**TITLE: PSYCHOLOGICAL FACTORS ARE ASSOCIATED WITH PAIN AT ALL
TIMEFRAMES AFTER BREAST CANCER SURGERY: A SYSTEMATIC REVIEW WITH META-
ANALYSES**

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ABSTRACT

Objective: This systematic review aimed to (1)to assess associations between psychological factors and pain following breast cancer (BC) treatment and, (2)to determine which pre-operative psychological factors predicted pain in the acute, sub-acute and chronic timeframes after BC surgery.

Design: A systematic review with meta-analysis

Subjects: Women with early-stage BC

Methods: Medline, EMBASE, CINAHL and Web of Science databases were searched between 1990 and January 2019. Studies that evaluated psychological factors and pain following surgery for early-stage BC were included. Associations between psychological factors and pain from early post-surgery to after 12 months were extracted. Effect size correlations (R equivalent) were calculated and pooled using random-effects meta-analysis models.

Results: From 4137 studies, 47 were included (n=15,987 participants; 26 studies within 12 months post-surgery and 22 studies after 12 months), the majority had low-moderate risk of bias. Higher pre-operative anxiety and depression were weak but significant predictors of pain at all time points up to 12 months (R equivalent: 0.15-0.22). Higher pre-operative pain catastrophising and distress were also weak but significant predictors of pain during the acute (0-7days) and chronic (3-12months) periods (R equivalent: 0.10-0.20). For the period after 12 months post-surgery, weak but significant cross-sectional associations with pain were identified for anxiety, depression, pain catastrophising and distress (R equivalent: 0.15, 0.17, 0.25, 0.14 respectively).

Conclusion: Significant pooled effect size correlations between psychological factors and pain were identified across *all* timeframes. While weak, these associations should encourage assessment of key psychological factors during pre-operative screening and pain assessments at all post-operative timeframes.

INTRODUCTION

Pain after breast cancer (BC) treatment affects up to 60% of women treated for BC (1). BC is the leading cause of mortality and morbidity among women globally, with 15.1 million disability adjusted life-years reported between 2005 and 2015 (2). With 5-year survival rates reaching 90% (3), there is a need to improve quality of life following treatment; pain is one important factor affecting this. Moderate-severe pain at long-term follow up affects 25% of women following BC treatment (4), and is commonly associated with disability (5). Unfortunately this pain is frequently under-treated (6), often due to inadequate assessment (7). Psychological factors have long been recognised as pivotal in the pain experience (8), thus their role is important to consider within pain assessments.

Psychological factors, such as post-traumatic stress, low mood and anxiety, are known to affect those with BC (9, 10). Psychological factors and pain commonly co-exist and influence each other via several mechanisms. Pain and mood disturbance share common neurobiological pathways and neurotransmitters, influencing each other directly (11). Further, functional MRI findings highlight connectivity between the limbic system and pre-frontal cortex with subsequent influence on descending pain modulation from the periaqueductal grey and rostro-ventral medulla (12). In recent clinical studies, links between dysfunctional pain modulation and both high stress responses (13), and pain catastrophizing have been identified in healthy populations and in women with pain following BC treatment (14), indicating that mood and pain-related cognitions impact on pain modulation specifically in this population. Therefore, understanding the association psychological factors have with pain, as well as how much they predict pain in this population is crucial to enhance appropriate assessment and treatment.

Risk factors for developing pain following BC treatment have attracted considerable attention. In a recent meta-analysis, Wang and colleagues identified high quality evidence that younger age, axillary lymph node dissection and radiotherapy increased the risk of persistent pain following BC with moderate quality evidence that pre-operative pain was a risk factor (15). Although not included in their meta-analyses, Wang et al. (15) reported that depression and previous stressful life events were associated with persistent pain following BC treatment, though the magnitude of association was likely to be small. They found little support for other psychological factors. A subsequent meta-analysis of 13 studies of pain predictors demonstrated that depression and anxiety were not predictive of pain, when

other factors are controlled for (16). Both of these reviews (15, 16) focused only on identifying predictors for persistent pain, that is pain that lasts for more than three months, following BC treatment. One further systematic review summarised data from 12 studies on psychological predictors for both acute and persistent pain following BC treatment(17). Their results suggest anxiety and distress may play more important roles than previously reported but overall, their results were mixed and limited by the lack of meta-analyses. In summary, these reviews provide conflicting results; therefore, information on risk factors for different stages of pain (acute, sub-acute and chronic) are currently unclear.

A second strategy in understanding pain profiles is to analyse psychological co-morbidities with pain (18). Clinically, this is important to build a multi-dimensional profile of the individual with pain and develop individualised treatment approaches. Knowledge of which factors most commonly present with pain is therefore important. In the aforementioned systematic reviews only predictive studies that provided adjusted analyses were included, thus excluding a large proportion of data available. Given the volume of data available on psychological factors and pain in this population, synthesising this evidence in order to guide future research and inform appropriate clinical assessments within BC populations is warranted.

The aims of this study, therefore, were to systematically review the literature (1) to assess whether psychological factors were associated with pain following BC treatment at different timeframes up to and after 12 months post diagnosis or surgery, and (2) to determine which psychological factors predicted pain across acute, sub-acute and chronic timeframes up to 12 months post-surgery.

METHODS

Identification and selection of studies

Eligibility criteria

This systematic review was registered with PROSPERO (Registration number; CRD42016029834) and conducted in accordance with PRISMA and other guidelines for reporting and conducting systematic reviews (19).

A literature search was undertaken using the following databases: Medline, EMBASE, CINAHL and Web of science. Studies were included if they were: full text in English language and published between 1990 and January 2019; cross sectional, longitudinal cohort, case control in design or presented baseline data from randomised controlled trials; assessed both psychological factors and pain in females over 18 years of age who presented with early stage breast cancer treatment (Stage 0-III) using standardized and valid psychological and pain measures. Further, studies had to present a measure of association between pain and psychological factors or present between group comparisons for these measures. In studies where this was not reported, data was sought by contacting authors directly, with up to three attempts made before exclusion. Because we aimed to analyse data according to various timeframes, studies were also excluded if the timeframes at which they assessed were unclear or we were unable to categorise them according to distinct categories. Studies were also excluded if they included participants with Stage IV cancer (given the impact on pain and treatment profiles), mixed types of cancer or reported symptom clusters, whereby pain and/or psychological data were not independently available.

Search strategies were developed with the aid of a medical librarian and used a combination of Medical Subject Heading (MeSH), key search terms and their derivatives for “breast cancer”, “pain” and “psychological factors”. An example of the MEDLINE search strategy is outlined in *Appendix 1*. Relevant systematic reviews were hand-searched to identify any further records.

Study records

After deleting duplicates, two pairs of reviewers (NP/NM/ED/ADG) independently screened titles and abstracts for inclusion. Full texts were subsequently independently assessed by two pairs of reviewers (NP/NM/ED/ADG) and disagreements resolved by consultation with a third reviewer (NM/ED).

Data items

Data extraction from the included studies was performed by one researcher (NM) and cross-checked by two other researchers (ADG/PLG). The study characteristics of interest included: study type, number of participants and participant characteristics including stage, treatments, and research setting where available. The time point at which data was collected, psychological factors measured, psychological scores, pain measurement tools

used, pain scores, measure of association/comparison and level of significance were extracted. Data were grouped according to the following timeframes following diagnosis or surgery: 0-7 days (acute pain); 7 days – 3 months (sub-acute pain); >3 months to ≤12 months (early chronic). We also grouped data from studies reporting pain after 12 months (late chronic).

Assessment of characteristics of studies

Risk of bias in individual studies

Study quality of each included study was assessed by two researchers independently (NM/ADG) using the Newcastle-Ottawa Quality Assessment Tools (NOQAT) for cross-sectional, longitudinal and case control studies (20). The NOQAT items are given 0, 1 or, for some questions, 2 points. More comprehensive information receives more points. Item points are summed to give an overall score whereby higher scores indicate a lower risk of bias. Based on the overall score and consideration of the impact of items missing, the two researchers independently rated the studies as low, moderate or high risk of bias. Differences were resolved by discussion or consultation with a third reviewer (ED) if necessary.

Data analysis

Studies were assessed for the presence and magnitude of associations between psychological factors and pain. Meta-analyses were performed when two or more studies reported data for a similar psychological construct for each of the specified timeframes described above as well as after 12 months. Specifically, for studies reporting pain outcomes up to 12 months post-surgery/diagnosis, meta-analyses were conducted to evaluate the longitudinal association between psychological factors assessed at baseline (pre-surgery) with pain assessed post-surgery. For pain outcomes beyond 12 months, meta-analyses of the cross-sectional association between psychological factors and pain assessed at the same time point were conducted. No other cross-sectional data were meta-analysed because of insufficient data available for specific measures and timeframes within the 12-month period.

For other studies, such as those reporting cross-sectional associations up to 12 months or those in which pain was used as the predictor, narrative summaries were reported.

For all meta-analyses, where more than one result was available from within the same study, we prioritised a multivariable regression coefficient over a univariate regression coefficient / correlation coefficient and a univariate regression coefficient / correlation

coefficient over results from between group analyses. Where results were available for two time points within the same study or cohort, the earlier data were used in meta-analyses for the acute/sub-acute stages and the later data were used in meta-analyses for the chronic stages (> 3months). For studies that presented data on both state and trait anxiety, we prioritised trait anxiety over state anxiety (21). For the psychological variable 'distress' we included both specific measures of distress as well as combinations of psychological measures of distress e.g. Hospital Anxiety and Depression combined scores.

To enable pooling across the studies, the effect size correlation (R equivalent) was calculated (22). Effect size correlation is a standardised measure of the magnitude and direction of the association between each psychological factor and pain and is equivalent to Pearson correlation with values between -1 and +1. According to Cohen (23), correlations around ± 0.1 are considered a small effect size, around ± 0.3 are considered a moderate effect size and around ± 0.5 are considered a large effect size. Effect size correlation can be estimated from any reported data such as regression coefficients, t-tests, odds ratios and so on making it an ideal measure when diverse statistical methods are used between and within studies to examine associations. Positive effect size correlation values indicate increasing pain with increasing psychological factor scores while negative effect size correlation indicates decreasing pain with increasing psychological factor scores.

Random effects meta-analysis models, using the restricted maximum likelihood (REML) estimator for between studies variability, were used to pool the effect size correlations at each time point of interest for each psychological factor. Heterogeneity was assessed using I^2 and τ^2 . I^2 measures the proportion of total variability in the meta-analysis model that is due to heterogeneity (24) while τ^2 is an estimate of the variability between studies. The Q-test was used to determine whether significant heterogeneity was present (24). Publication bias was assessed visually using funnel plots and via the Egger bias test (25). The bias test was only conducted for meta-analyses with at least 10 studies included, as per Cochrane guidelines(26).

R statistical software using the meta package was used for all analyses (27). P-values less than 0.05 were considered significant (28).

Results

Flow of studies through review

We identified 4137 records; 47 papers were eventually retained (Figure 1). This included 10 studies that were added following receipt of information directly from authors (29-38).

During title, abstract and full text screen, the percentage of agreement between two independent reviewers was 84%, with independent review by a third reviewer or group discussion sufficient for resolving any remaining disagreement.

Studies were divided into those which presented data within 12 months of diagnosis or surgery (n=26 studies, 8 cross-sectional; 18 longitudinal, Table 1) and those which presented data after 12 months of diagnosis or surgery (n=22 studies, 12 cross-sectional, 10 longitudinal, Table 2) with one study providing data for both periods (29). In total, 15,987 participants with breast cancer were included: n=6979 (range 32-1499) within 12-month follow up; n=9008 (range 42-2582) after 12-month follow up. One cross sectional study, which collected data between six and 15 months after surgery, was included 'within 12 month follow-up' analysis (39). A further study (40), evaluated risks for pain between one and 12 months after the start of aromatase inhibitors, a treatment usually commencing late in the treatment regimen; it was grouped with studies 'after 12 months'. Two studies were derived from the same cohort but provided analyses for separate timeframes (41, 42). Of the studies included, 11 (2 cross-sectional, 9 longitudinal) covered the acute timeframe; 6 (3 cross-sectional, 3 longitudinal) the sub-acute timeframe 14 (4 cross-sectional, 10 longitudinal) the early chronic timeframe and 21 (11 cross-sectional, 10 longitudinal) the late chronic (>12months) timeframe.

Risk of bias (RoB) across studies

Results for RoB are presented within Tables 3 and 4, with more detail presented in Appendix Table 2. Generally, most studies had a representative or somewhat representative cohort. Minor bias was introduced by some studies applying exclusion criteria such as age (36, 40, 43-45) and excluding certain stages of cancer or treatment modalities (46-50).

Concerning comparability, higher scores were awarded if the study controlled for baseline or pre-existing pain. Correction for additional factors was conducted in two cross-sectional studies (31, 51), nine cohort studies (35-37, 40-42, 52-54) and two case-control studies (55, 56) decreasing the RoB. For this review, self-report measurements were considered the

most appropriate assessment for pain and of psychological factors in research studies. Therefore, all studies were allocated maximum scores for the criterion 'outcome assessment'. For cross-sectional studies, sample sizes were considered large in most studies. However, only five studies used a power calculation (31, 46, 50, 57, 58). Non-responder rate and/or characteristics were described in three studies only (59-61).

For longitudinal studies, additional criteria were considered. Only one study demonstrated that the outcome of interest was not present at baseline, reducing its RoB (40). All included studies reported a reasonable follow-up period; however, nine studies lost more than 15% of participants at follow-up (29, 33, 38, 40, 52, 54, 62-64). Selection of controls was biased in all studies and the response rate of the controls was only reported in one study (55).

When determining the overall grading for all studies, the authors accounted for unequal weighting of individual items where assumptions had to be made regarding the degree of bias with that item (i.e. each item of grading was not weighted equally). As a result, for the studies reporting results before 12 months post-surgery four studies had a high risk of bias (i.e. low scores on the NOQAT), 10 moderate risk of bias and 13 low risk of bias (i.e. high scores on the NOQAT). For studies reporting results after 12 months post-surgery, two studies had high risk of bias, nine moderate risk of bias and eight low risk of bias. The percentage of agreement between the two reviewers who conducted the RoB analysis was 74.4% with all remaining cases resolved by discussion or in consultation with a third reviewer (ED) as necessary.

Characteristics of the studies

Study characteristics are presented in Tables 1 and 2 with outcomes, predictors and results described in Tables 3a-d. Study participants were recruited from a variety of settings including oncology and surgical departments, university hospitals, specialist clinics or through cancer registries. All but three studies were conducted in countries classified as developed at the time of their data collection. The type of cancer treatments used included axillary lymph node dissection or sentinel node biopsy, total mastectomy or breast conserving surgery, radiotherapy, chemotherapy, immunotherapy and hormonal treatments.

Synthesis of results for timeframes up to 12 months

The results for pain and psychological measures used as well as measures of association are presented in Tables 3a-3c, for the acute (0-7 days), subacute (7 days – 3 months) and chronic (3-12 months) timeframes, respectively). For the outcome measures anxiety, depression, distress and pain catastrophizing, meta-analyses were possible (Table 5 and Supplementary Figures 2-5). Results from these psychological factors not included in the meta-analyses are given descriptively.

Anxiety

Meta-analyses revealed a weak but significant correlation between pre-operative anxiety and pain at all timeframes up to 12 months (n=6, 2 and 7 studies for **acute**, **sub-acute** and **chronic** timeframes respectively (Table 5; Supplementary Figures 2a-c). Results for R equivalent (95%CI) ranged from: 0.16 (0.09-0.24) for **sub-acute** to 0.22 (0.15-0.28) for the **acute** timeframe. Heterogeneity was low throughout ($I^2 = 0-51\%$; $p > 0.06$). Sensitivity analyses (Table 5), in which estimates from multivariate models were replaced with univariate estimates from the same study (where possible), had little impact on results; the pooled R equivalent increased in the second decimal place and CIs widened slightly. There was no evidence of funnel plot asymmetry (Appendix 3, Figure 1) and there were too few studies to be able to perform an Egger bias test.

Of the studies not included in meta-analyses, one cross-sectional study showed no significant relationship between pain and anxiety on day 1 or day 2 post-operatively (**acute**)(44); while mixed associations were identified in two studies within the **sub-acute** timeframe (53, 57) and one cross-sectional study within the **chronic** timeframe (39).

Depression

Meta-analyses revealed a weak but significant correlation between pre-operative depression and pain at all timeframes up to 12 months (n=6, 2 and 7 studies for **acute**, **sub-acute** and **chronic** timeframes respectively (Table 5; Supplementary Figures 3a-c). Results for R equivalent (95%CI) ranged from: 0.15 (0.07-0.23) for **chronic** to 0.24 (0.03-0.45) for the **sub-acute** timeframe. Heterogeneity was significant for the **chronic** timeframe ($I^2 = 70.4\%$; $p = 0.003$). Sensitivity analyses (Table 5), in which estimates from multivariate models were replaced with univariate estimates from the same study (where possible), removed the significant heterogeneity in the **chronic** model ($p = 0.30$), and for both **sub-acute** and **chronic**, reduced the interval width and increased the R equivalent slightly. There was no evidence

of funnel plot asymmetry (Appendix 3, Figure 2) and there were too few studies to be able to perform an Egger bias test.

Of the studies not included in meta-analyses pre-operative severe pain predicted higher levels of depression in the **acute** timeframe (OR: 2.64, 95%CI: 1.53-4.55) (65). For the **sub-acute** timeframe depression was correlated with pain intensity and interference in one study (57), although depression was not found to be associated with pain at 3 months in another (53).

Within the **chronic** timeframe, three studies were not included in meta-analyses. Higher depression scores and positive associations with depression were noted in those with chronic pain by (39, 66) respectively. However, pain was not found to be contributor to changes in depression (67).

Pain Catastrophising

Meta-analyses revealed a weak but significant correlation between pre-operative pain catastrophising and pain within the **acute** (n=3 studies, R equivalent (95%CI): 0.20 (0.08-0.32), and **chronic** timeframes (n=4 studies, R equivalent (95%CI): 0.11 (0.05-0.18), (Table 5; Supplementary Figures 4a-b). Heterogeneity was not significant ($I^2 = 25.4$ & 42.1% ; $p > 0.18$). Sensitivity analyses in the **chronic** group (Table 5) changed the pooled R equivalent by 0.01 units and reduced the interval width for the **acute** but not the **chronic** studies.

No meta-analyses were conducted for the **sub-acute** timeframe as only one study was available. It showed higher pre-operative pain catastrophising increased the odds of clinically meaningful pain ($>3/10$) 2 months post-surgery(68). Neither meta-analysis indicated evidence of funnel plot asymmetry (Appendix 3, Figure 3); there were too few studies to be able to perform an Egger bias test.

Distress

Meta-analyses revealed a weak but significant correlation between pre-operative distress and pain during the **acute** (n= 3 studies; R equivalent (95%CI) = 0.17 (0.07-0.26)) and **chronic** timeframes (n=3 studies; R equivalent (95%CI) = 0.16 (0.09-0.22)), (Table 5; Supplementary Figures 5a-b). Heterogeneity was low for both ($I^2 = 42.3$ and 0% ; $p > 0.18$). Sensitivity analyses were not possible since no other estimates were available. No meta-analyses were

conducted for the **sub-acute** timeframe. Once again, there was no evidence of funnel plot asymmetry (Appendix 3, Figure 4) and there were too few studies to be able to perform an Egger bias test.

For studies not included in meta-analyses, two studies from the same cohort showed no difference in distress between those with or without pain at the **sub-acute** timeframe (52, 53), while lower **emotional function** was associated with more pain in the **chronic** timeframe ($r = -0.40$, $p < 0.001$) (51).

Other psychological measures

0 -7 days

Acute pain was not correlated with **risk of mood disorders** (69), **cognitive coping** (45) or **alexithymia** (68). No difference in pre-operative **somatosensory amplification** was noted between those with and without acute pain (52). Bruce et al. reported no significant difference in **positive and negative affect scores** between those with and without acute pain; however, those with acute pain had lower **optimism**. Further their composite measure pre-operative **psychological robustness** was associated with lower acute pain scores (OR = 0.63, 95%CI = 0.48-0.82) (42). **Expectations of post-operative pain** significantly correlated with maximal pain intensity (70).

7 days - 3 months

Pre-operative alexithymia was associated with increased odds of pain at 3 months post-surgery but not at 2 months (68). Neither **somatosensory amplification nor illness behaviours** were found to be associated with pain or to differ between pain versus no pain groups (52, 53). **Emotional functioning** revealed mixed results in between group comparisons (31, 52, 53). Lower **mental health scores** were identified in those with pain versus those without (31).

3 - 12 months

The presence of chronic pain was not associated with **positive and negative affect** or **dispositional optimism**, nor did pre-operative **psychological robustness** predict chronic pain at 9 months (OR = 0.70, 95%CI = 0.49-0.99) (41). **Coping styles** were not associated with chronic pain intensity (66). **Alexithymia** at baseline increased the odds of pain at both 6 and

12 months (6mo OR = 1.09, 95%CI = 1.0-1.18 and 12mo OR = 1.16, 95%CI = 1.04- 1.29).

Lower internal locus of control scores were also associated with greater pain.(34)

Synthesis of results for timeframes after 12 months (late chronic)

The results for pain and psychological measures used as well as measures of association are presented in Table 3d.

For studies reporting cross-sectional associations after 12 months meta-analyses revealed a weak but significant effect size correlation between **anxiety and pain** (n=7 studies, R equivalent (95%CI) = 0.15 (0.10- 0.20)), (Table 5; Supplementary Figure 2d); **depression and pain** (n=10 studies, R equivalent (95%CI) = 0.17 (0.12- 0.22)), (Table 5; Supplementary Figure 3d); **pain catastrophising** (n=3 studies, R equivalent (95%CI) = 0.25 (0.15- 0.35) (Table 5; Supplementary Figure 4c)); and **distress** (n=2 studies, R equivalent (95%CI) = 0.14 (0.08 - 0.20) (Table 5; Supplementary Figure 5c)). There was no significant heterogeneity for any of these analyses ($p > 0.07$). None of the meta-analyses indicated evidence of funnel plot asymmetry (Appendix 3, Figure 5). The depression and pain meta-analysis had 10 studies enabling Egger's test for publication bias, which was not significant ($p=0.234$).

For studies not included in meta-analyses, one longitudinal study found that both higher **anxiety and depression** scores were predictive of both shoulder /arm pain and breast pain (64). Bell et al. reported that presence of pain was associated with **anxiety and depressed mood** more than 5 years after diagnosis(71). **Anxiety and depression** were found to be associated with mastectomy related pain but not phantom breast pain (5). Mustonen et al. reported that both **preoperative anxiety and depression** were higher in those who developed chronic postsurgical neuropathic pain (72) while **anxiety** but not **depression or pain catastrophizing** were found to be associated with neuropathic pain/symptoms (40, 63).

Other psychological factors

Poorer mental health, psychiatric symptomatology and somatising tendency were mainly associated with higher pain scores (46, 48, 49, 58, 59), except for one study that did not find a difference in mental health between patients with and without persistent pain(56). **Pain vigilance** and **awareness** as well as **negative affect** demonstrated weak correlations with

pain (32, 62). Neither **emotional stability** nor **positive wellbeing** were not significantly associated with pain burden (59) or the presence of pain respectively (71).

DISCUSSION

This systematic review and meta-analyses investigating the association between psychological factors and pain following BC surgery identified moderate evidence of consistent weak but significant correlations between pre-operative anxiety, depression, distress and pain catastrophising with post-operative pain at all timeframes up to 12 months. Additionally, in the period following 12 months post-surgery, weak but significant correlations between psychological factors and pain were identified. The majority of studies had low-moderate risk of bias. Anxiety and depression were the most comprehensively studied psychological constructs across studies, hence we can be reasonably confident that these results are generalisable. However, only a small number of studies were available for meta-analyses for the sub-acute timeframe (7days-3months) and for pain catastrophising and distress. Therefore, future data may influence the results of these meta-analyses.

Two important findings emerged from this systematic review that add to our current understanding of the role of psychological factors for pain following BC treatment. First, significant correlations were evident across all timeframes covering the acute, sub-acute and chronic pain timeframes up to and beyond 12 months, although we did not identify differences between timeframes. Previous meta-analyses have not covered all of these timeframes, while one previous systematic review without meta-analyses highlighted conflicting results across acute and chronic timeframes (17). However, our results indicate that the role of psychological factors should be considered both clinically and in research studies across all time-frames.

The second main finding from this review is that all meta-analysed psychological factors displayed significant correlations with pain at each timeframe. While these correlations were weak, they should still be considered important for pain assessment and treatment. Interestingly, these findings differed from previous systematic reviews. For example, Wang et al.(15) reported that depression was predictive of persistent pain but was not included in their meta-analyses. They did not find an association between anxiety and persistent pain, which was again not included in meta-analyses. Further, meta-analyses by Johannsen et al. did not find that psychological factors significantly predicted persistent pain. One reason for

the differences between our findings and those of Johannsen et al.(73) may have been that our inclusion of data from both univariate and multivariate associations led to stronger pooled effect correlations. This, of course, is a valid consideration, i.e. that when other factors are controlled for, the association or predictive capacity of psychological factors for pain becomes negligible and non-significant. However, it is worth noting that apart from axillary lymph node dissection (ALND), no factors have been found to be strongly predictive for persistent pain. ALND increased the odds of pain by 21%, while all other risk factors only increased the risk of persistent pain by 7% or less (15). Further, many of the known predictive factors for pain following BC treatment are non-modifiable, such as, age, while risk factors related to treatment, such as ALND, may effectively be 'non-modifiable' in certain circumstances because their selection reflects optimal medical treatment for the cancer presentation.

In their clinical prediction model, Meretoja and colleagues (74) identified ALND, higher BMI and more severe acute post-operative pain as increasing the risk of persistent pain (at 20% risk level); however, this combination had high specificity but low sensitivity (32-47%). This clinical prediction model was derived from a small number of studies, albeit well-conducted and longitudinal in design, and as such it is possible that future well designed studies may influence these results. Meretoja et al. argued in that paper that a list of risk factors is not helpful given the difficulty in implementing this clinically. While we agree with this to a point, the fact that current methods of identifying those at risk carry low sensitivity, consideration of broader factors, particularly modifiable factors, should continue to be studied and may well influence future prediction models.

Our results indicate that psychological factors should be considered in pain assessment, management and prevention, even if their association is small by comparison to other non-modifiable factors. In those who present with pain following BC treatment, a multidimensional pain assessment considerate of biopsychosocial contributions is warranted, similar to other pain populations(75, 76). Further interventions that target psychological factors, such as cognitive behavioural therapy, mindfulness based stress reduction and yoga, have all demonstrated positive effects on anxiety, depression and pain specifically in this population(77-79).

Finally, given our finding that pre-operative psychological factors correlated with acute post-operative pain, a known risk factor for persistent pain (15, 74), assessment of these factors during pre-operative assessment and targeting these factors during early pain management warrants consideration and further investigation.

Strengths and Limitations

The results of this systematic review should be considered in the light of its strengths and limitations.

Strengths of this review include its scope, reporting data from a large number of cross-sectional and longitudinal studies (n=47; n=16,137 participants). We were able to meta-analyse a variety of psychological variables. We also evaluated the effects of psychological factors on pain at timeframes extending from the early post-operative period to many years later. We recognise that our more liberal inclusion criteria and the analyses of univariate as well as multivariate associations may have led to stronger pooled effects; however, sensitivity analysis suggested little impact of using multivariate versus univariate effects. Collating data from the large range of studies included in this study is also a strength of this review that contributes to our understanding of associations of co-morbid psychological load associated with pain.

Nonetheless, the limited number of studies within the sub-acute timeframe (7days- 3 months) prevented meta-analyses of pain catastrophising and distress, and meant that a small number of studies were pooled for anxiety and depression. Further data on factors associated with pain for this timeframe are warranted. Anxiety and depression were widely reported on; however, other psychological variables warrant more attention. For example, pain self-efficacy was not reported on, yet it is considered an important variable in other pain research. We did not identify differences between timeframes after diagnosis/surgery. Again as few studies were available for meta-analyses for factors other than depression and anxiety, future research may allow identification of other key predictors of pain across different timeframes. Further, future longitudinal studies should extend follow-ups beyond 12 months. This is important given the lengthy treatment regimens many breast cancer patients undergo; hence defining pain as 'chronic' from 3 months post diagnosis or surgery might be considered too early in this population. Further, risk factors for 'late' chronic pain need to be identified.

We included participants with Stage 0 to Stage 3 cancer. However, while it is common for these stages to be grouped together in research studies, it should be acknowledged that participants' treatment profiles would likely differ considerably, with stage 3 involving more extensive surgery and more frequent chemotherapy and radiotherapy, all factors known to increase the risk of pain. This was not controlled for in these analyses. Furthermore, all but three studies were conducted in developed countries and as such, further data from developing countries would shed light on whether the relationship between psychological factors and pain differs compared with developed countries. Finally, although a systematic search was performed in multiple databases and experts were contacted, it is possible that relevant studies were not included in this review.

Conclusion

Moderate quality evidence yielded significant pooled effect size correlations between psychological factors and pain were identified across all timeframes. While weak, these associations should encourage assessment of key psychological factors during pre-operative screening and pain assessments at all post-operative timeframes.

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