Persistent pain after breast cancer surgery

Prepared by

Professor Michael J. Cousins AM

May 2007

ACHR
AUSTRALIAN CENTRE FOR HEALTH RESEARCH

AUSTRALIAN CENTRE FOR HEALTH RESEARCH LTD ABN 87 116 781 965
114 Albert Road, South Melbourne Victoria 3205 Phone 03 9697 0283 Website www.achr.com.au

PAIN MANAGEMENT RESEARCH CENTRE

and

AUSTRALIAN CENTRE FOR HEALTH RESEARCH LTD

RESEARCH PROGRAM

PERSISTENT PAIN AFTER BREAST CANCER SURGERY

Special Note: The objective of the Australian Centre For Health Research Limited (ACHR) is to undertake activities aimed at improving the provision of health and ageing services in Australia. To this end, the ACHR commissions independent research on topics of importance in health and ageing, in order to stimulate further exploration of areas of shared concern. The presentation of factual matters, and the ideas and conclusions expressed in the independent research reflect the views of the author of that research, and do not necessarily represent all of the views of ACHR or its individual officers.

INTRODUCTION

One in eight women will develop breast cancer of which approximately 60 per cent are treated surgically for axillary node staging and primary breast tumour resection. It is estimated that over 50 per cent of women suffer chronic pain following the treatment for breast cancer surgery. It seriously affects quality of life through the combined impact of physical disability and emotional distress. The breast cancer incidence rate in Australia has risen in recent years while survival rates have improved; this has effectively increased the numbers of women for whom post-treatment quality of life is important. In this context, chronic pain following treatment for breast cancer surgery is a significantly under-recognized and under-treated problem.

Neuropathic pain is the most prevalent type of pain and it may be derived from the breast cancer, breast cancer surgery and non-surgical treatment. The surgery-related pain syndromes present as pain in the surgical scar, chest wall and upper arm, as well as shoulder discomfort and phantom breast dysesthesias and paresthesias.

Other neuropathic pain syndromes that may add to functional impairment include tumour recurrence pain, paraneoplastic processes, complex regional pain syndrome, chemotherapy-associated neuropathy (especially paclitaxel), radiation plexitis and plexopathy.

EPIDEMIOLOGY

In a recent review, Jung et al[1]found that the literature was inconsistent in defining chronic pain after breast cancer surgery. Earlier studies analysing prevalence did not distinguish between the various neuropathic pain syndromes. To improve comparability between future studies, Jung et al suggested a consistent time frame definition of chronic neuropathic pain and syndrome classification based on potential etiology. They further suggested that neuropathic pain syndromes due to breast cancer surgery should be considered chronic after 3 months and that shorter time frames should raise a consideration of pain associated with tumour recurrence.

In Jung et al's review, there were 21 studies with follow-up periods from 1-96 months (one study of 210 months), which revealed the following widely varying ranges of prevalence estimates:

- Phantom breast pain 3-44 per cent;
- Intercostobrachial neuralgia (ICN) 16-39 per cent for all breast cancer surgery;
- ICN in breast conserving surgery 14-61 per cent;
- Neuroma pain 23-49 per cent.[1]

Trial sizes to date have ranged from 22 to 283 patients, leaving considerable uncertainty about the overall size of the problem. However, even estimates at the lower end of these ranges suggest that the problem is considerable.

Variations in the reported size of the problem are also due to other factors including duration of time since surgery, type of surgery, research method, diagnostic criteria, pain assessment methods, and the distribution of various demographic and clinical characteristics in the samples studied.

In addition, very few studies differentiate pain syndromes according to the type of surgical procedure used. Wallace et al[2] analysed the incidence, intensity and character of pain after four types of breast surgery: mastectomy for breast cancer; mastectomy with reconstruction for breast cancer; cosmetic augmentation; and breast reduction. The highest incidence occurred in the combined mastectomy and reconstruction with breast implants at 53 per cent. There was equal incidence of about 30 per cent in those undergoing reconstruction without implants and mastectomy without reconstruction. Breast augmentation with subglandular implants and breast reduction were the lowest at 21 per cent.

In a recent study, Dijkstra et al[3] found the prevalence of phantom breast sensations or pain to be lower than in most previous studies. They attributed these differences to research methodology. In comparing their methods with those of the accompanied literature review of 29 studies, they found prospective studies on average showed higher prevalence of Phantom Breast pain and lower prevalence of Phantom Breast sensation compared to cross-sectional studies. Data collection by interview revealed lower prevalence in both compared to questionnaires.

CLASSIFICATION OF PAIN AFTER BREAST CANCER SURGERY

Jung et al[1] distinguished four different types of chronic neuropathic pain following breast cancer surgery due to surgical trauma.

1. **Phantom Breast Pain** is pain experienced in the area of a removed breast.

2. **Intercostobrachial Neuralgia** is pain often accompanied with sensory changes, in the distribution of the intercostobrachial nerve following breast cancer surgery with or without axillary dissection. The intercostobrachial nerves run from the chest wall through the axilla to innervate the shoulder and upper arm. With axillary node dissection, these nerves are impossible to spare.

   Unfortunately, the risk of damage to the intercostobrachial nerve in breast conserving surgery can be at times equivalent to that which occurs with complete mastectomy. Granek et al[4] revealed a wide variation in the size, location and branching of the intercostobrachial nerve which may explain the high risk of damage to these nerves irrespective of surgical approach.

   Sensory symptoms have been shown to vary depending on the origin at which the nerve is sectioned. For example, Paredes et al[5] found that patients who underwent modified radical mastectomy where the nerve was sectioned at the chest wall origin presented commonly with paresthesia rather than pain.

   Post-mastectomy pain syndrome (PMPS) consists of pain and sensory changes localized to the axilla, medial upper arm, and/or the anterior chest wall on the ipsilateral side of the surgery. Damage to the intercostobracial nerve has been identified as the most common cause of PMPS.[1, 6]

3. **Neuroma pain** (including scar pain) is pain in the region of a scar on the breast, chest, or arm that is provoked or exacerbated by percussion. A neuroma is formed from masses of tangled axons formed at the end of severed peripheral nerves. Neuromas

trapped in scar tissue have been shown to cause chronic neuropathic pain, spontaneous pain and severe sensitivity to pressure on the breast surgery area. Excision to enable relocation of the neuroma to a protected site may be beneficial, but may risk an increase in neuropathic pain

4. **Other nerve injury pain** may result from damage or traction to the medial and lateral pectoral, long thoracic, or thoracodorsal nerves.

PROGNOSIS

There is some evidence that chronic pain and sensory abnormalities do decrease over time.[7] Unfortunately, there are very few studies looking at the natural history of pain duration of individual neuropathic pain syndromes. Most are retrospective studies using data combined from all sources of pain following surgery. In the best existing population-based study of long-term outcomes, Macdonald et al[8] found that 7-12 years post-surgery, 52 per cent of women who had PMPS at four year follow-up still had PMPS; these women had significantly lower quality of life compared with those women whose PMPS had resolved.

QUALITY OF LIFE

The negative impact on a patient's physical and psychosocial functioning is consistent with many chronic and cancer pain syndromes. It has been reported that up to half of patients report negative impact of pain on their activities and up to one-quarter report moderate to high impact on their daily activities at home and work.[9]

Not surprisingly, studies have also found that breast cancer surgery patients with chronic pain have a greater psychological stress and psychiatric morbidity than the general population.[10, 11]

RISK FACTORS

There are a number of assumed factors causing or perpetuating persistent neuropathic pain after breast cancer surgery. There is however a lack of large scale multiple risk factor studies identifying the variables as independent risk factors or evaluating their relationships with other variables, which are known to affect the development of chronic pain.

From the literature currently available, the most well-established risk factors for developing phantom breast pain and other related-neuropathic pain syndromes are severe acute post-operative pain and greater post-operative use of analgesics.[9, 10, 12-15] These are consistent with all persistent post-surgical neuropathic pain syndromes. Hence, it is assumed that the relief of severe acute pain may reduce the risk of chronic pain. [16]

Pre-operative breast pain correlated with increased phantom breast sensation and phantom breast pain. [17, 18]

Underlying each of the four classifications of pain after breast cancer surgery is damage to various nerves during surgery. Nerve preservation approaches have shown reduced incidence

of sensory deficits (53 per cent vs. 84 per cent of women) but nerve sparing is only successful in 65 per cent of the cases where it was attempted. [19]

Evidence to support age as a risk factor is currently inconclusive. Younger patients however (under 35 years of age) have poorer prognosis due to more aggressive cancers or higher rates of recurrence. [20]

Chemotherapy and radiation therapy are reported not to be direct risk factors of phantom breast pain but may cause additional pain through peripheral neuropathy, plexopathy, and plexitis.

Psychosocial distress has been found to be both a consequence of chronic pain and a risk factor for its development.[10, 11] In particular, Katz et al [20] found that greater preoperative anxiety independently predicted both clinically meaningful pain in the immediate post-operative period as well as for a period of up to 30 days post surgery. While younger age and being unmarried were also independently associated with persisting acute pain, these were postulated to reflect the psychosocial affects of reduced social support.

PREVENTION TECHNIQUES

Based upon current incomplete evidence, the goals of these strategies could first target optimal perioperative pain control and minimizing damage to nerves during surgery.

Peri-operative Pain Control

Medications traditionally used for persistent neuropathic pain such as topical EMLA[21], gabapentin[22] and mexilitine[22] have been used in patients undergoing breast cancer surgery and have been reported in some studies to have benefits in reducing acute post-operative pain, one of the identified risk factors. However, more effective treatment regimens need to be evaluated. Kehlet et al[16] have suggested that simply aggressively treating perioperative pain is inadequate. A broad based approach targeting the mechanisms involved in persistent neuropathic pain after breast cancer surgery is also required.

Minimizing damage to nerves during surgery

Improved screening methods detect breast cancer at earlier stages. Earlier detection means smaller tumour sizes, which has made breast-conserving surgical treatments possible and widely used. These currently account for up to 40 per cent of breast cancer surgery[23]. Breast conserving techniques include lumpectomy, conservative breast surgery, wide local excision, partial mastectomy, segmentectomy, or tylectomy. Such approaches include reducing the number of axillary dissections required. Combining reduced surgical trauma with nerve preservation techniques may reduce the risk of sensory deficits and the occurrence of ICN.[24-26]

In this regard, the increased use of less invasive staging techniques such as sentinel lymph node biopsy has helped to reduce the number of patients undergoing axillary dissection and the resulting trauma to intercostobrachial nerves.[27-29]

TREATMENTS FOR ESTABLISHED NEUROPATHIC PAIN

In 2005, Finnerup et al[30] reviewed all randomized, doubled-blinded, placebo-controlled trials for evidence to support a neuropathic pain treatment algorithm. One hundred and five trials were included covering a number of neuropathic conditions. The main groups of oral medications studied included anti-depressants, anticonvulsants, opioids, NMDA antagonists, mexilitine, topical lidocaine, cannabinoids, topical capsaicin, and glycine antagonist.

For persistent post-breast cancer surgery neuropathic pain, there exists very few randomized, double-blind, placebo-controlled trials. The use of topical capsaicin [31-33]or amitryptiline [34] have reported benefit in the treatment of pain in patients after breast cancer surgery. However, many unanswered questions remain about the optimal doses, timing and co-ordination of therapy with ongoing adjuvant treatment for breast cancer. There are also a number of medications and multidisciplinary approaches showing benefit for other types of neuropathic pain that have yet to be trialled.
in women with early-onset or established post-breast cancer surgery neuropathic pain.

Neuromodulation techniques such as motor cortex stimulation[35, 36], spinal cord stimulation[37], and intrathecal drug therapies[38, 39] have been used to treat various neuropathic pain syndromes. Early case reports of the use of peripheral nerve stimulation[40, 41] for persistent neuropathic pain syndromes such as occipital neuralgia, trigeminal post-herpetic neuralgia, and trigeminal post-traumatic neuropathic pain may hold promise for its use in post-surgical pain syndromes. To date, there have been no reported studies in this area.

FUTURE DIRECTIONS

The small scale of existing studies into persistent pain after breast cancer surgery creates considerable uncertainty regarding the generalizability of their findings, and also regarding the identification of potentially modifiable risk factors. Recent improvements in neuropathic pain screening tools now make early identification and syndrome classification of neuropathic pain more achievable.[42]

Many important questions remain about persistent neuropathic pain after breast cancer surgery including the natural history, the predisposing risk factors, current awareness and management approaches by treating surgeons and oncologists.

To explore the size of the problem in Australia, associated factors, detection and optimal management strategies for persistent pain after breast cancer surgery, we are collaborating with Associate Professor Fran Boyle (Medical Oncologist, Mater Hospital, North Sydney) and Associate Professor Grantley Gill (Head of Breast, Endocrine & Surgical Oncology Unit, Royal Adelaide Hospital)

Currently, we have in principle agreement to access the SNAC database (Royal Adelaide Hospital) which is a large clinical trial (1,000 patients) comparing different surgical techniques for initial removal of breast cancers and their impact on quality of life. This trial is several times larger than existing published studies on persistent pain following breast cancer surgery. We will also be studying the development of persistent pain in women undergoing

chemotherapy or radiotherapy after breast cancer surgery at the Royal North Shore Hospital and the Mater Hospital in Sydney.

These study outcomes will be used to establish guidelines for providing information to patients; timely diagnosis of pain by treating surgeons and oncologists; and early pain management involving Pain Medicine specialists. On a broader level, these studies will also help us identify the issues affecting optimal access and use of pain management centres in general.

References

1. Jung, B., et al., *Neuropathic pain following breast cancer surgery: proposed classification and research update.* Pain, 2003. **104**: p. 1-13.
2. Wallace, M., et al., *Pain after Breast Surgery: a survey of 282 women.* Pain, 1996. **66**(2-3): p. 195-205.
3. Dijkstra, P., J. Rietman, and J. Geertzen, *Phantom breast sensations and phantom breast pain: A 2-year prospective study and a methodological analysis of literature.* European Journal of Pain, 2007. **11**: p. 99-108.
4. Granek, I., R. Ashikari, and K. Foley, *The post-mastectomy pain syndrome: clinical and anatomical correlates.* Proceedings of the American Society of Clinical Oncology, 1984. **3**: p. 122.
5. Paredes, J., J. Puente, and J. Potel, *Variations in sensitivity after sectioning the intercostobrachial nerve.* American Journal of Surgery, 1990. **160**: p. 525-8.
6. Vecht, C., H. Van de Brand, and O. Wajer, *Post-axillary dissection pain in breast cancer due to a lesion of the intercostobrachial nerve.* Pain, 1989. **38**: p. 171-6.
7. Ivens, D., et al., *Assessment of morbidity from complete axillary dissection.* British Journal of Cancer, 1992. **66**: p. 136-8.
8. Macdonald, L., et al., *Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome.* British Journal of Cancer, 2005. **92**: p. 225-30.
9. Tasmuth, T., et al., *Pain and other symptoms after different treatment modalities of breast cancer.* Annals of Oncology, 1995. **6**: p. 453-9.
10. Tasmuth, T., A. Estlanderb, and E. Kalso, *Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer.* Pain, 1996a. **68**: p. 343-7.
11. Akechi, T., et al., *Biomedical and psychosocial determinants of psychiatric morbidity among postoperative ambulatory breast cancer patients.* Breast Cancer Research and Treatment, 2001. **65**(3): p. 195-202.
12. Tasmuth, T., et al., *Chronic post-treatment symptoms in patients with breast cancer operated in different surgical units.* European Journal of surgical oncology, 1999. **25**: p. 38-43.
13. Tasmuth, T., B. Hartel, and E. Kalso, *Venlafaxine in neuropathic pain following treatment of breast cancer.* European Journal of Pain, 2002. **6**: p. 17-24.
14. Tasmuth, T., et al., *Treatment-related factors predisposing to chronic pai in patients with breast cancer: a multivariate approach.* Acta oncologica, 1997. **37**: p. 625-30.
15. Tasmuth, T., K. von Smitten, and E. Kalso, *Pain and other symptoms during the first year after radical and conservative surgery for breast cancer.* British Journal of Cancer, 1996b. **74**: p. 2024-31.
16. Kehlet, H., T. Jensen, and C. Woolf, *Persistent postsurgical pain: risk factors and prevention.* Lancet, 2006. **367**: p. 1618-25.
17. Kroner, K., et al., *Immediate and long-term phantom breast syndrome after mastectomy: incidence, clinical characteristics and relationship to pre-mastectomy breast pain.* Pain, 1989. **36**: p. 327-34.
18. Kroner, K., et al., *Long-term phantom breast syndrome after mastectomy.* Clinical Journal of Pain, 1992. **8**: p. 436-50.
19. Abdullah, T., et al., *Prospective randomized controlled trial of preservation of the intercostobrachial nerve during axillary node clearancee for breast cancer.* British Journal of Surgery, 1998. **85**(10): p. 1443-5.
20. Katz, J., et al., *Risk Factors for acute pain and its persistence following breast cancer surgery.* Pain, 2005. **119**: p. 16-25.

21. Fassoulaki, A., C. Sarantopoulos, and A. Melemeni, *EMLA reduces acute and chronic pain after breast surgery for cancer.* Regional anaesthesia & Pain Medicine, 2000. **25**: p. 350-5.
22. Fassoulaki, A., et al., *The analagesic effect of gabapentin and mexiletine after breast surgery for cancer.* Anesthesia & Analgesia, 2002. **95**: p. 985-91.
23. Iglehart, D. and C. Kaelin, *Diseases of the breast* in *Sabiston textbook of surgery*, C. Townsend, Editor. 2001, W.B. Saunders: Philadelphia.
24. Rietman, J., et al., *Long term treatment related upper limb morbidity and quality of life after sentinel lymph node biopsy for stag I or II breast cancer.* European Journal of surgical oncology, 2006. **32**: p. 148-52.
25. Mansel, R., et al., *Standard Axillary Treatment in Operable Breast Cancer: The ALMANAC trial.* Journal of National Cancer Institute, 2006. **98**(9): p. 599-609.
26. Peintinger, F., et al., *Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients.* British Journal of Cancer, 2003. **89**: p. 648-52.
27. Veronesi, U., F. Rilke, and A. Luini, *Distribution of axillary node metastases by level of invasion.* Cancer, 1987. **1987**(4): p. 682-7.
28. Berg, J., *The significance of axillary node levels in the study of breast cancer.* Cancer, 1955. **8**(4): p. 776-8.
29. Lyman, G., et al., *American Society of Clinical Oncology Guideline Recommendations for Sentinel Lymph node biopsy in early-stage breast cancer.* Journal of clinical oncology, 2005. **23**(30): p. 7703-7720.
30. Finnerup, N., et al., *Algorithm for neuropathic pain treatment: An evidence based proposal.* Pain, 2005. **118**: p. 289-305.
31. Watson, C. and R. Evans, *The post-mastectomy pain syndrome and topical capsaicin: a randomized trial.* Pain, 1992. **51**: p. 375-9.
32. Dini, D., et al., *Treatment of the post-mastectomy pain syndrome with topical capsaicin.* Pain, 1993. **54**: p. 223-6.
33. Watson, C., R. Evans, and V. Watt, *The post-mastectomy pain syndrome and the efect of topical capsaicin.* Pain, 1989. **38**: p. 177-86.
34. Kalso, E., T. Tasmuth, and P. Neuvonen, *Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer.* Pain, 1995. **64**: p. 293-302.
35. Brown, J. and J. Tilitsis, *Motor Cortex Stimulation.* Pain Medicine, 2006. **7**(S1): p. S140-45.
36. Nuti, C., et al., *Motor cortex stimulation for refractory neuropathic pain: Four year outcome and predictors of efficacy.* Pain, 2005. **118**(1-2): p. 43-52.
37. De Andres, J. and J. Van Buyten, *Neural Modulation by Stimulation.* Pain Practice, 2006. **6**(1): p. 39-45.
38. Hassenbusch, S., et al., *Polyanalgesic Consensus Conference 2003: An Update on the Managment of Pain by Intraspinal Drug Delivery-Report of an Expert Panel.* Journal of Pain and Symptom Management, 2004. **27**(6): p. 540-63.
39. Hassenbusch, S., et al., *Long-term Intraspinal Infusions of Opioids in the Treatment of Neuropathic Pain.* Journal of Pain and Symptom Management, 1995. **10**(7): p. 1995.
40. Johnson, M. and K. Burchiel, *Peripheral stimulation for treatment of trigeminal postherpetic neuralgia and trigeminal posttraumatic neuropathic pain: a pilot study.* Neurosurgery, 2004. **55**: p. 135-42.
41. Weiner, R., *Occipital Neurostimulation (ONS) for treatment of intractable headach disorders.* Pain Medicine, 2006. **7**(S1): p. S137-9.
42. Bennet, M., et al., *Using screening tools to identifiy neuropathic pain.* Pain, 2007. **127**: p. 199-203.