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Review Article

PAIN

Prevalence and intensity of persistent post-surgical pain following breast cancer surgery: a systematic review and meta-analysis of observational studies

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Abstract

Background: The prevalence and intensity of persistent post-surgical pain (PPSP) after breast cancer surgery are uncertain. We conducted a systematic review and meta-analysis to further elucidate this issue.
Methods: We searched MEDLINE, Embase, CINAHL, and PsycINFO, from inception to November 2018, for observational studies reporting persistent pain (≥3 months) after breast cancer surgery. We used random-effects meta-analysis and the Grading of Recommendations, Assessment, Development and Evaluations approach to rate quality of evidence.
Results: We included 187 observational studies with 297 612 breast cancer patients. The prevalence of PPSP ranged from 2% to 78%, median 37% (inter-quartile range: 22–48%); the pooled prevalence was 35% (95% confidence interval [CI]: 32–39%). The pooled pain intensity was 3.9 cm on a 10 cm visual analogue scale (95% CI: 3.6–4.2 cm). Moderate-quality evidence supported the subgroup effects of PPSP prevalence for localized pain *vs* any pain (29% *vs* 44%), moderate or greater *vs* any pain (26% *vs* 44%), clinician-assessed *vs* patient-reported pain (23% *vs* 36%), and whether patients underwent sentinel lymph node biopsy *vs* axillary lymph node dissection (26% *vs* 43%). The adjusted analysis found that the prevalence of patient-reported PPSP (any severity/location) was 46% (95% CI: 36–56%), and the prevalence of patient-reported moderate-to-severe PPSP at any location was 27% (95% CI: 10–43%).

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Conclusions: Moderate-quality evidence suggests that almost half of all women undergoing breast cancer surgery develop persistent post-surgical pain, and about one in four develop moderate-to-severe persistent post-surgical pain; the higher prevalence was associated with axillary lymph node dissection. Future studies should explore whether nerve sparing for axillary procedures reduces persistent post-surgical pain after breast cancer surgery.

Keywords: breast cancer; chronic postoperative pain; intensity; meta-analysis; persistent post-surgical pain; prevalence; systematic review

Editor's key points

- Persistent pain after breast cancer surgery is common, but reported prevalence varies widely.
- In this systematic review and meta-analysis, the authors found that almost half of all women undergoing breast cancer surgery develop persistent pain, and about one in four develop moderate-to-severe pain. Greater prevalence was associated with axillary lymph node dissection.
- Future studies should explore whether nerve sparing for axillary procedures reduces persistent pain after breast cancer surgery.

Worldwide, there were 2.1 million newly diagnosed cases of breast cancer in 2018, accounting for almost 25% of all cancers amongst women.[1] Breast cancer survival rates have increased over time as a result of improvements in early detection and treatment, particularly in developed countries. The 5 and 10 yr survival rates were 90% and 83%, respectively, in the USA from 2008 to 2014,[2–4] 87% and 78% in the UK from 2010 to 2011,[5] and 88% and 82% in Canada from 2012 to 2014.[6] However, persistent post-surgical pain (PPSP) is a potential complication of breast cancer surgery, and is associated with reduced quality of life, increased risk of unemployment, and greater healthcare costs.[7–10]

The most recent systematic review concluded, based on 30 studies (3746 patients), that 30% of breast cancer patients experienced PPSP after breast cancer surgery.[11] However, this review calculated a weighted average without consideration of variation between studies; combined patient-reported and clinician-assessed rates, pain that was and was not localised to the surgical site, and pain of different severities without exploring for subgroup effects; and did not evaluate risk of bias amongst individual studies or the overall quality of evidence. We conducted a systematic review and meta-analysis of observational studies to investigate the prevalence and intensity of persistent pain following breast cancer surgery, which addresses these limitations.

Methods

We followed the reporting of Meta-analysis of Observational Studies in Epidemiology statement,[12] and registered our protocol (PROSPERO identifier: CRD42015024504). Before analysis, we added three additional subgroup analyses, assuming higher rates of PPSP were associated with higher-income *vs* low- or middle-income countries,[13] and axillary lymph node dissection (ALND) *vs* sentinel lymph node biopsy (SLNB), and that higher rates of neuropathic pain were associated with clinical assessment *vs* use of a validated instrument (e.g. Douleur Neuropathique 4 Questions [DN4], Leeds Assessment of Neuropathic Symptoms and Signs [LANSS], or Self-Report LANSS [S-LANSS]). We also added a subgroup analysis for PPSP intensity assuming greater severity in patients reporting PPSP than amongst all patients who underwent breast cancer surgery. After registration of our protocol, but before analysis, we committed to conduct meta-regression to explore whether studies enrolling a greater proportion of patients with breast-conserving surgery, breast reconstruction, radiotherapy, chemotherapy, or endocrine therapy were associated with higher prevalence and intensity of PPSP after breast cancer surgery.

Data sources and searches

We searched MEDLINE, Embase, CINAHL, and PsycINFO from inception to November 2018, with database-specific search strategies developed by an academic librarian (Supplementary Appendix, section 1.1). We screened the reference lists of all eligible studies and three previous systematic reviews for additional studies.[11,14,15]

We included prospective and retrospective cohort or cross-sectional studies that (i) enrolled ≥100 breast cancer patients and (ii) reported the prevalence or intensity of PPSP (≥3 months after surgery); Supplementary Appendix, section 1.2. We excluded conference abstracts, letters, and non-English-language articles. We excluded RCTs, which, because of restrictive eligibility criteria, often highly select patients undergoing breast cancer surgery and limit their generalisability. We excluded case-control studies of PPSP, as the number of cases and controls is preselected, which produces an artificial prevalence. When study populations overlapped >50% between articles, we included only the study with the larger sample size. Studies excluded for population overlap are listed in Supplementary Appendix, section 1.3.

Study selection

Paired reviewers independently screened the titles and abstracts of identified citations and full texts of potentially eligible studies. Reviewers resolved any disagreements by discussion or with the help of an adjudicator (LW). We used online systematic review software (DistillerSR; Evidence Partners, Ottawa, Canada; http://systematic-review.net/) to facilitate literature screening.

Risk-of-bias assessment in individual studies

We used the following criteria from the Users' Guides to the Medical Literature[16] to assess eligible studies for risk of bias: (i) representativeness of the study population, (ii) validity of

outcome assessment, and (iii) loss to follow-up (≥20% was considered high risk of bias).

Data extraction

We used standardised, pilot-tested data extraction forms and a detailed instruction manual to facilitate data extraction. All reviewers extracted a common set of 10 articles as a calibration exercise before data extraction. After consensus was achieved on all calibration studies, paired reviewers, independently and in duplicate, extracted data from the remaining articles. Data abstracted included study and patient information, details regarding breast cancer treatment, the prevalence and intensity of PPSP, and pain characteristics.

Our primary outcome was the prevalence of PPSP at the longest follow-up time reported. Secondary outcomes were (i) prevalence of moderate-to-severe (≥4 cm on a 10 cm visual analogue scale [VAS]) and severe (≥7 cm on a 10 cm VAS) persistent pain; (ii) overall intensity of PPSP; (iii) prevalence and intensity of PPSP at 3–12 months, 13–24 months, and >2 yr after breast cancer surgery; (iv) prevalence and intensity of PPSP at different locations, including breast, axilla, arm/shoulder, or incisional scar; and (v) prevalence and intensity of persistent, post-surgical, neuropathic pain.

Data synthesis and analysis

We calculated an adjusted kappa statistic (κ) to assess inter-rater agreement for full-text screening.[17] We used random-effects models to pool data for prevalence of PPSP across studies, which consider both within- and between-study variability.[18] We used Freeman–Tukey double arcsine transformation to stabilise the variance and to ensure that confidence intervals (CIs) contained only admissible values.[19,20] Without this transformation, very high or very low prevalence estimates can produce CIs that contain values lower than 0% or higher than 100%.[20] We used the DerSimonian and Laird[21] method to compute the pooled estimate based on the transformed values and their variances, and then the harmonic mean of sample sizes for the back-transformation to the original units of proportions.[22] We pooled pain intensity after converting all pain instruments to the 10 cm VAS using linear transformation by assuming that instruments assessing pain share similar measurement properties (Supplementary Appendix, section 2).[23] We used this approach, *vs* pooling different instruments as a standardised mean difference (SMD), as the SMD is difficult to interpret and is vulnerable to baseline heterogeneity of enrolled patients.[24,25]

If a study reported multiple types of persistent pain, we chose the one that most closely approximated the following definition of PPSP[26]: (i) pain persists ≥3 months after surgery, (ii) pain develops or increases in intensity after the surgical procedure, (iii) pain is either localised to the surgical field or a referred area, and (iv) other causes of pain have been excluded. If a study only reported persistent pain for independent subgroups of patients, we estimated the overall PPSP prevalence and intensity by combining subgroups.[18] If a study reported pain at multiple locations or sites, we used the data for breast or arm pain for estimating the overall prevalence, which was the site most commonly reported across studies eligible for our review. If a study reported PPSP at different follow-up times, we used the longest follow-up for pooling overall PPSP prevalence and intensity. If authors reported pain intensity as the worst, least, and average pain, we used data for average pain. We derived the mean and standard deviation (SD) of pain intensity when reported as ordinal data (e.g. as mild, moderate, and severe pain). We estimated mean from median and SD from inter-quartile range (IQR) and range.[18] If not reported, we imputed the SD from a linear regression of log(SD) on log(mean).[18]

Patient involvement

To optimise reporting of our results, we engaged two breast cancer patients during the planning phase of our review to determine if they prioritised (i) persistent pain reported by patients or by their clinician, (ii) pain anywhere or associated with the surgical site, and (iii) persistent pain of any severity or moderate-to-severe pain. Both patients endorsed that persistent pain should be based on patient report, and in any location, but were divided over severity. We therefore used multivariable meta-regression to estimate the prevalence of PPSP as reported by patients, at any location, for both 'any pain' and 'moderate-to-severe pain'. We also asked the same patients and three clinical experts what prevalence of PPSP would be considered important for any pain, moderate pain, and severe pain.

Small-study effects

We explored for small-study effects by visual assessment of asymmetry of funnel plots and calculation of Egger's test, when there were at least 10 studies in a meta-analysis.[18,27]

Subgroup analyses, meta-regression, and sensitivity analyses

We examined heterogeneity for all pooled estimates through visual inspection of forest plots.[27] Some statistical tests of heterogeneity (I^2 and Cochrane's *Q*) can be misleading when sample sizes are very large and associated measures of precision are therefore very narrow[28]; therefore, we used τ^2 to estimate the extent of variation amongst the effect size parameters (e.g. PPSP prevalence or intensity) observed in different studies (between-study variance).[28]

We generated the following *a priori* hypotheses to explain variability between studies assuming a higher prevalence but less severity of PPSP with (i) patient-reported *vs* clinician-assessed pain; (ii) pain at any location *vs* pain associated with the surgical site or referred areas; (iii) pain of any severity *vs* moderate-to-severe pain; (iv) high-income *vs* low- or middle-income countries, according to the United Nations[13] classification; (v) greater *vs* lower risk of bias, on a criterion-by-criterion basis; and (vi) whether studies used a less rigorous *vs* a more rigorous definition of PPSP; and we assumed (vii) higher prevalence and greater severity of PPSP for ALND *vs* SLNB. We also explored whether prevalence of persistent neuropathic pain was higher when clinically diagnosed *vs* use of a validated instrument. We conducted a subgroup analysis for PPSP intensity assuming greater severity in patients with PPSP than amongst all breast cancer surgery patients. We conducted within-study subgroup analyses when possible to reduce risk of confounding, and between-study when not.

We performed meta-regression to explore the relationship between year of publication (as a surrogate for advancement in surgical techniques); length of follow-up; proportion of loss to follow-up; mean/median age; and proportion of patients undergoing breast-conserving surgery, breast reconstruction, radiotherapy, chemotherapy, and endocrine therapy with the prevalence and intensity of PPSP. All significant factors were explored with multivariable meta-regression.

We performed sensitivity analyses to examine (i) the impact of logit transformation *vs* Freeman–Tukey double arcsine transformation for PPSP prevalence,[20,29] (ii) imputing data for missing SD of PPSP intensity, and (iii) estimation from ordinal data for intensity of PPSP. We used Stata statistical software version 15 (StataCorp, College Station, TX, USA) for all analyses. All comparisons were two-tailed, with a threshold *P*-value of 0.05.

Quality of evidence

We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to summarise the quality of evidence for all meta-analyses as high, moderate, low, or very low.[27] Based on feedback from two patients and three clinicians, we used the following thresholds for determining imprecision regarding prevalence of PPSP: 20% for any pain, 10% for moderate pain, and 5% for severe pain.

Results

Of 9849 unique citations, 197 articles from 187 cohorts with 297 612 patients proved eligible (Fig. 1; Supplementary Appendix, section 1.2). There was near-perfect agreement (κ=0.87) between reviewers for full-text screening. Amongst eligible

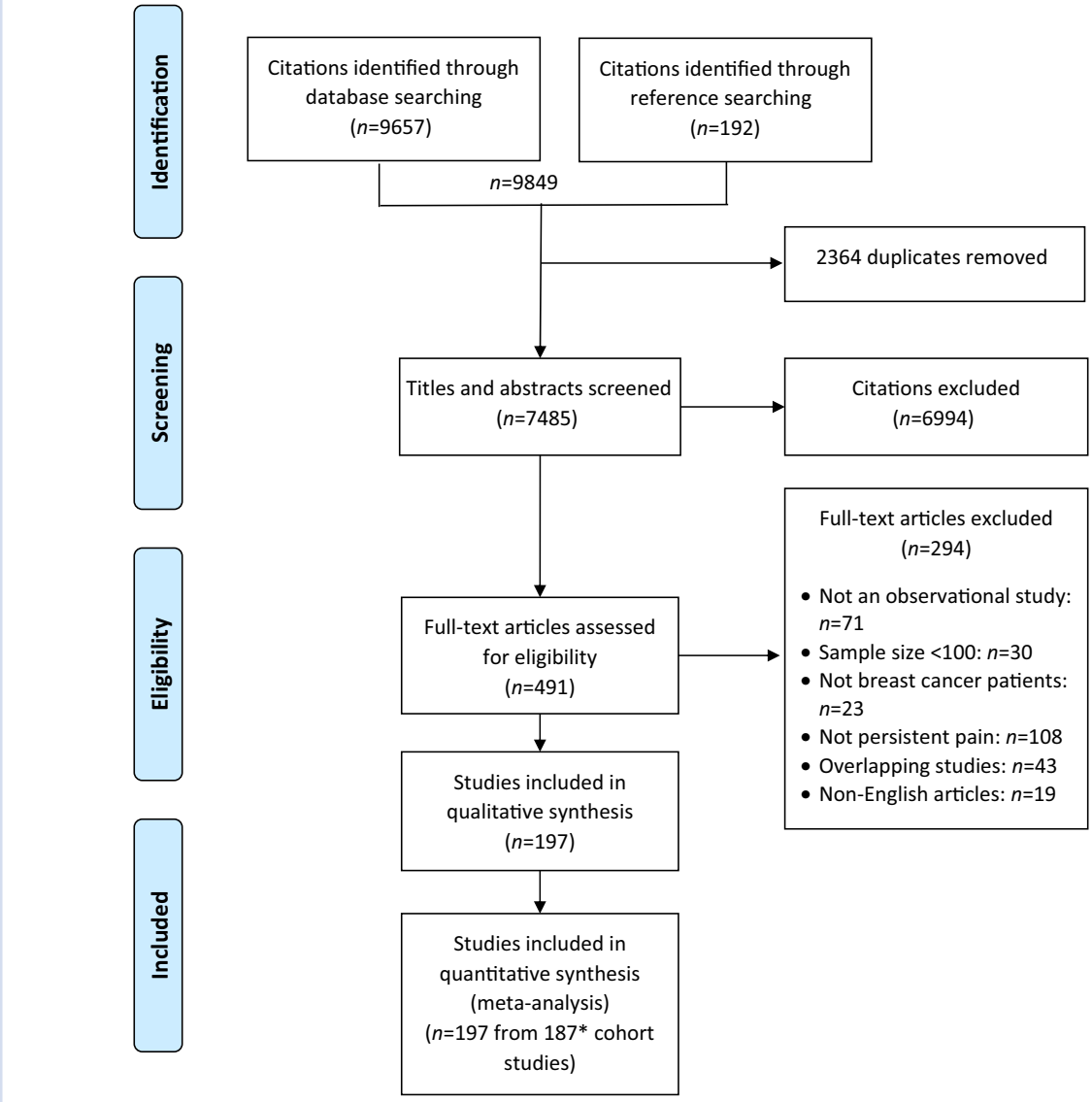

Fig 1. Flow diagram of study selection. *Each of 10 cohort studies was published in two articles, which reported different aspects of the same cohort (e.g. one reported pain prevalence, whereas the other reported pain intensity or neuropathic pain).

studies, 165 (88%) were conducted in high-income countries, 22 (12%) in middle-income countries, and none in low-income countries. The median sample size was 300 (IQR: 178–529; range: 100–119 576), the median of the mean age was 56 (IQR: 53–60), length of follow-up ranged from 3 months to >10 yr, and 10 studies (5%) only reported clinician-assessed pain (Supplementary Appendix, sections 3.1 and 3.2).

Risk of bias and outcome reporting

Amongst 187 eligible studies, 83% (n=155) enrolled representative samples, 69% (n=129) used validated pain measures, and 62% (n=116) reported <20% missing data. All studies defined persistent pain as ≥3 months, the majority (132 studies; 71%) as localised to the surgical site or a referred area, and most (106 studies; 57%) as distinct from pain before surgery, but only a minority (22 studies; 12%) explicitly excluded other possible causes of persistent pain (Supplementary Appendix, section 3.2).

Prevalence of persistent post-surgical pain after breast cancer surgery

One hundred forty-six studies (137 675 patients) reported the prevalence of persistent pain, which ranged from 2% to 78%; median prevalence was 37% (IQR: 22–48%). The pooled overall prevalence for PPSP of any severity was 35% (95% CI: 32–39%). Moderate-quality evidence found that the pooled prevalence for moderate-to-severe pain was 20% (95% CI: 17–23%; 78 studies; 29 939 patients), and 4% (95% CI: 3–5%; 58 studies; 24 002 patients; Supplementary Appendix, section 3.3) for severe persistent pain (Table 1). Seventy-three studies reported PPSP prevalence at specific locations. The pooled prevalence of PPSP involving the breast was 30% (95% CI: 24–38%; 42 studies; 97 780 patients), 27% (95% CI: 22–33%; 43 studies; 15 965 patients) for the arm/shoulder, 29% (95% CI: 18–41%; 19 studies; 7389 patients) for the axilla, and 33% (95% CI: 17–52%; 10 studies; 2529 patients) for the incisional scar (Supplementary Appendix, section 3.4).

A within-study subgroup analysis (34 studies; 18 089 patients)[30–63] provided moderate-quality evidence that ALND was associated with higher prevalence of PPSP than SLNB (43%; 95% CI: 36–51% *vs* 26%; 95% CI: 21–32%; test of interaction, P=0.001; Table 1; Figs. 2 and 3; Supplementary Appendix, section 3.5).

For PPSP of any severity, we found significant between-study subgroup effects for any pain *vs* localised pain (44% [95% CI: 41–48%] *vs* 29% [95% CI: 24–34%]; test of interaction, P<0.001), any severity *vs* moderate-to-severe pain (44% [95% CI: 41–48%] *vs* 26% [95% CI: 20–32%]; test of interaction, P<0.001), and patient-reported *vs* clinician-assessed pain (36% [95% CI: 33–40%] *vs* 23% [95% CI: 12–35%]; test of interaction, P=0.03); all moderate-quality evidence (Table 1; Fig. 2; Supplementary Appendix, section 3.5). All subgroup factors remained significant in multivariable meta-regression (Supplementary Appendix, section 3.6). Our adjusted analysis found that the prevalence of patient-reported PPSP, of any severity, at any location, was 46% (95% CI: 36–56%), and the prevalence of patient-reported moderate-to-severe PPSP at any location was 27% (95% CI: 10–43%).

Amongst 79 studies that reported prevalence of persistent pain at discrete time intervals, the pooled estimates were 39% (95% CI: 29–49%) at 3–12 months (54 studies; 110 050 patients), 31% (95% CI: 23–41%) at 1–2 yr (18 studies; 6364 patients), and 29% (95% CI: 22–37%) at >2 yr (30 studies; 94 655 patients) (Supplementary Appendix, section 3.7). Random-effects meta-regression found no significant association between prevalence of PPSP and length of follow-up (P=0.43; Supplementary Appendix, section 3.8).

Intensity of persistent post-surgical pain after breast cancer surgery

Amongst 127 studies (30 832 patients) that reported the intensity of PPSP, the pooled intensity on a 10 cm VAS was 3.0 cm (95% CI: 2.8–3.2 cm; Supplementary Appendix, section 3.9); however, pain scores amongst studies reporting on all breast cancer patients were significantly lower *vs* those reporting on patients with PPSP (2.1 cm [95% CI: 1.9–2.3 cm] *vs* 3.9 cm [95% CI: 3.6–4.2 cm]; test of interaction, P<0.001; Supplementary Appendix, sections 3.9 and 3.10).

Twenty-two studies reported PPSP intensity scores for the breast (22 studies; 4461 patients) and 19 studies (2404 patients) for the arm/shoulder. We found a significant subgroup effect for less pain severity in studies that reported on all patients *vs* patients with PPSP (test of interaction ≤0.001; Supplementary Appendix, sections 3.9 and 3.10) at these locations. The pooled pain intensity amongst patients with PPSP on a 10 cm VAS was 3.9 cm (95% CI: 3.6–4.3 cm) at the breast and 4.4 cm (3.6–5.3 cm) at the arm/shoulder (Supplementary Appendix, section 3.9).

Amongst 127 studies that reported intensity of persistent pain at discrete time intervals, the pooled estimates for patients reporting PPSP were 3.7 cm (95% CI: 3.1–4.4 cm) at 3–12 months (12 studies; 2023 patients), 3.1 cm (95% CI: 2.7–3.6 cm) at 1–2 years, and 4.3 cm (95% CI: 3.7–4.8 cm) at >2 yr (6 studies; 705 patients) (Supplementary Appendix, section 3.11). Random-effects meta-regression found no significant association between intensity of persistent pain and length of follow-up (P=0.88; Supplementary Appendix, section 3.12).

Persistent neuropathic pain after breast cancer surgery

Moderate-quality evidence suggested that the pooled prevalence of persistent neuropathic pain amongst patients undergoing breast cancer surgery was 29% (95% CI: 23–35%; 31 studies [9263 patients]; Table 1). The pooled pain intensity amongst patients who developed persistent neuropathic pain after surgery was 3.8 cm (95% CI: 3.1–4.5 cm on a 10 cm VAS; 10 studies [901 patients]) (Supplementary Appendix, section 3.9).

Additional subgroup analysis and meta-regression

Aside from those reported previously, no subgroup analysis was significant, including high-income *vs* middle-income countries, representativeness of patients, validity of outcome assessment, rigor of PPSP definition, and rigor of neuropathic pain assessment; test of interaction P-values ranged from 0.32 to 0.99 for pain prevalence (Supplementary Appendix, section 3.5) and from 0.19 to 0.51 for pain intensity (Supplementary Appendix, section 3.10). In addition, meta-regression found no significant association between prevalence or intensity of PPSP and year of publication; length of follow-up; proportion of loss to follow-up; mean/median age; or the proportion of patients receiving breast-conserving surgery, breast reconstruction, radiotherapy, chemotherapy, and endocrine therapy (P-values ranged from 0.16 to 0.89 for pain prevalence and

Table 1 Grading of Recommendations, Assessment, Development and Evaluations evidence profile: prevalence of persistent post-surgical pain (PPSP) following breast cancer surgery. ALND, axillary lymph node dissection; CI, confidence interval; SLNB, sentinel lymph node biopsy. Localised pain: pain associated with the surgical site (e.g. breast, axilla, arm/shoulder, or incisional scar). *τ^2 reduced by 20%, 3%, and 17%, respectively, after introducing subgroup analysis of localised pain or high threshold pain vs any pain of any severity, patient-reported pain vs clinician-assessed pain, and ALND vs SLNB. [1]Significant subgroup effect was found for pain at any location vs localised pain (interaction P<0.001). [2]Significant subgroup effect was found for pain with low threshold vs high threshold (interaction P<0.001). [3]Significant subgroup effect was found for patient-reported vs clinician-assessed pain (interaction P=0.03). [4]Significant subgroup effect was found for pain after ALND vs SLNB (interaction P=0.001). [5]We did not rate down for risk of bias, because our subgroup analyses and meta-regression did not identify any significant difference between each risk-of-bias component and the estimates of prevalence. [6]We did not rate down for imprecision because the 95% CI associated with the pain prevalence did not include our threshold of 20% for any pain prevalence (pain present or ≥1 on a 0–10 scale); 10% for moderate-to-severe pain prevalence (pain ≥4 on a 0–10 scale or equivalent definitions by authors). [7]We rated down for imprecision because the 95% CI (3.1–5.4%) associated with the pain prevalence included our threshold of 5% for severe pain (pain ≥7 on a 0–10 scale or equivalent definitions by authors), which means clinical actions based on the estimates in the lower or upper boundary may be different.

Outcomes	Study characteristics			Quality assessment						Summary of findings	
	No. of studies	No. of participants	Length of follow-up (months)	Risk of bias	Inconsistency	Indirectness	Imprecision	Small-study effects	Overall quality of evidence	Absolute PPSP prevalence	
										Prevalence (%)	95% CI (%)
Any pain[1,2,*]	65	27 889	3 to >120	No serious risk of bias[5]	Serious inconsistency; τ^2=0.015	No serious indirectness	No serious imprecision[6]	Undetected; symmetric funnel plot; Egger's test P=0.52	Moderate because of inconsistency	44	41–48
Localised pain[1*]	61	100 817	5–96	No serious risk of bias[5]	Serious inconsistency; τ^2=0.026	No serious indirectness	No serious imprecision[6]	Undetected; symmetric funnel plot; Egger's test P=0.70	Moderate because of inconsistency	29	24–34
High threshold pain[2*]	20	8969	3–96	No serious risk of bias[5]	Serious inconsistency; τ^2=0.021	No serious indirectness	No serious imprecision[6]	Undetected; symmetric funnel plot; Egger's test P=0.38	Moderate because of inconsistency	26	20–32
Patient-reported pain[3*]	136	133 959	3 to >120	No serious risk of bias[5]	Serious inconsistency; τ^2=0.025	No serious indirectness	No serious imprecision[6]	Undetected; symmetric funnel plot; Egger's test P=1.0	Moderate because of inconsistency	36	33–40
Pain after ALND[4*]	34	8310	3–95	No serious risk of bias[5]	Serious inconsistency; τ^2=0.030	No serious indirectness	No serious imprecision[6]	Undetected; symmetric funnel plot; Egger's test P=1.0	Moderate because of inconsistency	43	36–51
Pain after SLNB[4*]	34	9779	3–95	No serious risk of bias[5]	Serious inconsistency; τ^2=0.020	No serious indirectness	No serious imprecision[6]	Undetected; symmetric funnel plot; Egger's test P=1.0	Moderate because of inconsistency	26	21–32
Neuropathic pain	31	9263	3–108	No serious risk of bias[5]	Serious inconsistency; τ^2=0.022	No serious indirectness	No serious imprecision[6]	Undetected; symmetric funnel plot; Egger's test P=0.90	Moderate because of inconsistency	29	23–35
Moderate-to-severe pain	78	29 939	3–96	No serious risk of bias[5]	Serious inconsistency; τ^2=0.023	No serious indirectness	No serious imprecision[6]	Undetected; symmetric funnel plot; Egger's test P=0.25	Moderate because of inconsistency	20	17–23
Severe pain	58	24 002	3–96	No serious risk of bias[5]	No serious inconsistency; τ^2=0.0001	No serious indirectness	Serious imprecision[7]	Undetected; symmetric funnel plot; Egger's test P=0.69	Moderate because of imprecision	4	3–5

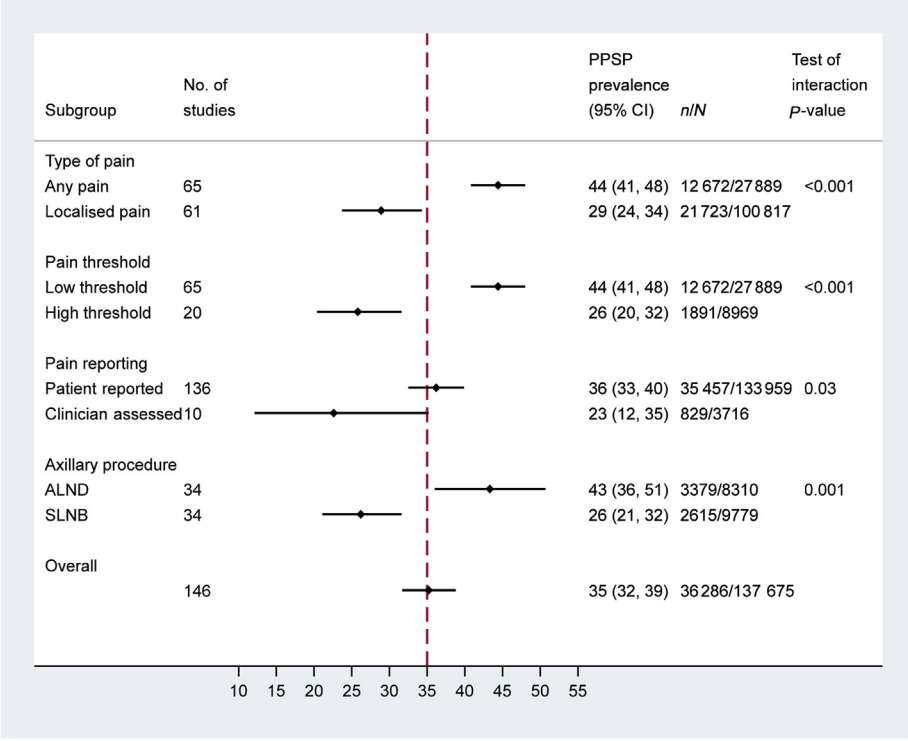

Fig 2. Persistent post-surgical pain prevalence subgroup analysis summary. Localised pain: pain associated with the surgical site (e.g. breast, axilla, arm/shoulder, or incisional scar). Low threshold: any pain present vs not; high threshold: moderate-to-severe pain vs no/mild pain. ALND, axillary lymph node dissection; CI, confidence interval; PPSP, persistent post-surgical pain; SLNB, sentinel lymph node biopsy.

from 0.07 to 0.89 for pain intensity; Supplementary Appendix, section 3.13).

Sensitivity analysis and small-study effects

Sensitivity analyses using logit transformation showed similar results in pooled pain prevalence (Supplementary Appendix, section 3.14). Sensitivity analyses, excluding data of missing SD imputed or estimated from IQR or range or excluding pain score derived from ordinal data, showed no important differences in pooled measures of pain intensity (Supplementary Appendix, section 3.15). No small-study effects were detected for prevalence and intensity of pain in general or neuropathic pain in particular (Supplementary Appendix, sections 3.16–3.19).

Discussion

Main findings

Persistent pain is common after breast cancer surgery with an average pain intensity, on a 10 cm VAS, of 3.9 cm in the breast and 4.4 cm in the arm and shoulder. When present, the intensity of persistent neuropathic pain after surgery was 3.8 cm. The prevalence of PPSP differs based on the location and severity of pain, whether pain is reported directly by patients or assessed by their clinician, and the surgical approach used. The prevalence of PPSP after breast cancer surgery is 46% when considering any location, any severity, and when captured directly from patients; the prevalence of patient-reported pain at any location reduces to 27% when restricted to moderate or greater severity. Higher prevalence of persistent pain is associated with ALND, likely because of sacrifice of the intercostobrachial nerve. Both prevalence and severity of persistent pain were stable for over 2 yr, suggesting that once PPSP develops, it may be unlikely to improve.

Relation to other studies and implications

Previous narrative reviews reported rates of PPSP after breast cancer surgery ranging from 10% to 69%,[64–66] and the only systematic review of overall PPSP reported a weighted average of 30%.[11] Our systematic review and meta-analysis found an overall pooled prevalence for PPSP of 35% (95% CI: 32–39%); however, we found evidence for a number of significant subgroup effects, suggesting a focus on the overall prevalence is misleading. Based on a qualitative assessment, the prior systematic review concluded the rate of PPSP had decreased from the 1990s to the 2010s.[11] Our meta-regression did not provide support for an association between the prevalence of PPSP after breast cancer surgery and year of study publication. A prior systematic review of neuropathic pain after breast

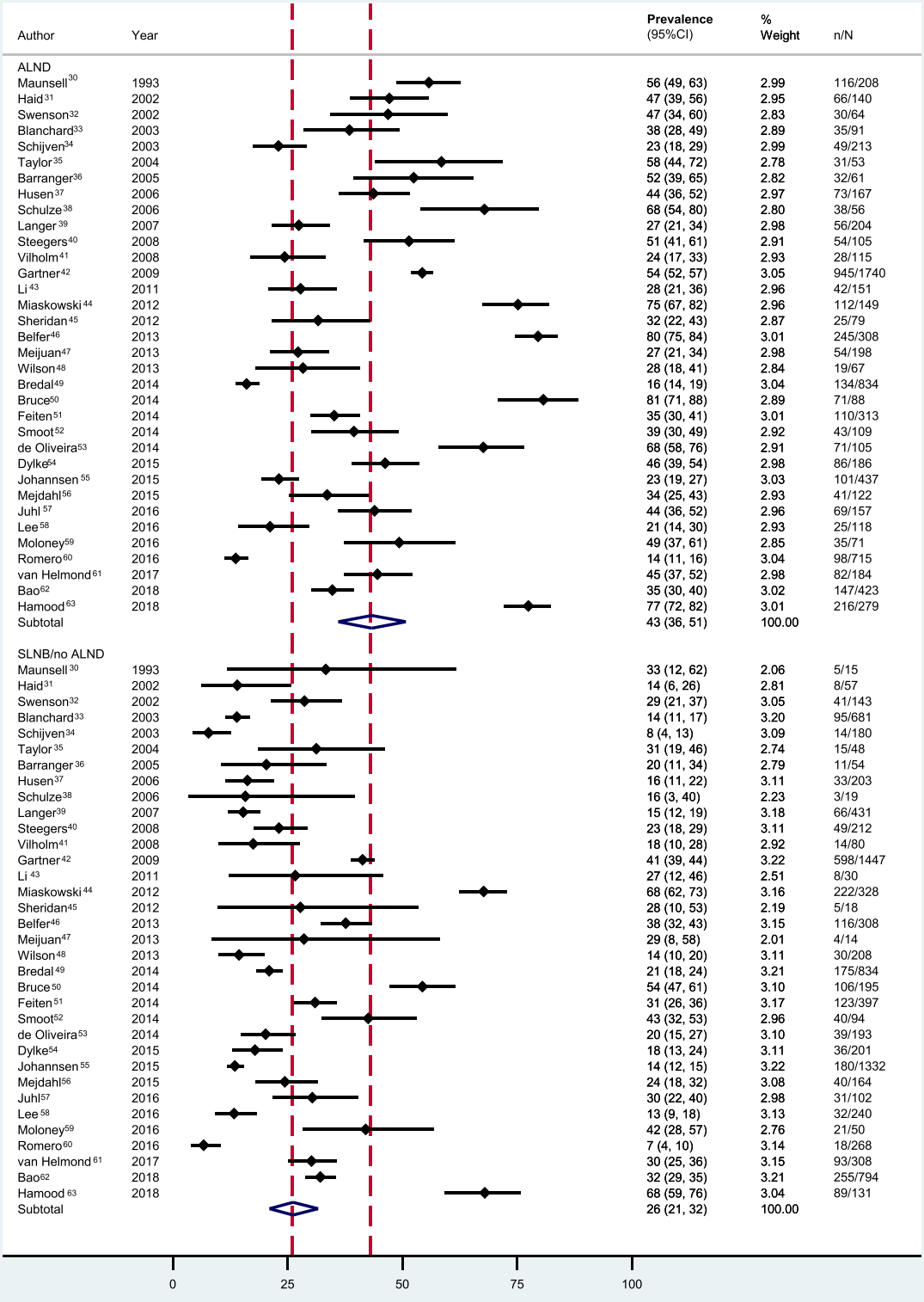

Fig 3. Persistent post-surgical pain prevalence subgroup analysis for axillary lymph node dissection (ALND) vs sentinel lymph node biopsy (SLNB). Test of interaction P=0.001. CI, confidence interval.

cancer surgery reported the prevalence ranged from 14% to 27%, based on the questionnaire used.[15] Our systematic review found a pooled prevalence of 29% for persistent neuropathic pain after surgery, and no evidence for a subgroup effect based on instrument-defined neuropathic pain (e.g. DN4, LANSS, or S-LANSS) *vs* clinically assessed neuropathic pain.

In our systematic review, we found a significant subgroup effect for patient-reported *vs* clinician-assessed pain, which indicates that clinical assessment may systematically underestimate pain prevalence. There is indirect evidence from other patient populations that support this finding. For example, 73% of patients with rheumatoid arthritis find it difficult to discuss pain with their healthcare provider, primarily because they do not want to be perceived as 'complaining'.[67]

Our review reaffirmed that ALND is associated with a higher prevalence of persistent pain after breast cancer surgery,[14] which is likely a result of sacrificing the intercostal brachial nerve.[79] A case series of breast cancer surgery patients who underwent ALND and developed post-surgical pain found that all showed evidence of a lesion of the intercostobrachial nerve.[68] Preservation of the intercostobrachial nerves during ALND reduces the incidence of post-mastectomy pain syndrome,[35,69] pain intensity,[70] and the risk of sensory deficits after axillary clearance without significant increase in total surgery time.[71] The American Society of Clinical Oncology recommends SLNB for patients with early-stage breast cancer, followed by dissection only if biopsy is positive,[72] as this approach may reduce PPSP and shows equivalent rates of axillary relapse compared with axillary dissection.[33,73,74]

Our review adds to a growing body of evidence that PPSP after breast cancer surgery is a major clinical problem.[64–66] Preliminary evidence suggests that education,[75] exercise therapy,[76] psychological or behavioural interventions,[77] and paravertebral blocks in addition to general anaesthesia[78] or ketamine infusion perioperatively[79,80] may reduce the rate of persistent pain after breast cancer surgery; however, further research is urgently needed to identify effective interventions, including the potential role of nerve sparing during ALND.

Strengths and limitations

The strengths of our review include explicit eligibility criteria and a comprehensive search that identified additional 113 observational studies, enrolling 137 123 patients that were not included in the previous systematic review. We converted different pain scales to a 10 cm VAS across studies to optimise interpretation of our findings. We used meta-analysis to estimate the prevalence and intensity of PPSP after breast cancer surgery, and Freeman–Tukey double arcsine transformation for pain prevalence to stabilise the variance.[20] We conducted sensitivity analyses to confirm robustness of our findings and the GRADE approach to appraise the quality of evidence.

There are some limitations to our systematic review. We excluded 19 non-English-language articles, and none of our included studies were conducted in low-income countries, which restricts the generalisability of our findings. Our pooled prevalence of PPSP showed considerable heterogeneity; however, subgroup analyses and meta-regression were able to explain some of the variability on the basis of how studies considered pain severity and location, if pain was assessed by clinicians or reported by patients, and if women underwent ALND or SLNB.

Conclusions

Moderate-quality evidence suggests that almost half of all women undergoing breast cancer surgery develop persistent pain, and one in four develop moderate-to-severe PPSP; higher prevalence is associated with ALND. Further, chronic pain after breast cancer surgery persists for years without significant improvement in either prevalence or intensity. Clinical trials are needed to determine whether axillary-nerve-sparing techniques are effective for reducing persistent pain after breast surgery involving ALND.

Authors' contributions

Study conception/design: LW, JWB
Literature search: RJC
Data acquisition: LW, JCC, ND, BYH, SK, DL, YO, SAK, BR, NA, HYK, KJ, MP, DJ, AL, GG, SN
Statistical analysis: LW
Data interpretation: LW, JWB, SR, JSK, MM
Drafting of manuscript: LW, JWB
Critical revision of manuscript for important intellectual content: all authors
LW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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