The Association of Axillary Clearance with Persistent Pain Following Breast Cancer Surgery:
A systematic review of observational studies
Conflicts of Interest

• This was an unfunded study

• I have no actual or potential conflicts of interest in relation to this presentation
Background

Breast cancer:
• The most common cancer in women
• 2nd leading cause of death in women in Canada

Source: CCS Breast cancer statistics: http://www.cancer.ca/
Persistent pain after breast cancer surgery

• Persistent postsurgical pain (PPSP) affects 25% to 60% of women undergoing breast cancer surgery

• Persistent pain after breast cancer surgery is associated with reduced health-related quality of life

• Predictors of chronic post-surgical pain are poorly understood, which complicates efforts to improve prognosis for patients at risk

Objective of Our Review

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

Eligible criteria

• P: Breast cancer surgery patients
• E: Evaluation of any predictor with an adjusted analysis
• O: Persistent pain after breast cancer surgery (IASP criteria, ≥2 months)

Study Design

• Cohort study
• Case-control study
Risk of bias assessment & Overall Quality

• Representativeness of the study population

• Accuracy of outcome assessment

• Proportion of missing data

• Predictive models appropriately adjusted for age, cancer severity, and adjuvant therapy (i.e. radiotherapy and chemotherapy)

• We used the GRADE approach to evaluate the quality of evidence on a predictor-by-predictor basis
Data Analysis

• When possible, we pooled all factors that were assessed for an association with persistent pain that were reported by >1 study, and presented the OR and the associated 95% CI.

• Studies were ineligible if they included, in all available models, significant associations with variables collected after baseline; in such instances the status of the predictor may be a result, rather than a cause, of pain.

• We imputed an OR of "1" for all missing non-significant associations and used the hot deck approach to acquire a measure of precision.

39% of studies included only variables significant in bi-variable analysis in their adjusted models.

74% of studies failed to present data for non-significant predictors in their adjusted analysis.
Results

Study selection:

Flow diagram
Persistent pain prevalence & intensity

Prevalence decreases, but intensity increases over time.
Age

- 21 studies with 11,030 patients
- Median follow-up was 12 months
- Younger women more likely to develop persistent pain
- Adjusted OR for every 10-year decrement (from age 70) = 1.36 (95% CI = 1.24 to 1.48)
- HIGH quality evidence

Baseline risk of PPSP is 30%
6% more (3% to 9% more) patients with PPSP per 10-year decrement of age from age 70
Axillary procedure

- 13 studies & 7,699 patients
- Median follow-up was 12 months
- Axillary procedures were more likely to result in PPSP
- Adjusted OR = 2.41 (95%CI = 1.73 to 3.35)
- HIGH quality evidence

Baseline risk of PPSP is 30%

21% more (13% to 29% more) patients with ALND experience persistent pain
Radiotherapy

- 16 studies, 9,468 patients
- Median follow-up was 24 months
- Radiotherapy is associated with PPSP
- Adjusted OR =1.35 (95%CI = 1.16 to 1.57)
- HIGH quality evidence

Baseline risk of PPSP is 30%

7% more (3% to 10% more) among patients who receive radiotherapy
Acute pre-op pain

• 8 studies & 2,504 patients

• Median follow-up was 8 months

• Acute post-op pain is associated with PPSP

• Adjusted OR = 1.29 (95%CI = 1.01 to 1.64)

• MODERATE quality evidence due to imprecision
Acute post-op pain

- 5 studies & 1,387 patients
- Median follow-up was 18 months
- Acute post-op pain is associated with PPSP
- Adjusted OR = 1.16 (95%CI = 1.03 to 1.30)
- HIGH quality evidence

Baseline risk of PPSP is 30%

3% more (1% to 6% more) patients with post-op pain experience persistent pain, per 1-cm increment of acute pain on a 10 cm pain scale
Independent variables that were not associated with PPSP

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Adjusted OR &amp; 95%CI</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (every 5-point increment over 25)</td>
<td>8</td>
<td>3,178</td>
<td>1.11 (0.99 to 1.24)</td>
<td>High</td>
</tr>
<tr>
<td>Breast surgery (M/MRM vs. BCS)</td>
<td>17</td>
<td>8,566</td>
<td>1.08 (0.90 to 1.30)</td>
<td>High</td>
</tr>
<tr>
<td>Chemotherapy (yes vs no)</td>
<td>17</td>
<td>8,481</td>
<td>1.12 (0.98 to 1.25)</td>
<td>High</td>
</tr>
<tr>
<td>Endocrine therapy (yes vs no)</td>
<td>11</td>
<td>8,312</td>
<td>1.07 (0.94 to 1.22)</td>
<td>High</td>
</tr>
</tbody>
</table>
Promising factors

• Investigators have tested 68 additional predictors, but the results precluded statistical pooling.

• Of these 68 predictors, studies of sufficient sample size (≥500) reported sufficiently large associations (OR≥2.0) that the following four predictors may warrant additional study:
  • physical exercise
  • overall comorbidity
  • radiotherapy dosage
  • depression
Summary

• With respect to modifiable risk, given the 30% risk of persistent pain in the absence of positive risk factors, we have postulated that targeting such a factor for an intervention would require an absolute increase in risk of at least 10%
  • ALND was the only potentially modifiable factor meeting this threshold

• With respect to non-modifiable risk, we postulated that increases of absolute risk of 20% or more would be required to warrant targeting a high risk population
  • none of the individual non-modifiable associations we identified met this threshold; however, a combination of risk factors might constitute a population warranting special attention
Study Team

• Li Wang
• Gordon H. Guyatt
• Sean A. Kennedy
• Beatriz Romerosa
• Henry Y Kwon
• Alka Kaushal
• Yaping Chang
• Samantha Craigie

• Carlos P.B. de Almeida
• Rachel J. Couban
• Shawn R. Parascandalo
• Zain Izhar
• Susan Reid
• James S. Khan
• Michael McGillion
• Jason W. Busse