OF PATIENT SUBGROUPS AND RISK FACTORS FOR PERSISTENT ARM/SHOULDER PAIN FOLLOWING BREAST CANCER SURGERY

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Abstract

Purpose—In this prospective, longitudinal study, we extend our findings on persistent breast pain in patients (n=398) following breast cancer surgery and evaluate the prevalence and characteristics of persistent pain in the arm/shoulder In addition, differences in the severity of common symptoms and quality of life outcomes measured prior to surgery, among the arm pain classes, were evaluated.

Methods and sample—Patients were recruited from Breast Care Centers located in a Comprehensive Cancer Center, two public hospitals, and four community practices. Patients were assessed prior to and monthly for six months following breast cancer surgery.

Results—Using growth mixture modeling, patients were classified into no (41.6%), mild (23.6%), and moderate (34.8%) arm pain classes based on ratings of worst arm/shoulder pain. Compared to the no pain class, patients in the moderate pain class were significantly younger, had a higher body mass index, and were more likely to report preoperative breast pain and swelling in the affected breast. In addition, patients in the moderate pain class reported higher levels of depression, anxiety, and sleep disturbance than the no pain class.

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Conclusions—Findings suggest that approximately 35% of women experience persistent levels of moderate arm/shoulder pain in the first six months following breast cancer surgery. Moderate arm/shoulder pain is associated with clinically meaningful decrements in functional status and quality of life.

Keywords

arm pain; shoulder pain; persistent postsurgical pain; risk factors; breast cancer surgery; growth mixture modeling; latent class analysis; chronic pain

INTRODUCTION

Persistent pain following breast cancer surgery occurs in 25% to 60% of patients (Gartner, et al., 2009). This pain problem is associated with mood disturbance, decrements in functional status, and decreases in quality of life (QOL) (Belfer, et al., 2013; Stevens, Dibble, & Miaskowski, 1995). However, in their recent review of persistent pain following breast cancer treatment, Andersen and Kehlet (2011) identified numerous limitations in the research studies done to date on this significant clinical problem. In addition to inconsistencies in the measurement of pain, only a limited number of studies have assessed for persistent pain in both the breast and shoulder/arm following breast cancer surgery.

In one of the earliest studies that compared occurrence rates based on anatomic site (Tasmuth, von Smitten, & Kalso, 1996), 10% of patients who underwent either mastectomy or breast conserving surgery reported pain in the ipsilateral arm. At one year, 39% of these patients reported persistent ipsilateral arm pain. Other studies have compared the prevalence of pain within the larger context of “arm and shoulder morbidities” in patients who had breast conserving surgery versus mastectomy (Carpenter, et al., 1999; Nesvold, Dahl, Lokkevik, Marit Mengshoel, & Fossa, 2008; Vilholm, Cold, Rasmussen, & Sindrup, 2008); sentinel lymph node biopsy (SNLB) versus an axillary lymph node dissection (ALND) (Andersen, et al., 2013; Brar, Jain, & Singh, 2011; Haid, et al., 2002; Langer, et al., 2007; Ronka, von Smitten, Tasmuth, & Leidenius, 2005; Vilholm, et al., 2008); and following receipt of radiation therapy (RT) (Deutsch & Flickinger, 2001; Hopwood, et al., 2010; Vilholm, et al., 2008). As noted by Andersen and Kehlet (2011), while the majority of studies reported no differences in arm pain between breast conserving surgery and mastectomy, these findings need to be interpreted with caution because the nociceptive effect of RT was not evaluated. In terms of SLNB versus ALND dissection, while inconsistent findings are noted in the literature, Andersen and Kehlet concluded that ALND is a risk factor for the development of persistent pain following breast cancer surgery.

Recently, our research group identified four subgroups of patients with distinct trajectories of persistent breast pain following breast cancer surgery (i.e., no (31.7%), mild (43.4%), moderate (13.3%), and severe (11.6%) pain) (Miaskowski, et al., 2012). These subgroups differed on a number of demographic, preoperative, intraoperative, and postoperative characteristics. As part of our longitudinal study, separate assessments of arm/shoulder pain were done monthly for six months following surgery. These separate assessments of arm/shoulder versus breast pain were purposely designed to be comparable so that differences in

persistent pain between the two distinct anatomic sites (e.g., different types of tissue at each site, different patterns of neural innervation) could be evaluated. Given that no studies were identified that evaluated for distinct subgroups and risk factors for persistent arm/shoulder pain following breast cancer surgery, the purposes of this prospective, longitudinal study, that recruited 398 women prior to surgery for breast cancer were to determine the prevalence of persistent pain in the arm/shoulder; characterize distinct persistent pain phenotype(s) using growth mixture modeling (GMM); and evaluate for differences among these pain classes in demographic, preoperative, intraoperative, and postoperative characteristics. In addition, differences in the severity of common symptoms and QOL outcomes measured prior to surgery, among the identified pain classes, were evaluated.

METHODS

A detailed description of the methods are published elsewhere (McCann, et al., 2012; Miaskowski, et al., 2012). In this section, an abbreviated version of the methods is described.

Patients and Settings

Patients were recruited from Breast Care Centers located in a Comprehensive Cancer Center, two public hospitals, and four community practices. Patients were eligible for this study if they were≥18 years of age; underwent surgery for cancer on one breast; were able to read, write, and understand English; agreed to participate, and provided written informed consent. Patients were excluded if they had surgery on both breasts and/or had distant metastasis at diagnosis. A total of 516 patients were approached to participate, 410 were enrolled in the study (response rate 79.4%), and 398 completed the study questionnaires. The major reasons for refusal were: too busy, overwhelmed with the cancer diagnosis, or insufficient time available to do baseline assessment prior to surgery.

Subjective Measures

A demographic questionnaire collected information on age, education, ethnicity, marital status employment status, living situation, financial status and functional status (Karnofsky, 1977; Karnofsky, Abelmann, Craver, & Burchenal, 1948). Comorbidities were assessed using the Self-Administered Comorbidity Questionnaire (SCQ) (Sangha, Stucki, Liang, Fossel, & Katz, 2003).

Persistent and postsurgical pain were evaluated using the Arm/Shoulder Symptoms Questionnaire (ASQ) and Postsurgical Pain Questionnaire. The ASQ is an adaptation of the Brief Pain Inventory (BPI) (Daut, Cleeland, & Flanery, 1983). The ASQ consisted of two parts. Part 1 obtained information on the occurrence of pain in the arm and shoulder area. If the patient had pain in the shoulder, arm, or hand, they completed Part 2 of the ASQ. Patients were asked to rate the intensity of their average and worst pain using a numeric rating scale (NRS) that ranged from 0 (no pain) to 10 (worst imaginable pain) (Jensen, 2003).

The Postsurgical Pain Questionnaire evaluated pain intensity, pain relief, and satisfaction with pain treatment in the first 24 to 48 hours after surgery. Average and worst pain were

rated using a 0 to 10 NRS. Pain relief was rated on a 0% (no relief) to 100% (complete relief) rating scale. Satisfaction with pain treatment was rated on a 0 (not satisfied at all) to 10 (extremely satisfied) NRS. This questionnaire was completed during the month 1 study visit.

The Center for Epidemiologic Studies-Depression (CES-D) scale was used to evaluate depressive symptoms. A CES-D score of ≥16 suggests the need for individuals to seek clinical evaluation for major depression (Carpenter, et al., 1998; Radloff, 1977; Sheehan, Fifield, Reisine, & Tennen, 1995). The Spielberger State-Trait Anxiety Inventories (STAI-S and STAI-T) were used to evaluate state and trait anxiety. Cuttoff scores of ≥31.8 and ≥32.2 indicate high levels of trait and state anxiety, respectively (Bieling, Antony, & Swinson, 1998; Kennedy, Schwab, Morris, & Beldia, 2001; Spielberger, Gorsuch, Suchene, Vagg, & Jacobs, 1983). The General Sleep Disturbance Scale (GSDS) was used to evaluate sleep disturbance in the past week. A GSDS total score of ≥43 indicates a significant level of sleep disturbance (Carney, et al., 2011; Fletcher, et al., 2008; Garrett, et al., 2011; Miaskowski, et al., 2006). The Lee Fatigue Scale (LFS) was used to evaluate physical fatigue and energy (Lee, Hicks, & Nino-Murcia, 1991). A cutoff score of ≥4.4 indicates high levels of fatigue. (Dhruva, et al., 2010) A cutoff score of ≤4.8 indicates low levels of energy (Dhruva, et al., 2010). The Attentional Function Index (AFI) was used to evaluate self-reported attentional function (i.e., ability to voluntarily direct and sustain attention) (Cimprich, 1992; Cimprich, Visovatti, & Ronis, 2011). AFI scores can be grouped into categories of functional status (i.e., patients who score <5.0 functioning poorly, patients who score 5.0 to 7.5 functioning moderately well, patients who score >7.5 functioning well) (Cimprich, So, Ronis, & Trask, 2005). The Quality of Life-Scale-Patient Version (QOL-PV) was used to evaluate four dimensions of QOL (i.e., physical well-being, psychological well-being, spiritual well-being, social well-being) as well as overall QOL. Higher scores indicating a better QOL (Ferrell, 1995; Ferrell, Dow, & Grant, 1995; Padilla, Ferrell, Grant, & Rhiner, 1990; Padilla, et al., 1983).

Objective Measures

Grip strength (in kilograms), in both hands, was measured using a Jamar hydraulic hand dynamometer (Sammons Preston). Grip strength was measured with women in a standing position with the arm held in a comfortable position (Spijkerman, Snijders, Stijnen, & Lankhorst, 1991). Grip strength was measured three times in each hand. If a variance of more than 20% occurred among the three readings on each hand, the test was repeated. The three readings from the affected and unaffected hands were averaged(Ribom, Piehl-Aulin, Ljunghall, Ljunggren, & Naessen, 2002; Spijkerman, et al., 1991).

Shoulder mobility was assessed using goniometric measurement of range of motion (ROM). While the patient was lying supine, ROM was measured twice on each side in four positions (i.e., flexion, abduction, internal rotation, external rotation) and these 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, determined her willingness to participate, and introduced the patient to the research nurse. The research nurse 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 objective measurements.

The research nurse met with the patients either in their home or in the Clinical Research Center at 1, 2, 3, 4, 5, and 6 months after surgery. During the study visits, the patients completed the study questionnaires, provided information on new and ongoing treatments, and had the objective measures done by the research nurse. Patients' medical records were reviewed for disease and treatment information.

Statistical analyses

Data were analyzed using SPSS Version 19.0(SPSS, 2010) and Mplus Version 6.11 (Muthen & Muthen, 1998-2010). Demographic and clinical characteristics and symptom severity scores were analyzed using descriptive statistics and frequency distributions.

Unconditional GMM with robust maximum likelihood estimation was carried out to identify latent classes of patients with distinct persistent arm pain trajectories. Arm/shoulder pain scores were assessed monthly for 6 months following breast cancer surgery. Prior to conducting GMM analyses, patients who reported no pain in their affected arm/shoulder for all 6 assessments were identified (n = 164, 41.6%) and not included in the GMM analysis. The remaining 230 women's ratings of worst arm/shoulder pain were used in the GMM analysis. These methods are described in detail elsewhere (Dunn, et al., 2011). In brief, a single growth curve that represented the "average" change trajectory was estimated for the sample. Then, the number of latent growth classes that best fit the data was identified using guidelines recommended in the literature (T. Jung & Wickrama, 2008; Nylund, Asparouhov, & Muthen, 2007; Tofighi & Enders, 2008).

Analyses of variance and Chi-square analyses were used to evaluate for differences, among the latent classes, in demographic, preoperative, intraoperative, and postoperative characteristics, symptom severity scores, and QOL scores at enrollment. Based on the recommendations of Rothman (1990), no adjustments were made for multiple testing. A p-value of <.05 was considered statistically significant.

RESULTS

GMM Analysis

A total of 164 patients (41.6%; no pain class) did not report any arm/shoulder pain for any of the six assessments. In the remaining 230 patients, two distinct latent classes of persistent arm/shoulder pain were identified using GMM (Figure 1). A two-class model was selected

because its BIC was smaller than the three-class model. In addition, comparisons of the other fit indices supported the choice of the two class model (Table 1).

As shown in Table 2, the mild pain class (n=93, 23.6%) maintained a similar level of pain throughout the study. Patients in the moderate pain class (n=137, 34.8%) had worst pain scores that decreased slightly to the month 4 assessment and then began to increase slightly during months 5 and 6.

Differences in Demographic Characteristics

As shown in Table 3, no differences were found among the three pain classes in living arrangements, marital status, and employment status. However, patients in the mild and moderate pain classes were significantly younger than patients in the no pain class. In addition, patients in the moderate pain class were more likely to be non-White compared to the no and mild pain classes. Finally, patients in the moderate pain class reported a lower level of education and less income than patients in the mild pain class.

Differences in Preoperative Clinical Characteristics

A large number of significant differences among the three pain classes was found in the preoperative characteristics (Table 4). In general, compared to patients in the no pain class, patients in the moderate pain class had a higher body mass index (BMI), a lower KPS score; a higher SCQ score, a higher number of breast biopsies, higher ratings of average and worst breast pain prior to surgery; decreased flexion in their affected arm; a higher stage of disease; were more likely to report pain and swelling in their affected breast prior surgery, and were more like to have received neoadjuvant chemotherapy (CTX).

Differences in Preoperative Symptom Severity Scores

As shown in Table 5, significant differences in preoperative symptom severity scores were found among the pain classes. In general, compared to the no pain class, patients in the moderate pain class reported significantly higher depression, trait anxiety, sleep disturbance, and fatigue scores, and lower attentional function scores prior to surgery.

Differences in Preoperative QOL Scores

As shown in Table 5, significant differences in QOL scores were found among the pain classes. In general, compared to the no pain class, patients in the mild and moderate pain classes reported significantly lower physical well-being, social well-being, and total QOL scores prior to surgery.

Differences in Intraoperative Characteristics

As shown in Table 6, significant differences were found among the three pain classes for several of the intraoperative characteristics. Compared to patients in the no pain class, patients in the moderate pain class had a higher number of lymph nodes removed, a higher number of positive lymph nodes, and a higher number of drains placed during surgery. In addition compared to the no pain class, a higher percentage of patients in the moderate pain class had a mastectomy and an axillary lymph node dissection (ALND).

Differences in Postoperative Characteristics

As shown in Table 7, significant differences in a number of postoperative characteristics were found among the three pain classes. Compared to the no pain class, patients in the moderate pain class experienced a higher number of postoperative complications; reported higher average and worst postoperative pain intensity scores, and were more likely to have had a surgical drain placed in the axilla or in the breast and axilla. In addition, compared to the no pain class, a higher percentage of patients in the moderate pain class had received physical therapy in the 6 months following breast cancer surgery.

DISCUSSION

This study is the first to use GMM to identify subgroups of patients with distinct persistent arm/shoulder pain trajectories following breast cancer surgery. In addition, a comprehensive list of demographic, preoperative, intraoperative, and postoperative characteristics was used to identify predictors of pain class membership. Over the six months of the study, 41.6% of the patients responded no to the question about having pain in their arm/shoulder. However, consistent with previous reports (Karki, Simonen, Malkia, & Selfe, 2005; Tasmuth, von Smitten, Hietanen, Kataja, & Kalso, 1995), 35% of the patients were classified as having moderate pain. These patients had worst arm/shoulder pain scores of approximately 6 that remained relatively constant over the six months of the study. Of note, compared to our GMM analysis of persistent breast pain that identified three distinct breast pain classes (i.e., mild (43.4%), moderate (13.3%), and severe (11.6%)) (Miaskowski, et al., 2012), only two persistent arm pain classes were identified. In addition, the percentage of women who did not report persistent arm/shoulder pain (i.e., 41.6%) was higher than the percentage of women who did not report persistent breast pain (i.e., 31.7%). These findings from the GMM analyses, as well differences in phenotypic characteristics discussed below, suggest that persistent breast pain and persistent arm/shoulder pain are distinct subtypes of persistent pain following breast cancer surgery.

Consistent with our previous study of persistent breast pain (Miaskowski, et al., 2012), four demographic characteristics, namely younger age, less education, being non-white, and having a lower total annual household income, were associated with being in the moderate pain class. Consistent with previous studies (Alves Nogueira Fabro, et al., 2012; Caffo, et al., 2003; Gartner, et al., 2009; Hack, Cohen, Katz, Robson, & Goss, 1999; Macdonald, Bruce, Scott, Smith, & Chambers, 2005; Peuckmann, et al., 2009; Poleshuck, et al., 2006; Smith, Bourne, Squair, Phillips, & Chambers, 1999; Steegers, Wolters, Evers, Strobbe, & Wilder-Smith, 2008; Swenson, et al., 2002; Vilholm, et al., 2008), younger age was associated with a higher risk of being in the mild or moderate pain classes identified in this study. While studies of racial/ethnic differences in experimental (Edwards, Doleys, Fillingim, & Lowery, 2001) and clinical pain (Edwards, Moric, Husfeldt, Buvanendran, & Ivankovich, 2005; Green, Ndao-Brumblay, Nagrant, Baker, & Rothman, 2004) have produced inconsistent results, the higher percentage of non- whites in the moderate pain class is consistent with one other study of breast cancer patients (Fecho, et al., 2009). However, this finding should be interpreted with caution because compared to White patients, non-white patients in our study were more likely to be diagnosed with more

advanced disease (p=.009) and to have had an ALND (p=.04) both of which may contribute to more severe pain. While lower levels of education (Krueger & Stone, 2008; Portenoy, Ugarte, Fuller, & Haas, 2004) and lower income levels (Cimmino, Ferrone, & Cutolo, 2011; Palmlof, et al., 2012) are associated with higher rates of chronic pain in the general population, in two studies of persistent pain after breast cancer surgery (Kudel, et al., 2007; Poleshuck, et al., 2006), no association was found between education and pain status.

Compared to our previous study of persistent breast pain (Miaskowski, et al., 2012), several preoperative risk factors were unique to persistent arm/shoulder pain. Compared to patients in the no arm/shoulder pain class, patients in the moderate pain class had a higher number of breast biopsies, were diagnosed with more advanced disease, and were more likely to have received neoadjuvant CTX. These preoperative risk factors are consistent with a number of intraoperative characteristics that were associated with membership in the moderate pain class. Consistent with previous reports, two of the intraoperative characteristics associated with membership in the moderate pain class were a higher number of lymph nodes removed (Alves Nogueira Fabro, et al., 2012; Johansen, Overgaard, Blichert-Toft, & Overgaard, 2000) and having an ALND (Alves Nogueira Fabro, et al., 2012; Caffo, et al., 2003; Gartner, et al., 2009). In addition, and distinct from predictors of persistent breast pain, patients in the moderate arm/shoulder pain class had a higher number of drains placed during surgery, were more likely to have a drain either in the axilla or in the breast and axilla, and to have a higher number of postoperative complications. Taken together these findings suggest that moderate, persistent arm/shoulder pain is more likely to occur in patients who have a surgical procedure that is associated with more trauma and inflammation.

Similar to persistent breast pain (Miaskowski, et al., 2012), two modifiable preoperative risk factors for persistent arm/shoulder pain were the occurrence of preoperative breast pain and changes in breast sensations. Women who reported the occurrence of pain or strange sensations in the breast were more likely to be classified into the moderate arm/shoulder pain class. Our results confirm the finding of a previous study (Kudel, et al., 2007) that found a relationship between preoperative breast pain and the occurrence of persistent pain following breast cancer surgery. However, research is warranted to determine additional risk factors for preoperative pain that may contribute to the development of persistent postsurgical pain. For example, we reported recently that variations in two cytokine genes (i.e., interleukin (IL) 1 receptor 1, IL13) were associated with the occurrence of preoperative breast pain (McCann, et al., 2012). Additional research is warranted on the mechanisms that underlie preoperative breast pain and its association with the development of persistent postsurgical pain in both the breast and/or the arm/shoulder.

A major modifiable risk factor for persistent arm/shoulder pain was unrelieved postoperative pain. Compared to the no pain class, ratings of worst postoperative pain were significantly higher in both the mild and moderate pain classes. These findings represent not only statistically significant differences but clinically meaningful differences in ratings of worst postoperative pain between the no pain versus the mild arm pain (d=.30) and the no pain versus the moderate pain (d=.87) latent classes (Guyatt, Osoba, Wu, Wyrwich, & Norman, 2002; Osoba, 1999; Osoba, Rodrigues, Myles, Zee, & Pater, 1998). In addition, these

findings are consistent with data from two retrospective studies (Steegers, et al., 2008; Tasmuth, et al., 1995), as well as our previous report of persistent breast pain (Miaskowski, et al., 2012), that found an association between higher postoperative pain scores and the development of persistent postsurgical pain. While detailed information is not available on the postoperative pain regimens that were ordered for the patients in our study, our data suggest that more effective postoperative pain management may reduce the occurrence of both persistent breast and arm/shoulder pain.

While the receipt of RT was associated with persistent breast pain in our previous study (Miaskowski, et al., 2012), it was not associated with persistent arm/shoulder pain. While it is well established that RT can cause neuropathic pain (B. F. Jung, Ahrendt, Oaklander, & Dworkin, 2003), the location of the radiation field may impact the development of persistent pain following breast cancer surgery (Andersen & Kehlet, 2011). In this study, detailed information was not obtained on the location of the radiation field. Therefore, patients cannot be subdivided into specific groups based on the location of RT (e.g., residual breast, chest wall, axilla).

It is interesting to note that a higher percentage of patients in the moderate pain group had received physical therapy during the six months following breast cancer surgery. The specific reason for the physical therapy consultation was not obtained as part of the patients' assessments. Patients could be referred to physical therapy for limitations in shoulder mobility that is associated with scar tissue formation after an ALND and/or lymphedema. Fear of exacerbating the pain associated with scar tissue formation and/or lymphedema prevents women from using their arm/shoulder which results in contractures and more pain. Because the rehabilitation exercises could contribute to increased pain in these patients, pre-emptive pain management strategies should be used during physical therapy. Future studies need to evaluate the association between pain and physical therapy in more detail.

Consistent with our previous study of persistent breast pain (Miaskowski, et al., 2012), patients classified in the moderate arm/shoulder pain class reported higher preoperative levels of depressive symptoms, trait anxiety, sleep disturbance, fatigue, and lower levels of attentional function. Of note, except for state anxiety (d=.18), all of the differences in symptom severity scores between the no pain and moderate arm pain classes represent clinically meaningful differences in depression (d=.29), trait anxiety (d=.33), fatigue (d=.46), energy (d=.24), sleep disturbance (d=.48) and attentional function (d=.41). These findings highlight the importance of addressing multiple concurrent symptoms that may worsen pain and have a negative impact on patients' QOL.

Additional research is warranted to identify specific risk factors for the development of persistent breast (Miaskowski, et al., 2012) versus persistent arm/shoulder pain. In this study, only 20% of the patients were classified in both the no breast and no arm/shoulder pain GMM groups. In contrast, only 7.9% of the patients were classified in both the severe breast and moderate arm/shoulder pain groups. This finding suggests that different factors and/or mechanisms may be associated with persistent pain in different locations following breast cancer surgery. Detailed evaluation of phenotypic characteristics for and molecular markers of persistent pain at each site may provide insights into potential pain mechanisms.

Several study limitations need to be acknowledged. While the sample size was adequate, additional latent classes may be identified with a larger sample. While the sample was representative of breast cancer patients in the United States, different latent classes and/or different risk factors may have been identified if a larger percentage of the sample was non-White, older, had more advanced disease, and/or required more extensive surgery. To increase the generalizability of the study findings, patients were recruited through referrals from twenty surgeons at seven different sites. Future studies need to evaluate how differences in surgical protocols, as well as postoperative pain management protocols influence the development of persistent arm/shoulder pain. In addition, future studies need to evaluate postoperative pain scores in a prospective manner rather than rely on patient recall. In our previous paper on persistent breast pain (Miaskowski, et al., 2012), a detailed evaluation of analgesic use was reported. Since the majority of these women were not prescribed analgesics over the six months of the study, a separate analysis of analgesic use for persistent arm/shoulder pain was not performed.

In conclusion, this study is one of the largest, prospective, longitudinal studies to evaluate the prevalence of and risk factors for persistent arm/shoulder pain following breast cancer surgery and to compare these findings with risk factors for persistent breast pain (Miaskowski, et al., 2012). Future analyses are focused on determining the specific pain characteristics for the two arm/shoulder pain classes identified using GMM as well as genomic predictors of latent class membership.

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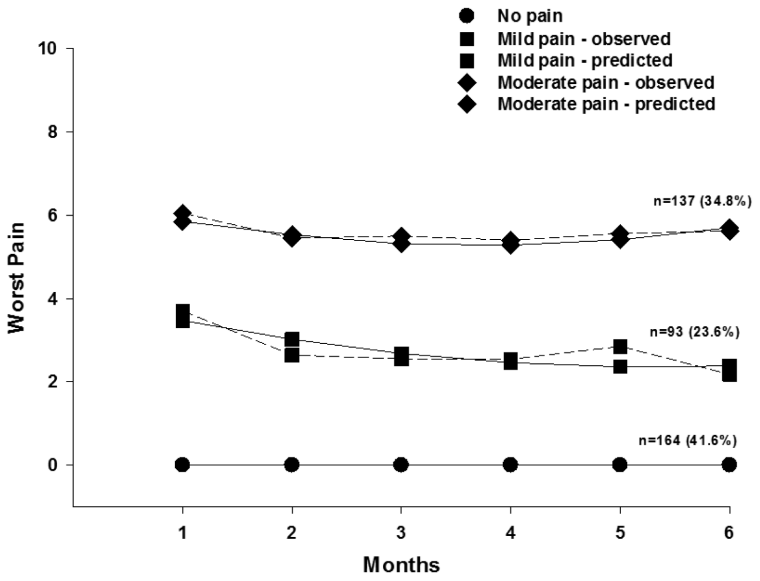

Figure 1.
Observed and estimated breast pain trajectories for patients in each of the latent classes.

Table 1

Fit Indices for the Growth Mixture Model Class Solutions for the Severity of Worst Arm/Shoulder Pain

GMM Solution	LL	AIC	BIC	Entropy	VLMR (df)	BLRT(df)
1-Class[a]	−1218.56	2457.12	2491.50	N/A	N/A	N/A
2-Class[b]	−1207.38	2442.75	2490.88	.46	22.37[ns] (4)	22.37[†] (4)
3-Class	−1201.79	2441.59	2506.91	.56	11.08[ns] (4)	11.08[ns] (4)

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; BLRT = parametric bootstrapped likelihood ratio test for K-1 (HO) vs K classes; CFI = Comparative Fit Index; df = degrees of freedom; GMM = Growth mixture model; LL = loglikelihood; N/A = not applicable; RMSEA = Root Mean Squared Error of Approximation; VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test for K-1 (HO) vs K classes.

[ns] = not significant;

[†] p < 0005

[a] Latent growth curve model with linear and quadratic components; Chi^2= 19.71, 17 df, p = . 29, CFI = 0.98, RMSEA = .03.

[b] 2-class model was selected based on the smallest BIC and a significant BLRT with 49 bootstrap draws.

Table 2

Parameter Estimates for Predicted Growtii Mixture Model Latent Classes from Six Assessments of Ratings of the Severity of Worst Arm/Shoulder Pain

Parameter Estimates[b]	**Class 1 N = 93 (40.4%)**	**Class 2 N = 137 (59.6%)**
	Mean (S.E.)	**Mean (S.E.)**
Intercept	3.48† (.38)	5.85† (.37)
Linear slope	-0.52* (.26)	-0.43* (.21)
Quadratic slope	0.06ns (.06)	0.08* (.04)
Variances[c]		
Intercept	0[c]	2.93† (.53)
Linear slope	0[c]	0[c]
Quadratic slope	0[c]	0[c]

Abbreviations: ns = not significant; GMM = growth mixture model; S.E. = standard error

*p<.05;

†P <.0005

[a]Trajectory group sizes are for classification of individuals based on their most likely latent class probabilities.

[b]GMM estimates were obtained with robust maximum likelihood.

[c]GMM could not be fit without fixing linear and quadratic slope variances to zero to allow model convergence.

Table 3

Differences in Demograpiiic Ciiaracteristics Among the Arm/Siioulder Pain Classes

Characteristic	No Pain (0) 164(41.6%)	Mild Pain (1) 93 (23.6%)	Moderate Pain (2) 137 (34.8%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	58.0(12.1)	52.7 (9.7)	52.9(11.3)	F=10.07, p<.0001 0>1 and 2
Education (years)	15.6(2.6)	16.3(2.7)	15.3(2.7)	F=3.70, p=.026 1>2
	% (N)	% (N)	% (N)	
Ethnicity White Non-white*	75.5(123) 24.5 (40)	68.8 (64) 31.2 (29)	50.0 (68) 50.0 (68)	X^2=21.90, p<.0001 0 and 1 < 2
Lives alone Yes No	25.3 (41) 74.7(121)	19.4(18) 80.6 (75)	24.6 (33) 75.4(101)	NS
Marital status Married/partnered Single, separated, widowed, divorced	43.2 (70) 56.8 (92)	35.5 (33) 64.5 (60)	43.0 (58) 57.0 (77)	NS
Currently working for pay Yes No	49.4 (80) 50.6 (82)	53.3 (49) 46.7 (43)	43.1 (59) 56.9 (78)	NS
Total annual household income <$10,000 to $19,999 $20,000 to $99,000 >$100,000	12.5(17) 47.1 (64) 40.4 (55)	14.5(12) 38.6 (32) 47.0 (39)	20.6 (22) 51.4 (55) 28.0 (30)	KW, p=.020 1>2

Abbreviations: KW = Kruskal Wallis; NS = Not significant

Table 4

Differences in Preoperative Clinical Characteristics Among the Arm/Shoulder Pain Classes

Characteristic	No Pain (0) 164(41.6%)	Mild Pain (1) 93 (23.6%)	Moderate Pain (2) 137 (34.8%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Body mass index (kg/m^2)	26.1 (5.2)	26.3 (6.2)	28.1 (6.9)	F=4.43, p=.013 0 < 2
Karnofsky Performance Status score	96.7 (6.8)	93.1 (10.0)	89.3(12.4)	F=21.50, p<.0001 0>1 and 2; 1>2
Self-Administered Comorbidity Scale score	3.9 (2.7)	3.8 (2.3)	5.0(3.1)	F=6.90, p=.001 0 and 1 < 2
Number of breast biopsies	1.3 (0.6)	1.6 (0.9)	1.6(0.9)	F=6.66, p=.001 0 < 1 and 2
Average breast pain	0.3(1.1)	0.5(1.0)	0.9(1.9)	F=7.56, p=.001 0 < 2
Worst breast pain	0.4(1.4)	1.0 (1.6)	1.5 (2.6)	F=10.90, p<.0001 0 < 2
Number of breast symptoms	0.5 (0.8)	0.7(1.0)	0.9(1.2)	F=6.09, p=.003 0 < 2
Grip strength – unaffected hand (kg)	23.6 (5.6)	24.2 (5.4)	23.6 (6.3)	NS
Grip strength – affected hand (kg)	23.5 (5.2)	23.9 (5.3)	22.9 (6.2)	NS
Flexion –unaffected arm	166.8 (8.4)	167.9 (8.6)	165.2 (11.3)	NS
Flexion – affected arm	166.3 (9.6)	167.7 (8.9)	163.0 (12.3)	F=6.12, p=.002 0 and 1 > 2
Abduction – unaffected arm	149.9 (17.1)	154.9 (16.8)	147.7 (20.2)	F=4.32, p=.014 1 > 2
Abduction – affected arm	149.2 (18.6)	154.4 (17.4)	144.8 (24.1)	F=6.05, p=.003 1>2
Internal rotation – unaffected arm	63.2 (8.1)	62.8 (9.1)	63.4 (8.5)	NS
Internal rotation – affected arm	62.7 (8.5)	63.5 (8.9)	62.5 (9.4)	NS
External rotation – unaffected arm	79.3 (7.4)	80.7 (6.6)	78.3 (9.1)	NS
External rotation – affected arm	79.3 (7.6)	80.5(7.1)	76.9(10.4)	F=5.64, p=.004 0 and 1 > 2
	% (N)	% (N)	% (N)	
Occurrence of comorbid conditions (% and number of women who reported each comorbid condition from the Self-Administered Comorbidity Questionnaire) Heart disease High blood pressure Lung disease Diabetes Ulcer Kidney disease Liver disease Anemia Depression Osteoarthritis Back pain Riieumatoid arthritis	4.3(7) 35.4 (58) 1.8(3) 5.5 (9) 2.4 (4) 0.6 (1) 1.2 (2) 4.9 (8) 22.0(36) 20.1 (33) 24.4 (40) 2.4 (4)	3.2 (3) 22.6 (21) 2.2 (2) 6.5 (6) 5.4 (5) 14.0(13) 12.9(12) 24.7 (23) 1.1 (1) 0.0 (0) 3.2 (3) 7.5 (7)	3.6 (5) 31.4 (43) 4.4 (6) 11.7(16) 4.4 (6) 1.5(2) 2.9 (4) 11.7(16) 27.0 (37) 17.5 (24) 34.3 (47) 5.8 (8)	NS NS NS NS NS NS NS NS NS NS NS NS
Exercise on a regular basis Yes No	74.4(122) 25.6 (42)	70.7 (65) 29.3 (27)	63.7 (86) 36.3 (49)	NS
Diagnosed with mastitis	15.4 (25)	10.9 (10)	8.9 (12)	NS

Characteristic	No Pain (0) 164(41.6%)	Mild Pain (1) 93 (23.6%)	Moderate Pain (2) 137 (34.8%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Yes No	84.6 (137)	89.1 (82)	91.1 (123)	
Diagnosed with fibrocystic disease Yes No	17.2 (27) 82.8 (130)	22.8 (21) 77.2 (71)	18.3 (24) 81.7 (107)	NS
Ever breast fed Yes No	54.0 (88) 46.0 (75)	43.0 (40) 57.0 (53)	41.6 (57) 58.4 (80)	NS
Surgery to affected breast unrelated to cancer Yes No	11.0 (18) 89.0 (146)	10.8 (10) 89.2 (83)	9.5 (13) 90.5 (124)	NS
Surgery on affected arm not related to cancer Yes No	4.3 (7) 95.7(157)	1.1 (1) 98.9 (92)	4.4 (6) 95.6 (131)	NS
Surgery on affected hand not related to cancer Yes No	6.1 (10) 93.9 (154)	4.3 (4) 95.7 (89)	5.1 (7) 94.9 (130)	NS
Injury to affected arm Yes No	15.2 (25) 84.8 (139)	15.1 (14) 84.9 (79)	13.1 (18) 86.9 (119)	NS
Injury to affected hand Yes No	7.3 (12) 92.7 (152)	9.7 (9) 90.3 (84)	12.4 (17) 87.6 (120)	NS
Prior hysterectomy Yes No	15.2 (25) 84.8 (139)	7.5 (7) 92.5 (86)	15.3 (21) 84.7 (116)	NS
Prior oophorectomy Yes No	12.9 (21) 87.1 (142)	7.5 (7) 92.5 (86)	10.2 (14) 89.8 (123)	NS
Gone through menopause Yes No	69.6 (112) 30.4 (49)	56.7 (51) 43.3 (39)	62.9 (83) 37.1 (49)	NS
Received neoadjuvant chemotherapy Yes No	8.0 (13) 92.0 (150)	23.7 (22) 76.3 (71)	31.4 (43) 68.6 (94)	X^2=26.76, p<.0001 0 < 1 and 2
On hormonal replacement therapy prior to surgery Yes No	21.1 (36) 77.9 (127)	12.9 (12) 87.1 (81)	14.0 (19) 86.0 (117)	NS
stage of disease Stage 0 Stage 1 Stage IIA and IIB Stage IIIA, IIIB, IIIMC, and IV	24.4 (40) 45.1 (74) 28.7 (47) 1.8 (3)	18.3 (17) 34.4 (32) 38.7 (36) 8.6 (8)	11.7 (16) 32.1 (44) 40.9 (56) 15.3(21)	KW, p<.0001 0 < 1 and 2
Estrogen receptor status Positive Negative	82.2 (134) 17.8(29)	73.1 (68) 26.9 (25)	74.5 (102) 25.5 (35)	NS
Progesterone receptor status Positive Negative	73.0 (119) 27.0 (44)	64.5 (60) 35.5 (33)	71.5 (98) 28.5 (39)	NS
HER2/neu receptor positive Yes No	12.8 (18) 87.2 (123)	17.6 (15) 82.4 (70)	19.4 (25) 80.6 (104)	NS
BRCA1 and BRCA2 genetic testing Positive Negative Not done	3.1 (5) 8.0 (13) 88.9 (144)	1.1 (1) 17.2 (16) 81.7 (76)	1.5 (2) 9.6 (13) 88.9 (120)	NS

Characteristic	No Pain (0) 164(41.6%)	Mild Pain (1) 93 (23.6%)	Moderate Pain (2) 137 (34.8%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Used NSAID preoperatively Yes No	3.7 (6) 96.3 (157)	0.0 (0) 100.0 (93)	3.7 (5) 96.3 (131)	NS
Pain in breast prior to surgery Yes No	15.0 (24) 85.0 (136)	35.2 (32) 64.8 (59)	38.5 (52) 61.5 (83)	X^2=23.15, p<.0001 0 < 1 and 2
Swelling in affected breast Yes No	4.3 (7) 95.7(157)	5.4 (5) 94.6 (88)	13.9 (19) 86.1 (118)	X^2=10.53, p=.005 0 < 2
Numbness in affected breast Yes No	1.8 (3) 98.2 (161)	4.3 (4) 95.7 (89)	6.6 (9) 93.4 (128)	NS
Strange sensations in affected breast Yes No	20.1 (33) 79.9 (131)	34.4 (32) 65.6 (61)	26.3 (36) 73.7 (101)	X^2=6.40, p=.041 0 < 1
Hardness in affected breast Yes No	14.0 (23) 86.0 (141)	16.1 (15) 83.9 (78)	24.1 (33) 75.9 (104)	NS

Abbreviations: KW = Kruskal Wallis; NS = Not significant, SD = standard deviation

Table 5

Differences in Preoperative Symptom and Quality of Life Scores Among the Breast Pain Classes

Symptom and Quality of Life Scores	No Pain (0) 164 (41.6%)	Mild Pain (1) 93 (23.6%)	Moderate Pain (2) 137 (34.8%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
SYMPTOM SCORES PRIOR TO SURGERY				
Center for Epidemiological Studies- Depression score	12.6 (9.6)	13.0 (9.8)	15.4 (9.6)	F=3.19, p=.042 0 < 2
Trait anxiety	34.3 (8.8)	34.3 (8.7)	37.3 (9.3)	F=4.83, p=.009 0 and 1 < 2
State anxiety	40.6 (14.2)	41.7 (12.6)	43.0 (13.0)	NS
General Sleep Disturbance Scale score	44.1 (20.9)	47.4 (22.2)	54.4 (20.9)	F=8.67, p<.0001 0 < 2
Lee Fatigue Subscale score	2.6 (2.3)	3.2 (2.2)	3.7 (2.4)	F=8.26, p<.0001 0 < 2
Lee Energy Subscale score	5.3 (2.7)	4.6 (2.2)	4.7 (2.4)	F=3.56, p=.029 No significant pairwise post hocs
Attentional Function Index score	7.0 (2.0)	6.5 (1.9)	6.2(1.9)	F=6.78, p=.001 0 > 2
QUALITY OF LIFE SUBSCALE AND TOTAL SCORES PRIOR TO SURGERY				
Physical well-being score	8.6 (1.2)	8.0 (1.5)	7.2 (1.8)	F=31.13, p<.0001 0 > 1 > 2
Psychological well-being score	6.3 (1.7)	5.8 (1.7)	5.2 (1.8)	F=14.32, p<.0001 0 and 1 > 2
Social well-being score	7.7 (1.6)	6.8 (1.9)	6.1 (2.1)	F=28.98, p<.0001 0 > 1 > 2
Spiritual well-being score	5.7 (1.8)	5.6 (1.6)	5.9 (1.9)	NS
Total quality of life score	6.9 (1.2)	6.4 (1.2)	5.9 (1.4)	F=23.46, p<.0001 0 > 1 > 2

Abbreviations: NS = Not significant, SD = standard deviation

Table 6

Differences in Intraoperative Characteristics Among the Arm/Shoulder Pain Classes

Characteristic	No Pain (0) 164 (41.6%)	Mild Pain (1) 93 (23.6%)	Moderate Pain (2) 137 (34.8%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Number of lymph nodes removed	3.3 (4.6)	6.6 (5.9)	8.0 (8.2)	F=20.91,p<.0001 0< 1 and 2
Number of positive lymph nodes	0.3 (1.1)	1.0 (1.9)	1.5 (3.1)	F=9.55, p<.0001 0 < 2
Number of drains placed during surgery	0.3 (0.6)	0.5 (0.7)	0.7 (0.8)	F=13.18, p<.0001 0 < 2
	% (N)	% (N)	% (N)	
Type of surgery Breast conserving Mastectomy	86.0 (141) 14.0 (23)	79.6 (74) 20.4 (19)	74.5(102) 25.5 (35)	X^2=6.36, p<.04 0 < 2
Location of cancer Right breast Left breast	43.3 (71) 56.7 (93)	46.2 (43) 53.8 (50)	51.8 (71) 48.2 (66)	NS
Surgery done on Dominant side Nondominant side	45.1 (74) 54.9 (90)	48.4 (45) 51.6 (48)	47.4 (65) 52.6 (72)	NS
Sentinel lymph node biopsy Yes No	79.9 (131) 20.1 (33)	86.0 (80) 14.0 (13)	83.9 (115) 16.1 (22)	NS
Axillary lymph node dissection Yes No	19.6 (32) 80.4 (131)	47.3 (44) 52.7 (49)	51.1 (70) 48.9 (67)	X^2=36.95, p<.0001 0 < 1 and 2
Intercostobrachial nerve sacrificed Yes No Unable to determine	0.6 (1) 10.4 (17) 89.0 (145)	3.2 (3) 11.8 (11) 84.9 (79)	6.6 (9) 8.0 (11) 85.4 (117)	NS
Intraoperative wound infiltration with local anesthetic Yes No Unable to determine	72.6 (119) 7.9 (13) 19.5 (32)	54.8 (51) 14.0 (13) 31.2 (29)	56.2 (77) 10.9 (15) 32.8 (45)	X^2=12.29, p=.015 0 > 1 and 2
Intraoperative radiation therapy Yes No	3.7 (6) 96.3 (158)	4.3 (4) 95.7 (89)	3.7 (5) 96.3 (131)	NS
Reconstruction at the time of surgery Yes No	20.7 (34) 79.3 (130)	20.7 (19) 79.3 (73)	24.1 (33) 75.9 (104)	NS

Abbreviations: NS = Not significant, SD = standard deviation

Table 7

Differences in Postoperative Clinical Characteristics Among the Arm/Shoulder Pain Classes

Characteristic	No Pain (0) 164 (41.6%)	Mild Pain (1) 93 (23.6%)	Moderate Pain (2) 137 (34.8%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Number of postoperative complications	0.2 (0.5)	0.2 (0.4)	0.3 (0.6)	F=3.67, p=.026 0 < 2
Severity of average postoperative pain	3.0 (2.3)	3.7 (2.3)	5.0 (2.2)	F=28.21, p<.0001 0 and 1 <2
Severity of worst postoperative pain	4.2 (2.7)	5.0 (2.6)	6.6 (2.4)	F=31.16, p<.0001 0 < 1 < 2
Amount of relief from analgesics (%)	81.1 (25.5)	81.3 (20.2)	74.8 (21.5)	F=3.16, p=.043 No significant pairwise post hocs
Satisfaction with postoperative pain treatment	9.0 (1.9)	8.6 (2.1)	8.1 (2.3)	F=6.39, p=.002 0 > 2
	% (N)	% (N)	% (N)	
Placement of surgical drain None Only in breast Only in axilla In both breast and axilla	75.0 (123) 17.7 (29) 6.7 (11) 0.6 (1)	57.0 (53) 16.1 (15) 20.4 (19) 6.5 (6)	48.9 (67) 13.1 (18) 27.7 (38) 10.2 (14)	X^2=42.72, p<.0001 None-0 > 1 and 2 Only in breast – NS Only in axilla – 0 < 1 and 2 In both – 0 < 2
Had one to four postoperative complications Yes No	12.2 (20) 87.8 (144)	14.0 (13) 86.0 (80)	24.1 (33) 75.9 (104)	X^2=8.24, p=.016 0 < 2
Had a seroma Yes No	7.3 (12) 92.7 (152)	7.5 (7) 92.5 (86)	14.6 (20) 85.4 (117)	NS
Had a hematoma Yes No	3.7 (6) 96.3 (158)	4.3 (4) 95.7 (89)	8.0 (11) 92.0 (126)	NS
Had bleeding Yes No	1.2 (2) 98.8 (162)	0.0 (0) 100.0 (93)	2.2 (3) 97.8 (134)	NS
Had a wound infection Yes No	3.0 (5) 97.0 (159)	4.3 (4) 95.7 (89)	5.1 (7) 94.9 (130)	NS
Received radiation therapy during the 6 months Yes No	59.1 (97) 40.9 (67)	54.8 (51) 45.2 (42)	54.7 (75) 45.3 (62)	NS
Received adjuvant chemotherapy during the 6 months Yes No	27.4 (45) 72.6 (119)	38.7 (36) 61.3 (57)	38.0 (52) 62.0 (85)	NS
Received hormonal therapy during the 6 months Yes No	45.1 (74) 54.9 (90)	45.2 (42) 54.8 (51)	38.0 (52) 62.0 (85)	NS
Received biological therapy during the 6 months Yes No	5.5 (9) 94.5 (155)	17.2 (16) 82.8 (77)	12.4 (17) 87.6 (120)	X^2=9.23, p=.010 0 < 1
Received complementary therapy during the 6 months Yes No	25.6 (42) 74.4 (122)	29.0 (27) 71.0 (66)	28.5 (39) 71.5 (98)	NS
Received physical therapy during the 6 months Yes No	10.4 (17) 89.6 (147)	12.9 (12) 87.1 (81)	24.8 (34) 75.2 (103)	X^2=12.47, p=.002 0 < 2

Characteristic	No Pain (0) 164 (41.6%)	Mild Pain (1) 93 (23.6%)	Moderate Pain (2) 137 (34.8%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Had breast reconstruction during the 6 months Yes No	6.1 (10) 93.9 (154)	7.5 (7) 92.5 (86)	8.0 (11) 92.0 (126)	NS
Breast cancer recurred during the 6 months Yes No	0.0 (0) 100.0 (164)	0.0 (0) 100.0 (93)	0.0 (0) 100.0 (137)	NS
Had re-excision or mastectomy during the 6 months Yes No	24.4 (40) 75.6 (124)	24.7 (23) 75.3 (70)	33.6 (46) 66.4 (91)	NS
Any other surgery during the 6 months Yes No	8.5 (14) 91.5 (150)	12.9 (12) 87.1 (81)	10.2 (14) 89.8 (123)	NS
Evidence of metastatic disease during the 6 months Yes No	0.0 (0) 100.0 (164)	1.1 (1) 98.9 (92)	0.0 (0) 100.0 (137)	NS

Abbreviations: NS = Not significant, SD = standard deviation