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Prediction of Persistent Pain Severity and Impact 12 Months After Breast Surgery Using Comprehensive Preoperative Assessment of Biopsychosocial Pain Modulators

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Abstract

Background.—Persistent post-mastectomy pain (PPMP) is a significant negative outcome occurring after breast surgery, and understanding which individual women are most at risk is essential to targeting of preventive efforts. The biopsychosocial model of pain suggests that factors from many domains may importantly modulate pain processing and predict the progression to pain persistence.

Methods.—This prospective longitudinal observational cohort study used detailed and comprehensive psychosocial and psychophysical assessment to characterize individual pain-processing phenotypes in 259 women preoperatively. Pain severity and functional impact then were longitudinally assessed using both validated surgery-specific and general pain questionnaires to survey patients who underwent lumpectomy, mastectomy, or mastectomy with reconstruction in the first postsurgical year. An agnostic, multivariable modeling strategy identified consistent predictors of several pain outcomes at 12 months.

Results.—The preoperative characteristics most consistently associated with PPMP outcomes were preexisting surgical area pain, less education, increased somatization, and baseline sleep disturbance, with axillary dissection emerging as the only consistent surgical variable to predict worse pain. Greater pain catastrophizing, negative affect, younger age, higher body mass index

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DISCLOSURE Andrea Pusic—co-developer of the Q-PROM portfolio and may receive royalties when these patient-reported outcome measures are used in for-profit, industry-sponsored clinical trials. There were no conflicts of interests.

(BMI), and chemotherapy also were independently predictive of pain impact, but not severity. Sensory disturbance in the surgical area was predicted by a slightly different subset of factors, including higher preoperative temporal summation of pain.

Conclusions.—This comprehensive approach assessing consistent predictors of pain severity, functional impact, and sensory disturbance may inform personalized prevention of PPMP and also may allow stratification and enrichment in future preventive studies of women at higher risk of this outcome, including pharmacologic and behavioral interventions and regional anesthesia.

Breast cancer is diagnosed for more than 250,000 women in the United States annually, and most of these women require at least one surgical procedure.[1] Persistent post-mastectomy pain (PPMP) is increasingly recognized as an important problem[2] after mastectomy and lumpectomy.[3–8] Likely due to the lack of a widely accepted definition, the reported incidence of PPMP varies from 20 to 65%. Past studies have used yes/no dichotomization, have included any level of pain severity (≥ 1/10),[9–12] or have included only moderately intense pain as PPMP (≥ 3/10 or ≥ 4/10 pain).[5,13–17] Although dichotomizing pain is appealingly simple, it eliminates important information about pain severity and decreases the power to test associations sensitively with risk factors and treatments.

The biopsychosocial model of pain implicates a broad array of characteristics as important modulators of pain.[18,19] In the context of postmastectomy pain, the contributions of disease characteristics, treatment differences, and individual biologic, psychological, and social factors have previously been investigated.[20–24] Together, these factors may meaningfully contribute to the development, maintenance, and impact of persistent pain states,[20] including PPMP.[22] The use of a comprehensive biopsychosocial model may capture the complexities of pain and provide insight into why pain varies between individuals. Furthermore, it may serve as a useful taxonomy for investigating acute[24,25] and chronic pain after breast surgery.

Some biologic variables previously associated with PPMP are younger age,[3,26–35] genetics,[9,36–38] and surgical factors such as type of procedure,[39,40] especially axillary dissection.[3,7,10,12,16,26,27,41] Psychophysical differences in pain processing between individuals can be assessed using quantitative sensory testing (QST).[42] Previously, QST measures have predicted acute[24,43,44] and persistent[4,11,45,46] postsurgical pain.

Psychosocial factors also have been associated with PPMP.[5,22] Anxiety and depression have been most commonly examined,[2,47,48] but higher pain catastrophizing, somatization, negative affect, and sleep disturbance also have been associated with greater PPMP[2,5,6,8,14,21,31,39,40,42,47,49–55] and psychological resilience with less PPMP.[4,5,10,12,37] Social factors, although less well studied, may include sociodemographic variables including lower education[56] and social engagement.

Importantly, few studies have simultaneously and preoperatively evaluated the comprehensive range of biopsychosocial variables in the prediction of PPMP. This study aimed to do just that using well-validated, brief measures at the time of surgical/anesthetic planning and then subsequently measuring multiple meaningful general and surgery-specific pain outcomes in the first year after surgery. The study aimed examine important associations between biopsychosocial predictors and PPMP that may help to explain the

variation observed between individuals, and to develop and internally validate multivariable models for predicting measures of pain severity and impact 12 months after mastectomy.

METHODS

Description of the Cohort

This prospective, observational longitudinal cohort study was approved by the institutional review board, and patients were recruited from the preoperative anesthesia clinic from September 2014 to October 2017 at a single academic medical center. The eligibility criteria specified women 18–80 years old scheduled to undergo breast surgery, English proficiency, and no cognitive impairments interfering with questionnaire completion.

Data Collection

After providing informed consent, the patients underwent brief bedside QST in nonsurgical areas (hands, extensor forearm, and trapezius). Validated questionnaires assessing psychosocial phenotypes, demographics, and pain at surgical sites and other body areas were sent to patients via an emailed link to a secure data entry system (Redcap) for them to complete before their scheduled surgery. Previous reports from this cohort on acute postsurgical pain and opioid use (up to 2 weeks after surgery)[24,57] and 6-month preliminary postsurgical outcomes[58] have been published.

Surgical and Treatment Variables

Clinical and pathologic factors as well as procedure details including type, laterality, duration, reconstruction type, axillary procedure, and subsequent surgeries or complications were extracted from patient medical records 1 year postoperatively. Breast surgical extent was categorized as breast-conservation surgery (partial mastectomy or excisional biopsy), mastectomy, or mastectomy with reconstruction. Axillary surgical extent was evaluated independently and categorized as 0 (no axillary surgery), 1 (sentinel lymph node biopsy [SLNB]), or 2 (axillary lymph node dissection [ALND]). The patients who underwent ALND after index surgery were recategorized in the ALND category. Similarly, the patients who underwent subsequent total mastectomy after a lumpectomy were recategorized in the total mastectomy category. The patients electronically reported their use of other breast cancer treatment or treatments including radiation, chemotherapy, or endocrine therapy 1 year after surgery.

Perioperative Care and Analgesic Use

The majority of the patients received general anesthesia, and regional anesthesia (ultrasound-guided thoracic paravertebral block, proximal intercostal block, and/or pectoralis nerve block) was offered preoperatively to most of the patients undergoing total mastectomy depending on regional anesthesia availability and surgeons' preferences. Additional intra- and postoperative analgesics including opioids, celecoxib, ketamine, and acetaminophen were administered according to anesthesia and surgical provider preference.

Psychosocial Assessment

Psychosocial measures previously associated with persistent pain in a retrospective cohort[5] and those with strong psychometric properties and brevity were selected.[24] The Pain Catastrophizing Scale (PCS),[59] was used to measure pain-associated catastrophic thinking. Depressive symptoms, anxiety, and sleep disturbance were assessed using the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) short form.[60] The Brief Symptom Index 18-Somatization Scale[61] was used to measure somatization. The Positive Affect Negative Affect Scale (PANAS)[62] was used to assess affect, and preferences for coping strategies were measured using the short-form Coping Strategies Questionnaire (CSQ).[54,63]

Psychophysical Assessment

Psychophysical assessment of baseline general pain sensitivity involved two brief, portable QSTs. Temporal summation of pain (TSP) and painful after-sensations (PAS) of mechanical pinprick pain were assessed with standardized weighted pinprick applicators using methods described by Rolke et al.[42] and in our previous studies.[4,24,25] Pressure pain threshold and tolerance were assessed using a digital pressure algometer (Wagner FDX, Greenwich, CT, USA) with a flat round transducer (probe area, 0.785 cm) bilaterally on the dorsal aspect of the proximal forearm approximately 3–4 cm distal to the elbow crease (extremity site) and over the trapezius muscle at the upper back approximately 2–3 cm above the scapular spine midway between the C7 prominence and humeral head (truncal site), as in previous studies.[4,24,25]

Pain Assessment

Persistent pain was measured at 2 weeks, then at 3, 6, and 12 months using the extended version of a surgery-specific questionnaire, the Breast Cancer Pain Questionnaire (BCPQ) (Appendix A), first developed by Gartner et al.[3] and used in subsequent studies.[47,49,64–71] The BCPQ queries patients about pain severity (scores 1–10) and frequency (scores 5 [constantly], 4 [daily], 3 [occasionally], 2 [weekly], 1 [monthly], and 0 [never]) in four surgically related body areas (breast, axilla, chest wall, arm). As in our previous studies,[4,5,25] a Pain Severity Index (PSI) score was calculated using the following equation:

$$\mathrm{PSI} = \Sigma(\text{pain score at each site } [0-10]) \times (\text{frequency } [1-5]).$$

The BCPQ includes questions about the impact of surgical pain on physical activities relevant to the body area (Physical Impact of Pain), the impact of surgical pain on cognitive and emotional functioning (Cognitive & Emotional Impact of Pain), and sensory disturbance in the surgical area, including both negative (numbness) and positive (burning) alterations in sensation (Sensory Disturbance).[17]

To promote generalizability to other surgical and nonsurgical pain samples, the patients also completed the widely used and well-validated Brief Pain Inventory (BPI),[72] wherein the average of the current, worst, least, and average pain ratings in the preceeding week produce the BPI Severity, and other questions evaluate pain intereference (BPI Interference).

Statistical Approach

Patient demographic, psychosocial, psychophysical, and pain outcome characteristics were summarized using frequencies and percentages, mean and standard deviations, or medians with interquartile ranges. To maximize power in the analyses, all pain outcomes were measured using a continuous scale reflective of the nonbinary nature of pain.

Uni- and multivariable analyses were modeled for several different pain outcomes, described earlier (Pain Severity Index, Physical Impact of Pain, Cognitive & Emotional Impact of Pain, Sensory Disturbance, BPI Severity, and BPI Interference). Candidate predictors were identical for all outcomes except the preoperative pain measure, which was provided from the corresponding baseline questionnaire (BCPQ or BPI).

In the univariable analysis, bivariable associations between all candidate predictors and each outcome were run using simple linear regression. Multivariable prediction models for outcomes were developed using linear regression with the least absolute shrinkage and selection operator (LASSO), a penalized regression method appropriate for preventing overfitting while creating a parsimonious model.[73] The study assessed LASSO model discrimination via root mean square error (RMSE), a measure of the average magnitude of the difference between observed pain severity and impact scores 12 months after mastectomy and scores predicted by the model.

Internal model validation was performed using 100 bootstrap samples with the incorporation of multiple imputation (described later) to obtain optimism-corrected estimates of the RMSE and shrinkage factors while accounting for missing data.[52,74] The shrinkage factor was estimated as the average slope obtained by regressing the observed scores for the original development sample on their predicted scores using models built on each bootstrap sample. Recalibration of the models using the shrinkage factor did not improve model RMSE or calibration, so original model coefficients are presented. Further, alternative modeling approaches (e.g., negative binomial regression) did not improve model discrimination or calibration or decrease heteroscedasticity of model residuals, so linear regression was chosen as the final approach.

To account for missing data, all models were built and internally validated using datasets imputed via the method of multivariate imputation by chained equations.[75] Specifically, predictive mean matching and logistic regression were used to impute continuous and categorical variables, respectively, to create 40 complete datasets per original and bootstrap sample. To allow for a single set of model predictors to be selected across all imputed datasets, MI-LASSO, a group LASSO method, was used.[76] Imputation models included corresponding outcome values measured at baseline, then at 6 months and 12 months.

Other variables included in the imputation model were selected based on maximizing the correlation with the variable imputed, as well as the proportion of cases with observed values on both the predictor and imputed variable. Beta coefficients, RMSE, and calibration metrics were calculated for each of the 40 imputed datasets and combined using Rubin’s rules.

To determine sample size, we used data from our previous study,[4,5] in which approximately 35% of the patients experienced persistent post-mastectomy pain longer than 1 year after mastectomy (defined in that study as pain ≥ 3/10). We calculated effect sizes for predictor variables and determined that 200 patients would provide 80% power at a two-sided alpha level of 0.05 to detect effect sizes of 0.40 or greater. Statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc, Cary, NC, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Participants

The baseline biopsychosocial assessments were completed by 259 patients, and 201 patients recruited from a single academic medical center completed the BCPQ at 1 year (Fig. 1). All the subjects were women, predominantly Caucasian (86.4%) with a mean age of 55.5, and 76% reported a college degree or higher (Table 1).

Surgical, Medical, and Anesthetic Treatment

The surgical indications were invasive cancer (77%), ductal carcinoma in situ (15%), prophylactic mastectomy (4.5%), and benign lesions (3.5%). The patients underwent a range of surgical procedures including breast-conserving surgery (54%) and mastectomy (46%), reconstruction involving tissue expander placement/implant (28%) or autologous reconstruction (8% deep inferior epigastric artery perforator [DIEP] or transverse rectus abdominis [TRAM] flap), sentinel lymph node biopsy (63%), and ALND (16%) (Table 1). Subsequent surgery after the index surgery was performed for 48 patients (18.5%), with 25 (52%) of these surgeries occurring within the first 3 months and 43 (90%) occurring within 6 months after the index surgery. Additional medical treatment of breast cancer included radiation (57.3%), chemotherapy (35.9%), and endocrine therapy (49.6%). The majority (96%) of the patients received general anesthesia for surgery. Of the patients who had total mastectomy, 44% also received regional anesthesia.

Pain Locations Over Time

Figure 2 depicts the number of surgically related body areas with pain reported at each time point (Fig. 2a). Similar to previous studies,[3,41] pain in the breast, axilla, or both was most commonly reported (Fig. 2b). Mild preoperative breast pain was common (38%), but surgery-related locations had notably higher pain prevalence and severity after surgery.

Incidence of PPMP and Pain Severity Index

To compare longitudinal prevalence of PPMP with rates reported in previous studies, we dichotomized PPMP using various cutoffs (≥ 1/10, ≥ 3/10, ≥ 5/10) to define PPMP (Fig. 3a). Approximately one third of the patients reported a pain level of 3/10 or higher in at least one body area, a proportion that remained constant at 3, 6, and 12 months.

To capture pain severity more thoroughly, we examined patients' Pain Severity Index (PSI) scores, which encompass pain severity, frequency, and number of body areas affected.[4,5,25]

The magnitude and time course of PSI varied between patients, with the highest values observed 2 weeks after surgery and stable values after 3 months (Fig. 3b).

Assessment of Pain Impact and Sensory Disturbance

The physical, cognitive, and emotional impact of pain was highest 2 weeks after surgery, with lower, relatively stable mean impact scores across the 3-, 6-, and 12-month time points (Appendix 2, Fig. 6). Notably, the impact on cognitive and emotional functioning appeared more sustained beyond 2 weeks than the impact on physical functioning. As with PSI, a large amount of inter-individual variability in pain impact scores was observed, with a proportion of patients still reporting a substantial impact of pain at later time points (Appendix 2, Fig. 6b). Sensory disturbance remained relatively consistent across time (Appendix 2, Fig. 6c). Sensory disturbance scores were moderately correlated with pain severity and impact outcomes (Spearman's rho, 0.41–0.68; $p < 0.001$). The BPI severity and interference scores were moderately to highly correlated with, but not identical to, the BCPQ Pain severity and impact scores (Appendix 3).

Association of Variables with Persistent Pain at 12 Months

Our prediction analysis focused on 12 months to avoid potentially confounding effects of radiation treatment (56% of the patients), subsequent surgical interventions (18.5% of the patients), or both that could lead to acute pain exacerbation, potentially confounding PPMP assessment at 3 and possibly 6 months.

Simple Univariable Associations of Preoperative Factors with Pain Outcomes at 12 Months

Factors were assessed for association of several PPMP outcomes at 12 months, including breast surgery-specific (BCPQ) and general (BPI) pain severity as well as impact measures (Table 1). The overlap of these associations is illustrated in a matrixed Venn diagram (Fig. 4). The factors associated with many outcomes (at the intersection of circles) included preexisting pain in surgical areas or elsewhere, ALND, chemotherapy, higher BMI, lower education, and higher sleep disturbance, somatization, pain catastrophizing, and negative affect. Several factors were associated with only some PPMP outcomes, including less exercise, radiation, higher depression and anxiety, younger age, greater weekly alcohol use, and baseline opioid use. The only QST associated with PPMP outcomes was temporal summation of pain, but only for sensory disturbance/neuropathic type pain in the surgical area.

Multivariable Prediction of Persistent Pain Outcomes at 12 Months

Given that many of the predictor variables were highly correlated, we next assessed them within a combined prediction model (multivariable prediction analysis) using LASSO (Table 2). The variables that independently and consistently contributed to prediction of all outcomes were preoperative pain, education, and sleep disturbance (Fig. 5). Other relatively consistent predictors were greater somatization, preoperative pain in other body areas, and baseline opioid use. Greater pain catastrophizing and negative affect, younger age, higher BMI, and chemotherapy were predictive of only pain impact, whereas ALND was predictive

of both BCPQ pain severity and impact. Greater breast surgical extent was not predictive of pain severity or impact.

Internal Validation of Models

Multivariable prediction models were internally validated via bootstrapping, and the accuracy of prediction (observed vs predicted values for each patient) was shown in scatterplots (Fig. 5). The most accurate prediction was observed for the BCPQ Cognitive and Emotional Impact of Pain (13% average difference between predicted and observed scores) compared with the less accurate predictions of pain severity (17% for PSI and 22% for BPI; Fig. 5) and sensory disturbance (22%; Appendix 4).

Analgesic Use

Opioid use 12 months after surgery was extremely uncommon. Only 8 (4%) of 201 patients reported taking any opioids, with only 5 (2.5%) of the 201 patients taking opioids for pain in the surgical area, thus precluding meaningful analysis of predictors of this outcome.

DISCUSSION

Previous studies have rarely evaluated all known pain modulators (demographic, biophysical, psychosocial) simulataneously and prospectively in a rigorous longitudinal assessment of diverse pain outcomes (severity, physical, cognitive and emotional functional impact, and sensory disturbance). This prospective longitudinal study examined associations between a comprehensive set of preoperative predictors and PPMP 12 months after surgery.

Using robust and agnostic modeling approaches, we developed reduced predictive models. The consistent independent predictors were preoperative pain, younger age, ALND, lower education, BMI, sleep disturbance, and the psychosocial variables somatization, catastrophizing, and depression. Notably, breast surgical extent (e.g., mastectomy vs breast-conserving surgery) or presence of reconstruction were absent from this list of predictors. Many predictors associated with greater pain severity and impact were consistent with those of previous studies.[8,22,48]

Our multivariable analysis yielded several notable findings. First, preoperative pain in the breast was found to be one of the strongest, most frequently selected predictors of PPMP. Preoperative surgery-specific site pain has rarely been reported in previous studies because it is seldom prospectively assessed with a rigorous, surgery-specific questionnaire. We observed a relatively high prevalence of at least mild pain among the participants at baseline (40%, Fig. 3a). Given that most of the participants in the study had a breast biopsy as part of their diagnostic workup in the month before surgery, it is conceivable that the high prevalence of breast pain may have resulted from the biopsy. However, future studies are needed to further explore the prevalence and duration of preoperative breast pain. Importantly, the severity, frequency, and number of pain locations increased substantially after surgery (Fig. 3b). Most, if not all, of the previous studies found that acute *post*operative pain is a predictor of subsequent pain. Although inclusion of acute postoperative pain in prediction models may increase the accuracy of prediction, this pain score is not accesible *pre*operatively, making it a less useful predictor for surgical and anesthetic planning.

Second, the only surgical variable consistently associated with PPMP was ALND, congruent with previous findings,[3] including our own studies, that did not detect a greater incidence of PPMP with mastectomy than with breast-conserving surgery, and a recent metaanalysis concluding that breast reconstruction was not associated with greater pain persistence.[77] Axillary dissection has consistently been associated with persistent pain[3,7,10,12,16,26,27,37,41] and sensory dysfunction,[78] particularly in the distribution of the intercostobrachial nerve (ICBN).

Third, and somewhat surprisingly, baseline sleep disturbance was a consistent independent predictor of both pain severity and pain impact. Previous evaluations identified preoperative fatigue and sleep as important predictors of PPMP,[55] which together with our findings bolsters the utility of sleep disturbance as a predictor and target of future study. The relationship between sleep and pain likely is bidirectional, with pain itself also disturbing sleep.[50,79,80] Evidence for this self-reinforcing maladaptive spiral has been noted among patients with cancer,[53,81] and both pharmacologic and behavioral interventions to improve sleep have been associated with chronic pain improvement.[82]

Fourth, psychosocial variables, including catastrophizing, anxiety, and depression, were more consistently predictive of pain impact than pain severity. Although this association does not constitute a causal link, some evidence is emerging that behavioral interventions directed at these factors in the peri- and postoperative period may improve pain.[83–86] Morevover, although decisions about surgical procedure may not be negotiable, modification of the psychological health of patients with breast cancer through behavioral interventions and acquisition of coping strategies pre-surgically has essentially no downside. Similarly, social factors, including peer support and group interventions, have shown efficacy in lessening pain impact.[87,88]

Fifth, despite our previous findings that QST-assessed temporal summation of pain (TSP) predicts acute pain after mastectomy[24] and total knee arthroplasty,[43] TSP did not emerge as a significant associate or predictor of pain severity or pain impact in the current study. Our previous cross-sectional study observed an association of several QSTs (lower pressure pain threshold and higher TSP) with PPMP,[4,11] similar to findings of a large cohort with orofacial pain.[89] Mechanical pain sensitivity may increase for patients who experience persistent pain, such that cross-sectional studies observe these associations, whereas preoperative testing is less predictive.

Although some previous studies have examined pain impact, usually as a secondary outcome, it has rarely been used as a criterion to define which predictors are most important. Assessing the functional impact of pain has been recognized in consensus guidelines as crucial to the study of acute[4] and chronic[90] pain. Differential prediction of pain severity and impact may be an important consideration because most patients and clinicians are interested in whether post-surgical pain has a meaningful impact on patient quality of life, including physical and mental functioning, relationships, and employment. Interestingly, the independent predictors of the impact of pain included more psychosocial variables, preoperative opioid consumption, and younger age.

Some important limitations of this study should be noted. First, the patients who declined participation in ths study often cited feeling overwhelmed, perhaps leading to an underestimation of anxiety and catastrophizing, reflected by the lower scores on these measures than in previous cohorts. Second, the low number of non-white participants precluded a meaningful estimation of race as a risk factor. Third, the low rate of opioid use at 12 months, although generally encouraging, limited our ability to discern risk factors for this outcome. Previous work has demonstrated that higher anxiety and depression may be risk factors for opioid use,[51] and our previous analysis showed sleep disturbace and TSP to be important predictors for opioid use at 2 weeks.[24]

The discernment of interindividual differences that predict risk of outcomes such as chronic pain is critically important to the development of personalized medicine. Even if perfect prediction is not possible, discernment of somewhat higher potential risk for persistent pain may help patients weigh the risks and benefits of surgery if other management options are available.

This study showed that the most consistent biopsychosocial predictors of PPMP are preoperative pain, lower education, sleep disturbance, and somatization, with axillary lymph node dissection and chemotherapy also playing an important role. Other important and potentially modifiable factors may include preoperative opioid use, sleep disturbance, and psychosocial state (catastrophizing, affect and depressive symptoms), many of which appear to predict the impact of pain better than severity. Recognition of these factors may help to identify patients most likely to benefit from preventive interventions that appear promising, including pharmacologic and behavioral interventions and regional anesthesia, and to inform definitive testing and efficient targetting of preventive therapies in future trials.

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APPENDIX 1 BREAST CANCER PAIN QUESTIONNAIRE

Breast Cancer Pain Questionnaire (BCPQ)

Outcomes were assessed using the corresponding questions:

- *Pain Severity Index (PSI): 4-13*
- *Sensory disturbance: 27-34*
- *Cognitive and emotional impact: 39-52*
- *Physical impact: 53-71*

1)	When were you diagnosed with breast cancer?	_____ (give approximate date)
2)	What is your level of physical activity in the last month?	○ Sedentary or nearly completely physically passive month? (e.g. tv, reading, movies) ○ Light physical activity 2-4 hours per week (minimum physical effort, e.g. a stroll. Cycle ride at a relaxed tempo, yoga, golf, a little light gardening) ○ Moderate physical activity, minimum 3 hours per week (not exhausting e.g. tennis, "keep fit" classes) ○ Hard physical activity for more than 4 hours per week (where your heartbeat is increased by running, spinning, circuit training)
3)	Has your activity level decreased because of treatment of breast cancer?	○ Yes ○ No
4)	Within the last month, have you experienced pain in the breast area, armpit, chest or arm on the side of your current breast cancer? (regardless of whether you have already had surgery for breast cancer, we would like you to answer this question)	○ Yes ○ No
5)	If so, indicate the area(s) in which you have had pain:	☐ breast ☐ armpit ☐ arm ☐ side of chest
6)	Please indicate the average severity of your breast pain, from 0 (no pain) to 10 (worst possible pain.)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
7)	Please indicate the frequency of your breast pain	○ Constantly ○ Daily ○ Weekly

	○ Monthly ○ Occasionally	
8) Please indicate the severity of your armpit pain, from 0 (no pain) to 10 (worst possible pain)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5	○ 6 ○ 7 ○ 8 ○ 9 ○ 10
9) Please indicate the frequency of your armpit pain	○ Constantly ○ Daily ○ Weekly ○ Monthly ○ Occasionally	
10) Please indicate the severity of your arm pain, from 0 (no pain) to 10 (worst possible pain)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5	○ 6 ○ 7 ○ 8 ○ 9 ○ 10
11) Please indicate the frequency of your arm pain	○ Constantly ○ Daily ○ Weekly ○ Monthly ○ Occasionally	
12) Please indicate the severity of your side of chest pain, from 0 (no pain) to 10 (worst possible pain)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5	○ 6 ○ 7 ○ 8 ○ 9 ○ 10
13) Please indicate the frequency of your side of chest pain	○ Constantly ○ Daily ○ Weekly ○ Monthly ○ Occasionally	
14) Do you experience chronic pain in any other area(s) of your body?	☐ No (none) ☐ Headache ☐ Neck/shoulders ☐ Lower back ☐ Hip	☐ Ankle/foot ☐ Stomachache ☐ Lower abdomen ☐ Other

	☐ Knee	
15) If other, please list	_____	
16) How severe is the pain is this/these areas (indicate for most severe area)?	O 0 O 1 O 2 O 3 O 4 O 5	O 6 O 7 O 8 O 9 O 10
17) How frequently do you experience the pain in this/these areas (indicate for most severe area)?	O Constantly O Daily O Weekly O Monthly O Occasionally	
18) Please raise your arm on the operated side/side to be operated 90 degrees to the side. Does this hurt?	O Yes O No	
19) If yes, how much pain does this movement cause?	O 0 O 1 O 2 O 3 O 4 O 5	O 6 O 7 O 8 O 9 O 10
20) Do you ever take painkillers?	O Yes O No	
21) Are you taking painkillers primarily for your pain related to breast cancer/ breast cancer surgery?	O Yes O No	
22) How often do you take painkillers?	O Daily O 2-3 times/week O 1 time/week O 1-3 times/month O < 1 time/month	
23) If so, please indicate the type of painkiller(s):	☐ weak over the counter medications (Ibuprofen, Acetaminophen...) ☐ opioids (Morphine, Oxycodone, Vicodin, Percocet, Tramadol...)	

	☐ special pain medicines (Gabapentin, Lyrica, Flexeril, Klonopin…) ☐ other	
24) If you indicate other painkiller, please list	_____	
25) How effective are painkillers at relieving your pain? (0 is no relief, 10 is complete relief)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5	○ 6 ○ 7 ○ 8 ○ 9 ○ 10
26) At this point in time, have you already had surgery for your breast cancer?	○ Yes ○ No	
27) Have you had pins and needles, "falling asleep", or stabbing sensations in or around the area of your surgery?	○ Yes ○ No	
28) Have you experienced an electric shock like sensation or jabbing feelings in the skin area in or around the area of your surgery?	○ Yes ○ No	
29) Have you experienced heat or burning sensations in or around the area of your surgery?	○ Yes ○ No	
30) Have you had numbness or decreased sensitivity in or around the area of your surgery?	○ Yes ○ No	
31) Have the lightest touches (i.e. from clothes) been a cause of pain in or around the area of your surgery?	○ Yes ○ No	
32) Have cold temperatures been a cause of pain in or around the area of your surgery?	○ Yes ○ No	
33) Have you experienced a painful itch in or around the area of your surgery?	○ Yes ○ No	
34) Gently rub the painful area with your index finger, and then rub a non-painful area of skin further away or on the opposite side from the painful area. How does this rubbing feel in the painful area?	○ The painful area feels no different from the non-painful area ○ I feel discomfort, pins and needles, tingling, or burning in the painful area that is different from the non-painful area	

35) In what part of your body do you feel these sensory disturbances?	☐ breast ☐ armpit ☐ arm ☐ side of chest	
36) In the last month, have you had sensory disturbances in any other part of your body (besides the surgical area)?	O Yes O No	
37) Within the last month, have you experienced swelling, tension, or heaviness in your breast, armpit, arm, or back of your hand in the side you had your surgery?	O Yes O No	
38) If so, where have your experienced the sensation of heaviness, swelling, or tension?	☐ breast ☐ armpit ☐ arm	☐ underarm ☐ back of hand

Below is a list of statements. Please indicate how you have been feeling during the last month.

39) I often say no to taking part in leisure activities because of discomfort due to my treatment.	O never O to some degree O quite a bit O very much
40) My reduced physical ability affects interactions with friends and family.	O never O to some degree O quite a bit O very much
41) My reduced physical ability gets me down.	O never O to some degree O quite a bit O very much
42) My discomfort after the treatment is a burden for my family and friends.	O never O to some degree O quite a bit O very much
43) My discomfort after the treatment makes me nervous.	O never O to some degree O quite a bit O very much
44) My discomfort after the treatment is an unpleasant reminder of my illness.	O never O to some degree O quite a bit O very much

45) My discomfort after the treatment for breast cancer is the reason I don't do the things I want to do.	O never O to some degree O quite a bit O very much
46) I sometimes think that pain could be an indication that I still have breast cancer.	O never O to some degree O quite a bit O very much
47) Discomfort consumes my daily life.	O never O to some degree O quite a bit O very much
48) My discomfort makes me feel like I am a bad partner.	O never O to some degree O quite a bit O very much
49) I have difficulty concentrating.	O never O to some degree O quite a bit O very much
50) I have more difficulty concentrating now than before my treatment for breast cancer.	O never O to some degree O quite a bit O very much
51) I feel that I don't have the energy to solve problems.	O never O to some degree O quite a bit O very much
52) I feel that I quickly get mentally fatigued after treatment.	O never O to some degree O quite a bit O very much
We are interested in whether pain from breast cancer and/or breast cancer surgery affects your daily activities. Think about how the last week has been for you in relation to the activities below:	
53) Doing laundry	O I can do this without a problem O I can do this, but with difficulty because of pain O I cannot do this because of pain O I don't do this because of another reason O Not relevant, I do not do this anyway

54) Reaching a high shelf	O I can do this without a problem O I can do this, but with difficulty because of pain O I cannot do this because of pain O I don't do this because of another reason O Not relevant, I do not do this anyway
55) Carrying grocery bags, luggage or heavy bags	O I can do this without a problem O I can do this, but with difficulty because of pain O I cannot do this because of pain O I don't do this because of another reason O Not relevant, I do not do this anyway
56) Kitchen chores or cooking	O I can do this without a problem O I can do this, but with difficulty because of pain O I cannot do this because of pain O I don't do this because of another reason O Not relevant, I do not do this anyway
57) Vacuuming, washing floors, cleaning house	O I can do this without a problem O I can do this, but with difficulty because of pain O I cannot do this because of pain O I don't do this because of another reason O Not relevant, I do not do this anyway
58) Walk a mile at normal tempo	O I can do this without a problem O I can do this, but with difficulty because of pain O I cannot do this because of pain O I don't do this because of another reason O Not relevant, I do not do this anyway
59) Go on a bike ride	O I can do this without a problem O I can do this, but with difficulty because of pain O I cannot do this because of pain O I don't do this because of another reason O Not relevant, I do not do this anyway
60) Swimming	O I can do this without a problem O I can do this, but with difficulty because of pain O I cannot do this because of pain O I don't do this because of another reason O Not relevant, I do not do this anyway

61) Opening a heavy door	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
62) Driving a car	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
63) Carry or lift children	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
64) Putting on socks	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
65) Washing hair	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
66) Bending down or kneeling	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
67) Taking a sweater/sweatshirt on or off	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway

68) Putting on a brassiere	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
69) Putting on a coat	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
70) Sleeping	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway
71) Getting out of bed	○ I can do this without a problem ○ I can do this, but with difficulty because of pain ○ I cannot do this because of pain ○ I don't do this because of another reason ○ Not relevant, I do not do this anyway

APPENDIX 2

See Fig. 6.

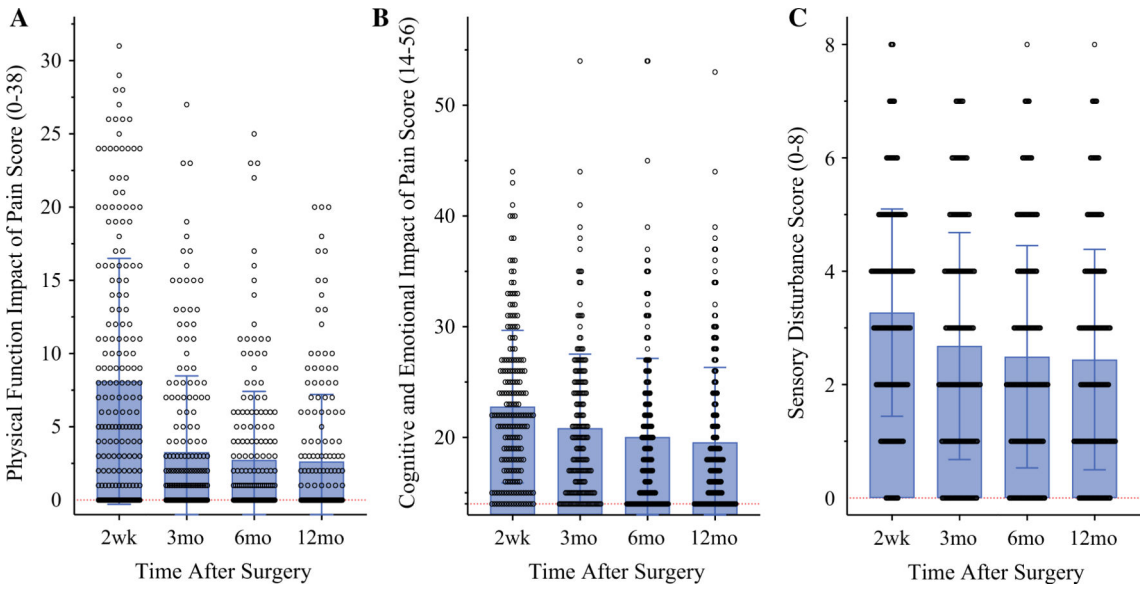

FIG. 6.

Longitudinal functional pain outcomes: functional impact of pain and sensory disturbance in the first year after breast surgery. **a** Extent of surgical area pain impact on patients' daily physical functioning. **b** Extent of surgical area pain impact on patients' cognitive and emotional functioning. **c** Extent of neuropathic-type sensory disturbance in surgical areas

APPENDIX 3

See Table 3.

TABLE 3

Correlation between scores from the Breast Surgery Specific Questionnaire (BCPQ) and General Pain Questionnaire (BPI)

			General Pain Questionnaire							
			Baseline		2 weeks		6 months		1 year	
			BPI Mean	BPI Interference	BPI Mean	BPI Interference	BPI Mean	BPI Interference	BPI Mean	BPI Interference
Breast Surgery Specific Questionnaire	Baseline	Pain Severity Index	0.335*	0.331*	0.402*	0.341*	0.357*	0.243*	0.273*	0.215*
		Cog/ Emot Impact	-	-	-	-	-	-	-	-
		Physical Impact	0.451*	0.419*	0.276*	0.206*	0.355*	0.325*	0.407*	0.388*
	2 weeks	Pain Severity Index	0.189*	0.247*	0.710*	0.623*	0.383*	0.405*	0.365*	0.349*
		Cog/ Emot Impact	0.145	0.233*	0.533*	0.745*	0.299*	0.447*	0.315*	0.407*
		Physical Impact	0.082	0.161	0.599*	0.740*	0.328*	0.435*	0.262*	0.333*
	6 months	Pain Severity Index	0.270*	0.277*	0.491*	0.406*	0.639*	0.567*	0.362*	0.300*
		Cog/ Emot Impact	0.154	0.227*	0.470*	0.586*	0.491*	0.659*	0.326*	0.380*
		Physical Impact	0.302*	0.333*	0.466*	0.511*	0.614*	0.727*	0.394*	0.469*
	1 year	Pain Severity Index	0.232*	0.273*	0.427*	0.355*	0.518*	0.425*	0.602*	0.408*
		Cog/ Emot Impact	0.267*	0.352*	0.449*	0.528*	0.435*	0.582*	0.528*	0.606*
		Physical Impact	0.248*	0.307*	0.376*	0.397*	0.495*	0.561*	0.568*	0.630*

Scores from the breast surgery specific questionnaire (BCPQ) and the general pain questionnaire (BPI) were significantly correlated at each time point they were assessed. Cognitive/Emotional impact was not assessed at baseline.

*Spearman correlation is significant at the 0.01 level (2-tailed)

BCPQ=Breast Cancer Pain Questionnaire; BPI=Brief Pain Inventory; Cog/Emot Impact= Cognitive & Emotional impact

APPENDIX 4

See Table 4.

TABLE 4

Performance of multivariable linear regression models for predicting pain severity and impact outcomes 1 year after mastectomy

	Surgery specific pain outcomes: Breast Cancer Pain Questionnaire (BCPQ)				General pain outcomes: Brief Pain Inventory (BPI)	
	Pain Severity Index	**Cognitive emotional impact**	**Physical impact**	**Sensory disturbance**	**BPI mean**	**BPI impairment**
(0–200, higher is worse)	**(14–56, higher is worse)**	**(0–38, higher is worse)**	**0–8 (higher is worse)**	**(0–10, higher is worse)**	**(0–100, higher is worse)**	
RMSE						
Apparent	16.69	4.85	3.75	1.65	1.30	14.87
Optimism-corrected	18.35	5.20	4.01	1.75	1.44	16.42
%RMSE (error as % of reported scores range)	17.64	13.34	20.06	21.91	22.16	19.78
Calibration						
Intercept	−0.47	−4.08	−0.48	−0.57	−0.16	−0.71
Slope	1.04	1.21	1.14	1.22	1.11	1.05

RMSE is a measure of the average magnitude of the difference between observed vs. predicted scores. Apparent RMSE reflects predictive performance on the model development sample, while optimism-corrected RMSE (estimated via bootstrapping) is adjusted to better estimate performance on future samples. The shrinkage factor, a measure of model calibration, was estimated as the average slope of the regression line between the observed scores for the original development sample vs. their predicted scores using models built on each bootstrap sample

RMSE root mean square error

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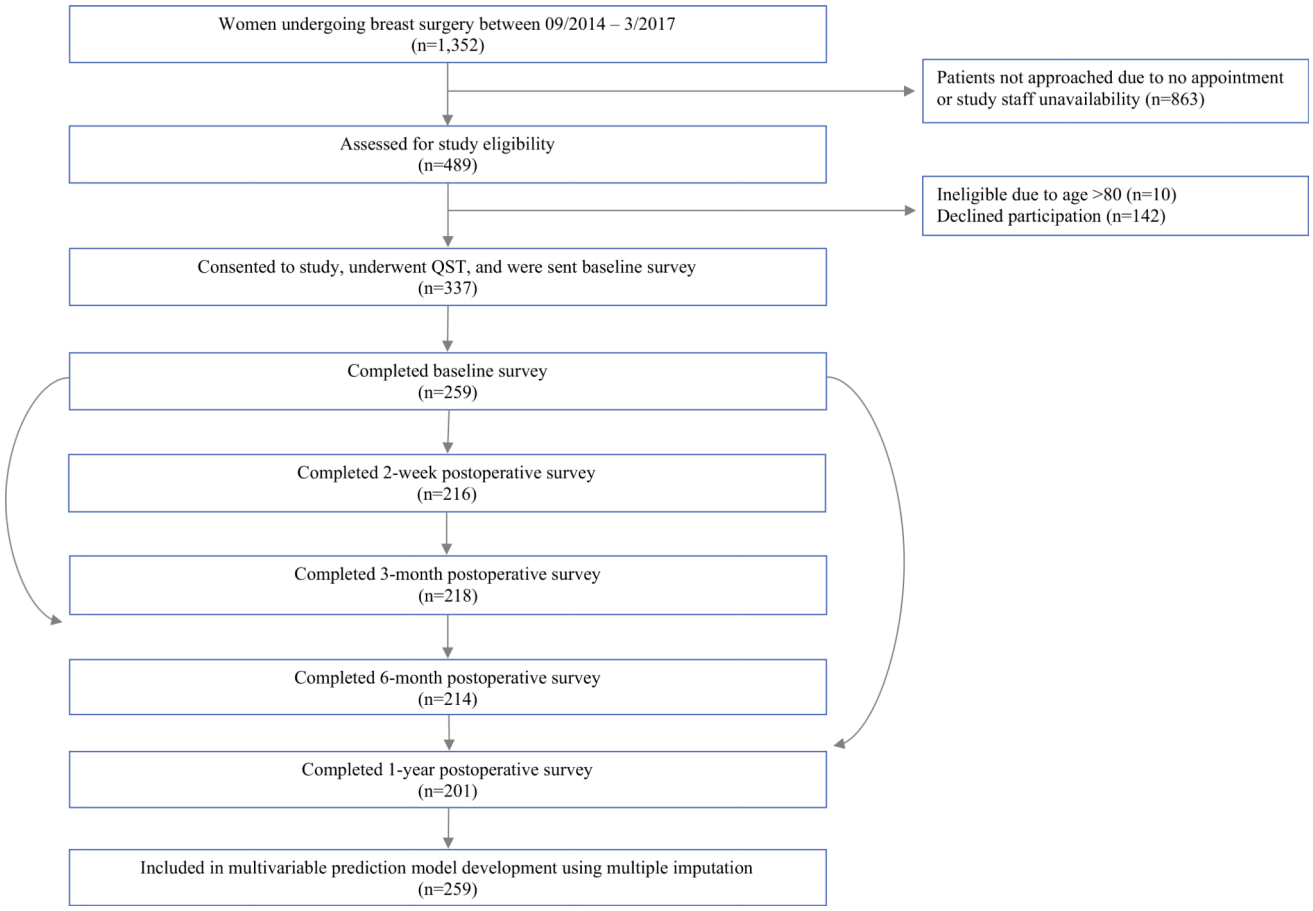

FIG. 1.

Study flow/consort diagram. Patients scheduled for breast surgery were approached at the anesthesia preoperative clinic and completed baseline and follow-up testing as indicated. The *n* listed is for the Pain Severity Index; *n* for completion of other pain outcomes. Physical Impact of Pain, Cognitive & Emotional Impact of Pain, Sensory Disturbance, Brief Pain Inventory (BPI) severity, and BPI interference ranged between 181 and 200, as indicated in Table 1. Subjects initially completing the baseline questionnaires who subsequently dropped out of the study did not differ from those not completing the 12-month questionnaires in terms of basic demographics or baseline psychosocial, psychophysical, or pain characteristics

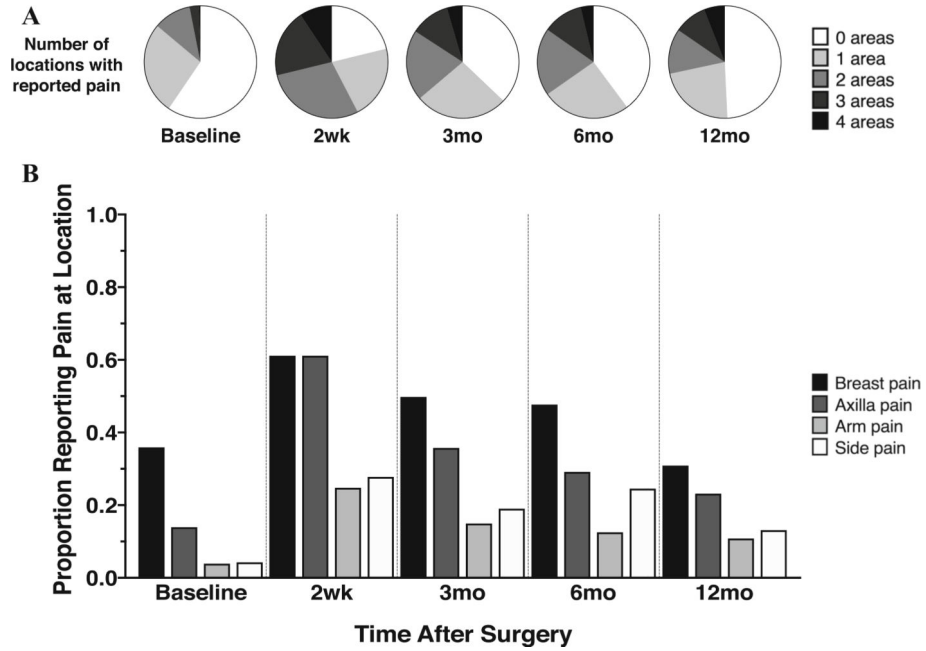

FIG. 2.

Longitudinal location and frequency of pain after breast surgery. Patients completed the Breast Cancer Pain Questionnaire at baseline and several times postoperatively. **a** Patient indication of pain in any of the four surgically related areas assessed. Pie charts show the number of surgically related body locations with some pain at each time point. **b** Proportion of patients reporting pain in each of the four specified surgically related areas across time

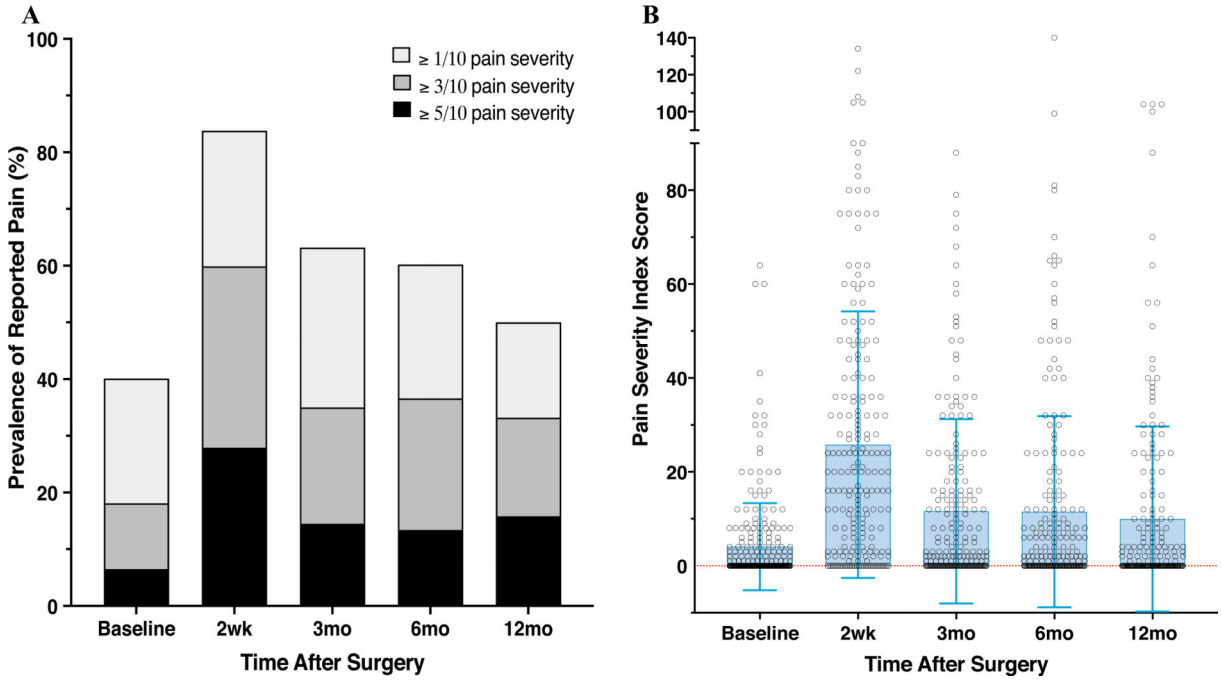

FIG. 3.

Pain Prevalence and Pain Severity Index. Patients completed the Breast Cancer Pain Questionnaire and indicated the severity and frequency of pain in surgically related body areas. **a** Patient rating of pain severity on a scale of 0–10. Nested bar graphs depict the prevalence of subjects reporting pain with various cutoffs (≥ 1, ≥ 3, ≥ 5/10) defining a clinically meaningful severity of pain. The highest rates and largest number of areas were reported at 2 weeks, and prevalence remained relatively consistent for 3 months and longer. **b** Distribution of subjects' scores on the Pain Severity Index (PSI), which estimates the extent of surgical pain using severity, frequency, and area according to the following formula: PSI = Σ pain score at each site (0–10) × frequency (0–5). The frequency was scored as follows: 5 (constantly), 4 (daily), 3 (occasionally), 2 (weekly), 1 (monthly), and 0 (never), with a possible range of 0–200

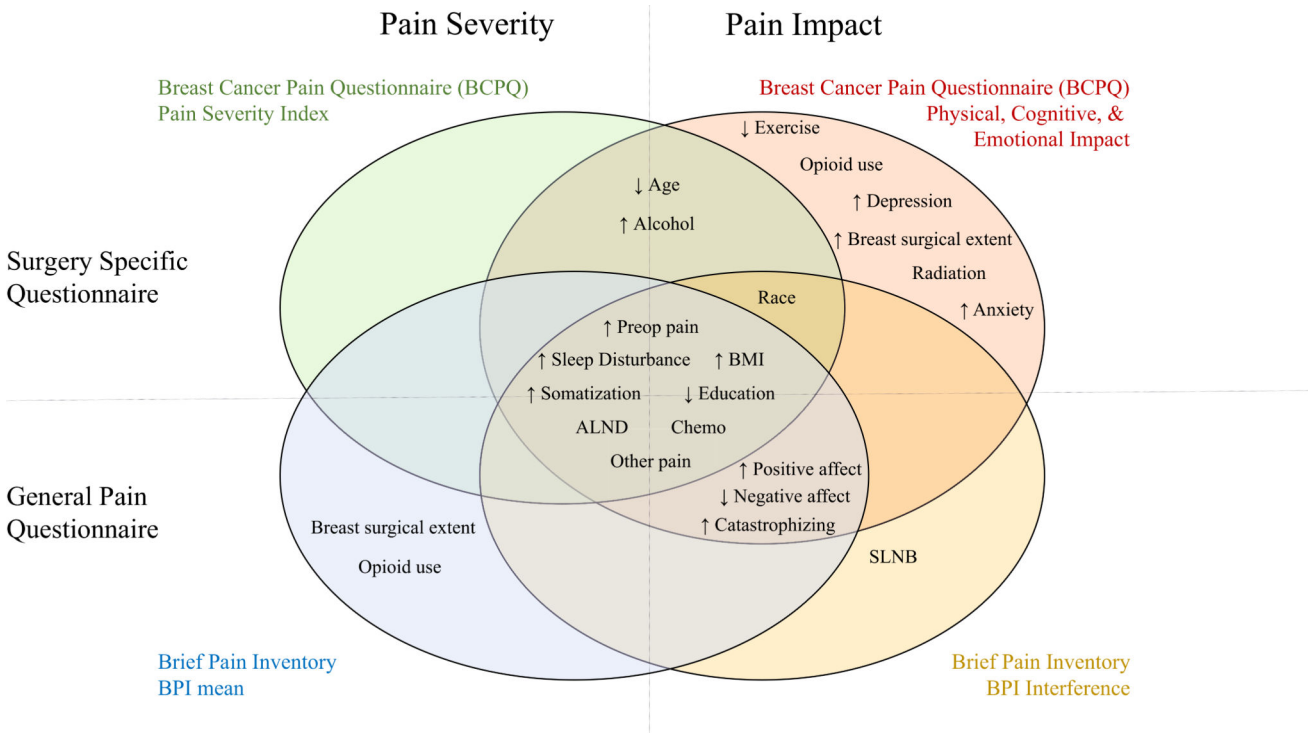

FIG. 4.

Univariate association of preoperative factors with pain outcomes. Factors significantly associated with at least one of the four main pain outcome types are shown, with factors associated with multiple outcomes falling within the overlapping areas. The top circles show the breast surgery-specific questionnaire (Breast Cancer Pain Questionnaire [BCPQ]) outcomes, and the bottom circles show the general pain questionnaire (BPI) outcomes. The circles on the left show the pain severity outcomes, and the circles on the right show the pain impact measures. ↑, higher value associated with higher pain; ↓, lower value associated with higher pain; ALND, axillary lymph node dissection; BMI, body mass index; SLNB, sentinel lymph node biopsy

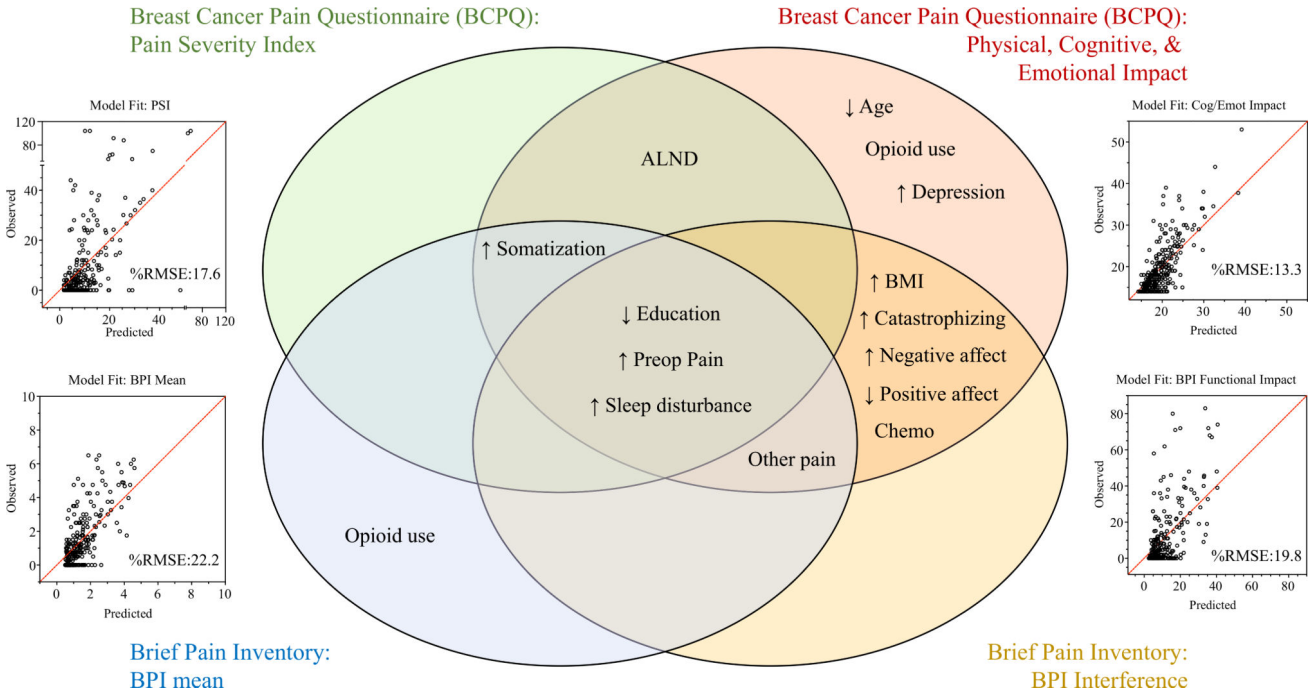

FIG. 5.

Predictors of persistent post-mastectomy pain (PPMP) at 12 months selected by least absolute shrinkage and selection operator (LASSO). Significant independent predictors of pain outcomes retained after multivariable regression with LASSO are shown. Surgery-specific questionnaire outcomes (*top*), general pain questionnaire outcomes (*bottom*), severity-related outcomes (*left*), and impact-related outcomes (*right*) are depicted, with factors most consistently associated across outcomes found in the intersection of circles. The diagonal line indicates perfect prediction. The average difference between the predicted and observed values for the subjects (%RMSE) was calculated, with lower values indicating better prediction. The model fit comparing predicted and observed values (scatterplots) is shown for each outcome, with the average percentage difference between predicted and observed values reported (%RMSE = RMSE/observed range of scores *100). The %RMSE was calculated by dividing the RMSE by the actual score range observed for the outcome. ↑, higher value associated with higher pain; ↓, lower value associated with higher pain; ALND, axillary lymph node dissection; BMI, body mass index; %RMSE, %Root mean squared error

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TABLE 1

Patient characteristics and univariate association with pain outcomes 12 months after surgery

	Baseline Values		Univariate Association with Pain Outcomes at 12 months after surgery											
			Surgery Specific Pain Outcomes: Breast Cancer Pain Questionnaire (BCPQ)								General Pain Outcomes: Brief Pain Inventory (BPI)			
			Pain Severity Index		Cognitive & Emotional Impact of Pain		Physical Impact of Pain		Sensory Disturbance		BPI Mean		BPI Impairment	
			n=201 (0–200, higher is worse)		n=186 (14–56, higher is worse)		n=183 (0–38, higher is worse)		n=181 (0–8, higher is worse)		n=200 (0–10, higher is worse)		n=183 (0–100, higher is worse)	
Variable	n	mean ± SD, median (Q1, Q3), n (%)	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (99% CI)	P value	β (99% CI)	P value
Demographics														
Age, mean ± SD	259	55.5 (12.4)	−1.03 (−2.15, 0.09)	0.071	−0.77 (−1.17, −0.38)	< 0.001	−0.33 (−0.58, −0.07)	0.012	−0.27 (−0.38, −0.17)	< 0.001	−0.02 (−0.12, 0.07)	0.626	−0.31 (−1.3, 0.68)	0.541
Body Mass Index (BMI), mean ± SD	259	27.4 (6.2)	0.37 (−0.05, 0.79)	0.085	0.19 (0.03, 0.35)	0.023	0.1 (−0.01, 021)	0.065	0.04 (−0.01, 0.08)	0.097	0.06 (0.02, 0.1)	0.005	0.71 (0.19, 1.23)	0.007
Education College graduate n (%)	257	196 (76.3)	−6.81 (−14.41, 0.79)	0.079	−1.84 (−4.16, 0.48)	0.121	−2.96 (−4.82, −1.1)	0.002	−0.47 (−1.17, 0.23)	0.187	−1.08 (−1.69, −0.46)	0.001	−8.83 (−15.85, −1.8)	0.014
Race/ethnicity *, n (%)	258													
Caucasian		223 (86.4)	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
African American		7 (2.7)	29.78 (−4.43, 63.98)	0.088	6.24 (0.07, 12.4)	0.047	7.33 (1.55, 13.11)	0.013	1.13 (−0.57, 2.82)	0.192	1.56 (−0.45, 3.58)	0.129	34.69 (9.16, 60.22)	0.008
Hispanic/ Latina		5 (1.9)	−5.25 (−12.52, 2.01)	0.156	−1.71 (−7.84, 4.42)	0.585	−0.04 (−4.03, 3.94)	0.982	1.18 (−1.13, 3.49)	0.316	−0.62 (−1.5, 0.26)	0.169	−4.82 (−15.6, 5.97)	0.379
Asian		11 (4.3)	−1.07 (−14.98, 12.83)	0.88	3.5 (−1.16, 8.15)	0.141	0.56 (−2.72, 3.84)	0.736	−0.53 (−2.09, 1.04)	0.506	−0.35 (−1.47, 0.77)	0.544	−2.64 (−14.54, 9.26)	0.663
Mixed race		8 (3.1)	−3.45 (−14.08, 7.19)	0.524	3.26 (−2.6, 9.12)	0.275	2 (−1.94, 5.94)	0.319	1.06 (−0.55, 2.68)	0.196	−0.63 (−1.38, 0.13)	0.104	−5.33 (−11.17, 0.51)	0.074

Variable	Baseline Values		Univariate Association with Pain Outcomes at 12 months after surgery											
			Surgery Specific Pain Outcomes: Breast Cancer Pain Questionnaire (BCPQ)								General Pain Outcomes: Brief Pain Inventory (BPI)			
			Pain Severity Index		Cognitive & Emotional Impact of Pain		Physical Impact of Pain		Sensory Disturbance		BPI Mean		BPI Impairment	
	n	mean ± SD, median (Q1, Q3), n (%)	n=201 (0–200, higher is worse)		n=186 (14–56, higher is worse)		n=183 (0–38, higher is worse)		n=181 (0–8, higher is worse)		n=200 (0–10, higher is worse)		n=183 (0–100, higher is worse)	
			β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (99% CI)	P value	β (99% CI)	P value
Other		4 (1.6)	1.47 (−20.66, 23.6)	0.896	−0.99 (−8.05, 6.07)	0.782	2.36 (−3.92, 8.63)	0.462	−0.34 (−2.65, 1.98)	0.775	0.85 (−1.59, 3.29)	0.493	5.35 (−16.8, 27.5)	0.635
Lifestyle														
Alcoholic beverages per week, n (%)	259													
None		97 (37.5)	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
1–4		105 (40.5)	−7.25 (−13.53, −0.96)	0.024	−0.73 (−2.79, 1.32)	0.483	−1.35 (−2.83, 0.13)	0.075	−0.61 (−1.2, −0.01)	0.047	−0.15 (−0.66, 0.36)	0.554	−1.04 (−6.45, 4.37)	0.706
5–10		48 (18.5)	−4.59 (−12.39, 3.2)	0.248	−1.36 (−3.82, 1.1)	0.277	−1.39 (−3.14, 0.36)	0.118	−0.68 (−1.45, 0.09)	0.082	−0.08 (−0.72, 0.56)	0.808	−1.6 (−8.34, 5.14)	0.642
10–20		9 (3.5)	−6.46 (−17.11, 4.2)	0.235	−2.16 (−7.12, 2.8)	0.393	−1.47 (−4.84, 1.89)	0.389	−0.73 (−2.17, 0.7)	0.316	0.73 (−0.56, 2.02)	0.266	8.31 (−5.54, 22.16)	0.239
Weekly exercise amount, median (Q1, Q3); Self-reported, each instance >15 min, 1 point mild, 2 points moderate, 3 points heavy exercise	259	12.0 (6.0, 19.5)	0.1 (−0.16, 0.37)	0.44	−0.1 (−0.18, −0.01)	0.031	−0.01 (−0.07, 0.06)	0.83	−0.01 (−0.03, 0.02)	0.499	0 (−0.02, 0.02)	0.817	−0.17 (−0.43, 0.09)	0.207
Surgical Variables														
Previous breast surgery, n (%)	259	66 (25.5)	2.21 (−4.58, 8.99)	0.524	0.5 (−1.56, 2.56)	0.632	0.35 (−1.09, 1.79)	0.634	−0.3 (−0.89, 0.29)	0.317	0.18 (−0.39, 0.75)	0.531	−0.34 (−5.9, 5.23)	0.906
Bilateral surgery, n (%)	257	53 (20.6)	−1.78 (−8.18, 4.63)	0.586	0.47 (−1.75, 2.69)	0.676	0.14 (−1.39, 1.66)	0.861	0.23 (−0.42, 0.88)	0.492	0.12 (−0.42, 0.66)	0.657	1.64 (−4.38, 7.67)	0.592

Variable	Baseline Values n	Baseline Values mean ± SD, median (Q1, Q3), n (%)	Univariate Association with Pain Outcomes at 12 months after surgery: Surgery Specific Pain Outcomes: Breast Cancer Pain Questionnaire (BCPQ) — Pain Severity Index n=201 (0–200, higher is worse) β (95% CI)	P value	Cognitive & Emotional Impact of Pain n=186 (14–56, higher is worse) β (95% CI)	P value	Physical Impact of Pain n=183 (0–38, higher is worse) β (95% CI)	P value	Sensory Disturbance n=181 (0–8, higher is worse) β (95% CI)	P value	General Pain Outcomes: Brief Pain Inventory (BPI) — BPI Mean n=200 (0–10, higher is worse) β (99% CI)	P value	BPI Impairment n=183 (0–100, higher is worse) β (99% CI)	P value
Surgery/ reconstruction type, n (%)	259													
Breast conserving surgery (Lumpectomy)		136 (52.5)	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Mastectomy		34 (13.1)	4.43 (−4.09, 12.94)	0.308	2.06 (−0.68, 4.81)	0.14	2.41 (0.27, 4.56)	0.028	1.12 (0.24, 2)	0.013	0.9 (0.18, 1.62)	0.015	5.32 (−2.47, 13.12)	0.181
Mastectomy with reconstruction - tissue expander		68 (26.3)	0.73 (−5.34, 6.8)	0.814	0.48 (−1.61, 2.57)	0.656	0.91 (−0.48, 2.3)	0.198	0.37 (−0.25, 0.98)	0.24	0.21 (−0.33, 0.75)	0.447	2.17 (−3.51, 7.84)	0.454
Mastectomy with reconstruction - autologous		21 (8.1)	−0.72 (−10.49, 9.05)	0.885	3.54 (0.19, 6.9)	0.039	2.22 (−0.65, 5.09)	0.13	1.17 (0.18, 2.17)	0.021	0.23 (−0.62, 1.08)	0.594	3.19 (−5.86, 12.24)	0.489
Node surgery type, n (%)	259													
No auxillary surgery		52 (20.1)	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---	Reference	---
Sentinel lymph node procedure		165 (63.7)	1.28 (−4.48, 7.05)	0.663	0.29 (−1.75, 2.34)	0.78	0.79 (−0.59, 2.17)	0.261	0.37 (−0.24, 0.99)	0.235	0.29 (−0.27, 0.84)	0.311	5.25 (0.46, 10.05)	0.032
Axillary lymph node dissection		42 (16.2)	15.17 (5.2, 25.13)	0.003	6.33 (2.96, 9.71)	< 0.001	4.03 (1.78, 6.29)	< 0.001	1.78 (0.95, 2.61)	< 0.001	0.7 (−0.05, 1.44)	0.066	8.45 (1.04, 15.85)	0.025
Medical Treatment within first year after surgery														
Radiation therapy, n(%)	256	146 (57.3)	3.28 (−2, 8.55)	0.223	1.57 (−0.2, 3.34)	0.082	0.74 (−0.49, 1.98)	0.236	0.25 (−0.27, 0.78)	0.344	−0.09 (−0.55, 0.37)	0.711	−0.22 (−5.03, 4.59)	0.928
Chemotherapy, n (%)	256	92 (35.9)	5.45 (0.1, 10.8)	0.046	3.89 (2, 5.78)	< 0.001	2.61 (1.21, 4.01)	< 0.001	1.11 (0.59, 1.63)	< 0.001	0.38 (−0.07, 0.83)	0.1	4.82 (−0.61, 10.25)	0.082

Variable	Baseline Values		Univariate Association with Pain Outcomes at 12 months after surgery											
			Surgery Specific Pain Outcomes: Breast Cancer Pain Questionnaire (BCPQ)								General Pain Outcomes: Brief Pain Inventory (BPI)			
			Pain Severity Index		Cognitive & Emotional Impact of Pain		Physical Impact of Pain		Sensory Disturbance		BPI Mean		BPI Impairment	
	n	mean ± SD, median (Q1, Q3), n (%)	n=201 (0–200, higher is worse)		n=186 (14–56, higher is worse)		n=183 (0–38, higher is worse)		n=181 (0–8, higher is worse)		n=200 (0–10, higher is worse)		n=183 (0–100, higher is worse)	
			β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (99% CI)	P value	β (99% CI)	P value
Hormone therapy, n (%)	255	126 (49.6)	4.01 (−1.16, 9.18)	0.129	−0.08 (−1.93, 1.77)	0.931	−0.21 (−1.46, 1.04)	0.738	0.44 (−0.09, 0.97)	0.102	−0.05 (−0.49, 0.39)	0.821	1.18 (−3.71, 6.06)	0.637
Baseline pain (Breast Cancer Pain questionnaire, BCPQ)														
Pain Severity Index (PSI) (severity × frequency in 4 surgical areas, median) (Q1, Q3)	258	0.0 (0.0, 4.0)	0.95 (0.44, 1.45)	< 0.001	0.34 (0.21, 0.47)	< 0.001	0.18 (0.08, 0.28)	< 0.001	0.07 (0.04, 0.1)	< 0.001	0.62 (0.48, 0.75)	<0.001	5.67 (3.64, 7.7)	<0.001
Highest Severity in surgical area median (Q1, Q3)	259	0.0 (0.0, 2.0)	3.77 (1.57, 5.97)	0.001	1.35 (0.71, 1.99)	< 0.001	0.81 (0.41, 1.22)	< 0.001	0.35 (0.21, 0.49)	< 0.001				
Physical Impact, median (Q1, Q3)	226	0.0 (0.0, 0.0)	3.06 (1.38, 4.74)	< 0.001	0.68 (0.2, 1.17)	0.006	0.74 (0.41, 1.07)	< 0.001	0.21 (0.09, 0.32)	< 0.001	0.05 (0.03, 0.06)	<0.001	0.51 (0.33, 0.7)	<0.001
Severity of chronic pain in other area(s), median (Q1, Q3)	228	0.0 (0.0, 3.0)	1.37 (0.06, 2.67)	0.04	0.6 (0.15, 1.05)	0.009	0.44 (0.13, 0.76)	0.006	0.09 (−0.01, 0.19)	0.087	0.33 (0.23, 0.43)	<0.001	3.39 (2.13, 4.65)	<0.001
Opioid use, n (%)	255	13 (5.1)	8.22 (−5.15, 21.59)	0.227	3.7 (−0.53, 7.93)	0.087	3.74 (0.74, 6.73)	0.015	0.1 (−1.19, 1.38)	0.884	1.87 (0.74, 3)	0.001	10.48 (−2.61, 23.57)	0.116
Psychosocial Variables														
Pain Catastrophizing Scale (PCS total), median (Q1, Q3)	246	4.0 (1.0, 9.0)	0.29 (−0.2, 0.78)	0.24	0.31 (0.14, 0.48)	< 0.001	0.12 (0, 0.24)	0.059	0.05 (0.01, 0.09)	0.008	0.06 (0.02, 0.09)	0.002	0.76 (0.34, 1.18)	<0.001
Anxiety (PROMIS SF), median (Q1, Q3)	256	17.0 (13.0, 20.0)	0.35 (−0.25, 0.94)	0.254	0.45 (0.26, 0.64)	< 0.001	0.09 (−0.02, 0.2)	0.126	0.06 (0, 0.11)	0.034	0.02 (−0.02, 0.06)	0.324	0.42 (−0.13, 0.98)	0.133

Variable	Baseline Values		Univariate Association with Pain Outcomes at 12 months after surgery											
			Surgery Specific Pain Outcomes: Breast Cancer Pain Questionnaire (BCPQ)								General Pain Outcomes: Brief Pain Inventory (BPI)			
			Pain Severity Index		Cognitive & Emotional Impact of Pain		Physical Impact of Pain		Sensory Disturbance		BPI Mean		BPI Impairment	
	n	mean ± SD, median (Q1, Q3), n (%)	n=201 (0–200, higher is worse)		n=186 (14–56, higher is worse)		n=183 (0–38, higher is worse)		n=181 (0–8, higher is worse)		n=200 (0–10, higher is worse)		n=183 (0–100, higher is worse)	
			β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (99% CI)	P value	β (99% CI)	P value
Depression (PROMIS SF), median (Q1, Q3)	259	11.0 (9.0, 14.0)	0.47 (−0.19, 1.13)	0.163	0.61 (0.4, 0.81)	< 0.001	0.14 (0, 0.28)	0.057	0.08 (0.02, 0.14)	0.006	0.04 (−0.02, 0.09)	0.18	0.52 (−0.11, 1.15)	0.103
Sleep Disturbance (PROMIS SF), median (Q1, Q3)	250	21.0 (16.0, 26.0)	0.85 (0.4, 1.31)	< 0.001	0.33 (0.19, 0.47)	< 0.001	0.18 (0.09, 0.28)	< 0.001	0.06 (0.03, 0.1)	0.001	0.06 (0.03, 0.09)	<0.001	0.61 (0.24, 0.99)	0.001
Negative Affect (PANAS), median (Q1, Q3)	246	17.0 (13.0, 20.0)	0.33 (−0.12, 0.79)	0.15	0.46 (0.28, 0.64)	< 0.001	0.13 (0.01, 0.26)	0.035	0.07 (0.02, 0.11)	0.009	0.04 (0, 0.07)	0.065	0.61 (0.11, 1.12)	0.018
Positive Affect (PANAS), median (Q1, Q3)	246	35.0 (30.0, 39.0)	−0.14 (−0.49, 0.2)	0.409	−0.28 (−0.4, −0.16)	< 0.001	−0.1 (−0.19, −0.01)	0.025	−0.05 (−0.09, −0.02)	0.004	−0.02 (−0.05, 0.01)	0.209	−0.21 (−0.55, 0.12)	0.207
Somatization (BSI), median (Q1, Q3)	248	7.0 (6.0, 8.0)	2.84 (1.07, 4.61)	0.002	1.11 (0.62, 1.6)	< 0.001	0.73 (0.39, 1.07)	< 0.001	0.23 (0.1, 0.35)	< 0.001	0.33 (0.23, 0.44)	<0.001	2.73 (1.22, 4.23)	<0.001
Coping Strategies Questionnaire subscales, median (Q1, Q3)														
Behavioral	250	5.0 (3.0, 7.0)	−0.07 (−0.88, 0.75)	0.871	−0.09 (−0.36, 0.18)	0.496	0.03 (−0.16, 0.22)	0.776	−0.03 (−0.11, 0.05)	0.472	−0.03 (−0.1, 0.04)	0.433	−0.31 (−1.1, 0.47)	0.434
Catastrophizing	249	0.0 (0.0, 2.0)	1.25 (−0.33, 2.83)	0.12	0.43 (−0.05, 0.91)	0.077	0.33 (−0.02, 0.068)	0.063	0.06 (−0.08, 0.21)	0.401	0.15 (0.02, 0.28)	0.027	2.11 (0.57, 3.64)	0.007
Diverting	251	4.0 (1.0, 6.0)	0.17 (−0.71, 1.05)	0.703	−0.08 (−0.37, 022)	0.612	0.02 (−0.19, 0.24)	0.819	−0.02 (−0.1, 0.07)	0.734	−0.02 (−0.1, 0.06)	0.601	−0.08 (−0.91,0.74)	0.843
Ignoring	249	5.0 (2.0, 6.0)	0.68 (−0.25, 1.6)	0.151	−0.22 (−0.52, 0.08)	0.158	0.01 (−0.21, 0.23)	0.917	−0.02 (−0.11, 0.07)	0.664	0.02 (−0.06, 0.1)	0.63	0.08 (−0.79, 0.94)	0.864

Variable	Baseline Values		Univariate Association with Pain Outcomes at 12 months after surgery											
			Surgery Specific Pain Outcomes: Breast Cancer Pain Questionnaire (BCPQ)								General Pain Outcomes: Brief Pain Inventory (BPI)			
			Pain Severity Index		Cognitive & Emotional Impact of Pain		Physical Impact of Pain		Sensory Disturbance		BPI Mean		BPI Impairment	
	n	mean ± SD, median (Q1, Q3), n (%)	n=201 (0–200, higher is worse)		n=186 (14–56, higher is worse)		n=183 (0–38, higher is worse)		n=181 (0–8, higher is worse)		n=200 (0–10, higher is worse)		n=183 (0–100, higher is worse)	
			β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (99% CI)	P value	β (99% CI)	P value
Praying	249	3.0 (0.0, 5.0)	0.11 (−0.85, 1.06)	0.826	0 (−0.33, 0.34)	0.978	0.09 (−0.13, 0.32)	0.427	0.03 (−0.07, 0.12)	0.612	−0.05 (−0.13, 0.03)	0.258	−0.16 (−1.01, 0.69)	0.711
Reinterpreting	251	1.0 (0.0, 3.0)	−0.31 (−1.29, 0.66)	0.526	−0.09 (−0.43, 0.24)	0.595	0.02 (−0.21, 0.26)	0.838	−0.02 (−0.12, 0.08)	0.705	−0.08 (−0.16, 0.01)	0.083	−0.17 (−1.08, 0.75)	0.719
Self Statements	251	5.0 (3.0, 8.0)	0.39 (−0.48, 1.27)	0.38	−0.08 (−0.36, 0.2)	0.569	0 (−0.2, 0.2)	0.975	−0.03 (−0.11, 0.06)	0.549	0 (−0.07, 0.07)	0.992	−0.1 (−0.89, 0.68)	0.798
Psychophysical Variables (Quantitative Sensor Testing, QST)														
Territorial Summation of Pain, median (Q1, Q3)	257	1.9 (1.0, 3.8)	0.13 (−1.34, 1.6)	0.861	0.27 (−0.2, 0.73)	0.256	0.08 (−0.26, 0.41)	0.643	0.13 (−0.01, 0.27)	0.065	0.06 (−0.06, 0.18)	0.343	0.36 (−1.01, 1.74)	0.607
Painful After-Sensations, median (Q1, Q3)	256	0.0 (0.0, 0.2)	0.81 (−6.28, 7.89)	0.823	−0.77 (−2.87, 1.34)	0.475	0.03 (−1.5, 1.56)	0.971	0.35 (−0.3, 1)	0.288	−0.28 (−0.83, 0.27)	0.318	−1.39 (−7.45, 4.67)	0.653
Pressure pain threshold-forearm, median (Q1, Q3)	257	4.8 (3.7, 6.2)	−0.03 (−0.18, 0.12)	0.714	−0.02 (−0.07, 0.03)	0.385	−0.01 (−0.04, 0.03)	0.678	−0.01 (−0.02, 0.01)	0266	0 (−0.01,0.01)	0.768	−0.03 (−0.17, 0.11)	0.695
Pressure pain threshold-trapezius, median (Q1, Q3)	254	7.2 (5.0, 9.6)	0.09 (−0.81, 1)	0.837	−0.12 (−0.4, 0.16)	0.392	0.03 (−0.16, 0.22)	0.759	0 (−0.08, 0.09)	0.983	0.02 (−0.05, 0.09)	0.573	0.04 (−0.72, 0.8)	0.915
Pressure pain tolerance-forearm median (Q1, Q3)	257	7.4 (5.4, 9.4)	−0.01 (−0.98, 0.97)	0.991	−0.04 (−0.34, 0.25)	0.774	0.04 (−0.17, 0.25)	0.736	0.03 (−0.06, 0.12)	0.539	0 (−0.08, 0.08)	0.955	0.14 (−0.68, 0.97)	0.738
Pressure pain tolerance-trapezius, median (Q1, Q3)	254	10.4 (7.3, 13.7)	−0.32 (−1.03, 0.4)	0.383	−0.13 (−0.37, 0.1)	0.268	−0.06 (−0.23, 0.1)	0.449	−0.02 (−0.09, 0.05)	0.513	0 (−0.06, 0.06)	0.999	−0.03 (−0.69, 0.62)	0.924

Beta coefficients, 95% confidence intervals, and p values were estimated using simple linear regression models of pain outcomes 12 months after surgery with multiple imputation to account for missing data

Darker colored cells indicate significance of univariate association at the 0.05 level, and lighter cells the 0.1 level; each outcome has an associated color which corresponds to colors in Fig. 4

PROMIS SF Patient-Reported Outcomes Measurement Information System Short Form, *PANAS* Positive And Negative Affect Schedule, *BSI* Brief Symptom Inventory

*Considered in univariate but not included in LASSO

TABLE 2

Multivariate prediction of pain outcomes using LASSO

	Multivariate Association with Pain Outcomes at 1 year					
	Surgery Specific Pain Outcomes: Breast Cancer Pain Questionnaire (BCPQ)			General Pain Outcomes: Brief Pain Inventory (BPI)		
	PSI (Pain Severity Index)	Cognitive Emotional Impact	Physical Impact	Sensory Disturbance	BPI Mean	BPI Impairment
	(0–200, higher is worse)	(14–56, higher is worse)	(0–38, higher is worse)	0–8 (higher is worse)	(0–10, higher is worse)	(0–100, higher is worse)
Variable	**β**	**β**	**β**	**β**	**β**	**β**
Intercept	−1.0678	11.6409	0.8335	3.3270	0.3037	0.1875
Age (per 5 years)		−0.0696		−0.1202		
BMI		0.0553				0.1233
College graduate	−0.5023		−1.4263		−0.4801	−1.2681
Alcohol (per increase in category)				−0.0045		
Total exercise						
Bilateral surgery						
SLNB vs. all other categories						
ALND vs. all other categories	5.0196	2.5070	1.0675	0.4625		
Mastectomy vs. all other categories						
Mastectomy with reconstruction - tissue expanders vs. all other categories						
Mastectomy with reconstruction - autologous vs. all other categories						
Previous breast surgery						
Radiation therapy						
Chemotherapy		1.3924	1.2587	0.3464		0.2378
Hormone therapy						
Opioid use			1.2349		0.4485	
Severity of other chronic pain		0.2369	0.0859		0.1090	1.2203
BSI - Total	0.1220	0.0616	0.0715	0.0004	0.0953	
Coping - Behavioral						

	Multivariate Association with Pain Outcomes at 1 year					
	Surgery Specific Pain Outcomes: Breast Cancer Pain Questionnaire (BCPQ)			General Pain Outcomes: Brief Pain Inventory (BPI)		
	PSI (Pain Severity Index)	Cognitive Emotional Impact	Physical Impact	Sensory Disturbance	BPI Mean	BPI Impairment
	(0–200, higher is worse)	(14–56, higher is worse)	(0–38, higher is worse)	0–8 (higher is worse)	(0–10, higher is worse)	(0–100, higher is worse)
Variable	**β**	**β**	**β**	**β**	**β**	**β**
Coping - Catastrophizing						0.1096
Coping - Diverting						
Coping - Ignoring						
Coping - Praying						
Coping - Reinterpreting						
Coping - Self Statements						
PANAS - Negative		0.0738				0.0178
PANAS - Positive		−0.0331		−0.0086		
PCS - Total		0.0334				0.0830
PROMIS - Anxiety						
PROMIS - Depression		0.2627				
PROMIS - Sleep Disturbance	0.3072	0.0510	0.0494	0.0057	0.0111	0.0944
QST - Painful After-Sensations						
QST - Temporal Summation of Pain				0.0682		
QST - Pressure pain tolerance - forearm						
QST - Pressure pain threshold - forearm						
QST - Pressure pain tolerance - trapezius						
QST - Pressure pain threshold - trapezius						
Preop Pain numerical severity in surgical area (BCPQ - Severity or BPI mean)			0.0960	0.0934	0.2718	1.1109
Preop severity index in surgical area (BCPQ - PSI)	0.5094	0.2052	0.0574	0.0122		
Pain functional impact (BCPQ - Physical Impact or BPI - Impairment)	1.2665		0.2870	0.0796	0.0033	0.2340

Beta coefficients for models to predict pain outcomes one year after surgery were estimated as averages over 40 imputed datasets using MI-LASSO, a group LASSO method that attempts to avoid model overfitting while accounting for missing data. Where no coefficient is shown, the LASSO shrank the coefficient to zero because the corresponding variable did not contribute substantively to the model.

LASSO= Least Absolute Shrinkage and Selection Operator; BMI=Body Mass Index; SLND= Sentinel Lymph Node Procedure; ALND=Axillary Lymph Node Dissection; BSI=Brief Symptom Inventory (somatization); PCS=Pain Catastrophizing Scale; QST=Quantitative Sensory Testing; BCPQ=Breast Cancer Pain Questionnaire; BPI=Brief Pain Inventory; PSI=Pain Severity Index