The psychological predictors of acute and chronic pain in women following breast cancer surgery: A systematic review.

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Abstract

Objectives: Numerous psychological factors have been found to be associated with acute and chronic pain following breast cancer surgery. However, individual studies tend to be limited to a small number of predictors and many fail to employ prospective designs. This study aimed to identify a broader range of psychological predictors of acute and chronic pain following breast cancer surgery through a systematic review of relevant prospective studies.

Methods: Web of Science, psychINFO, PubMed, and MEDLINE databases were searched to identify relevant prospective cohort studies. Studies were included if women were to undergo mastectomy or wide local excision, if psychological factors were assessed before surgery, and pain assessed after surgery.

Results: Twelve studies (representing 11 independent cohorts) met the inclusion criteria and described 10 psychological predictors. Anxiety and depression were the most frequently assessed psychological factors, and were measured in nine of the 12 studies. Anxiety and psychological robustness emerged as significant predictors of acute pain. Distress was the strongest predictor of chronic pain. The relationship between depression and chronic post-surgical pain was, at best, mixed.

Discussion: This review has identified a range of psychological predictors of acute and chronic pain following breast cancer surgery, however the evidence was conflicting and limited. Future studies should demonstrate adequate power and take account of known confounders.

Key Words: Breast cancer surgery, acute pain, chronic pain, risk factors, psychological factors, depression, anxiety

INTRODUCTION

Breast cancer is the most common female cancer in the UK and USA, accounting for a third of all new cases of cancer in women.[1,2] In the UK, approximately three quarters of breast cancer patients receive surgery as part of their treatment.[3] Although surgery for breast cancer varies, from procedures involving the breast (mastectomy, lumpectomy or breast conserving surgery (wide local excision)), to those involving the axilla (axillary lymph node dissection or sentinel lymph node biopsy),[4] post-surgical pain is experienced by many patients regardless of the type of surgery.[5] This post-surgical pain has significant negative impacts on physical and psychological well-being.[6]

Whilst acute post-surgical pain (APSP) is an expected consequence of tissue damage due to surgery, patients also experience chronic pain following breast cancer surgery, with prevalence estimates for chronic post-surgical pain (CPSP) ranging from 20-60%.[5,7] This variability in prevalence rates of CPSP might be explained methodologically, by differences in the measures of pain used between studies[8,9] and clinically, by differences in the type of surgery received.[10]

The transition from acute post-surgical pain to persistent chronic pain is complex and can be influenced by a variety of factors, including psychological factors.[11,12] Research from mixed surgical populations has identified several psychological factors that predict post-surgical pain including: depression, anxiety, and pain catastrophizing.[13-15] Pre-surgical depression is moderately correlated with CPSP up to one year after surgery.[14,16] Similarly, pre-surgical anxiety and higher pain catastrophizing are all risk factors for the development of CPSP.[13,15]

That said, breast cancer surgery formed a small minority of the patients under scrutiny in studies reporting mixed surgical populations. Whilst, a recent review examined the role of demographic and clinical factors in the prediction of post-surgical pain solely following breast cancer surgery, consideration of psychological factors were notably absent.[17] Anxiety,

depression, and pain catastrophising, are commonly experienced psychological sequelae amongst cancer patients.[18,19] Further, elevated levels of these psychological factors can occur as a response to cancer diagnosis, treatment, and adjustment to life thereafter.[20] Thus understanding the role of psychological factors in post-surgical pain in breast cancer patients is of particular importance, especially because these factors are amenable to change.

Two reviews have attempted to address the role of psychological factors in persistent pain after breast cancer surgery.[21,22] However, the range of psychological predictors included in the reviews was limited and inclusion of cross-sectional and retrospective designs restricts the conclusions that can be drawn.[9] However, in general, correlational analyses indicated that pre-surgery anxiety, depression and pain catastrophising were associated with CPSP.[22] Thus, the role of psychological factors as predictors of post-surgical pain remains to be investigated fully. Both reviews focussed on chronic post-surgical pain and whilst acute and chronic post-surgical pain are distinct constructs, on average one in five patients develop CPSP from an initial APSP,[23] therefore it is important to identify whether the predictors of acute and chronic pain differ.[24]

Gaining an understanding of the role pre-surgical psychological factors in relation to acute and chronic pain following breast cancer surgery is important for the prevention of CPSP.[21] This understanding may inform the generation of pre-surgical, preventative strategies to reduce the risk of the development of CPSP and enable better management of APSP.[21] Therefore, the aim of this systematic review was to identify the range of psychological predictors of acute and chronic pain following breast cancer surgery, described in evidence from prospective cohort studies exclusively.

METHODS

The protocol for this review was registered with PROSPERO international prospective register of systematic reviews (registration: CRD42017065098) on 10th May 2017.

Search Strategy

MEDLINE, Web of Science, PubMed, and psychINFO were searched from 1997 to 2017 with the search being carried out on May 1st 2017. The search strategy combined keywords pertaining to surgery type, pain outcomes, psychological factors, predictor terms and study design. Minor adjustments were made to search terms where necessary for individual databases (full search terms and the database specific modifications are listed in Supplemental Digital Content 1). Reference lists of systematic reviews identified through the database search were checked to identify additional eligible studies.

Eligibility Criteria

Studies were included if they met the following criteria: 1) the population were women[1] aged 18+ years scheduled to undergo breast cancer surgery (studies that included a mixed surgical populations were eligible if they presented a separate analysis of the breast cancer sample); 2) the surgical interventions for breast cancer were defined as mastectomy or wide local excision; including lymph node surgery, e.g. axillary lymph node dissection, sentinel lymph node biopsy, and lymph node excision; 3) psychological factors were measured before surgery; 4) the outcome of the study was acute and/or chronic pain assessed after surgery, whereby acute pain was defined as pain lasting less than three months. Chronic pain was defined as pain lasting at least three months or longer;[25] 5) the design was a prospective cohort study, published as a fully accessible paper, in the English language from 1997 – 2017 (this time frame ensured surgical techniques were currently relevant).

Studies were excluded if they were: 1) retrospective or cross-sectional in design and a systematic review or meta-analysis; 2) if psychological factors were not assessed before surgery; 3) if breast reconstruction, chemotherapy, or radiotherapy were the only interventions; 4) pre-operative psychological factors were measured but not used to predict post-operative pain.

[1] women only were included because the prevalence of male breast cancer patients is low and it is likely that their psychological profile will be different

Study Selection

Following removal of duplicates, the primary reviewer (M.M.) independently screened all titles and abstracts of identified articles against the inclusion/exclusion criteria. Where articles were regarded as fulfilling eligibility criteria, full-text versions were obtained and assessed for inclusion. In order to assess how reliably eligibility criteria were applied, a second reviewer (J.V.) independently applied eligibility criteria to a random sample (50%) of articles at both the title/abstract and full-text selection stages. Agreement between the primary and secondary reviewer for application of eligibility criteria was tested using Cohen's kappa.[26,27] Any disagreements were resolved through discussion.

Data Extraction

The following data were extracted: sample size, mean age, recruitment procedures, type of surgical procedure, psychological factors investigated and their measurement, definition of acute or chronic pain, and measures used to assess pain outcomes, statistical analysis conducted, and the extent of the relationship between pre-surgical psychological factors and post-surgical pain. Any missing information was recorded as not reported. M.M. undertook data extraction for the studies independently and J.V. checked the data extracted from 50% of the studies; no data extraction errors were noted.

Quality Assessment

Study quality was assessed using the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies.[28] The tool assesses studies against 14 quality criteria (the criteria are described in full in Supplemental Digital Content 2). Each criterion is judged to either be met or not met; the instrument does not generate an overall quality score. When it could not be determined whether a criterion was met due to insufficient information, a rating of 'cannot determine' was given. Similarly, a rating of 'not reported' was given when all necessary information required to establish whether a criterion had been met was not given. Each study was given an overall quality

rating of good (study met 10 or more of the criteria), fair (study met between seven and nine criteria), or poor (study met less than seven criteria). Studies were not excluded from review on the basis of poor quality. M.M. independently assessed each study and a second reviewer (J.V.) checked the quality assessment of 50% of the sample; there were no disagreements in the quality assessment ratings.

Analysis

Studies were analysed separately on the basis of pain outcomes by dividing the studies into either or both of two categories: a) those which assessed APSP, and b) those which assessed CPSP. This facilitated an examination of psychological factors within each pain category, and also across both pain categories, in order to identify if the same or different psychological factors predict APSP and CPSP. The diversity of psychological predictors and outcomes precluded meta-analyses therefore qualitative data synthesis and summary of results are presented.

RESULTS

Study Selection

The initial search identified 412 studies; after removing duplicates, 115 remained. An additional three studies were identified through hand searching of reference lists of systematic reviews identified by the electronic database search. The title and abstracts were screened for eligibility, of which 82 studies were excluded. Therefore, 36 full-text studies were retrieved for detailed evaluation of eligibility; 24 were excluded and 12 studies were included in the final review, which reported on 11 independent cohorts (see Figure 1) (details of excluded studies are provided in Supplemental Digital Content 3). Agreement between reviewers when applying inclusion and exclusion criteria at title and abstract stage was excellent (κ=.82) and at full-text assessment was good (κ=.73).[29]

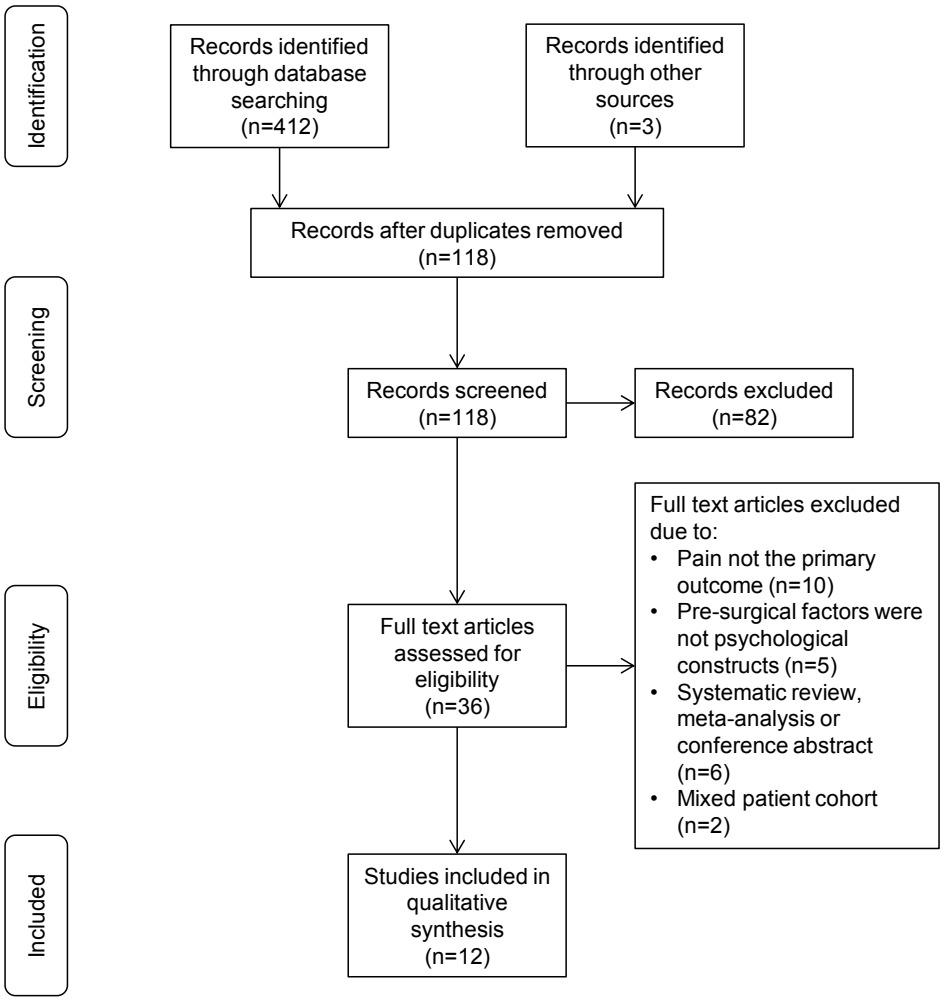

Figure 1. PRISMA flow diagram of the study selection process

Study Characteristics

Seven studies were European (Denmark (two studies),[30,31] UK (three),[32-34] France (one)[35] and Finland (one)[36]) and five were from the USA.[37-40] Size of cohorts varied, ranging from *N*=63 to *N*=537. The 12 studies reviewed reported on 11 independent cohorts; two studies

reported on the same patient cohort.[37,38] Participant mean age across the majority of studies fell within the range 50-59 years. Exceptions to this included two studies where the mean age was younger, 45-49 years[39,41] and two studies that reported a median age of 60 and 61 respectively.[30,31] The percentage of women undergoing each type of surgical procedure differed widely across studies (Table 1).

Table 1 Study characteristics

Author, year	Country	Population, recruitment	Cancer status and stage (% or mean, SD)	Location of pain	Surgery (% or mean, SD)	Sample size	Age (yrs) (SD), range
Acute Pain							
Baudic et al. 2016[35]	France	Women 18-85 years, recruited May 2008-June 2011 from Rene Huguenin Hospital	Data unavailable	Breast, axilla, chest wall of operated side, medial upper arm	Mastectomy (64%), wide local excision (36%) Both including axillary lymph node dissection	100	55.24 (12.10), 32-80
Bruce et al. 2012[32]	UK	Women, 18+ years, recruited over 18 months from four breast cancer centres across North of Scotland	Invasive (95%), Non-invasive (5%). Tumour Grade I (13%), II (51%), III (37%)	Data unavailable	Wide local excision (64%), mastectomy (26%), mastectomy with concurrent reconstructive surgery (4%). Sentinel lymph node biopsy (42%), axillary node clearance (31%), or axillary four node sample (28%)	338	59.1 (10.8)
Katz et al. 2005[33]	UK	Women 18+ years	Benign (29.4%), malignant (70.6%)	Data unavailable	Lumpectomy (simple lumpectomy without axillary node dissection or lumpectomy with sentinel lymph node biopsy and without axillary dissection) (56%), lumpectomy with nodes or	114	58.2 (12.0), 21-81

					mastectomy (lumpectomy with axillary dissection, simple mastectomy, or modified radical mastectomy) (44%)		
Montgomery et al. 2004[39]	USA	Women 18+ years, recruited from Mount Sinai Medical Centre	Lumpectomy patients only: Stage 0 (48%), Stage I (39%), Stage II (13%)	Data unavailable	Wide local excision (30%), excisional breast biopsy (70%)	63	48.71 (12.42)
Montgomery et al. 2010[41]	USA	Women 18+ years, recruited Feb 2000-2006 from Mount Sinai Medical Centre	Only reported post-surgery: cancer negative (65%), Stage 0 (9%), Stage I (17%), Stage II (9%)	Data unavailable	Wide local excision (30%), excisional breast biopsy (70%)	101	49.43 (14.06)
Chronic Pain							
Andersen et al. 2015[30]	Denmark	Women 18+ years, recruited November 2011 – October 2013 from Department of Breast Surgery at Rigshospitalet	Data unavailable	Breast, axilla, side of chest, arm	Wide local excision (66%), mastectomy (34%). Both including sentinel lymph node biopsy (68%) or axillary lymph node dissection (32)	537	Median = 60, IQR (50-68)
Baudic et al. 2016[35]	France	Women 18-85 years, recruited May 2008-June 2011 from Rene Huguenin Hospital	Data unavailable	Breast, axilla, chest wall of operated side, medial upper arm	Mastectomy (64%), wide local excision (36%) Both including axillary lymph node dissection	100	55.24 (12.10), 32-80
Bruce et al. 2014[34]	UK	Women 18+ years,	Invasive cancer (95%), Non-invasive (5%)	Breast/breast area, axilla, upper arm	Wide local excision (63.9%), mastectomy (25.8%), mastectomy	362	59.1 (10.8)

		recruited over 18 months from four breast cancer centres across North of Scotland			with concurrent reconstruction (4.2%). Sentinel lymph node biopsy (42.1%), axillary node sample (26%), or axillary node clearance (29.6%)		
Mejdahl et al. 2015[31]	Denmark	Women 18+ years, Recruited October 2008-October 2009 from Department of Breast Surgery at Rigshospitalet	Stage I (34.6%), Stage II (41.3%), Stage III (20.3%), Unfit (0.3%), Missing (3.5%)	Breast area, axilla, arm, side of body, and/or shoulder of operated side	Mastectomy (42.7%), wide local excision (66.8%). Sentinel lymph node biopsy (57.3%), axillary lymph node dissection (42.7%)	357	Median = 61, IQR (54-66)
Miaskowski et al. 2012[37]	USA	Women 18+ years, recruited from Comprehensive Cancer Centre, two public hospitals, and four community practices	No pain = Stage 0 (17.5, 22), Stage I (41.3, 52), Stage IIA and IIB (35.7, 45), Stage IIIA, IIIB, IIIC, IV (5.6, 7) Mild pain = Stage 0 (20.8, 36), Stage I (35.8, 62), Stage IIA and IIB (35.8, 62), Stage IIIA, IIIB, IIIC, IV (7.5, 13) Moderate pain = Stage 0 (17, 9), Stage I (39.6, 21), Stage IIA	Breast	No pain = breast conserving surgery (84.1, 106), mastectomy (15.9, 20) Mild pain = breast conserving surgery (77.5, 134), mastectomy (22.5, 39) Moderate pain = breast conserving surgery (75.5, 40), mastectomy (24.5, 13) Severe pain = breast conserving surgery (82.6, 38), mastectomy (17.4, 8)	398	Mean age for pain categories: No pain = 58.6(11.4) Mild pain = 53.4(11.5) Moderate pain = 53.4(12.1) Severe pain = 52.4(9.4)

			and IIB (30.2, 16), Stage IIIA, IIIB, IIIC, IV (13.2, 7) Severe pain = Stage 0 (13, 6), Stage I (34.8, 16), Stage IIA and IIB (39.1, 18), Stage IIIA, IIIB, IIIC, IV (13, 6)				
Miaskowski et al. 2014[38]	USA	Women 18+ years, recruited from Comprehensive Cancer Centre, two public hospitals, and four community practices	No pain = Stage 0 (24.4, 0) Stage 1 (45.1, 74) Stage IIA and IIB (28.7, 47) Stage IIIA, IIIB, IIIC, IV (1.8, 3) Mild pain = Stage 0 (18.3, 7) Stage I (34.4, 32) Stage IIA and IIB (38.7, 36), Stage IIIA, IIIB, IIIC, IV (8.6, 8) Moderate pain = Stage 0 (11.7, 16) Stage 1 (32.1, 44) Stage IIA and IIB (40.9, 56) Stage IIIA, IIIB, IIIC, IV (15.3, 21)	Arm, shoulder	No pain = breast conserving surgery (86, 141), mastectomy (14, 23) Mild pain = breast conserving surgery (79.6, 74), mastectomy (20.4, 19) Moderate pain = breast conserving surgery (74.5, 102), mastectomy (25.5, 35)	398	Mean age for pain categories: No pain = 58 (12.1) Mild pain = 52.7(9.7) Moderate pain = 52.9(11.3)

Poleshuck et al. 2006[40]	USA	Women 18 + years	Benign (29.5%), Malignant (70.5%)	Data unavailable	Lumpectomy (simple lumpectomy without axillary node dissection or lumpectomy with sentinel lymph node biopsy and without axillary dissection) (56.8%), lumpectomy with nodes or mastectomy (lumpectomy with axillary dissection, simple mastectomy, or modified radical mastectomy) (43.2%)	95	58.5 (11.7), 28-81
Sipila et al. 2012[36]	Finland	Women 18-75 years, recruited from Helsinki University Central Hospital	Data unavailable	Breast, axilla, upper arm, lower arm	Wide local excision with sentinel node biopsy (41.7%), wide local excision with axillary evacuation (22.5%), mastectomy with sentinel node biopsy (12.9%), mastectomy with axillary evacuation (22.9%)	489	56.4 (9.28), 30-75

IQR = Interquartile Range

A total of ten different psychological predictors were reported (Table 2). Anxiety and depression were the most commonly assessed psychological factors, being reported in nine of the 12 studies.[30,32-38,40] Two measures were used to assess anxiety; the Hospital Anxiety and Depression Scale (HADS) and the Spielberger State-Trait Anxiety Inventory (STAI); the STAI was the most frequently used (eight studies).[32-38,40] Three measures were used to assess depression; the Beck Depression Inventory (BDI), the HADS and Centre for Epidemiological Studies-Depression (CED-S); the most frequently used measure was the BDI (four studies).[33,35 36,40]

One study assessed both acute and chronic pain;[35] four assessed acute pain only[32,33,39,41] and five assessed chronic pain only.[30,31,34,36,40] Two additional studies used growth mixture modelling to identify latent classes of pain using data collected pre-operatively through 6 months (6-7 assessments).[37,38] Data from these studies have been considered as representing chronic pain. Five different measures were used to assess APSP and CPSP, however numerical rating scales were the most frequently utilised measure for both types of pain. None of the studies formally defined acute pain and only three studies provided standard definitions for chronic pain as proposed by IASP.[31,34 40] The time to follow-up for APSP assessment ranged from immediately after surgery[39] until two month post-surgery.[35] Similarly, the follow-up for CPSP assessment varied from three[35,37,38,40] to 12 months post-surgery.[30,35,37,38]

Table 2 Psychological predictors and outcome measurement

Author, year	Psychological predictors: measures used	Pain measure	Post-surgery follow-up period	Statistical analysis (univariate, multivariate)
Acute Pain				
Baudic et al. 2016[35]	Anxiety: STAI-FV; Depression: BDI-FV; Catastrophising: PCS-FV; Alexithymia: TAS-FV	BPI	2 days, 2 months	t-test, logistic regression
Bruce et al. 2012[32]	Anxiety: STAI; Depression: HADS; Catastrophising: PCS; Affect: PANAS; Dispositional optimism: LOT; Psychological robustness: higher positive affect and optimism, with lower anxiety and depression	NRS	7 days	t-test, logistic regression
Katz et al. 2005[33]	Anxiety: STAI; Depression: BDI; Disease-specific emotional functioning: FACT-E	NRS	2, 10, 30 days	t-test, logistic regression
Montgomery et al. 2004[39]	Distress: VAS; Pain Response Expectancies: VAS	VAS	Immediately and before discharge from hospital	Pearson correlation, linear regression
Montgomery et al. 2010[41]	Distress: SV-POMS (tension anxiety subscale); Pain response expectancies: VAS	BPI	7 days	Pearson correlation, multiple regression
Chronic Pain				
Andersen et al. 2015[30]	Anxiety and Depression: HADS; Catastrophising: PCS; Distress: DT	NRS	6 months, 1 year	Pearson correlation, logistic regression
Baudic et al. 2016[35]	Anxiety: STAI-FV; Depression: BDI-FV; Catastrophising: PCS-FV; Alexithymia: FV-TAS	BPI	3, 6, 12 months	t-test, logistic regression
Bruce et al. 2014[34]	Anxiety: STAI; Depression: HADS ; Catastrophising: PCS; Affect: PANAS; Dispositional optimism: LOT; Psychological Robustness: higher positive affect and optimism, with lower anxiety and depression	BPI	4, 9 months	t-test, logistic regression
Mejdahl et al. 2015[31]	Distress: DT	NRS	8 months	X^2, logistic regression
Miaskowski et al. 2012[37]	Anxiety: STAI; Depression: CES-D	BSQ and NRS	3, 4, 5, 6 months	ANOVA
Miaskowski et al. 2014[38]	Anxiety: STAI; Depression: CES-D	ASQ and NRS	3, 4, 5, 6 months	ANOVA
Poleshuck et al. 2006[40]	Depression: BDI; Anxiety: STAI; Disease specific emotional functioning: FACT-E	NRS	3 months	t-test, logistic regression
Sipila et al. 2012[36]	Anxiety: STAI; Depression: BDI	NRS	6 months	Pearson correlation, Bayesian method

Measures: ASQ, Arm/Shoulder Symptoms Questionnaire; BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; BSQ, Breast Symptoms Questionnaire; CES-D, Centre for Epidemiological Studies-Depression; CSQ, Coping Strategies Questionnaire; DT, Distress Thermometer; FACT-E, Functional Assessment of Cancer Treatment Emotional Scale; FV, French Version; HADS, Hospital Anxiety and Depression Scale; LOT, Life Orientation Test; NRS, Numerical Rating Scale; PANAS, Positive and Negative Affect Scale; PCS, Pain Catastrophising Scale; STAI, Spielberger State-Trait Anxiety Inventory; SV-POMS, Short Version-Profile of Mood States; TAS, Toronto Alexithymia Scale; VAS, Visual Analogue Scale Statistical analyses: ANOVA, Analysis of Variance; X^2, Chi-square; GMM, growth mixture modelling

Quality Assessment

Eleven studies were rated Good[30,35,36,37,38,39,41] and one rated Fair.[33] Studies were least likely to meet the criterion of providing a justified sample size, power description, variance or effect estimates (criterion 5), which was met by only two studies.[32,34] None of the studies met criterion 10 (Was the exposure(s) assessed more than once over time?). All the included studies measured the psychological factors on one occasion only prior to surgery and therefore failed to meet this criterion. However, it could be argued that unless the psychological factors are likely to change within a short time frame, their measurement on more than one occasion prior to surgery is unnecessary. That said, recoding of criterion 5 as not applicable would not alter the overall rating of any study.

Psychological Predictors Of Acute Pain

A total of five studies assessed psychological predictors of APSP (See Table 4). There was little commonality across the majority of studies in relation to which psychological predictors were investigated; anxiety[33,35] distress and response expectancies[39,41] were each assessed in two studies. The predictive utility of depression,[35] catastrophising,[35] alexithymia (a disorder which reflects a disturbance in psychological functioning and is characterised by a deficit in emotional awareness, whereby difficulties exist in identifying and describing emotions)[35] and psychological robustness (defined as a combination of positive affect and dispositional optimism)[32] were also investigated.

Table 3 Quality assessment of included studies

Criteria*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall
Andersen et al. 2015[30]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	N	Good
Baudic et al. 2016[35]	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	Y	Y	N	Good
Bruce et al. 2012[32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NR	Y	Y	Good
Bruce et al. 2014[34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NR	Y	Y	Good
Katz et al. 2005[33]	N	N	Y	CD	N	Y	Y	Y	Y	N	Y	N	N	Y	Fair
Mejdahl et al. 2015[31]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	Good
Miaskowski et al. 2012[37]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Good
Miaskowski et al. 2014[38]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	Good
Montgomery et al. 2004[39]	Y	Y	Y	CD	N	Y	Y	Y	Y	N	Y	N	Y	Y	Good
Montgomery et al. 2010[41]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	CD	Y	Good
Poleshuck et al. 2006[40]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	CD	Y	Y	Good
Sipila et al. 2012[36]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	N	Good

CD = Cannot determine; N = No; NR = Not reported; Y = Yes

*Criteria: 1. Was the research question or objective in this paper clearly stated? 2. Was the study population clearly specified and defined? 3. Was the participation rate of eligible persons at least 50%? 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants? 5. Was a sample size justification, power description, or variance and effect estimates provided? 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome? 9. Were the exposure measures clearly defined, valid, reliable, and implemented consistently across all study participants? 10. Was the exposure(s) assessed more than once over time? 11. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? 12. Were the outcome assessors blinded to the exposure status of participants? 13. Was loss to follow-up after baseline 20% or less? 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure and outcome?

Anxiety

The association between pre-surgery anxiety and APSP was absent or weak. One study failed to find an association between pre-surgery state anxiety and APSP.[35] Whilst, another found a weak association between pre-surgery anxiety (overall STAI anxiety score) and APSP at two and 30 days post-surgery (OR: 1.06, 95% CI: 1.02-1.10 and OR: 1.08, 95% CI: 1.01-1.17 respectively).[33]

Depression, Distress And Response Expectancies

Depression was not predictive of APSP two days post-surgery.[35] Two studies investigated the association between pre-surgery distress, response expectancies and APSP.[39,41] Response expectancies were defined as specific expectations regarding surgical outcomes which were beyond individual volition, such as the expected level of post-surgical pain. Both studies demonstrated that pre-surgery distress did not predict APSP. However pre-surgery response expectancies, i.e. expecting to experience pain after surgery, predicted acute pain immediately after surgery, explaining 29% of the variance in APSP intensity and this relationship was maintained one-week later.[41]

Other Predictors

Psychological robustness, defined as a combination of positive affect and dispositional optimism, predicted two forms of acute pain, namely, pain at rest (OR: 0.63, 95% CI: 0.48-0.82) and movement evoked pain (OR: 0.71, 95% CI: 0.54-0.93) seven days post-surgery.[32] Catastrophising was not predictive of APSP two days post-surgery, but was weakly associated with APSP at two months follow-up (OR: 0.95, 95% CI: 0.90-0.99)[35]. Alexithymia did not predict APSP.[35]

Table 4 Psychological predictors of acute pain

Author, year	Follow-up	Psychological predictors	*P*-value	Odds ratio	95% CI
Baudic et al. 2016[35]	2 days	State Anxiety	0.12	0.97	(0.93-1.01)
		Depression	0.52	0.95	(0.79-1.13)
		Catastrophising	0.41	0.98	(0.94-1.03)
		Alexithymia	0.97	1.00	(0.93-1.07)
	2 months	State Anxiety	0.60	1.02	(0.96-1.07)
		Depression	0.19	0.91	(0.79-1.05)
		Catastrophising	0.01	0.95	(0.90-0.99)
		Alexithymia	0.42	0.97	(0.89-1.05)
Bruce et al. 2012[32]	7 days	Psychological robustness	0.001	0.63	(0.48-0.82)
	7 days	Psychological robustness	0.01	0.71	(0.54-0.93)
Katz et al. 2005[33]	2 days	Anxiety	0.003	1.06	(1.02-1.10)
	30 days	Anxiety	0.03	1.08	(1.01-1.17)
Montgomery et al. 2004[39a]	Immediately after surgery	Distress	0.20	.29 (R^2)	
		Response expectancies	<.001		
Montgomery et al. 2010[41b]	7 days	Distress	0.05	.28 (R^2)	β = .17
		Response expectancies	<.001		β = .37

[a]study reported total model R^2 and *p*-values only. [b]study reported standardised beta-weight co-efficient (β) and *p*-values for each predictor, alongside total model R^2. 95% CI = 95% confidence intervals

Psychological Predictors Of Chronic Pain

Eight studies assessed psychological predictors of CPSP (see Table 5). Anxiety and depression were both assessed in six studies.[30,35-38,40] Catastrophising,[35] psychological robustness,[34] distress,[31] alexithymia,[35] and disease specific emotional functioning[40] were each assessed in one study.

Anxiety

The associations between pre-surgery anxiety and post-surgical chronic pain were mixed. One study found a significant correlation between state (r = .17) and trait anxiety (r = .23) and CPSP at six months.[36] Another found a weak association between pre-surgery state anxiety and CPSP at three months (OR: 1.08, 95% CI: 1.01-1.15).[35] Other studies did not find an association between pre-surgery anxiety and CPSP at three,[40] six, or 12 months.[30,35] Two studies classified women according to their level of post-surgical pain and then compared their pre-surgical level of anxiety.[37,38] Women classified as having severe or moderate pain six months post-surgery reported higher levels of anxiety than women who reported no pain post-surgery.[37] Similarly, women classified as having moderate arm/shoulder post-surgical pain up to six months after surgery reported greater pre-surgical trait anxiety scores compared to women classified as having no pain in the arm/shoulder.[38]

Depression

One study found a weak correlation between pre-surgery depression and CPSP at three months (r = .17).[36] Other studies demonstrated that pre-surgery depression was not a significant predictor of chronic pain at three,[35,40] six or twelve months[35] post-surgery. Women who reported severe or moderate pain up to six months after surgery reported significantly higher pre-surgical depression scores compared to women who reported no pain up to 6 months after surgery.[37] Similarly, women reporting moderate arm/shoulder pain up to 6 months after surgery reported significantly higher pre-surgery depression scores compared to women classified as having no arm/shoulder pain up to 6 months after surgery.[38]

Other Predictors

Alexithymia was found to be a significant predictor of CPSP at three (OR: 1.12, 95% CI: 1.01-1.24), six (OR: 1.09, 95% CI: 1.00-1.18), and twelve months (OR: 1.16, 95% CI: 1.04-1.29).[35] Pain catastrophising was not associated with CPSP at any point after surgery.[35]

Psychological robustness was a significant predictor of CPSP at four months (OR: 0.70, 95% CI: 0.49-0.99), indicating that psychological robustness was associated with a decreased likelihood of CPSP but this relationship was absent at 9 months follow-up.[34]

One study identified pre-surgery distress as a significant predictor of CPSP at eight months (OR: 2.05, 95% CI: 1.18-3.56).[31]

Lastly, disease specific emotional functioning, characterised as low mood and anxiety specifically in cancer patients, assessed via the Functional Assessment of Cancer Treatment-Emotional Scale, was did not predict CPSP.[40]

Table 5 Psychological predictors of chronic pain

Author, year	Pain follow-up	Psychological predictors	*P*-value	Odds ratio	95% CI
Andersen et al. 2015[30]	1 year	Anxiety	0.12	1.41	(0.91-2.22)
Baudic et al. 2016[35]	3 months	State Anxiety	0.03	1.08	(1.01-1.15)
		Depression	0.67	0.96	(0.78-1.18)
		Catastrophising	0.14	0.95	(0.89-1.02)
		Alexithymia	0.03	1.12	(1.01-1.24)
	6 months	State Anxiety	0.05	1.05	(1.00-1.11)
		Depression	0.55	1.05	(0.89-1.25)
		Catastrophising	0.20	0.97	(0.92-1.02)
		Alexithymia	0.04	1.09	(1.00-1.18)
	12 months	State Anxiety	0.31	1.03	(0.97-1.10)
		Depression	0.74	1.04	(0.84-1.28)
		Catastrophising	0.22	.096	(0.90-1.02)
		Alexithymia	0.01	1.16	(1.04-1.29)
Bruce et al. 2014[34]	4 months	Psychological robustness	0.04	0.70	(0.49-0.99)
	9 months	Psychological robustness	0.14	0.78	(0.56-1.09)
Mejdahl et al. 2015[31]	8 months	Distress	0.01	2.05	(1.18-3.56)
Miaskowski et al 2012[37]	6 months	State Anxiety	0.002	$F = 4.88$	
		Trait Anxiety	< .001	$F = 7.22$	
		Depression	< .001	$F = 9.15$	
Miaskowski et al 2014[38]	6 months	State Anxiety	Not significant data		
		Trait Anxiety	unavailable	$F = 4.83$	
		Depression	0.009	$F = 3.19$	
			0.04		
Poleshuck et al. 2006[40a]	3 months	Anxiety	0.49		
		Depression	0.14		
		Disease specific emotional functioning	0.11		
Sipila et al. 2012[36b]	6 months	Depression	< .001	$r = .17$	
		State anxiety	< .001	$r = .17$	
		Trait anxiety	< .001	$r = .23$	

[a]psychological predictors not included in multivariate analysis. [b]Univariate (correlation) results available only; 95%CI = 95% confidence intervals

DISCUSSION

This systematic review included 12 prospective cohort studies across 11 independent cohorts that assessed psychological predictors of acute and chronic pain following breast cancer surgery. Overall the evidence base was limited with only 11 independent cohorts available for scrutiny and many of the predictors were only measured in a single cohort.

The results demonstrated inconclusive evidence that pre-surgery anxiety, distress, and psychological robustness predict APSP and CPSP. There was no evidence demonstrating that pre-surgery depression or pain catastrophizing or disease specific emotional functioning were predictors of either form of post-surgical pain.

Evidence for pre-surgery anxiety as a predictor of APSP and CPSP was weak. Studies found either only a weak association, indicated by small odds ratios, or no association at all. Similarly, there was little evidence to support pre-surgery depression as a predictor of postsurgical pain. Whilst previous reviews have identified pre-surgery anxiety and depression as predictors of post-surgical pain[14,15] these reviews were based on studies that included a variety of surgery types. In both of the earlier reviews surgery for musculoskeletal problems, primarily elective joint replacement surgery, were dominant. Patients undergoing surgery for breast cancer were a small minority of studies under review (one study out of 18[15] and nine out of 50[14] reported on breast cancer sugery). There was some evidence in both reviews that the risk factors for post-surgical pain differ by surgery type. For example, in the Theunissen et al review[15] approximately two thirds of the musculoskeletal studies reported a significant association between anxiety or pain catastrophising and CPSP. In contrast, only 36% of the studies reporting other types of surgery found an association. The single study of breast cancer surgery included in the review did not find an association between anxiety and CPSP. Similarly, in the Hinrichs-Roker[14] review pre-surgical depression was predictive of CPSP in a variety of musculoskeletal surgeries whereas the results for

breast cancer surgery were mixed. Five of the nine breast cancer studies reviewed examined pre-surgical psychological factors; pre-surgical depression predicted CPSP in two of the five studies. Thus, the results of the current review are not dissimilar to previous findings when the focus is on breast cancer surgery rather than mixed surgical types. It is possible to speculate why the findings might be more variable in women undergoing surgery for breast cancer compared to other surgery types. Elective joint replacement surgery is the dominant form of surgery within the mixed surgical cohorts and there are three obvious differences between joint replacement surgery and surgery for breast cancer that might go some way to account for these differences. First, surgery for breast cancer is not elective whereas joint replacement surgery is. Second, joint replacement surgery is uniform whereas the type of surgery for breast cancer is very variable. Third, the timescale experienced by patients undergoing each type of surgery is hugely different. Patients with osteoarthritis will generally have been living with the condition for many years prior to electing for surgery. In contrast, the time between diagnosis and surgery for breast cancer is usually measured in weeks or months rather than years. Thus the time course of presurgical psychological factors will be different; likely chronic in osteoarthritis and acute in breast cancer.

Similarly, the majority of existing research that identifies pre-surgery catastrophising as a predictor of post-surgical pain involves other surgical procedures.[15] Consequently, pre-surgical catastrophising as a risk factor for post-surgical pain may also depend on the surgical model and population sampled.

A range of novel psychological predictors were identified which have not been previously reviewed, including: distress, response expectancies, alexithymia, and psychological robustness. However, these factors tended to be examined in single studies and not all studies employed standard measures of the psychological construct of interest. For example, pre-surgery distress was associated with a significant risk of CPSP. However, distress was conceptualised broadly including a variety of emotional responses, assessed via the Distress Thermometer.[31] It would, therefore, be useful to assess the predictive utility

of distress using other measures such as the Brief Symptom Inventory,[42] which may also help to elucidate specific facets of distress as predictors of post-surgical pain.

Study quality varied and the included studies had some limitations. Half the studies failed to control for factors that could have impacted on pre-surgical psychological factors and the experience of acute and/or chronic surgical pain such as receiving adjuvant therapy after surgery or existing pre-surgical pain. Radiotherapy in particular presents a higher risk of developing CPSP.[9] For example, radiotherapy predicted a seven percent increase in the absolute risk of developing CPSP.[17] Additionally, radiotherapy and ongoing treatment in the context of cancer have been associated with increased emotional distress.[43] Pre-surgical pain is also a risk factor for post-surgical pain[17,44,45] and existing pain has also been associated with psychological comorbidities, in particular depression. Therefore, pre-surgical pain could have impacted on levels of pre-surgical psychological variables[44] and the failure to control for this association is concerning.

There are some limitations to this review. The search may have missed studies as it was conducted primarily across electronic databases and grey literature was not consulted. Consequently, the possibility of publication bias cannot be excluded. However, reference lists of systematic reviews identified through the search were scanned, in an attempt to reduce this issue. In addition, the review was limited to prospective studies thus, the role of other psychological factors, assessed in other study designs, such as post-traumatic stress[46] and personality[47] may merit consideration in future reviews. Further, whilst the focus of the review was on psychological factors alone, it is recognised that those factors are a component of a larger complex of sociodemographic and clinical factors that together act to influence post-surgical pain.

Conclusion

This systematic review identified a range of psychological predictors of acute and chronic pain following breast cancer surgery. Common predictors of both APSP and CPSP were

identified, alongside distinctive predictors for each type of pain. There was some evidence that pre-surgery anxiety, response expectancies, and psychological robustness predict APSP and some evidence that pre-surgery anxiety, distress, psychological robustness, and alexithymia predict CPSP. However, overall the evidence was limited, making it difficult to draw reliable conclusions. There were relatively few studies (only 11 independent cohorts) and many of the predictors were only assessed in a single cohort. This review identifies psychological factors that merit future study, however, additional work is also required to establish reliably the broader range of psychological predictors in order to identify the most important predictors of post-surgical pain. It would perhaps be useful if that work could focus on those predictors that are amenable to change.

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