Predictors for persistent pain after breast cancer surgery:
A systematic review of observational studies

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Faculty/Presenter Disclosure

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• **Other:** NONE
Systematic Review of Predictors for Persistent Postsurgical Pain

Following all types of surgery

- Breast cancer surgery
- Cardiac surgery
- Thoracotomy
- Amputation
- Hernia repair
- Caesarean section
- Others...

- Persistent postsurgical pain (PPSP): 10–50%
- Predictors of PPSP are poorly understood, which complicates efforts to improve prognosis for patients at risk
Background

Two systematic reviews and 3 narrative reviews published:

Persistent pain after breast cancer surgery:

• Median 31% (IQR: 21.5–47.3%) - 1st SR for persistent pain prevalence only
• Range 25 - 60% - 2nd SR for both prevalence and predictor
• Severe pain: 10% (2nd SR); 10 -15% (from narrative review)

Persistent pain after breast cancer surgery is associated with

• Other symptoms: lymphedema, sensory disturbance, sleep disturbance, upper limb dysfunction...
• Poorer heath-related quality of life
Risk factors/predictors for persistent pain

Preoperative factors:
- Psychosocial factors
- Age
- Obesity
- Ethnicity
- Preop pain (breast or other locations)
- Nociceptive function
- Genetics

Intraoperative factors:
- Mastectomy vs BCS
- ALND vs. SLNB
- ICBN
- Analgesia and preemptive analgesia...

Postoperative factors:
- Adjuvant therapy
- Recurrence
- Acute pain
- Pain treatment
- Sensory disturbances
- Lymphedema
- Complications
- Follow-up
Limitations of existing reviews

Most reviews are narrative summaries
  • Overestimation of predictive power (often only positive results)

The sole systematic review of the predictors:
  • Outdated searching: from 1995 to March 2010
  • Included results without adjustment
  • Did not assess the quality of included studies
  • Did not attempt any statistical pooling of data
    • No overall assessment of predictive power for any predictors
Objectives

To identify the predictors for persistent pain following breast cancer surgery using meta-analysis when possible

Eligibility criteria

P: Patients underwent breast cancer surgery
E: Any predictor with an adjusted analysis
O: Persistent pain - any pain after breast cancer surgery
   • Time frame: >=2 months (IASP criteria for chronic pain)

Design

• Cohort study
• Case-control study
Searching strategies

Databases: From the inception to August 04, 2014

- MEDLINE/PubMed
- EMBASE
- CINAHL
- PsycInfo

No language limitation

Risk of bias assessment

- Representativeness of the study population
- Accuracy of outcome assessment
- Proportion of missing data
- Predictive models appropriately adjusted for
  - age, cancer stage/type of surgery, and adjuvant therapy
Data selection, coding & extraction

10 reviewers screened, independently and in duplicate

Calibration exercises for screening and data extraction

Screening & Data extraction: standardized forms and instruction

Code-book for all predictors

10 reviewers extracted data, and then verified by Li Wang
Data analysis

Meta-analysis:
- Random effects model to pool data for each predictor across studies
- Odds ratios & 95% confidence interval.
- Converting other measures (e.g. RR, HR) to an odds ratio
- Heterogeneity using both a chi-squared test and the \( I^2 \) statistic

Data imputation:
- For predictors tested, not significant, not reported
- Attributing adjusted OR=1 to minimize overestimation
- Variance from “hot deck approach”
Explanations of heterogeneity

Subgroup analyses

1) Different threshold for pain:
   High vs. low threshold

2) Whether adjusted for age, cancer stage/type of surgery, and adjuvant therapy

Meta-regression for interaction

1) Mean age
2) Duration of follow-up
3) Proportion of loss to follow-up
Results

Study selection:

Identification

Records identified through database searching (n = 9,233)
Additional records identified through other sources (n = 0)

Screening

Records after duplicates removed (n = 6,476)

Eligibility

Records screened (n = 6,476)

Full-text articles assessed for eligibility (n = 512)

Included

Studies included (n = 30)

Records excluded (n = 5,964)

Full-text articles excluded, with reasons:
- Excluded: 457
- Unreviewed: 25
Baseline characteristics

Year published
• 1997-1999: 3
• 2000-2009: 7
• 2010-2014: 20

Countries
• Europe: 15
• North America: 11
• Australia: 1
• South America: 2
• Asia: 1

Study design
• All cohort study

• Sample size
  • Median & IQR: 416 (262-611)
  • Range: 113-2750

• Mean age
  • Median & IQR: 57 (54-59)
  • Range: 41-64

• Mean duration of follow-up(months)
  • Median & IQR: 26 (17-42)
  • Range: 3-72.5
Persistent pain prevalence & intensity

Prevalence decreases, but intensity increases over time.
Risk of bias

The representativeness of the study population
- Low risk: 19
  - Random sampling: 1
  - Cancer registry: 2
  - Consecutive sampling: 16
- Not reported: 11

The proportion of lost to follow-up
- Median & IQR: 16.6% (8.2%-30.5%)
- Range: 4.2% – 43.4%
- >20%: 8 studies

The accuracy of outcome assessment
- Low risk: 13
- High risk: 17

Whether or not predictive models are appropriately adjusted
- Low risk: 27
- High risk: 3
Predictor: Age

21 studies, 10,240 patients

Older women less likely to develop persistent pain

Adjusted OR & 95%CI: 0.77 (0.68 to 0.87)
Predictor: Age – subgroup analyses

Low vs. high threshold

Appropriately adjusted vs. not

interaction p = 0.22

<table>
<thead>
<tr>
<th>Refid</th>
<th>Sample size</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
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Interaction p = 0.23

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NOTE: Weights are from random effects analysis
Predictor: Axillary procedure

Studies, 6,839 patients

Axillary clearance more likely to result in PPSP

Adjusted OR & 95% CI: 2.4 (1.6 to 3.5)

None of hypotheses factors explained heterogeneity

<table>
<thead>
<tr>
<th>refid</th>
<th>axilla analysis</th>
<th>sample</th>
<th>Adjusted OR (95% CI)</th>
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<tr>
<td>69</td>
<td>ALND vs SLNB</td>
<td>174</td>
<td>1.00 (0.33, 3.00)</td>
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<tr>
<td>80</td>
<td>ALND vs SLNB</td>
<td>1631</td>
<td>1.46 (1.08, 1.97)</td>
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<tr>
<td>186</td>
<td>ALND vs no</td>
<td>532</td>
<td>1.00 (0.52, 1.93)</td>
</tr>
<tr>
<td>364</td>
<td>ALND vs SLNB</td>
<td>235</td>
<td>2.97 (1.09, 8.01)</td>
</tr>
<tr>
<td>662</td>
<td>ALND vs no</td>
<td>300</td>
<td>7.70 (4.30, 13.8)</td>
</tr>
<tr>
<td>1305</td>
<td>ALND vs no</td>
<td>370</td>
<td>6.30 (3.30, 12.0)</td>
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<tr>
<td>1930</td>
<td>ALND vs SLNB</td>
<td>2406</td>
<td>2.04 (1.60, 2.60)</td>
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<tr>
<td>2736</td>
<td>ALND vs no</td>
<td>103</td>
<td>3.83 (1.72, 8.50)</td>
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<tr>
<td>2778</td>
<td>ALND vs SLNB</td>
<td>247</td>
<td>4.85 (1.78, 13.2)</td>
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<tr>
<td>3104</td>
<td>ALND vs SLNB</td>
<td>470</td>
<td>1.32 (0.64, 2.81)</td>
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<tr>
<td>3150</td>
<td>ALND vs no</td>
<td>183</td>
<td>1.16 (0.38, 3.54)</td>
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<tr>
<td>3727</td>
<td>ALND vs no</td>
<td>188</td>
<td>2.49 (1.12, 5.51)</td>
</tr>
<tr>
<td></td>
<td><strong>Overall</strong> (I-squared = 78.3%, p = 0.000)</td>
<td></td>
<td><strong>2.40 (1.64, 3.49)</strong></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Radiotherapy is associated with PPSP

Adjusted OR & 95%CI: 1.34 (1.11 to 1.61)

None of hypotheses factors explained heterogeneity
Predictor: Acute postop pain
- 6 studies, 1,608 patients
- Acute post-op pain is associated with PPSP

Adjusted OR & 95%CI:
1.18 (1.07 to 1.30)

*Converting to same scale NRS 0-10

NOTE: Weights are from random effects analysis
Other predictors:

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Adjusted OR &amp; 95%CI</th>
<th>Heterogeneity p</th>
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<tbody>
<tr>
<td>Breast surgery (MRM vs. BCS)</td>
<td>16</td>
<td>7,805</td>
<td>0.92 (0.75 to 1.13)</td>
<td>0.16</td>
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<tr>
<td>Chemotherapy (yes vs no)</td>
<td>17</td>
<td>7,813</td>
<td>1.07 (0.93 to 1.24)</td>
<td>0.97</td>
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<tr>
<td>Endocrine therapy (yes vs no)</td>
<td>12</td>
<td>8,162</td>
<td>1.03 (0.89 to 1.18)</td>
<td>1</td>
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<tr>
<td>Preoperative pain (yes vs no)</td>
<td>7</td>
<td>2,011</td>
<td>1.41 (0.95 to 2.09)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

50+ predictors reported, not able to be pooled
Summary

Younger age, axillary procedures, radiotherapy and acute post-op pain are associated with persistent pain after breast cancer surgery.

Large unexplained heterogeneity:
- particularly age, axillary procedures

Future studies for intervention:
- explore the effect of
  - targeting post-operative pain
  - nerve sparing techniques for axillary procedures
Suggestions for future research

Definition of persistent pain after breast cancer surgery/PMPS

Validated instrument of pain intensity/severity

Adequate sample size for pre-specified important risk factors
  - Ten patients with/without event (pain/no pain) for each predictor

Appropriate data analysis

Following observational study reporting guideline – e.g. STROBE

Complete reporting of data
Acknowledgement

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