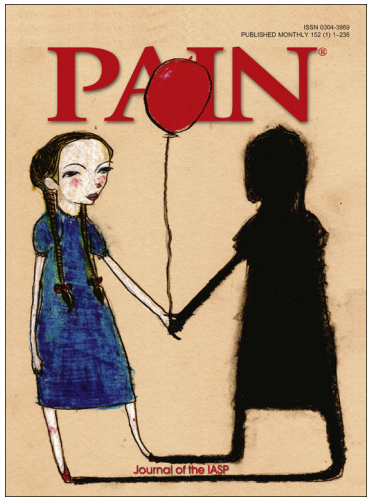


# Psychological, surgical and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study

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**TITLE PAGE**

**(i) Title**

Psychological, surgical and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study

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## INTRODUCTION

Improvements in breast cancer survival resulting from earlier diagnosis and advances in therapy have refocused efforts towards reducing the long-term sequelae of cancer treatment. Persistent or chronic post-surgical pain (CPSP) is a well-recognised adverse event, with prevalence studies suggesting up to half of women report pain persisting for 1 to 2 years after breast cancer surgery [1; 20]. We previously reported on the long-term prognosis and impact of persistent pain after mastectomy, whereby half of women reporting chronic pain at 3 years postoperatively continued to experience painful symptoms up to 12 years postoperatively, with associated reduced quality of life compared to those whose chronic pain had resolved [30; 50].

Recent research has focused attention upon the identification of subgroups at greatest risk of adverse painful outcomes, with calls made for prospective surgical studies incorporating detailed assessment of multiple factors at repeated time points [24; 28; 54]. Epidemiological studies with larger sample sizes are required to elucidate the relative contribution of psychosocial and clinical risk factors for acute pain onset and pain chronicity.

Current thinking, supported by empirical evidence, accepts that CPSP is predominantly, but not entirely, neuropathic in character. A recent review suggested that two-thirds of women with CPSP after breast cancer surgery experience neuropathic pain, although this judgement was retrospectively applied to older studies undertaken before the development of standardised neuropathic assessment instruments [21]. To date, no studies have assessed the contribution of *preoperative* neuropathic pain to CPSP after breast cancer surgery; it is theoretically plausible that women experience continuation of pre-existing painful symptoms. No large-scale epidemiological studies have accounted for the contribution of intraoperative nerve handling, as a potential risk factor or effect modifier, to pain development. In breast cancer surgery, the intercostobrachial nerve (ICBN) can be sacrificed during axillary dissection for lymph node sampling or clearance, but there is lack of

agreement regarding attribution of postoperative chest and upper arm pain to intraoperative nerve damage [18; 33; 45]. Despite changes in surgical technique with increasing rates of breast conservation surgery and sentinel lymph node biopsy (SLNB), the proximity of the ICBN to surgical incision and sentinel node(s) may result in nerve irritation, damage or division, potentially contributing to subsequent postoperative sequelae. Acute postoperative numbness and sensory abnormalities may mask painful symptoms that subsequently become apparent after wound and tissue healing.

Depression, pain catastrophizing and psychological distress are associated with established CPSP and predict acute postoperative outcome when measured preoperatively. Certain psychological traits, such as dispositional optimism, appear to be protective, predicting improved recovery and a range of favourable postoperative outcomes [38; 39; 48]. We have previously reported acute postoperative pain outcomes from our prospective epidemiological study of women undergoing surgery for breast cancer; chronic preoperative pain and dispositional psychological robustness were independent predictors of severe acute pain in the first week after surgery [11]. Our primary aim, herein reported, was to investigate the relative contribution of psychological, sociodemographic, perioperative and acute postoperative factors associated with the persistence of pain at 4 and 9 months after breast cancer surgery.

## METHODS

*Study design and participants*

The Study of Recovery after Breast Cancer Surgery (The Recovery Study) was an epidemiological, prospective cohort study that recruited women from four breast cancer units, serving a large catchment population across the North of Scotland. Study methodology and calculation of sample size has been fully described in a previous publication [11]. In brief, we aimed to recruit 405 women aged 18 years or over, with newly diagnosed, histologically proven primary invasive or non-invasive breast cancer, requiring surgical excision of tumour with or without axillary surgery. Males, women aged <18 years, pregnant women and those with a history of major psychiatric disorder, previous breast or axillary surgery, bilateral surgery, recurrent disease or detectable metastatic disease at the time of initial diagnosis, were excluded.

*Recruitment procedure*

Participant recruitment and consent was undertaken at breast clinics and screening centres or on the hospital ward when patients were admitted prior to surgery. Clinical or research staff invited patients to participate and provided packs containing an information sheet, consent form and baseline questionnaire. Consent was obtained for access to medical records for research purposes. Ethical approval was granted by Fife and Forth Valley National Health Service (NHS) Multicentre Research Ethics Committee with local governance approvals obtained from each regional NHS organisation.

*Data collection*

Data collection was undertaken at four time points: preoperatively, and at 1 week, 4 and 9 months postoperatively. Questionnaires and data collection tools were modelled on our previous studies investigating CPSP and informed by literature review [2; 9; 30; 43; 50].

Instruments were piloted on a sample of women to assess face validity. Sociodemographic variables including age, marital status, highest educational qualification achieved, employment status and residential location, were measured preoperatively by questionnaire. Social deprivation was captured using a geographical-based relative measure of deprivation based upon postcode: participants were allocated to a Scottish Index of Multiple Deprivation (SIMD) quintile, whereby 1 equates to most deprived, and 5, most affluent) [11].

*Preoperative Pain*

Preoperative pain history, incorporating pain character, location and duration of any existing pain was assessed by self-completion questionnaire. The International Association for the Study of Pain (IASP) definition of continuous or intermittent pain lasting for 3 months or longer was used to define chronicity of preoperative pain [22]. Participants reporting any ache, pain, discomfort, altered sensations or numbness experienced in the previous week were asked to complete upper body maps, pain-related symptom grids and validated neuropathic pain instruments. Upper body diagrams were modified from standard 4-view body diagrams widely used in chronic pain research. Pain diagrams were redrawn to illustrate different positions, including arms raised, to allow reporting of location of reported symptoms. Neuropathic pain scales included the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) [3; 4], the 'Douleur Neuropathique 4' (DN4) questionnaire [6] and the Brief Pain Inventory [13]. The S-LANSS and DN4 have been used in epidemiological surveys, whereby scores of $\geq$12 and $\geq$3 respectively are indicative of pain with neuropathic characteristics.

Given that preoperative investigative tests can cause pain and restrict function, we assessed arm morbidity before surgery using the Functional Assessment of Cancer Therapy-Breast questionnaire (FACT-B+4) arm subscale [14]. This scale captures ipsilateral and contralateral swelling/tenderness, numbness, painful movement, poor range of movement and stiffness in arm/side of planned breast surgery. Lower scores indicate greater arm

morbidity (range 0-20). A chronicity question was added to distinguish pain potentially arising from diagnostic/investigative tests (e.g. fine needle biopsy) from chronic symptoms: participants were asked whether preoperative painful symptoms had lasted for more than 3 months before surgery.

*Preoperative comorbidity and Quality of Life*

Participants were asked to report existing co-morbidity, selecting from a predetermined list of 15 medical conditions. Of these, 10 conditions were considered to be 'painful' (e.g. migraine, angina, back problems, peripheral neuropathy etc). Quality of life was captured using the EORTC QLQ-C30 questionnaire [16].

*Psychological variables*

Standardised instruments were used to measure psychological vulnerability (anxiety, depression, pain catastrophizing and surgical worry); and protective/ resilience factors (positive affect and dispositional optimism) before surgery. The State Trait Anxiety Inventory (STAI) measures state and trait anxiety whereby higher scores indicate greater anxiety (range 20-80) [51]. The Hospital Anxiety and Depression Scale (HADS) depression sub-scale was used to capture anxious and depressed mood, with higher scores indicating poorer mental health (range 0-21) [56]. The 13-item Pain Catastrophizing Scale (PCS) was used to capture pain catastrophizing, defined as an exaggerated negative orientation to aversive stimuli [37]. Total PCS scores range from 0-52 with higher values indicating greater catastrophizing. Worry about forthcoming breast surgery was captured using a single item asking women to rate '*how worried you are about your operation'* (4-category response) modified from previous studies [7]. The full Positive and Negative Affect Scale (PANAS) was used to capture affect, with higher scores indicating greater positive affect (range 10-50) [55]. The timing of the stem question 'how you generally feel' was applied. Two indicators of psychological 'robustness' were assessed: the tendency to experience general positive affect, captured using the positive affect scale of the PANAS (PANAS-PA); and dispositional

optimism, defined as generalized outcome expectancies that good things, rather than bad things will happen, measured using the Life Orientation Test (LOT) (scale range 0-32) [23; 46].

*Clinical and surgical variables*

Body mass index (BMI) was calculated from height and weight measured on admission for surgery. Data on tumour grade and status were extracted from medical records. Operative data were captured on day of surgery and cross-tabulated against medical records. Breast surgery was categorised as wide local excision (WLE) or mastectomy with or without immediate reconstruction. Axillary procedures were categorised as sentinel lymph node biopsy (SLNB), axillary node sample (ANS) or axillary node clearance (ANC).

*Intercostobrachial nerve (ICBN) handling*

Nerve handling data were collected intraoperatively or postoperatively. Senior operating surgeons were asked to record whether or not the ICBN was identified, and, if identified, whether the nerve was preserved with no apparent damage, preserved with potential damage, the main trunk was divided or some branches divided and others preserved at the time of surgery. Data were analysed as nerve divided or damaged versus nerve preserved or not identified e.g. due to anatomical variation or surgery not within vicinity of nerve.

*Anaesthetic variables*

A pragmatic, open protocol was permitted for anaesthetic regimes. General anaesthesia was induced with propofol and fentanyl or alfentanil with volatile maintenance using isoflurane, sevoflurane or desflurane together with nitrous oxide or air. Intraoperative morphine up to 10mg intravenous was used for mastectomy or axillary clearance, with bupivacaine infiltration of the breast around the site of skin incision used for WLE's at the end of surgery. Bupivacaine infiltration was also administered to the axillary wound following ANS or SLNB. Usual analgesia included intravenous paracetamol (1g) and 10mg or 30mg IV

ketorolac, dependent upon age and comorbidity. Postoperative analgesia was 1g paracetamol 6-8 hourly as required.

*Radiotherapy, Chemotherapy and Endocrine*

Treatment regimens accorded with local and national guidelines. Data on chemotherapy, radiotherapy and endocrine therapy were extracted from medical records using piloted data extraction forms. Patients who had breast conservation surgery always underwent radiotherapy to the breast; those who had undergone mastectomy only received radiotherapy to the chest wall if there was deemed to be an increased risk of local recurrence. Patients with an involved sentinel lymph node or positive axillary sample underwent either axillary radiotherapy or a surgical axillary clearance. Patients with grade III tumours or those with positive lymph nodes received a standard anthracycline-based chemotherapy of 6 cycles at three weekly intervals postoperatively. Radiation therapy and chemotherapy, when administered, were commenced within 4 months of surgery.

Patients with hormone receptor positive tumours received Tamoxifen if premenopausal, or if post-menopausal, received an aromatase inhibitor if at an increased risk of recurrence (e.g. grade III, large primary tumour size or lymph node positive disease) for five years. Those patients undergoing chemotherapy and whose tumours overexpressed HER2 received adjuvant trastuzumab for a 12 month period.

*Acute postoperative pain*

Acute postoperative pain character at the wound or related area was captured using the following pain descriptors: ‘ache, pain, discomfort, altered sensations or numbness’ [11]. These descriptors were based upon the literature and from our previous qualitative interviews with women reporting chronic post-mastectomy pain [2; 30; 50]. Participants were asked to select the ‘best’ descriptor for their most painful wound or area. Presence of numbness and altered sensations in the first week after surgery were considered

neuropathic-type symptoms. Pain intensity at rest and evoked by movement was captured using a numerical rating scale (NRS 0-10), administered by telephone on the 7th postoperative day.

*Definition of chronic pain*

Incidence of chronic pain at 4 and 9 months, was defined as any ache, pain, discomfort, altered sensation or numbness in the upper body, first present *after* the primary breast operation and reported to have been present in the week prior to questionnaire completion. We selected a timeframe of 4 months postoperatively rather than the generally accepted 3 month period to define postoperative pain chronicity, to account for the likelihood that other active adjuvant treatment may still have been underway at 3 months. Women reporting chronic pain at follow-up were asked about analgesic use in the previous 24 hours and use of alternative therapies. They were also asked whether they thought their symptoms were due to their breast surgery.

*Statistical Analysis*

The primary research aim was to identify psychological, sociodemographic and acute postoperative factors associated with chronic pain at 4 and 9 months after surgery. Initial analyses were conducted to compare women with and without chronic pain at 4 and at 9 months postoperatively. These unadjusted analyses were treated as exploratory and no adjustment was made for repeated testing. For continuous variables, the independent samples t-test or Mann-Whitney test was used, depending on whether data were normally distributed. For unordered and ordered categorical variables, the chi-squared test with continuity correction and the chi-squared test for trend were used respectively.

Two multiple logistic regression models were then developed to predict chronic pain status (presence or absence of chronic pain) at 4 and 9 months after controlling for other variables. Included variables were specified *a priori* by the Study Group, based upon previous

literature: age; type of breast surgery (mastectomy or wide local excision); type of axillary surgery; whether the ICBN was divided or damaged; having more than one breast or axillary procedure (a second procedure in relation to the primary surgery); presence of preoperative chronic pain, pain at rest in the first postoperative week; presence of altered sensations or numbness on the 7$^{th}$ postoperative day, and adjuvant therapy (chemotherapy, radiotherapy and endocrine therapy). As described previously [11], many of the psychological variables were correlated, therefore a factor analysis of preoperative psychological measures (STAI, HADS depression, PCS, PANAS positive affect, LOT and surgical worry) was used to reduce these to a smaller number of variables. The exploratory factor analysis approach was used using principal component analysis with promax rotation and Kaiser normalisation. The Eigenvalues and scree plot suggested a single derived component which was given the label "psychological robustness" because it was particularly associated with higher values of PANAS-PA and LOT dispositional optimism, also lower values of STAI trait anxiety and HADS depression. This single variable therefore represented low levels of psychological vulnerability factors and high levels of psychological resilience factors. The component was termed psychological robustness because it appeared to fit with broader dimensions of resources that characterise psychological positivism, combining a 'habitual style of anticipating favourable outcomes' [11; 47].

Our *a priori* analysis was based on 'any' chronic pain after breast cancer surgery. An additional secondary analysis was conducted to explore the magnitude and potential impact of clinically meaningful chronic pain. Using a threshold of $\geq$4 on the BPI pain intensity question (0-10 NRS), we used logistic regression models to investigate risk factors predictive of moderate to severe chronic pain intensity at 4 and 9 months postoperatively.

## RESULTS

The full sample size was achieved, with 406 women being recruited from participating breast cancer units across Northern Scotland. Forty-four women (10.8%) were excluded after recruitment and a further 20 women were excluded or withdrawn at different stages during follow-up, therefore sample size varied by time point. Preoperative data were available for 362 women, complete acute pain data for 338, 4 and 9 month chronic pain data for 308 and 293 women respectively (Figure 1). Study retention rates were high, with 89% and 87% of questionnaires returned at 4 and 9 months respectively.

Median (IQR) time from completion of the baseline questionnaire to surgery was 1 day (1-4 days); 90% of women underwent surgery within two weeks of completion of the baseline questionnaire. Time from surgery to acute pain assessment was median 8 days (IQR 7-10), with subsequent follow-up at 4 months (IQR 16.6-19.4 weeks) and 9 months (IQR 38.7-41.4 weeks). Sociodemographic, surgical and psychological characteristics for the full sample are presented in Table 1.

*Preoperative pain*

Overall, 151/362 (42%) reported painful symptoms in the upper body in the week before surgery. Of these, a subset of women, 56/362 (15%) had *chronic* painful symptoms in the upper body persisting for 3 months before breast surgery, suggesting that the remainder had pain potentially related to preoperative core biopsy. Prevalence of preoperative chronic pain of predominantly neuropathic origin was low: 8/362 (2%) were S-LANSS positive and 12/362 (3%) DN4-positive. Location of chronic symptoms included the breast or breast area, axilla and/or upper arm (Table 2).

*Incidence of chronic pain*

Using the primary study definition, 210/308 (68%) women reported chronic pain at 4 months and 184/293 (63%) at 9 months respectively. Rates are based on any symptom of ache, pain, discomfort, altered sensation or numbness in the upper body, experienced in the previous week, but absent before breast cancer surgery. Relaxing the stipulation that painful symptom(s) were experienced in the previous week, 255/308 (83%) and 235/293 (80%) women reported any chronic pain at 4 and 9 months respectively. Symptom onset was variable, with only half of women (54%) being aware of pain-related symptoms in the first postoperative week (Table 3). The pattern of symptoms, in terms of location and frequency, was relatively stable rather than dynamic, when compared across follow-up time points. By 9 months postoperatively, more than half of women felt that their symptoms were unchanged, rather than improving over time (Table 3). Regarding symptom attribution, breast surgery was reported to be the cause of symptoms for 94% women with chronic pain at 4 months and 89% of women at 9 months after surgery.

*Pain intensity and character*

Most women reported chronic pain of mild intensity (Table 4). Incidence of moderate to severe/unbearable chronic pain was 23% (47/202) and 27% (49/183) amongst those reporting chronic pain at 4 and 9 months respectively. Only a small proportion of those with chronic pain reported having taken analgesics in the previous 24 hours (38% and 22% at 4 and 9 months respectively). At 4 months after surgery, only 7% of women had tried alternative therapies for their pain; by 9 months postoperatively this had increased slightly to 11%. At 4 and 9 months postoperatively, approximately 40% of those with persistent pain had neuropathic characteristics, categorised as S-LANSS or DN4-positive (Table 4). Using the full postoperative sample as denominator, incidence of predominantly neuropathic pain was 26% and 24% at 4 and 9 months respectively (81/308; 69/293).

*Predictors of chronic pain at 4 and 9 months, unadjusted analysis*

Table 5 presents preoperative, perioperative and postoperative variables for women with and without chronic pain at 4 and 9 months. Women experiencing chronic pain at 4 months were younger, had axillary node clearance, had ICBN division or damage and were more likely to have received chemotherapy. They were also more likely to report more severe pain, altered sensations or numbness in the first postoperative week. Factors with a statistically significant association with chronic pain at 9 months included younger age, intraoperative ICBN division or damage, having mastectomy, having axillary node clearance, and having received chemotherapy.

Preoperative quality of life, arm morbidity and psychological factors were associated with chronic pain at either 4 or 9 months. Chronic pain at 4 months was associated with worse preoperative scores on the FACT-B+4 arm morbidity scale, HADS anxiety, STAI trait anxiety, negative affect (PANAS), pain catastrophizing and surgical worry. Preoperative quality of life, arm morbidity, HADS depression, pain catastrophizing and anxiety (HADs and STAI-state) were significantly associated with chronic pain at 9 months.

*Predictors of chronic pain at 4 and 9 months, adjusted analysis*

Nine variables were included in the multiple logistic regression models predicting chronic pain at 4 and 9 months. In the adjusted analysis, there was evidence that younger women, those with greater preoperative psychological vulnerability and decreased psychological robustness, and higher acute pain scores at rest in the first postoperative week were more likely to have chronic pain at 4 months (Table 6). At 9 months, younger women, those undergoing axillary node clearance and those with more severe pain at rest in the first postoperative week were more likely to have persistent chronic pain.

*Predictors of moderate to severe chronic pain at 4 and 9 months, adjusted analysis*

Logistic regression analyses, adjusted for the predetermined clinical, psychological and sociodemographic factors, revealed that more severe pain at rest within the first week of surgery was associated with clinically meaningful pain of moderate to severe intensity at 4 months postoperatively (Table 7). Decreased psychological robustness, type of axillary surgery and more severe acute postoperative pain at rest increased the risk of experiencing moderate to severe pain at 9 months postoperatively. Several risk factors were of borderline statistical significance: younger age and having had multiple surgical procedures were associated with greater pain intensity at 4 months, and chronic preoperative pain was associated with greater pain intensity at 9 months postoperatively.

## DISCUSSION

This multicentre prospective cohort study investigated psychological, sociodemographic, and surgical risk factors, adjusted for intraoperative nerve handling, on painful adverse outcomes captured at multiple time points after resectional surgery for primary breast cancer.

We found a high incidence of chronic pain, with two-thirds of women reporting pain-related symptoms in the upper body region, 4 and 9 months after surgery. There was little change in the proportion reporting chronic persistent pain over time. Rather than restricting our definition to pain *per se*, our broad definition also accepted any ache, discomfort, altered sensations or numbness in the area of surgical incision that was not present preoperatively; this may account for the high incidence. Other population surveys accept any 'aches or pains' within definitions of regional or widespread pain [31]. We deliberately included nociceptive pain descriptors (ache/discomfort), to identify whether postoperative non-neuropathic symptoms are associated with later functional impairment and long-term pain-related disability. One recent Danish survey found that 50% of women reported 'sensory disturbances' (yes/no) at 5 to 7 years postoperatively [34], although no preoperative assessment was undertaken. We captured pre- and postoperative altered sensations and numbness ~~by location~~ and investigated whether acute postoperative symptoms predicted painful symptoms later in the recovery timeline. Indeed, acute postoperative numbness and altered sensations were associated with chronic pain at 4 and 9 months, but were not statistically significant after adjustment for other factors, nor were they predictive of pain intensity. A quarter of women experienced pain of moderate or severe intensity and 40% screened positive on DN4 and S-LANSS.

At 4 months, younger age and acute postoperative pain were independent predictors of CPSP, as was our composite variable representing psychological robustness, which was associated with a 30% reduction in the odds of reporting CPSP. Severity of acute pain

predicted moderate to severe chronic pain at 4 and 9 months. Evidence that sensory abnormality immediately after surgery may predict long-term adverse outcome is scant, but emerging: neuropathic characteristics occurring within 2 days of thoracic surgery predicted chronic neuropathic pain at 3 months postoperatively [49].

At 9 months, CPSP was 3 times more likely after axillary clearance, with younger age and acute postoperative pain also associated with persistent pain. Younger age independently predicted CPSP and pain intensity at 4 months~~,~~ this finding differs from previous work whereby younger women were more likely to report clinically meaningful pain in the acute postoperative period, but not by 3 months postoperatively [41]. Explanations for this finding may relate to increased expectation related to functional recovery or may be biological, with younger patients potentially having more heightened central nervous system responsiveness [34]. Younger age has been associated with CPSP in numerous other surgical procedures, [27; 40; 42], although studies of breast cancer surgery are less conclusive [8; 20; 34; 50; 53]. Younger women are more likely to have a higher histopathological tumour grade and undergo more aggressive adjuvant treatment, particularly chemotherapy [29]. Unadjusted analyses suggested that chemotherapy was associated with chronic pain at 4 and 9 months, however, this relationship was attenuated after adjustment. We found no evidence of increased risk of CPSP associated with adjuvant therapy; this finding is comparable with other literature [17; 41], although the large national Danish study identified a relationship between chronic pain and radiotherapy, but not site of radiotherapy [20].

Increased psychological distress, captured using scales assessing emotions and cognition, was predictive of moderate to severe acute postoperative pain and chronic pain intensity. The few prospective studies investigating psychological status *before* breast cancer surgery have focused upon individual distress variables e.g. anxiety, depression, catastrophizing [25; 40], rather than more general emotional and cognitive resilience. We explored the role of psychological robustness to investigate resilience and capacity to withstand adverse

circumstances when faced with a potentially life threatening illness and pending surgery. Our study is novel in examining the role and contribution of both negative and positive psychological states on pain outcomes after breast cancer surgery. Psychological robustness indicates the adoption of positive coping strategies in the face of external threats and suggests a positive postoperative recovery trajectory [12]. Katz [24] reasonably argues that different risk factors may contribute to the onset and maintenance of pain; indeed, we found that our derived variable, psychological robustness was protective earlier in the recovery trajectory, and although a similar effect size was found at 9 months, this did not maintain significance in multivariate analysis.

We hypothesized that apparent ICBN damage would predict CPSP. Nerve injury is necessary, but not sufficient for the development of chronic postoperative neuropathic pain [32]. Findings from small ~~clinical~~ trials of ICBN division have been contradictory: one found a greater degree of postoperative numbness, pain severity and arm stiffness after ICBN division during axillary dissection, compared with nerve preservation [33]. Conversely, another study concluded that nerve preservation was unnecessary as there was no difference in postoperative functional outcome after nerve division or preservation [45]. Studies of ICBN handling are methodologically weak, either hampered by small sample size or lacking in preoperative pain characterisation. Breast conserving surgery is less invasive than mastectomy, with lower risk of tissue damage, although ICBN irritation may still occur. We adjusted for type of axillary surgery, distinguishing between the extent of axillary surgery performed. Previous studies have categorised surgery as lumpectomy/mastectomy with or without axillary node surgery [41], whereas our more refined classification highlights the extent of axillary node surgery performed. The practice of axillary node clearance is decreasing but is still appropriate for patients with axillary node involvement.

One methodological and clinical challenge, hitherto not acknowledged in previous studies of CPSP after breast surgery, was the high rate of second operations on the breast, particularly

in women undergoing breast conservation surgery. The need for secondary procedures (usually to excise margins in those undergoing breast conservation surgery or to undertake mastectomy when conservation surgery has been attempted but adequate tumour clearance has not been achieved), is well acknowledged within surgical oncology but not in the pain literature. One US centre reported that approximately half of women required repeat surgery for margin or axillary clearance because of a staging procedure (axillary sample or SLNB) having shown axillary nodal involvement by tumour [36]. We found a marginal association between repeat surgery and moderate to severe chronic pain at 4 months. Central sensitization may reflect both neuropathic mechanisms associated with nerve injury and inflammatory processes associated with the surgical wound [8; 26; 27]. It ishighly plausible that repeated surgical insult to a previously inflamed area may heighten CNS responsiveness and contribute to central sensitization. This is an area worthy of future investigation.

Our study is limited by number of participants but our sample is geographically representative of the Northern and Eastern Scotland, incorporating remote-rural, urban and socially diverse populations. We did not adjust for pain treatment modalities because perioperative analgesia regimes were standardised, however, this may impact upon pain reporting. Given the epidemiological design, we accepted self-reported neuropathic characteristics without confirmation by clinical examination as this was impractical to achieve on a large, geographically scattered population. However, evidence suggests good discriminant ability of neuropathic pain screening tools [5; 6].

The strengths of our study include being the first epidemiological study to investigate multiple pain predictors adjusted for intercostobrachial nerve handling. The lack of surgical pain studies investigating the contribution of nerve handling was recently highlighted in the *BMJ* [34]. Participating surgeons were supportive of our study and assisted with the design of intraoperative data collection forms; we achieved 97% complete data on nerve handling.

We adjusted for other potential confounding factors, specified *a priori,* identified from existing literature and from our own research [9-11; 30; 43; 50; 54]. Other strengths include the detailed preoperative assessment of baseline health status and pain history, often neglected from surgical cohort studies [2; 17; 20; 44] and experimental studies incorporating sensory testing [15; 19; 32]. Identification of preoperative upper body pain provided incidence data on persistent pain arising as a consequence of surgery and related treatment. As with any large epidemiological study, we were unable to exclude with absolute certainty that the small subset reporting chronic preoperative breast pain did not have continuing painful symptoms rather than surgically-induced incident pain; this can only be attempted by detailed clinical assessment and investigation at the individual level. However, a compelling finding was that the majority of women (~90%) *attributed* breast surgery as the cause of their painful symptoms after cancer treatment.

**CONCLUSION**

This study highlights the frequency and persistence of pain-related outcomes as a consequence of breast cancer treatment and identifies clinical and psychological factors potentially amenable to intervention. Incidence of pain, altered sensations and numbness is very high after primary breast cancer surgery, with about one quarter experiencing neuropathic pain up to 9 months postoperatively. We provide insights into those at risk of persistent adverse outcomes, namely younger women, those with psychological vulnerability, axillary clearance surgery and more severe acute postoperative pain. Preventive strategies should target these risk factors to reduce adverse sequelae of treatment, supplemented with broader efforts to support the longer term physical and psychological recovery in cancer survivors.

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**Conflict of Interest statement**

We declare that there are no conflicts of interest.

## REFERENCES

[1] Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. J Pain 2011;12(7):725-746.

[2] Baron RH, Fey JV, Borgen PI, Stempel MM, Hardick KR, Van Zee KJ. Eighteen sensations after breast cancer surgery: a 5-year comparison of sentinel lymph node biopsy and axillary lymph node dissection. Ann Surg Oncol 2007;14(5):1653-1661.

[3] Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. J Pain 2005;6(3):149-158.

[4] Bouhassira D, Attal N. All in one: is it possible to assess all dimensions of any pain with a simple questionnaire? Pain 2009;144(1-2):7-8.

[5] Bouhassira D, Attal N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. Pain 2011;152(3 Suppl):S74-83.

[6] Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lantéri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114(1-2):29-36.

[7] Broadbent E, Petrie KJ, Alley PG, Booth RJ. Psychological stress impairs early wound repair following surgery. Psychosom Med 2003;65(5):865-869.

[8] Bruce J. Post-surgical pain. In: P Croft, Blyth F.M., van der Windt, D., editor. Chronic pain epidemiology: from aetiology to public health. Oxford: Oxford University Press, 2010. pp. 235-248.

[9] Bruce J, Drury N, Poobalan AS, Jeffrey RR, Smith WC, Chambers WA. The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. Pain 2003;104(1-2):265-273.

[10] Bruce J, Poobalan AS, Smith WC, Chambers WA. Quantitative assessment of chronic postsurgical pain using the McGill Pain Questionnaire. Clin J Pain 2004;20(2):70-75.

[11] Bruce J, Thornton AJ, Scott NW, Marfizo S, Powell R, Johnston M, Wells M, Heys SD, Thompson AM. Chronic preoperative pain and psychological robustness predict acute postoperative pain outcomes after surgery for breast cancer. Br J Cancer 2012;107(6):937-946.

[12] Carver CS, Pozo C, Harris SD, Noriega V, Scheier MF, Robinson DS, Ketcham AS, Moffat FL, Clark KC. How coping mediates the effect of optimism on distress: a study of women with early stage breast cancer. J Pers Soc Psychol 1993;65(2):375-390.

[13] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23(2):129-138.

[14] Coster S, Poole K, Fallowfield LJ. The validation of a quality of life scale to assess the impact of arm morbidity in breast cancer patients post-operatively. Breast Cancer Res Treat 2001;68(3):273-282.

[15] Edwards RR, Mensing G, Cahalan C, Greenbaum S, Narang S, Belfer I, Schreiber KL, Campbell C, Wasan AD, Jamison RN. Alteration in Pain Modulation in Women With Persistent Pain After Lumpectomy: Influence of Catastrophizing. J Pain Symptom Manage 2012.

[16] Fayers PM AN, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 Scoring Manual. European Organisation for Research and Treatment of Cancer. Brussels: European Organisation for Research and Treatment of Cancer, 2001.

[17] Fecho K, Miller NR, Merritt SA, Klauber-Demore N, Hultman CS, Blau WS. Acute and persistent postoperative pain after breast surgery. Pain Med 2009;10(4):708-715.

[18] Freeman SR, Washington SJ, Pritchard T, Barr L, Baildam AD, Bundred NJ. Long term results of a randomised prospective study of preservation of the intercostobrachial nerve. Eur J Surg Oncol 2003;29(3):213-215.

[19] Granot M. Can we predict persistent postoperative pain by testing preoperative experimental pain? Curr Opin Anaesthesiol 2009;22(3):425-430.

[20] Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 2009;302(18):1985-1992.

[21] Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013;154(1):95-102.

[22] IASP. (International Association for the Study of Pain) Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Pain 1994;24 (S):226.

[23] Johnston M, Wright, S., Weinman, J. Measures in Health Psychology: A user's portfolio. Individual and demographic differences. In: nPC Ltd. editor. London, 1995.

[24] Katz J. One man's risk factor is another man's outcome : Difference in risk factor profiles for chronic postsurgical pain maintenance vs transition. Pain 2012;153(3):2.

[25] Katz J, Poleshuck EL, Andrus CH, Hogan LA, Jung BF, Kulick DI, Dworkin RH. Risk factors for acute pain and its persistence following breast cancer surgery. Pain 2005;119(1-3):16-25.

[26] Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 2009;9(5):723-744.

[27] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367(9522):1618-1625.

[28] Kehlet H, Rathmell JP. Persistent postsurgical pain: the path forward through better design of clinical studies. Anesthesiology 2010;112(3):514-515.

[29] Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. BMJ 2000;320(7233):474-478.

[30] Macdonald L, Bruce J, Scott NW, Smith WC, Chambers WA. Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome. Br J Cancer 2005;92(2):225-230.

[31] Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, McBeth J, Jones GT, Team MS. The prevalence and management of low back pain across adulthood: results from a population-based cross-sectional study (the MUSICIAN study). Pain 2012;153(1):27-32.

[32] Martinez V, Ben Ammar S, Judet T, Bouhassira D, Chauvin M, Fletcher D. Risk factors predictive of chronic postsurgical neuropathic pain: the value of the iliac crest bone harvest model. Pain 2012;153(7):1478-1483.

[33] Maycock LA, Dillon P, Dixon JM. Morbidity related to intercostobrachial nerve damage following axillary surgery for breast cancer. The Breast 1998;7:209-2012.

[34] Mejdahl MK, Andersen KG, Gärtner R, Kroman N, Kehlet H. Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. BMJ 2013;346:f1865.

[35] Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1(3):277-299.

[36] Mullenix PS, Cuadrado DG, Steele SR, Martin MJ, See CS, Beitler AL, Carter PL. Secondary operations are frequently required to complete the surgical phase of therapy in the era of breast conservation and sentinel lymph node biopsy. Am J Surg 2004;187(5):643-646.

[37] Pavlin DJ, Sullivan MJ, Freund PR, Roesen K. Catastrophizing: a risk factor for postsurgical pain. Clin J Pain 2005;21(1):83-90.

[38] Peters ML, Sommer M, de Rijke JM, Kessels F, Heineman E, Patijn J, Marcus MA, Vlaeyen JW, van Kleef M. Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. Ann Surg 2007;245(3):487-494.

[39] Peters ML, Sommer M, van Kleef M, Marcus MA. Predictors of physical and emotional recovery 6 and 12 months after surgery. Br J Surg 2010;97(10):1518-1527.

[40] Pinto PR, McIntyre T, Almeida A, Araújo-Soares V. The mediating role of pain catastrophizing in the relationship between presurgical anxiety and acute postsurgical pain after hysterectomy. Pain 2012;153(1):218-226.

[41] Poleshuck EL, Katz J, Andrus CH, Hogan LA, Jung BF, Kulick DI, Dworkin RH. Risk factors for chronic pain following breast cancer surgery: a prospective study. J Pain 2006;7(9):626-634.

[42] Poobalan AS, Bruce J, King PM, Chambers WA, Krukowski ZH, Smith WC. Chronic pain and quality of life following open inguinal hernia repair. Br J Surg 2001;88(8):1122-1126.

[43] Powell R, Johnston M, Smith WC, King PM, Chambers WA, Krukowski Z, McKee L, Bruce J. Psychological risk factors for chronic post-surgical pain after inguinal hernia repair surgery: a prospective cohort study. Eur J Pain 2012;16(4):600-610.

[44] Reyes-Gibby C, Morrow PK, Bennett MI, Jensen MP, Shete S. Neuropathic pain in breast cancer survivors: using the ID pain as a screening tool. J Pain Symptom Manage 2010;39(5):882-889.

[45] Salmon RJ, Ansquer Y, Asselain B. Preservation versus section of intercostal-brachial nerve (IBN) in axillary dissection for breast cancer--a prospective randomized trial. Eur J Surg Oncol 1998;24(3):158-161.

[46] Scheier MF, Carver CS. Optimism, coping, and health: assessment and implications of generalized outcome expectancies. Health Psychol 1985;4(3):219-247.

[47] Scheier MF, Carver CS. Dispositional optimism and physical well-being: the influence of generalized outcome expectancies on health. J Pers 1987;55(2):169-210.

[48] Scheier MF, Matthews KA, Owens JF, Magovern GJ, Lefebvre RC, Abbott RA, Carver CS. Dispositional optimism and recovery from coronary artery bypass surgery: the beneficial effects on physical and psychological well-being. J Pers Soc Psychol 1989;57(6):1024-1040.

[49] Searle RD, Simpson MP, Simpson KH, Milton R, Bennett MI. Can chronic neuropathic pain following thoracic surgery be predicted during the postoperative period? Interact Cardiovasc Thorac Surg 2009;9(6):999-1002.

[50] Smith WC, Bourne D, Squair J, Phillips DO, Chambers WA. A retrospective cohort study of post mastectomy pain syndrome. Pain 1999;83(1):91-95.

[51] Spielberger C, Gorsuch R, Lushene P, Vagg P, Jacobs G. Manual for the State-Trait Anxiety Inventory (Form Y). http://www.mindgarden.com/products/staisad.htm: Mind Garden Inc., 1983.

[52] Tasmuth T, Estlanderb AM, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. Pain 1996;68(2-3):343-347.

[53] Tasmuth T, von Smitten K, Hietanen P, Kataja M, Kalso E. Pain and other symptoms after different treatment modalities of breast cancer. Ann Oncol 1995;6(5):453-459.

[54] VanDenKerkhof EG, Peters ML, Bruce J. Chronic pain after surgery: time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. Clin J Pain 2013;29(1):2-8.

[55] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070.

[56] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-370.

## Figure Captions

Figure 1. Flow chart of recruited participants

**Figure 1. Flow chart of recruited participants**

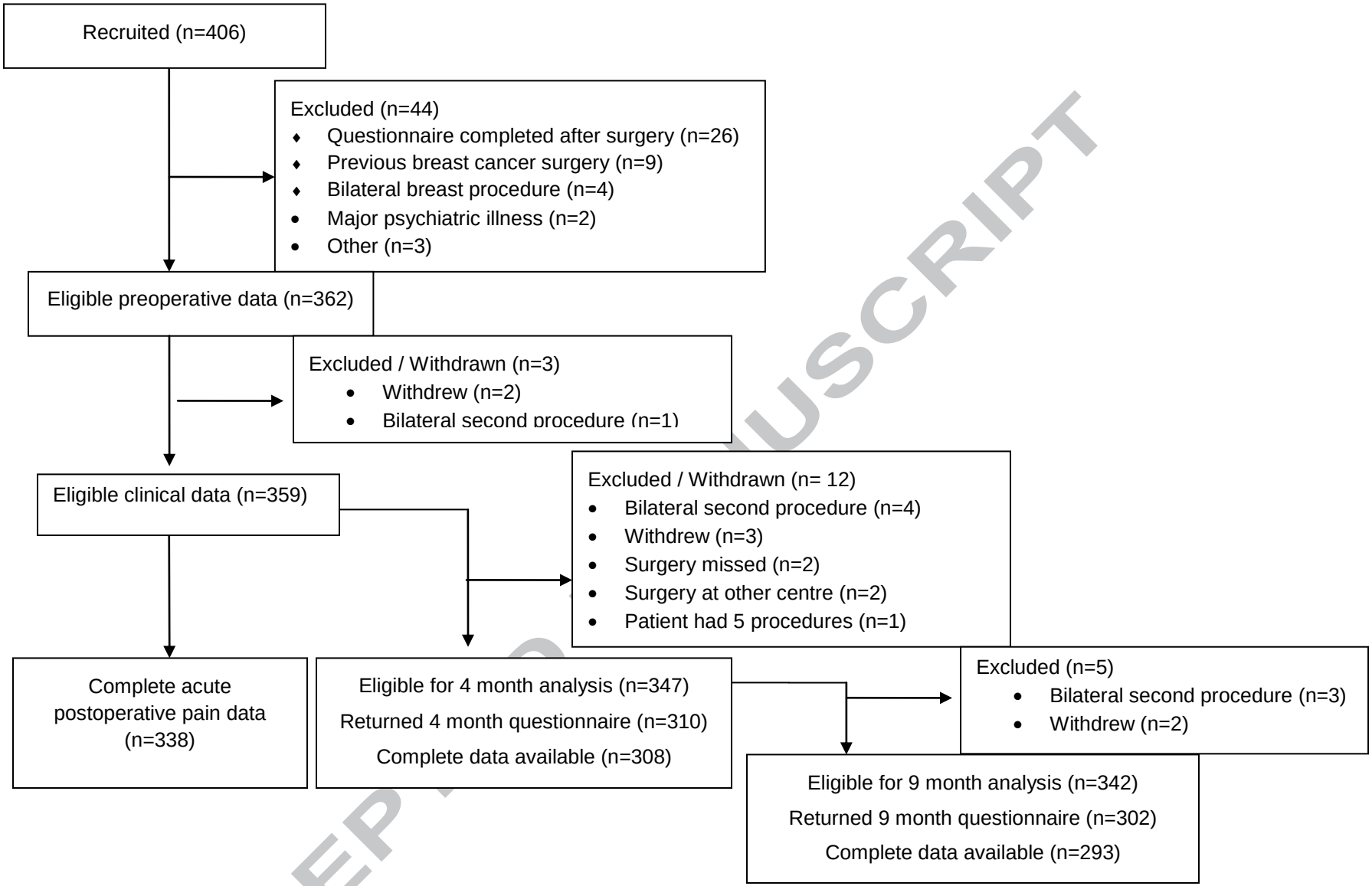

**Table 1: Sociodemographic, surgical and pre-operative psychological characteristics [Eligible N=362]**

| | |
|---|---|
| | Mean (SD) [N] |
| Age, years, | 59.1 (10.8) [356] |
| BMI, | 28.0 (5.9) [350] |
| | N (%) |
| Married | 241/362 (66.6) |
| | |
| **Highest Educational level** | N (%) |
| School only | 109 (30.3) |
| Work or college qualification | 180 (50.0) |
| Degree qualification | 71 (19.7) |
| Missing | 2 |
| | |
| **Deprivation score quintile (SIMD)** | N (%) |
| 1 (most deprived) | 17 (4.7) |
| 2 | 35 (9.7) |
| 3 | 65 (18.0) |
| 4 | 145 (40.1) |
| 5 (most affluent) | 100 (27.6) |
| | |
| **Arm morbidity** | Median (IQR) [N] |
| FACT-B arm subscale | 20 (20-20) [361] |
| | |
| **Preoperative psychological health** | Median (IQR) [N] {Cronbach's α} |
| STAI State | 40 (30-50) [347] {0.86} |

| | |
|---|---|
| STAI Trait | 32.5 (26-42) [350] {0.94} |
| HADS Anxiety | 7 (3-10) [360] {0.89} |
| HADS Depression | 1.5 (0-4) [360] {0.85} |
| LOT | 24 (16-32) [345] {0.51} |
| | Median (IQR) [N] {Cronbach's α} |
| PANAS Positive | 30.5 (4.9) [355] {0.76} |
| PANAS Negative | 23.0 (4.5) [355] {0.64} |
| PCS Total Score | 11.0 (9.2) [349] {0.94} |
| | |
| **Surgical worry** | N (%) |
| Not at all/a little | 221 (61.7) |
| Quite a bit/very much | 137 (38.3) |
| Missing | 4 |
| | |
| **Any painful co morbidity** | N (%) |
| Yes | 231 (63.8) |
| No | 131 (36.2) |
| | |
| **Chronic pain (>3 months) before surgery*** | N (%) |
| Yes | 56 (15.6) |
| No | 303 (84.4) |
| Missing | 3 |
| **Breast surgery** | N (%) |
| WLE | 228 (63.9) |
| Mastectomy | 92 (25.8) |

| | |
|---|---|
| Mastectomy with reconstruction | 15 (4.2) |
| Missing | 5 |
| | |
| **Axillary surgery** | N (%) |
| SLNB | 146 (42.1) |
| ANS | 94 (26.0) |
| ANC | 107 (29.6) |
| Missing | 15 |
| | |
| **ICBN status** | N (%) |
| Not identified | 96 (27.4) |
| Preserved | 144 (41.1) |
| Divided /damaged | 110 (31.4) |
| Missing | 12 |
| | |
| **Cancer status** | N (%) |
| Invasive | 342 (95%) |
| Non-invasive | 17 (5%) |

*Including women with ache, pain, discomfort, altered sensations or numbness in the upper body in the previous week

SD: standard deviation; BMI: body mass index; SIMD: Scottish Index of Multiple Deprivation; WLE: wide local excision; SLNB: sentinel lymph node biopsy; ANS: axillary node sample; ANC: axillary node clearance; FACT: Functional Assessment of Cancer Therapy; IQR: interquartile range; STAI: State Trait Anxiety Inventory; HADS: Hospital Anxiety and Depression Scale; PANAS: Positive and Negative Affect Scale; PCS: Pain Catastrophizing Scale; LOT: Life Orientation Test. Table published [reference 11]

**Table 2: Location and character of chronic pain and related symptoms***

| | **Chronic preoperative pain [N=56]** | **Chronic pain at 4 months [N=210]** | **Chronic pain at 9 months [N=184]** |
|---|---|---|---|
| | **n (%)** | **n (%)** | **n (%)** |
| **Breast or breast area** | | | |
| Pain | 9 (16) | 58 (28) | 46 (25) |
| Ache or discomfort | 30 (54) | 106 (50) | 90 (49) |
| Numbness or altered sensations | 9 (16) | 98 (47) | 92 (50) |
| **Axilla** | | | |
| Pain | 2 (4) | 33 (16) | 20 (11) |
| Ache or discomfort | 12 (21) | 77 (37) | 72 (39) |
| Numbness or altered sensations | 4 (7) | 119 (57) | 84 (46) |
| **Upper arm** | | | |
| Pain | 3 (5) | 17 (8) | 11 (6) |
| Ache or discomfort | 10 (18) | 39 (19) | 46 (25) |
| Numbness or altered sensations | 5 (9) | 99 (47) | 79 (43) |

*Symptoms occurred in the last week. Where preoperative, symptoms persisting for at least 3 months. Postoperatively, symptoms must be first present after the primary breast operation.

**Table 3: Onset and pattern of pain-related symptoms**

| | Chronic pain at 4 months [N=210] | Chronic pain at 9 months [N=184] |
|---|---|---|
| | **n (%)** | **n (%)** |
| When did you first notice these symptoms? | | |
| Within the first week | 112 (54) | n/a |
| More than 1 week but within 1 month | 61 (29) | n/a |
| Between 1- 2 months after surgery | 19 (9) | n/a |
| Between 2-4 months after surgery | 15 (7) | n/a |
| More than 4 months after my surgery | n/a | 30 (16) |
| Not known | 3 | 1 |
| How often have you had these symptoms? | | |
| Continuously | 92 (44) | 89 (48) |
| Once or more a day | 70 (33) | 48 (26) |
| Once or more a week | 38 (18) | 36 (20) |
| Once or more a month | 6 (3) | 6 (3) |
| Less than once a month | 1 (0) | 0 |
| Not known | 3 | 5 |
| Do you think these symptoms are due to your breast surgery? | | |
| Yes | 194 (94) | 158 (89) |
| No | 13 (6) | 20 (11) |
| Not known | 3 | 6 |
| Do you think these symptoms are: | | |
| Getting better | 123 (59) | 67 (36) |

| | | |
|---|---|---|
| Getting worse | 7 (3) | 11 (6) |
| Staying just the same | 78 (38) | 105 (57) |
| Not known | 2 | 1 |

**Table 4: Pain intensity and neuropathic characteristics**

| | **Preoperative chronic pain [N=56]** | **Chronic pain at 4 months [N=210]** | **Chronic pain at 9 months [N=184]** |
|---|---|---|---|
| **Pain intensity in previous week [NRS 0-10]~~24 hours~~** | **n (%)** | **n (%)** | **n (%)** |
| None (0) | 3 (5) | 28 (14) | 27 (15) |
| Mild (1-3) | 34 (61) | 127 (63) | 107 (58) |
| Moderate (4-7) | 15 (27) | 44 (22) | 43 (23) |
| Severe /Unbearable (8-10) | 4 (7) | 3 (2) | 6 (3) |
| Missing | 2 | 8 | 1 |
| | | | |
| **BPI** | Median (IQR) [N] | Median (IQR) [N] | Median (IQR) [N] |
| BPI Pain severity (4 items) | 2 (1-4) [53] | 1.25 (0.75-2.75) [202] | 1.75 (0.75-3) [182] |
| BPI Pain intensity (7 items) | 1 (0.29-3) [55] | 0.43 (0-1.71) [206] | 0.43 (0-1.86) [183] |
| **Treatment** | **N (%)** | **N (%)** | **N (%)** |
| Taking pain medication | 17/56 (30) | 46/210 (38) | 40/184 (22) |
| Tried alternative therapies for pain | 10/53 (19) | 13/197 (7) | 20/174 (11) |
| | | | |
| **S-LANSS** | 5 (0-18) [55] | 11 (0-24) [194] | 10 (0-24) [169] |
| S-LANSS negative < 12 | 47 (85) | 113 (58) | 100 (59) |
| S-LANSS positive ≥12 | 8 (15) | 81 (42) | 69 (41) |
| Missing | 1 | 16 | 15 |
| | | | |

| | | | |
|---|---|---|---|
| **DN4** | 1 (0-7) [51] | 2 (0-7) [189] | 2 (0-7) [178] |
| DN4 negative (%) | 39 (76) | 114 (60) | 105 (59) |
| DN4 positive (%) | 12 (24) | 75 (40) | 73 (41) |
| Missing | 5 | 21 | 6 |

**Table 5: Sociodemographic, clinical and psychological factors associated with chronic pain at 4 and 9 months after breast cancer surgery**

| | | 4 months | | | 9 months | | |
|---|---|---|---|---|---|---|---|
| | | **Chronic pain (max N=210)** | **No chronic pain (max N=98)** | | **Chronic pain (max N=184)** | **No chronic pain (max N=109)** | |
| | | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** |
| **Age** | | 57.7 (10.3) [206] | 64.1 (9.4) [96] | <0.001 | 58.1 (10.2) [181] | 62.3 (10.3) [108] | 0.001 |
| | | **N (%)** | **N (%)** | **p-value ($\chi^2$ test)** | **N (%)** | **N (%)** | **p-value ($\chi^2$ test)** |
| **Marital status** | Single | 13 (65) | 7 (35) | 1.00 | 11 (58) | 8 (42) | 0.39 |
| | Living with partner | 13 (69) | 6 (32) | | 10 (59) | 7 (41) | |
| | Married | 142 (69) | 64 (31) | | 121 (61) | 78 (39) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Separated | 6 (67) | 3 (33) | | 8 (89) | 1 (11) | |
| | Divorced | 10 (67) | 5 (33) | | 12 (80) | 3 (20) | |
| | Widowed | 26 (67) | 13 (33) | | 22 (65) | 12 (35) | |
| | | | | | | | |
| | | **N (%)** | **N (%)** | **p-value ($\chi^2$ test for trend)** | **N (%)** | **N (%)** | **p-value ($\chi^2$ test for trend)** |
| **SIMD Deprivation category** | 1 (most deprived) | 5 (42) | 7 (58) | 0.24 | 4 (40) | 6 (60) | 0.60 |
| | 2 | 22 (69) | 10 (31) | | 20 (59) | 14 (41) | |
| | 3 | 38 (67) | 19 (33) | | 35 (70) | 15 (30) | |
| | 4 | 88 (71) | 36 (29) | | 76 (64) | 43 (36) | |
| | 5 (most affluent) | 57 (69) | 26 (31) | | 49 (61) | 31 (39) | |
| | | | | | | | |
| **Surgical Unit** | 1 | 72 (65) | 38 (35) | 0.49 | 69 (65) | 37 (35) | 0.15 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 | 89 (73) | 33 (27) | | 70 (61) | 44 (39) | |
| | 3 | 21 (68) | 10 (32) | | 23 (77) | 7 (23) | |
| | 4 | 28 (62) | 17 (38) | | 22 (51) | 21 (49) | |
| | | | | | | | |
| | | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** |
| **Body mass index** | | 27.8 (5.5) [204] | 28.6 (5.8) [94] | 0.24 | 28.1 (5.4) [178] | 27.7 (5.5) [105] | 0.48 |
| | | | | | | | |
| | | **N (%)** | **N (%)** | **p-value ($\chi^2$ test)** | **N (%)** | **N (%)** | **p-value ($\chi^2$ test)** |
| **Any painful comorbidity preoperatively** | Yes | 136 (68) | 65 (32) | 0.89 | 59 (57) | 44 (43) | 0.19 |
| | No | 74 (69) | 33 (31) | | 125 (66) | 65 (34) | |
| **Multiple procedures** | Yes | 49 (77) | 15 (23) | 0.14 | 134 (60) | 90 (40) | 0.08 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | No | 161 (66) | 83 (34) | | 50 (72) | 19 (28) | |
| | | | | | | | |
| **Type of breast surgery** | WLE | 127 (65) | 69 (35) | 0.12 | 108 (57) | 82 (43) | 0.006 |
| | Mastectomy | 83 (74) | 29 (26) | | 76 (74) | 27 (26) | |
| **Type of axillary surgery** | ANC | 74 (81) | 17 (18) | 0.006 | 71 (81) | 17 (19) | <0.001 |
| | ANS | 54 (63) | 32 (37) | | 41 (52) | 38 (48) | |
| | SLNB | 76 (62) | 46 (38) | | 65 (56) | 51 (44) | |
| | Not known | 6 | 3 | | 7 | 4 | |
| **ICBN status** | Not identified/ preserved | 111 (60) | 74 (40) | <0.001 | 91 (52) | 83 (48) | <0.001 |
| | Divided/ damaged | 93 (80) | 23 (20) | | 89 (78) | 25 (22) | |
| | Not known | 6 | 1 | | 4 | 2 | |
| | | **N(%)** | **N(%)** | **p-value ($\chi^2$ test)** | **N(%)** | **N(%)** | **p-value ($\chi^2$ test)** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Chemotherapy** | Yes | 80 (76) | 25 (24) | 0.04 | 81 (76) | 25 (24) | <0.001 |
| | No | 130 (64) | 73 (36) | | 103 (55) | 84 (45) | |
| **Radiotherapy** | Yes | 106 (69) | 48 (31) | 0.90 | 136 (61) | 86 (39) | 0.41 |
| | No | 104 (68) | 50 (32) | | 48 (68) | 23 (32) | |
| **Endocrine therapy** | Yes | 118 (64) | 65 (36) | 0.12 | 144 (62) | 90 (38) | 0.46 |
| | No | 92 (74) | 33 (26) | | 40 (68) | 19 (32) | |
| | | | | | | | |
| | | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** |
| **EORTC QLQ-C30** | Baseline Global health status/QoL | 77.4 (18.9) [210] | 80.8 (18.3) [97] | 0.13 | 75.7 (19.2) [184] | 82.3 (18.1) [108] | 0.004 |
| | | | | | | | |
| | | **Median (IQR) [N]** | **Median (IQR) [N]** | **p-value (Mann-Whitney)** | **Median (IQR) [N]** | **Median (IQR) [N]** | **p-value (Mann-Whitney)** |
| **FACT-B+4** | Baseline arm | 20 (20-20) [210] | 20 (20-20) [97] | 0.05 | 20 (20-20) | 20 (20-20) | 0.02 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | morbidity subscale | | | | [184] | [109] | |
| **HADS** | Baseline depression | 2 (0-4) [208] | 1 (0-4) [98] | 0.20 | 2 (0-5) [182] | 1 (0-3.5) [109] | 0.05 |
| | Baseline anxiety | 7 (4-11) [208] | 6 (2-8) [98] | <0.001 | 7 (4-11) [182] | 6 (2.5-9) [109] | 0.003 |
| **STAI** | Baseline state anxiety | 43.3 (30-50) [207] | 36.7 (26.7-48.3) [89] | 0.10 | 40 (30-50) [179] | 36.7 (26.7-46.7) [102] | 0.03 |
| | Baseline trait anxiety | 33 (27-42) [207] | 29 (24-39) [93] | 0.01 | 33 (27-43) [179] | 30.5 (25-39.3) [106] | 0.10 |
| **LOT** | Baseline | 24 (17-31) [200] | 24 (16-32) [92] | 0.72 | 24 (16-32) [176] | 24 (17-32) [104] | 0.65 |
| **Pain Catastrophizing Score (PCS)** | Baseline total score | 10 (5-16) [206] | 6 (1-14) [91] | 0.005 | 9 (5-15.8) [180] | 7 (3-15.8) [104] | 0.07 |
| | | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **PANAS** | Baseline positive affect | 30.4 (5.0) [208] | 30.7 (4.9) [95] | 0.63 | 30.4 (4.9) [182] | 30.6 (4.9) [108] | 0.74 |
| | Baseline negative affect | 23.4 (4.8) [208] | 21.8 (3.8) [95] | 0.001 | 23.0 (4.7) [182] | 22.3 (4.2) [108] | 0.15 |
| | | **N(%)** | **N(%)** | **p-value ($\chi^2$ test for trend)** | **N(%)** | **N(%)** | **p-value ($\chi^2$ test for trend)** |
| **How worried about operation** | Not at all | 17 (61) | 11 (39) | 0.03 | 14 (50) | 14 (50) | 0.20 |
| | A little | 108 (65) | 59 (35) | | 96 (61) | 61 (39) | |
| | Quite a bit | 54 (77) | 16 (23) | | 52 (75) | 17 (25) | |
| | Very much | 31 (78) | 9 (23) | | 21 (58) | 15 (42) | |
| | Not known | 0 | 3 | | 1 | 2 | |
| | | | | | | | |
| | | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** | **Mean (SD) [N]** | **Mean (SD) [N]** | **p-value (t-test)** |
| **Component 1 at** | "Psychological | 0.024 (1.01) | -0.293 (1.00) | 0.02 | -0.002 | -0.304 (0.98) | 0.02 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **baseline** | robustness" | [193] | [81] | | (0.98) [167] | [94] | |
| | | | | | | | |
| | | **N(%)** | **N(%)** | **p-value ($\chi^2$ test)** | **N(%)** | **N(%)** | **p-value ($\chi^2$ test)** |
| **Chronic pain at baseline** | Yes | 39 (83) | 8 (17) | 0.03 | 34 (72) | 13 (28) | 0.18 |
| | No | 169 (65) | 90 (35) | | 149 (61) | 96 (39) | |
| | Not known | 2 | 0 | | 1 | 0 | |
| | | | | | | | |
| | | **Median (IQR) [N]** | **Median (IQR) [N]** | **p-value (Mann-Whitney)** | **Median (IQR) [N]** | **Median (IQR) [N]** | **p-value (Mann-Whitney)** |
| **Acute pain at rest*** | | 3 (2-5) [199] | 2 (1-4) [95] | 0.001 | 3 (2-5) [177] | 2 (1-4) [104] | 0.11 |
| | | **N(%)** | **N(%)** | **p-value ($\chi^2$ test)** | **N(%)** | **N(%)** | **p-value ($\chi^2$ test)** |
| **Altered** | Yes | 93 (77) | 28 (23) | 0.005 | 81 (69) | 36 (31) | 0.07 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **sensations or numbness (acute)**** | | | | | | | |
| | No | 106 (61) | 69 (39) | | 96 (58) | 70 (42) | |
| | Not known | 11 | 1 | | 6 | 3 | |

*Pain at rest in first postoperative week. **First postoperative week.

**Table 6: Multiple logistic regression models predicting chronic pain at 4 and 9 months**

| | | Chronic pain at 4 months (N=243) | | Chronic pain at 9 months (N=235) | |
|---|---|---|---|---|---|
| | | **Odds ratio (95% CI)** | **p-value** | **Odds ratio (95% CI)** | **p-value** |
| **Age** | | 0.91 (0.87, 0.95) | <0.001 | 0.95 (0.91, 0.98) | 0.002 |
| | | | | | |
| **Type of breast surgery** | WLE | 1 | 0.44 | 1 | 0.88 |
| | Mastectomy | 1.38 (0.60, 3.15) | | 1.07 (0.43, 2.67) | |
| | | | | | |
| **Type of axillary surgery** | SLNB | 1 | 0.11 | 1 | 0.02 |
| | ANS | 0.70 (0.31, 1.54) | | 0.62 (0.30, 1.29) | |
| | ANC | 2.40 (0.82, 6.94) | | 2.97 (1.09, 8.06) | |
| | | | | | |
| **ICBN status** | Not identified/preserved | 1 | 0.25 | 1 | 0.49 |
| | Divided/damaged | 1.72 (0.68, 4.30) | | 1.35 (0.57, 3.16) | |
| | | | | | |
| **Preoperative chronic pain** | No | 1 | 0.19 | 1 | 0.73 |

| | | | | | |
|---|---|---|---|---|---|
| | Yes | 1.98 (0.71, 5.47) | | 1.16 (0.50, 2.66) | |
| | | | | | |
| **Preoperative psychological robustness*** | | 0.70 (0.49, 0.99) | 0.04 | 0.78 (0.56, 1.09) | 0.14 |
| | | | | | |
| **Multiple procedures** | No | 1 | 0.06 | 1 | 0.10 |
| | Yes | 2.44 (0.95, 6.24) | | 2.00 (0.87, 4.57) | |
| | | | | | |
| **Pain at rest in first postoperative week (VAS 0-10)** | | 1.34 (1.12, 1.60) | 0.001 | 1.17 (1.00, 1.37) | 0.05 |
| | | | | | |
| **Numbness / altered sensations within first postoperative week** | No | 1 | 0.09 | 1 | 0.41 |
| | Yes | 1.80 (0.90, 3.59) | | 1.31 (0.69, 2.46) | |
| | | | | | |
| **Chemotherapy** | No | 1 | 0.05 | 1 | 0.60 |
| | Yes | 0.29 (0.81, 1.01) | | 0.80 (0.35, 1.85) | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | |
| **Radiotherapy** | No | 1 | 0.24 | 1 | 0.34 |
| | Yes | 1.69 (0.71, 4.00) | | 0.62 (0.24, 1.66) | |
| | | | | | |
| **Endocrine therapy** | No | 1 | 0.19 | 1 | 0.99 |
| | Yes | 0.49 (0.17, 1.41) | | 1.01 (0.45, 2.23) | |

*Composite psychological variable based upon factor analysis.

The model performance was adequate for both logistic regression models (Hosmer and Lemeshow goodness of fit test: $\chi^2$=6.11, df=8, p=0.64 (4 months); $\chi^2$=5.73, df=8, p=0.68 (9 months)).

**Table 7: Multiple logistic regression models predicting chronic pain of moderate to severe intensity (≥4) at 4 and 9 months**

| | | Moderate to severe chronic pain at 4 months (N=237) | | Moderate to severe chronic pain at 9 months (N=234) | |
|---|---|---|---|---|---|
| | | **Odds ratio (95% CI)** | **p-value** | **Odds ratio (95% CI)** | **p-value** |
| **Age** | | 0.96 (0.91, 1.00) | 0.08 | 1.00 (0.95, 1.04) | 0.82 |
| | | | | | |
| **Type of breast surgery** | WLE | 1 | 0.75 | 1 | 0.47 |
| | Mastectomy | 0.86 (0.32, 2.26) | | 0.47 (0.17, 1.24) | |
| | | | | | |
| **Type of axillary surgery** | SLNB | 1 | 0.19 | 1 | 0.007 |
| | ANS | 0.41 (0.14, 1.21) | | 0.31 (0.09, 1.01) | |
| | ANC | 1.25 (0.37, 4.18) | | 2.72 (0.87, 8.46) | |
| | | | | | |
| **ICBN status** | Not identified/preserved | 1 | 0.60 | 1 | 0.59 |
| | Divided/damaged | 0.75 (0.25, 2.18) | | 0.76 (0.28, 2.05) | |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Preoperative chronic pain** | No | 1 | 0.13 | 1 | 0.05 |
| | Yes | 2.05 (0.81, 5.16) | | 2.41 (0.99, 5.87) | |
| | | | | | |
| **Preoperative psychological robustness*** | | 0.86 (0.58, 1.26) | 0.44 | 0.52 (0.35, 0.77) | 0.001 |
| | | | | | |
| **Multiple procedures** | No | 1 | 0.05 | 1 | 0.68 |
| | Yes | 2.77 (0.98, 7.81) | | 1.25 (0.43, 3.61) | |
| | | | | | |
| **Pain at rest in first postoperative week (VAS 0-10)** | | 1.54 (1.27, 1.87) | <0.001 | 1.30 (1.08, 1.56) | 0.006 |
| | | | | | |
| **Numbness / altered sensations within first postoperative week** | No | 1 | 0.66 | 1 | 0.21 |
| | Yes | 0.83 (0.36, 1.89) | | 0.60 (0.26, 1.34) | |
| | | | | | |
| **Chemotherapy** | No | 1 | 0.57 | 1 | 0.91 |

| | | | | | |
|---|---|---|---|---|---|
| | Yes | 0.62 (0.12, 3.14) | | 1.10 (0.21, 5.71) | |
| | | | | | |
| **Radiotherapy** | No | 1 | 0.37 | 1 | 0.15 |
| | Yes | 0.60 (0.20, 1.80) | | 0.47 (0.16, 1.33) | |
| | | | | | |
| **Endocrine therapy** | No | 1 | 0.59 | 1 | 0.77 |
| | Yes | 0.68 (0.16, 2.78) | | 1.26 (0.27, 5.87) | |

*Composite psychological variable based upon factor analysis.

The model performance was adequate for both logistic regression models (Hosmer and Lemeshow goodness of fit test: $\chi^2$=10.05, df=8, p=0.26 (4 months); $\chi^2$=9.39, df=8, p=0.31 (9 months)).

**ABSTRACT**

Chronic post-surgical pain (CPSP) is a common postoperative adverse event affecting up to half of women undergoing breast cancer surgery, yet few epidemiological studies have prospectively investigated the role of pre-, intra- and postoperative risk factors for pain onset and chronicity. We prospectively investigated preoperative sociodemographic and psychological factors, intraoperative clinical factors and acute postoperative pain in a prospective cohort of 362 women undergoing surgery for primary breast cancer. Intraoperative nerve handling (division or preservation) of the intercostobrachial nerve was recorded. At 4 and 9 months after surgery, incidence of chronic painful symptoms, not present preoperatively, was 68% and 63% respectively. Univariate analysis revealed that multiple psychological factors and nerve division was associated with chronic pain at 4 and 9 months. In a multivariate model independent predictors of CPSP at 4 months included younger age and acute postoperative pain (OR 1.34, 95% CI 1.12, 1.60), whereas preoperative psychological 'robustness' (OR 0.70, 95% CI 0.49, 0.99), a composite variable comprising high dispositional optimism, high positive affect and low emotional distress, was protective. At 9 months, younger age, axillary node clearance (OR 2.97, 95% CI 1.09, 8.06) and severity of acute postoperative pain (OR 1.17, 95% CI 1.00, 1.37) were predictive of pain persistence. Of those with CPSP, a quarter experienced moderate to severe pain and 40% ~~25%~~ were positive on DN4 and S-LANSS. Overall, A high proportion of women report painful symptoms, altered sensations and numbness, in the upper body within the first 9 months after resectional breast surgery and cancer treatment.