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Topical review

Neuropathic pain following breast cancer surgery: proposed classification and research update

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1. Introduction

Chronic pain following surgical procedures for breast cancer was once thought to be rare. The results of recent studies, however, suggest that the incidence of chronic pain following breast cancer surgery may be over 50% (Tasmuth et al., 1995; Kwekkeboom, 1996; Fassoulaki et al., 2000). Post-operative sensations reported by patients can be transient or long-lasting, and can include pain, phantom sensations, and sensory loss or changes. Chronic pain can be a source of considerable disability and psychological distress. In patients undergoing diagnostic studies, surgical procedures, and other treatments for breast cancer, persisting pain is an additional burden for individuals already suffering from many psychosocial and medical stressors (Wyatt and Friedman, 1998; Velanovich and Szymanski, 1999; Kuehn et al., 2000). Chemotherapy and radiotherapy can be additional sources of pain and related symptoms and make diagnosis difficult.

More patients are surviving breast cancer as a result of progress in diagnosis and treatment. The population at risk for chronic pain and other late complications can therefore be expected to increase in coming years. Although most surgical advances are less invasive and have fewer complications, the rapid pace of change in treatment complicates outcomes research.

This article reviews the types of breast cancer surgery and research on the epidemiology and natural history, pathophysiologic mechanisms, treatment, and prevention of chronic pain following these procedures. We emphasize neuropathic pain because it is the most prevalent type, and propose a classification of chronic neuropathic pain following breast cancer surgery that takes into account recent advances in surgical procedures. This classification includes only chronic neuropathic pain syndromes that are a direct consequence of breast cancer surgery. There are other neuropathic pain syndromes that occur following breast cancer surgery that are a consequence of breast cancer and its non-surgical treatment. These syndromes, which include neuropathic pain caused by tumor recurrence and paraneoplastic processes, chemotherapy-associated neuropathy, and radiation plexitis and plexopathy, are beyond the scope of this article.

Breast cancer occurs in men with a low incidence (Meguerditchian et al., 2002). Unfortunately, no studies have systematically compared chronic pain in men and women patients following breast cancer surgery; indeed, to our knowledge, only one study of chronic pain following breast cancer surgery has included men (Miaskowski and Dibble, 1995). The nature of the samples studied therefore limits our conclusions to women with breast cancer.

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Table 1
Surgical procedures for breast cancer

Surgical procedure	Tissue removed	Radiation therapy	Chemotherapy
Mastectomy			
Radical mastectomy (Halsted)	Skin and breast tissue, all axillary lymph nodes, pectoralis major and minor muscles	Not routine	Not routine
Modified radical mastectomy	Skin and breast tissue, all axillary lymph nodes	Not routine	Not routine
Breast-conserving surgery			
Lumpectomy	Breast lump and a margin of normal tissue	Routine	No
Lumpectomy with axillary node dissection	Breast lump, margin of normal tissue, axillary nodes	Routine	If disease present in axillary nodes
Lumpectomy with sentinel node biopsy	Breast lump, margin of normal tissue, axillary nodes only if positive sentinel node biopsy	Routine	If disease present in axillary nodes

2. Types of breast cancer surgery

Table 1 presents a summary of surgical procedures for breast cancer.

2.1. Radical mastectomy

This operation was developed by Halsted in the late 19th century (Iglehart and Kaelin, 2001). It involves removing the breast, skin and fat, pectoralis major and minor muscles of the chest, and all the lymph nodes under the ipsilateral arm. It is the most disfiguring breast cancer surgery, and exploration of other options began in the 1970s when it was realized that most breast cancer recurrences are not in the chest muscles.

2.2. Modified radical mastectomy

Clinical trials conducted in the 1970s compared radical mastectomy with less extensive procedures. One was the modified radical mastectomy, in which the pectoralis muscles are not removed but all other aspects of radical mastectomy are retained (Shons and Cox, 2001). Although removal of pectoralis minor was included with the initial modifications, it is now rarely performed.

2.3. Breast conserving surgery (lumpectomy)

Breast-conserving surgical treatments have evolved rapidly in recent years and currently account for as much as 40% of breast cancer surgery (Iglehart and Kaelin, 2001). Although commonly referred to as lumpectomy, these procedures have also been termed breast preservation, conservative breast surgery, wide local excision, partial mastectomy, segmentectomy, or tylectomy (Shons and Cox, 2001). Lumpectomy involves removal of the primary tumor and a margin of normal tissue, and it is important to distinguish lumpectomy from lumpectomy with axillary node dissection and lumpectomy with sentinel node biopsy. Patients who undergo only lumpectomy generally have earlier breast cancer (in situ disease) than those who require an axillary procedure.

2.3.1. Lumpectomy with axillary node dissection

Outcomes of lumpectomy with axillary node dissection were first studied in the 1970s. The primary tumor and a margin of normal tissue are removed, and axillary node dissection is performed through a separate incision in the armpit. Post-operative radiation therapy is administered to the remaining breast and the tumor bed. When disease is found in the axillary nodes, post-operative chemotherapy is administered (Iglehart and Kaelin, 2001; Shons and Cox, 2001).

2.3.2. Lumpectomy with sentinel lymph node biopsy

This is the most recent and least invasive option. A sentinel lymph node (i.e. the first axillary lymph node to receive drainage from the breast tumor) is identified by injecting a dye or radiolabelled colloid into the area of the tumor before surgery and then the labeled node is identified and removed for pathologic examination. If no tumor is found within this node, the patient does not undergo axillary dissection. With sentinel node biopsy, only those patients with disease in the sentinel lymph node undergo axillary dissection, sparing many patients from axillary dissection and its complications. Post-operative breast radiation therapy is administered to all patients.

2.4. The role of chemotherapy and radiation therapy

Chemotherapy is typically initiated after surgery and before radiotherapy when disease is found in axillary nodes.

It is also used in selected patients, including those with locally advanced disease as well as those with inflammatory breast cancer, as an initial treatment to reduce tumor size in preparation for later surgical removal. Radiation therapy is now a standard part of breast-conserving treatment. Patients undergoing lumpectomy with axillary node dissection or sentinel node biopsy are routinely administered post-operative radiotherapy that targets the breast and tumor bed and possibly the axillary area (Iglehart and Kaelin, 2001). Although use of brachytherapy (implantation of small radioactive particles into the tumor bed) is increasing, it is not widely practiced. There are many side effects of chemotherapy and radiation, including pain and associated symptoms such as fatigue. Peripheral neuropathy, often painful, is common after paclitaxel, a second-line therapy for metastatic disease, and also occurs with other chemotherapeutic agents.

3. Anatomical considerations

The innervation of the cutaneous and subcutaneous (adipose, lactiferous) structures of the breast is simple, with somatic and preganglionic sympathetic innervation being supplied through the medial and lateral cutaneous branches of the ventral ramus of the third through sixth intercostal nerves. The lateral cutaneous branch of T_2 (intercostobrachial nerve) crosses the axilla to innervate the upper medial portion of the arm while the lateral and anterior branches innervate the anterior chest and upper back. T_3 innervates the skin of the axilla as well as the anterior and posterior torso, and T_4 and below are restricted to the torso. The nipple is primarily innervated by T_4.

Axillary dissection poses risks to the intercostobrachial nerve, from stretch during retraction as well as from frank transection. Many patients will be left with an area of numbness on the upper inner arm, signifying damage to the intercostobrachial nerve, but only a minority of these will be painful. Other nerves at risk for damage from axillary dissection include the medial cutaneous nerve of the arm, which contains fibers from C_8 and T_1 and arises from the medial cord of the brachial plexus. It can be harmed during section of the tributaries of the axillary vein, leaving patients with sensory loss on the lower medial skin of the upper arm. Pain accompanied by sensory loss in one of these areas provides the basis for a diagnosis of injury to these specific nerves.

Neuropathic pain arises from damage to nociceptive axons; damage to primarily motor nerves is less likely to cause chronic pain. However, even motor nerves have sensory *nervi nervorum* and *vasorum*. Vulnerable motor nerves in the area include the medial and lateral pectoral nerves, which innervate the pectoralis minor and major muscles and are lost during resection of these muscles. The long thoracic nerve to the serratus anterior muscle runs along the posterior part of the medial wall of the axilla behind the axillary nodes. Damage produces 'winging' of the scapula. The thoracodorsal nerve to the latissimus dorsi muscle runs vertically through the axilla in close proximity to the subscapular artery and vein. Preservation of these neurovascular structures is required if a latissimus dorsi flap is needed for reconstructive breast surgery. Weakness of the latissimus dorsi (which adducts the upper arm) can usually be compensated for by the teres major and pectoralis major muscles.

4. Classification of chronic neuropathic pain following breast surgery

Persistent pain in a patient with a prior surgical procedure for breast cancer can occur for many reasons, including tumor recurrence, complications of radiotherapy or chemotherapy, or surgical injury (Watson and Evans, 1982; Foley, 1987). Chronic pain that is a direct consequence of surgery can be either nociceptive – for example, resulting from injury to ligament or muscle – or neuropathic in origin. Nociceptive pain usually resolves as damaged tissues heal, whereas pain from neuronal dysfunction can persist indefinitely. Neuropathic pain, defined as pain 'initiated or caused by a primary lesion or dysfunction in the nervous system' (Merskey and Bogduk, 1994), has been the focus of greater clinical attention and research effort because it is considerably more common.

We distinguish four different types of chronic neuropathic pain following breast cancer surgery (Table 2). This proposed classification is based on the results of studies of the epidemiology, mechanisms, and treatment of chronic pain following breast cancer surgery. Because of recent advances in the surgical treatment of breast cancer, few studies have investigated chronic pain following the different types of breast conserving surgery discussed above. The goal of our classification, therefore, is to stimulate future research that will result in a taxonomy of chronic pain following breast cancer surgery that is valid with respect to differences in pain mechanisms and treatment response. Such research is required not only to refine the descriptions of these four syndromes, but also to develop reliable and valid diagnostic criteria and assessment methods.

4.1. Phantom breast pain (versus non-painful phantom breast sensation)

Patients commonly experience the sensation that the removed breast is still present after a radical mastectomy or a modified radical mastectomy. In considering chronic pain following breast cancer surgery, it is important to distinguish non-painful phantom sensation from phantom pain. Non-painful phantom breast sensation is a sensory experience of a removed breast that still feels present. Phantom breast pain is a sensory experience of a removed

Table 2
Classification of chronic neuropathic pain syndromes following breast cancer surgery

Syndrome	Description
Phantom breast pain[a]	Sensory experience of a removed breast that is still present and is painful
Intercostobrachial neuralgia (includes post-mastectomy pain syndrome)	Pain, typically accompanied by sensory changes, in the distribution of the intercostobrachial nerve following breast cancer surgery with or without axillary dissection
Neuroma pain (includes scar pain)	Pain in the region of a scar on the breast, chest, or arm that is provoked or exacerbated by percussion
Other nerve injury pain	Pain outside the distribution of the intercostobrachial nerve consistent with damage to other nerves during breast cancer surgery (e.g. medial and lateral pectoral, long thoracic, thoracodorsal, and other intercostal nerves)

[a] To be distinguished from non-painful phantom breast sensations.

breast that is still present and is painful. Phantoms, either painful or non-painful, can occur after removal of any innervated body part.

4.2. Intercostobrachial neuralgia

Foley and colleagues (Granek et al., 1984; Foley, 1987) described a distinct syndrome of pain and sensory abnormalities following mastectomy that they termed post-mastectomy pain syndrome (PMPS). In PMPS, pain is typically localized to the axilla, medial upper arm, and/or the anterior chest wall on the affected side (Stevens et al., 1995). Damage to the intercostobrachial nerve, which can occur with axillary node dissection, has been considered the most common cause of PMPS. For example, in a series of 38 patients who had undergone mastectomy with axillary node dissection, a lesion of the intercostobrachial nerve was considered the cause of pain in seven of eight patients with persistent pain on neurologic examination (Vecht, 1990).

Further evidence that the intercostobrachial nerve plays an important role in post-mastectomy pain is provided by a study that compared post-operative findings in three different surgical approaches to the intercostobrachial nerve during modified radical mastectomy (Paredes et al., 1990). Abnormal sensation was more common in patients whose intercostobrachial nerve was sectioned at its origin on the chest wall than when only the axillary branches were sectioned (with the trunk remaining intact); sensation was the most normal in patients whose intercostobrachial nerve was preserved.

As breast conserving surgery has become common, it has been recognized that chronic pain can also occur after lumpectomy. The risk of damage to the intercostobrachial nerve seems to be at least as great in lumpectomy with axillary dissection as in mastectomy, judging by the incidence of 'post-mastectomy' and ipsilateral arm pain found in patients who had breast conserving surgery versus those who had mastectomy (Tasmuth et al., 1995, 1996b, 1997; Carpenter et al., 1999).

Abdullah et al. (1998) randomly assigned patients to intercostobrachial nerve preservation or section, but noted that the nerve was only preserved in 65% of those assigned to the preservation group. Pain, numbness, and other sensory changes were significantly greater at the time of hospital discharge in the patients whose nerve had been sectioned. By 3 months the difference in pain was no longer significant, but the incidence of sensory deficits remained greater in those assigned to nerve section (84%) than preservation (53%). Some patients with sensory loss had no sensory symptoms and others with symptoms had no sensory loss, a common finding in neuropathic pain. This study demonstrates both the technical difficulty in preserving the intercostobrachial nerve, and the variable relationship between sensory signs and symptoms. Importantly, wide variation in the size, location, and branching of the intercostobrachial nerve has been found when the nerve is carefully dissected during mastectomy (Granek et al., 1984). These variations may provide an anatomical basis for differences among surgical procedures and among patients in outcomes.

Because patients with chronic pain following lumpectomy with axillary node dissection, as well as those with PMPS, can have neuropathic pain, at present intercostobrachial neuralgia (ICN) is a more appropriate term than PMPS for the neuropathic pain syndrome that appears to result from damage to the intercostobrachial nerve (Fromm, 2000). This term can be applied to patients who have neuropathic pain caused by damage to the intercostobrachial nerve irrespective of the type of surgical procedure that has been performed.

4.3. Neuroma pain

Neuromas can form whenever peripheral nerves are severed or injured. Macroneuromas consist of a palpable mass of tangled axons unable to regenerate to their target, fibroblasts, and other cells, whereas microneuromas contain small numbers of axons and may not be palpable. Clinical experience and animal models indicate that the formation of a neuroma in scar tissue can cause chronic neuropathic pain.

Both mastectomy and lumpectomy leave a scar in which neuromas can form (Rosso et al., 2000). Axons entrapped within these scars can cause spontaneous pain and severe mechanosensitivity.

Neuroma pain may be more common following lumpectomy than mastectomy; Tasmuth et al. (1995) reported that patients who had lumpectomy, axillary dissection, and radiotherapy were significantly more likely to have scar pain than those who had a modified radical mastectomy. Anecdotal reports suggest that resection of intercostal neuromas may alleviate chronic pain after breast cancer surgery (Wong, 2001). However, because a neuroma can reform following excision, relocation to a protected site and attempts to improve regeneration using nerve grafts are the major neurosurgical treatment options (Burchiel, 1997; Campbell, 1997).

4.4. Other nerve injury pain

The three chronic neuropathic pain syndromes we have discussed – phantom breast pain, ICN, and neuroma pain – do not exhaust the types of chronic neuropathic pain found after breast cancer surgery. For example, Carpenter et al. (1999) reported that two of four patients who had lumpectomy without axillary dissection had 'post-mastectomy pain' on medical record review, as did four of 18 whose records documented sparing of the intercostobrachial nerve during surgery. One explanation of these findings is that other intercostal nerves are involved in some patients with chronic neuropathic pain following breast cancer surgery (Granek et al., 1984; Watson et al., 1989). Of course, these patients may have had neuroma pain with symptoms that mimicked PMPS (Carpenter et al., 1998), and it is also possible that fascicles or small branches of the intercostobrachial nerve were damaged during surgery in these patients despite the absence of axillary node dissection and efforts to preserve the nerve. Other sources of neuropathic pain following breast cancer surgery are damage to the medial and lateral pectoral, long thoracic, or thoracodorsal nerves, which are routinely spared but may be injured by scarring or by traction during mastectomy (Wallace and Wallace, 1997).

5. Epidemiology and natural history

Unfortunately, the research literature on chronic pain following breast cancer surgery has used a variety of definitions of chronic pain, ranging from two (Macrae and Davies, 1999) to six (Kwekkeboom, 1996) months postoperatively. The convention established by the International Association for the Study of Pain (IASP) is that pain can be considered chronic when it has persisted beyond the normal time of healing, with 3 months being considered 'the most convenient point of division between acute and chronic pain' (Merskey and Bogduk, 1994). To facilitate comparison of research results, this definition of chronic pain should be used in all future studies of phantom breast pain, ICN, and neuroma pain following breast cancer surgery. Although it was further proposed in the IASP taxonomy that when pain is associated with cancer, '3 months can be too long to wait before considering the pain as chronic' (Merskey and Bogduk, 1994), we believe that for research purposes this qualification should apply only to pain associated with tumor recurrence, and not to neuropathic pain syndromes caused by breast cancer surgery.

5.1. Prevalence

A summary of the results of studies that have examined the prevalence of chronic neuropathic pain following breast cancer surgery is presented in Table 3. Data are presented for phantom breast pain, ICN, and neuroma pain. There are many other studies that have not specified the type of chronic pain following breast cancer surgery, and the results of such studies are not included in the table. For ICN, the table includes only the results of studies clearly referring to PMPS or pain in the ipsilateral axilla or arm; studies reporting the prevalence of chest or shoulder pain were not included because damage to the intercostobrachial nerve may not be the cause of such pain. For neuroma pain, the table includes only the results of studies referring to neuroma pain, scar pain, or cicatrix pain. Many of the studies summarized in the table have examined small samples of patients, and most have important methodological shortcomings, including use of retrospective samples of convenience.

Estimates of the prevalence of phantom breast sensation in patients following mastectomy have been as high as 60–80% (Jamison et al., 1979; Lierman, 1988). As can be seen from Table 3, reports of the prevalence of phantom breast pain range from 13 to 44%. Estimates of the prevalence of ICN (or PMPS) also vary widely. Stevens et al. (1995) reported that the prevalence of PMPS was 20% after breast cancer surgery, and that patients with PMPS constituted 58% of those who reported pain following their surgery (the remainder had somatic or visceral pain directly associated with tumor involvement). Estimates of the risk of a painful neuroma following breast cancer surgery also vary widely, ranging from 23 to 49% (Table 3).

Wallace et al. (1996) conducted one of the few studies of pain following breast cancer surgery that specifically examined breast reconstruction and found that the prevalence of any pain was greatest in patients who had had mastectomy with reconstruction (49%) versus those who had undergone mastectomy without reconstruction (31%). Women whose reconstruction had included breast implants had a greater prevalence of pain (53%) than patients who had reconstruction without implants (30%), who had a very similar prevalence of pain as patients who had mastectomy without reconstruction.

Table 3
Prevalence of chronic neuropathic pain syndromes following breast cancer surgery

Author, year	*N*	Time after surgery (months)[a]	Prevalence (%)
Phantom breast pain			
Jamison et al. (1979)	41	22	44
Krøner et al. (1989)	110	12	13
Krøner et al. (1992)	69	72	17
Intercostobrachial neuralgia (including post-mastectomy pain syndrome and ipsilateral axillary or arm pain)			
Vecht (1990)	38	1–6	18
Keramopoulos et al. (1993)	104	3	16
Polinsky (1994)	223	96	33–39
Stevens et al. (1995)	95	NA[b]	20
Tasmuth et al. (1995)			
Modified radical mastectomy	283	32	28–41
Breast conserving surgery	184	28	37–61
Tasmuth et al. (1996b)			
Modified radical mastectomy	53	6	23
		12	13
Breast conserving surgery	40	6	35
		12	23
Wallace et al. (1996)			
Mastectomy	103	12–72	56
Mastectomy + reconstruction	78	12–72	42
Abdullah et al. (1998)			
Nerve preserved	40	3	14
Nerve removed	80	3	32
Carpenter et al. (1998)	134	38	27
Kakuda et al. (1999)	95	1–210	20
Tasmuth et al. 1999)			
High-volume hospitals	129	12	43
Low-volume hospitals	92	12	56
Fassoulaki et al. (2000)			
Control group	22	3	50–68
Johansen et al. (2000)	266	78	15
Fassoulaki et al. (2002)			
Control group	24	3	33
Neuroma pain (including scar pain)			
Krøner et al. (1989)	110	12	23
Krøner et al. (1992)	69	72	31
Polinsky (1994)	223	96	31
Tasmuth et al. (1995)			
Modified radical mastectomy	283	32	32–40
Breast conserving surgery	184	28	45–49

[a] Mean, median, or range of follow-up duration after surgery.
[b] NA = not available.

Tasmuth et al. (1999) examined whether there is a volume-outcome relationship in the development of chronic pain following breast cancer surgery. Although the incidence of pain and abnormal sensations was reduced in high-volume hospitals, such outcome differences likely reflect multiple factors, including the availability of better support services in high-volume hospitals.

There can be little doubt that the variability in estimates of the incidence of chronic pain following breast cancer surgery – whether phantom pain, ICN, or neuroma pain – is due to multiple factors, including duration of time since surgery, type of surgery, research method (retrospective versus prospective), diagnostic criteria, pain assessment methods, and the distribution of various demographic and clinical characteristics in the samples studied (e.g. age, use of chemotherapy and radiotherapy, tumor recurrence).

5.2. Prognosis

Assessments of the overall duration of pain following breast cancer surgery are complicated by sources of pain that follow surgery. These include radiotherapy and

chemotherapy, reconstruction, restrictions in shoulder range of motion and arm strength, and disease progression. Patients may also undergo treatment for their pain, which makes it difficult to evaluate whether decreased pain is a result of natural history or treatment effects. Most studies of the prognosis of chronic pain following breast cancer surgery have used retrospective methods, and it is very likely that the results of these studies include various recall and selection biases.

There is some evidence that the incidence of chronic pain following breast cancer surgery, its intensity (de Vries et al., 1994), and associated sensory abnormalities decrease over time. For example, Ivens et al. (1992) found that the likelihood of chronic pain diminished from 31% at 1–2 years following breast cancer surgery to 20% after more than 4 years following surgery. With respect to phantom breast sensations, it was found that 26% of patients reported phantom sensation 3 weeks after surgery, with approximately half of these patients reporting pain; when recontacted 6 years later, the incidence of phantom breast sensation remained the same but only 17% of these patients reported pain (Krøner et al., 1989, 1992).

5.3. Quality of life

As is generally true of chronic and cancer pain syndromes (Glover et al., 1995), phantom breast pain, ICN, and neuroma pain following breast cancer surgery can have a profound negative impact on a patient's physical and psychosocial functioning. In one study, approximately half of patients following breast cancer surgery reported some impact of pain on their activities, with one-quarter of patients reporting that their pain had moderate or greater impact on their daily lives (Tasmuth et al., 1995). The impact of pain following breast cancer surgery occurs at work and at home (Polinsky, 1994), and because of their pain some patients must apply for disability benefits or reduce their work schedule to part-time (Stevens et al., 1995).

Several studies have examined whether patients with chronic pain following breast cancer surgery have elevated levels of psychosocial distress. Compared to the general population, patients with chronic pain following breast cancer surgery have been found to have significantly greater psychological distress (Tasmuth et al., 1996a), although not in all studies (Hack et al., 1999). The results of other research suggest that the presence and intensity of chronic pain and discomfort following breast cancer surgery is, not surprisingly, associated with greater psychological or psychiatric morbidity, including depression and anxiety (Maunsell et al., 1993; Glover et al., 1995; Miaskowski and Dibble, 1995; Tasmuth et al., 1996b; Carpenter et al., 1998; Akechi et al., 2001). Such cross-sectional relationships between psychosocial distress and the presence and intensity of pain are certainly consistent with elevated levels of distress being a consequence of chronic pain. However, it is also possible that these relationships reflect psychosocial risk factors for chronic pain; as will be seen below, only the results of prospective studies have the potential to disentangle these causal relationships.

5.4. Risk factors for chronic pain following breast cancer surgery

Identification of risk factors for phantom pain, ICN, and neuroma pain after breast cancer surgery not only provides important information about the natural history of these syndromes but may increase understanding of their pathophysiologic mechanisms. In addition, knowledge of risk factors can be used to design interventions intended to prevent the development of chronic pain following breast cancer surgery, and will identify the important covariates that should be examined in clinical trials of such preventive interventions. Finally, determining the risk factors for chronic pain following breast cancer surgery makes it possible to identify those patients who have greatest need for preventive efforts because of their increased risk of chronic pain.

5.4.1. Demographic risk factors

The results of research examining whether age is a risk factor for chronic pain following breast cancer surgery are inconsistent. Although several studies suggest that younger patients are at greater risk (de Vries et al., 1994; Tasmuth et al., 1995; Smith et al., 1999), others find no relationship between age and pain after breast surgery (Krøner et al., 1989; Ivens et al., 1992; Carpenter et al., 1999). Importantly, breast cancer patients under 35 years of age have a poorer prognosis, which may explain the results of studies reporting a greater likelihood of chronic pain in younger patients. Tumors in younger patients are more likely to be estrogen-receptor negative, of higher tumor grade, more proliferating, and more vessel invasive (Kroman et al., 2000; Yildirim et al., 2000), and age independently predicts increased relapse and decreased survival (Colleoni et al., 2002).

5.4.2. Medical and surgical risk factors

Chemotherapy and radiation therapy seem not to increase the risk of phantom breast pain (Krøner et al., 1989; de Vries et al., 1994) but have been found to be associated with other types of pain after lumpectomy or mastectomy in some studies (Tasmuth et al., 1995, 1997; Smith et al., 1999) but not others (Carpenter et al., 1999). However, chemotherapy and radiotherapy are related to age and disease stage and can themselves be the cause of various neuropathic pain syndromes and it is therefore unclear whether they make an independent contribution to the development of ICN or neuroma pain.

5.4.3. Acute pain

The presence of breast pain before mastectomy predicted

the presence of phantom breast pain 3 weeks after surgery but not 1 year later; however, pre-operative breast pain did predict the presence of phantom breast sensation at the 1-year follow up in this study (Krøner et al., 1989). Greater intensity of acute post-operative pain and greater post-operative analgesic use have been found to be associated with chronic breast and ipsilateral arm pain following breast cancer surgery in both retrospective and prospective research studies (Tasmuth et al., 1995, 1996a, 1997; Jung et al., 2002).

5.4.4. Psychosocial risk factors

As noted above, cross-sectional associations between chronic pain and psychosocial distress are consistent with distress being either a consequence of chronic pain or one of its risk factors. For this reason, only the results of prospective studies can provide compelling evidence that psychological variables are risk factors for chronic pain (Dworkin and Banks, 1999). In the first study to prospectively examine psychosocial risk factors for chronic pain following breast cancer surgery, pre-operative depression and anxiety were non-significantly greater in patients who developed chronic pain than in those who did not (Tasmuth et al., 1996a). Interim analyzes of the results of an ongoing prospective study provide further support for the possibility that psychosocial distress prior to breast cancer surgery is a risk factor for chronic pain after surgery (Jung et al., 2002).

5.4.5. Necessity of multivariate analyzes of risk factors

It is very likely that there are significant associations among risk factors for chronic pain following breast cancer surgery. For example, patients with more advanced disease undergo more invasive treatment and may have greater psychological distress. It is important to identify whether such variables and others (e.g. age, chemotherapy) are independent risk factors or whether their association with the development of chronic pain is explained by their relationships with other variables. This will require studies in which all of these demographic, clinical, and psychosocial characteristics are carefully assessed and then analyzed using multivariate statistics. Prospective studies in which interventions that modify putative risk factors are administered prior to surgery also have the potential to further clarify the role of these factors in the development of chronic pain.

6. Pathophysiologic mechanisms

Because it is caused by tissue damage and inflammation, post-operative pain immediately following breast cancer surgery has both nociceptive and neuropathic components. As healing occurs, neuropathic pain mechanisms associated with breast removal and surgical insult to the intercostobrachial and other nerves become predominant. The pathophysiologic basis for the development of chronic phantom breast pain, ICN, and neuroma pain is provided by the damage to peripheral nerve fibers that occurs during breast cancer surgery. Identifying the specific pathophysiologic mechanisms that are involved in peripheral neuropathic pain syndromes has recently become the focus of intense research effort. Current understanding of these mechanisms, however, is largely based on studies of animal and human experimental models of neuropathic pain rather than on the results of studies of human clinical syndromes.

6.1. Mechanisms of phantom breast pain

Few studies have sought to identify the mechanisms of phantom breast pain. In an early study, Aglioti et al. (1994) examined responses to pinprick and light touch in patients with phantom breast sensations, including some whose phantom sensations had resolved. When testing on operated and non-operated sides, upper and lower limbs, head and neck, back, and facial areas, stimulation of skin areas well outside the dermatomes of the operated breast in patients who still had phantom sensations produced a phantom that reflected the kind of stimulus given. The duration of time that had elapsed between surgery and these assessments varied greatly among patients, suggesting that remapping of peripheral input and cortical reorganization may begin very soon after surgery. Appearance of this type of cortical plasticity within a few days of surgery provides evidence for unmasking of extant non-functional connections.

Flor et al. (2000) have proposed a model of the development of phantom limb pain and its perpetuation by peripheral factors that provides a valuable guide to future research on the development of phantom breast pain following breast cancer surgery. In this model, presence of pain before amputation can lead to the development of a cortical pain memory, which promotes the cortical reorganization after amputation that underlies phantom limb pain. Reorganization of the amputation zone in the somatosensory cortex is perpetuated by peripheral input, including ectopic discharges from central and/or peripheral neurons, sympathetic activation, and loss of nociceptive input. Different contributions by these different peripheral and central mechanisms may explain different symptoms and responses to regional analgesia. In some amputees, elimination of both phantom pain and cortical reorganization occurred during brachial plexus anesthesia, whereas in other patients, pain and cortical reorganization remained unchanged (Birbaumer et al., 1997).

An important question for future research is whether cortical reorganization provides the mechanism of phantom pain or whether reorganization is a concomitant or consequence of the experience of a phantom sensation (and can perhaps serve as a biomarker for it). It can be expected, however, that relationships between phantom

breast pain and cortical reorganization will differ from those found between phantom limb pain and reorganization. This is because the cortical representation of breasts presumably differs from that of limbs, which convey detailed somatosensory information, including proprioception and joint sensation that breasts do not.

6.2. Mechanisms of ICN

In an important study addressing mechanisms, Gottrup et al. (2000) did extensive psychophysical testing in 15 patients with pain after mastectomy or lumpectomy and in 11 patients without persistent pain after breast cancer surgery. There were increased warm and cold thresholds on the operated side in both groups, but compared to those without pain, patients with pain had less sensory deficit, that is, their thermal sensation was relatively preserved. Patients with pain also had lower pressure pain thresholds and more cutaneous blood flow on the operated compared to the non-operated side (differences that were not seen in the pain-free group). Temporal summation, demonstrated by greater evoked pain intensity after repetitive tactile stimulation, was found near the surgical site in the patients with pain, but was not seen on their unaffected side or in the pain-free patients. Finally, stimulus-evoked pain and spontaneous pain intensity were associated in the patients with pain.

Considered together, these results are reminiscent of those reported in patients with postherpetic neuralgia by Rowbotham et al. (1998), who propose that such patterns of sensory findings and symptoms reflect the maintenance of central sensitization by input from damaged primary afferent nociceptors that remain in continuity with their central targets. It is difficult, however, to determine the extent to which peripheral versus central sensitization accounts for these results. Moreover, tactile allodynia presumably involves low-threshold mechanoreceptors; these sprout into the superficial nociceptive layers of the dorsal horn, allowing cross-stimulation of nociceptive as well as non-nociceptive central pathways in animals with nerve injuries (Woolf et al., 1992).

6.3. Mechanisms of neuroma pain

Chronically painful scars can develop after mastectomy and lumpectomy, and abnormal neuronal activity originating in neuromas or entrapped axons within this scar tissue is the likely mechanism of such pain. It is well-established that neuromas can be a source of ectopic discharges that contribute to pain (Devor, 1997; Kretschmer et al., 2002). These can be either spontaneous or evoked by mechanical stimuli; the abnormal activity is thought to result from upregulation and/or ectopic placement of energy transducers normally deployed only at the receptive field. Tapping of neuromas is associated with increased activity in C fibers as well as increased pain, and greater phantom limb pain is associated with lower stump pressure pain thresholds (Nikolajsen and Jensen, 2001).

7. Treatment

There are very few randomized, double-blind, placebo-controlled trials of treatments for chronic pain following breast cancer surgery. In open-label trials of topical capsaicin for patients diagnosed with PMPS, Watson et al. (1989) reported that eight of 14 patients (who completed the trial) had good or excellent results, and Dini et al. (1993) reported that after treatment two of 21 patients had complete pain relief and another 11 had less pain. In the only randomized controlled trial of topical capsaicin, crossover treatment with capsaicin versus placebo in 25 patients diagnosed with PMPS was associated with significantly greater pain relief and reduction in jabbing pain, although the treatment groups did not differ in the relief of steady pain and allodynia (Watson and Evans, 1992). It was noted that burning caused by capsaicin made it probable that the integrity of the double-blind in this trial was compromised.

Amitriptyline has been examined in a randomized, double-blind, placebo-controlled, crossover trial of neuropathic pain following breast cancer surgery (Kalso et al., 1995). Pain relief was significantly greater with amitriptyline than placebo, and eight of 15 patients reported at least 50% decrease in their pain intensity; five of these patients, however, did not want to continue treatment after the trial ended because of adverse effects. A recent randomized, double-blind, placebo-controlled, crossover trial failed to find a significant benefit of venlafaxine versus placebo on the primary endpoint (daily pain diary ratings) but did find greater relief associated with venlafaxine treatment for two secondary endpoints, pain relief and maximum pain (Tasmuth et al., 2002).

These few clinical trials of chronic pain following breast cancer surgery do not provide a basis for evidence-based treatment of phantom breast pain, ICN, and neuroma pain. However, there have been recent major advances in the treatment of neuropathic pain that are based on the results of randomized controlled trials in other chronic peripheral neuropathic pain syndromes that likely share similar mechanisms. The extent to which the results of clinical trials of one chronic neuropathic syndrome apply to other chronic neuropathic syndromes cannot be determined at present. Nevertheless, the results of published clinical trials and current knowledge of pathophysiologic mechanisms and patterns of symptoms and signs suggest that treatments found to be efficacious in one chronic neuropathic pain syndrome may be efficacious in other neuropathic pain syndromes (Sindrup and Jensen, 1999). In considering treatment with medications not studied in phantom breast pain, ICN, and neuroma pain, potential risks and benefits should be carefully evaluated by considering the medication's safety and tolerability in light of the patient's

medical condition, age, pain severity, degree of suffering, and previous treatment history.

For many years, amitriptyline was considered the first-line treatment for chronic neuropathic pain. However, a recent study of patients with postherpetic neuralgia demonstrated that nortriptyline and amitriptyline provide equivalent analgesic benefits but that nortriptyline is better tolerated (Watson et al., 1998). Therefore, secondary amine tricyclic antidepressants, in particular nortriptyline and desipramine, should be used in place of amitriptyline and the other poorly tolerated tertiary amine tricyclics.

In addition to tricyclic antidepressants, recent placebo-controlled trials have demonstrated the efficacy of gabapentin, tramadol, and lidocaine patch 5% in patients with various chronic neuropathic pain syndromes, especially painful peripheral neuropathy (Sindrup and Jensen, 2000) and postherpetic neuralgia (Dworkin and Schmader, 2003). In addition to its analgesic benefit, the lidocaine patch 5% provides a protective barrier that may be especially beneficial in patients whose allodynia makes it difficult to wear clothing.

Although the role of opioid analgesics in the treatment of neuropathic pain was controversial for many years, the efficacy of controlled-release oxycodone (Watson and Babul, 1998) and morphine (Raja et al., 2002) has recently been demonstrated in patients with postherpetic neuralgia. The results of these studies provide compelling evidence that opioid analgesics can be effective in neuropathic pain, and should be considered in the treatment of the often-refractory patient with neuropathic pain following breast cancer surgery.

Although multidisciplinary treatment – which includes psychological interventions and physical therapy as well as medical and interventional treatments – has not been studied in patients following breast cancer surgery, it has very well established efficacy in the treatment of other chronic pain syndromes. Indeed, patients with metastatic carcinoma of the breast treated with group therapy with or without self-hypnosis training reported significantly less pain and suffering compared to control patients over the course of 1 year (Spiegel and Bloom, 1983). There is therefore no reason to doubt that the multidisciplinary approach would provide as significant a benefit in treating phantom breast pain, ICN, and neuroma pain as it does in all of the other chronic pain syndromes in which it has been studied.

8. Prevention

The risk of chronic pain following breast cancer surgery can be attenuated by the surgical procedure employed. Although it can be technically difficult to preserve the intercostobrachial nerve, preservation or careful dissection reduces the risk of sensory deficits and may reduce the risk of ICN (Paredes et al., 1990; Abdullah et al., 1998). Because only patients with disease in their lymph nodes undergo axillary dissection, increasing use of sentinel lymph node biopsy may also reduce the incidence of sensory deficits and ICN (Dentsman et al., 2003).

Despite these and other advances in breast cancer surgery, some patients will still develop chronic pain following mastectomy and lumpectomy. Severe acute pain is a risk factor for several pain syndromes, including chronic pain following breast cancer surgery, and it has been suggested that relief of acute pain may therefore reduce the risk of chronic pain (Dworkin, 1997; Dworkin et al., 2000). Recent placebo-controlled studies have examined whether peri-operative treatment with eutectic mixture of local anesthetics (EMLA), gabapentin, or mexiletine reduces the risk of chronic pain following breast cancer surgery. Patients undergoing mastectomy or lumpectomy with axillary dissection who were treated with EMLA beginning before surgery and continuing for six post-operative days had a lower incidence and intensity of chronic pain 3 months later compared with placebo-treated patients (Fassoulaki et al., 2000). Although peri-operative treatment with gabapentin and mexiletine did not reduce the incidence or intensity of chronic pain in a subsequent study by the same research group (Fassoulaki et al., 2002), burning pain was significantly more common in the placebo group at the 3-month assessment (burning pain was reported by 7/24 placebo-treated patients, versus 1/20 mexiletine-treated and 1/22 gabapentin-treated patients). In these studies, peri-operative treatment with EMLA, mexiletine, or gabapentin also reduced acute post-operative pain, including spontaneous and movement-associated pain, and decreased post-operative analgesic consumption (Fassoulaki et al., 2000, 2002).

Considered together, the results of these studies have two important implications. The first is that treatments for chronic neuropathic pain can be effective for acute post-operative pain, which is caused by a combination of nociceptive and neuropathic mechanisms. Moreover, by reducing acute post-operative pain, these agents might attenuate the risk that chronic pain will develop following breast cancer surgery. However, studies of the efficacy of pre-, intra-, and post-operative epidural analgesia in preventing phantom limb pain have had mixed results (Nikolajsen and Jensen, 2001). Whether chronic neuropathic pain following breast cancer surgery (or limb amputation) can be prevented by optimizing peri-operative pain management is an important question that demands further research.

9. Future directions

We have reviewed chronic neuropathic pain syndromes that develop following breast cancer surgery. Unfortunately, few studies have directly compared the natural history, mechanisms, or treatment response of the different neuro-

pathic pain syndromes within the same sample of patients. This is unfortunate, because such studies would make it possible to examine the unique aspects of each of these different neuropathic pain syndromes by holding constant across all three groups the presence of cancer and cancer treatment. Stratification by mechanism of pain should be encouraged in future studies.

We have not discussed breast surgery procedures that do not involve malignancy. Evidence of malignancy is sometimes not found after surgical procedures for breast cancer, and there are, of course, cosmetic and reconstructive breast surgeries that do not involve a diagnosis of cancer. These surgical procedures provide an opportunity to study chronic neuropathic pain following breast surgery in patients free of the physical and psychological consequences of cancer, chemotherapy, and radiotherapy (Wallace et al., 1996). Such patients would provide a valuable comparison group in studies of physical and psychosocial functioning and mechanisms of neuropathic pain following breast cancer surgery, making it possible to identify what is unique about chronic neuropathic pain following breast cancer surgery and what are more general concomitants of breast surgery.

The aging of the population and advances in diagnosis and treatment of breast cancer that prolong survival will increase the challenge of controlling chronic pain and other late complications and their negative impacts on quality of life. Chronic neuropathic pain following breast cancer surgery is one of the few types of neuropathic pain in which large samples of patients known to be at risk for chronic pain can be first assessed before their pain has developed and then followed until their chronic pain is well established. Such prospective studies will not only increase understanding of the natural history of these chronic pain syndromes, but will also provide an important opportunity to investigate mechanisms accounting for the transition from acute to chronic pain. This knowledge of natural history and mechanisms will inform and enhance efforts to develop interventions to prevent chronic neuropathic pain following breast cancer surgery.

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References

Abdullah TI, Iddon J, Barr L, Baildam AD, Bundred NJ. Prospective randomized controlled trial of preservation of the intercostobrachial nerve during axillary node clearance for breast cancer. Br J Surg 1998; 85:1443–5.

Aglioti S, Cortese F, Franchini C. Rapid sensory remapping in the adult human brain as inferred from phantom breast perception. Neuroreport 1994;5:473–6.

Akechi T, Okuyama T, Imoto S, Yamawaki S, Uchitomi Y. Biomedical and psychosocial determinants of psychiatric morbidity among postoperative ambulatory breast cancer patients. Breast Cancer Res Treat 2001; 65:195–202.

Birbaumer N, Lutzenberger W, Montoya P, Larbig W, Unertl K, Topfner S, Grodd W, Taub E, Flor H. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. J Neurosci 1997;17:5503–8.

Burchiel KJ. Neurosurgical procedures of the peripheral nerves. In: North RB, Levy RM, editors. Neurosurgical management of pain. New York: Springer-Verlag; 1997. p. 133–61.

Campbell JN. Peripheral nerve injury and sympathetically maintained pain: mechanisms and surgical approach. In: North RB, Levy RM, editors. Neurosurgical management of pain. New York: Springer-Verlag; 1997. p. 75–82.

Carpenter JS, Andrykowski MA, Sloan P, Cummingham L, Cordova MJ, Studts JL, McGrath PC, Sloan D, Kenady DE. Postmastectomy/postlumptectomy pain in breast cancer survivors. J Clin Epidemiol 1998;51:1285–92.

Carpenter JS, Sloan P, Andrykowski MA, McGrath P, Sloan D, Rexford T, Kenady D. Risk factors for pain after mastectomy/lumpectomy. Cancer Pract 1999;7:66–70.

Colleoni M, Rotmensz N, Robertson C, Orlando L, Viale G, Renne G, Luini A, Veronesi P, Intra M, Orecchia R, Catalano G, Galimberti V, Nole F, Martinelli G, Goldhirsch A. Very young women (<35 years) with operable breast cancer: features of disease at presentation. Ann Oncol 2002;13:273–9.

Dentsman S, Wallace A, Wallace M, Muchmore E. Pain and neurosensory findings after sentinel node biopsy and axillary node dissection in women with breast cancer. Presented at the meeting of the American Society of Regional Anesthesia and Pain Medicine, San Diego, CA, April 2003.

Devor M. Phantom pain as an expression of referred and neuropathic pain. In: Sherman RA, editor. Phantom pain. New York: Plenum; 1997. p. 33–58.

de Vries JE, Timmer PR, Erftemeier EJ, van der Weele LT. Breast pain after breast conserving therapy. Breast J 1994;3:151–4.

Dini D, Bertelli G, Gozza A, Forno G. Treatment of the post-mastectomy pain syndrome with topical capsaicin. Pain 1993;54:223–6.

Dworkin RH. Which individuals with acute pain are most likely to develop a chronic pain syndrome? Pain Forum 1997;6:127–36.

Dworkin RH, Banks SM. A vulnerability-diathesis-stress model of chronic pain: herpes zoster and the development of postherpetic neuralgia. In: Gatchel RJ, Turk DC, editors. Psychosocial factors in pain: critical perspectives. New York: Guilford Press; 1999. p. 247–69.

Dworkin RH, Schmader KE. The treatment and prevention of postherpetic neuralgia. Clin Infect Dis 2003;36:877–82.

Dworkin RH, Perkins FM, Nagasako EM. Prospects for the prevention of postherpetic neuralgia in herpes zoster patients. Clin J Pain 2000;16: S90–S100.

Fassoulaki A, Sarantopoulos C, Melemeni A. EMLA reduces acute and chronic pain after breast surgery for cancer. Reg Anesth Pain Med 2000; 25:350–5.

Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002;95:985–91.

Flor H, Birbaumer N, Sherman RA. Phantom limb pain. Pain Clin Update 2000;8(3):1–4.

Foley KM. Pain syndromes in patients with cancer. Med Clin North Am 1987;71:169–84.

Fromm GH. The neuralgias. In: Joynt RJ, Griggs RC, editors. Baker's clinical neurology. Philadelphia: Lippincott Williams & Wilkins; 2000.

Glover J, Dibble SL, Dodd MJ, Miaskowski C. Mood states of oncology patients: does pain make a difference? J Pain Symptom Manage 1995; 10:120–8.

Gottrup H, Andersen J, Arendt-Nielsen L, Jensen TS. Psychophysical examination in patients with post-mastectomy pain. Pain 2000;87: 275–84.

Granek I, Ashikari R, Foley K. The post-mastectomy pain syndrome: clinical and anatomical correlates. Proc Am Soc Clin Oncol 1984;3: 122.

Hack TF, Cohen L, Katz J, Robson LS, Goss P. Physical and psychological morbidity after axillary lymph node dissection for breast cancer. J Clin Oncol 1999;17:143–9.

Iglehart DJ, Kaelin CM. Diseases of the breast. In: Townsend CM, editor. Sabiston textbook of surgery, 16th ed. Philadelphia: W.B. Saunders; 2001. p. 556–90.

Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. Br J Cancer 1992;66: 136–8.

Jamison K, Wellisch DK, Katz RL, Pasnau RO. Phantom breast syndrome. Arch Surg 1979;114:93–5.

Johansen J, Overgaard J, Blichert-Toft M, Overgaard M. Treatment morbidity associated with the management of the axilla in breast-conserving therapy. Acta Oncol 2000;39:349–54.

Jung BF, Hogan LA, Kulick DI, Andrus C, Dworkin RH. Chronic pain following breast cancer surgery: prevalence and risk factors. Presented at the Fifth International Conference on the Mechanisms and Treatment of Neuropathic Pain, Bermuda, November 2002.

Kakuda JT, Stuntz M, Trivedi V, Klein SR, Vargas HI. Objective assessment of axillary morbidity in breast cancer treatment. Am Surg 1999;65:995–8.

Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 1995;64: 293–302.

Keramopoulos A, Tsionou C, Minaretzis D, Michalas S, Aravantinos D. Arm morbidity following treatment of breast cancer with total axillary dissection: a multivariate approach. Oncology 1993;50:445–9.

Kretschmer T, Nguyen DH, Beuerman RW, Happel LT, England JD, Tiel RL, Kline DG. Painful neuromas: a potential role for a structural transmembrane protein, ankyrin G. J Neurosurg 2002;97:1424–31.

Kroman N, Jensen M, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: population based study. Br Med J 2000;320:474–9.

Krøner K, Krebs B, Skov J, Jorgensen HS. Immediate and long-term phantom breast syndrome after mastectomy: incidence, clinical characteristics and relationship to pre-mastectomy breast pain. Pain 1989;36:327–34.

Krøner K, Knudsen UB, Lundby L, Hvid H. Long-term phantom breast syndrome after mastectomy. Clin J Pain 1992;8:436–50.

Kuehn T, Klauss W, Darsow M, Regele S, Flock F, Maiterth C, Dahlbender R, Wendt I, Kreienberg R. Long-term morbidity following axillary dissection in breast cancer patients: clinical assessment, significance for life quality and the impact of demographic, oncologic and therapeutic factors. Breast Cancer Res Treat 2000;64:275–86.

Kwekkeboom K. Postmastectomy pain syndromes. Cancer Nurs 1996;19: 37–43.

Lierman LM. Phantom breast experiences after mastectomy. Oncol Nurs Forum 1988;15:41–4.

Macrae WA, Davies HTO. Chronic postsurgical pain. In: Crombie IK, editor. Epidemiology of pain. Seattle: IASP Press; 1999. p. 125–42.

Maunsell E, Brisson J, Deschenes L. Arm problems and psychological distress after surgery for breast cancer. Can J Surg 1993;36:315–20.

Meguerditchian AN, Falardeau M, Martin G. Male breast carcinoma. Can J Surg 2002;45:296–302.

Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms, 2nd ed. Seattle: IASP Press; 1994.

Miaskowski C, Dibble SL. The problem of pain in outpatients with breast cancer. Oncol Nurs Forum 1995;22:791–7.

Nikolajsen L, Jensen TS. Phantom limb pain. Br J Anaesth 2001;87: 107–16.

Paredes JP, Puente JL, Potel J. Variations in sensitivity after sectioning the intercostobrachial nerve. Am J Surg 1990;160:525–8.

Polinsky ML. Functional status of long-term breast cancer survivors: demonstrating chronicity. Health Soc Work 1994;19:165–73.

Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, Royall RM, Max MB. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002;59:1015–21.

Rosso R, Scelsi M, Carnevali L. Granular cell traumatic neuroma: a lesion occurring in mastectomy scars. Arch Pathol Lab Med 2000;124: 709–11.

Rowbotham MC, Petersen KL, Fields HL. Is postherpetic neuralgia more than one disorder? Pain Forum 1998;7:231–7.

Shons AR, Cox CE. Breast cancer: advances in surgical management. Plastic Recons Surg 2001;107:541–9.

Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999;83:389–400.

Sindrup SH, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. Neurology 2000;55:915–20.

Smith WCS, Bourne D, Squair J, Phillips DO, Chambers WA. A retrospective cohort study of post mastectomy pain syndrome. Pain 1999;83:91–5.

Spiegel D, Bloom JR. Group therapy and hypnosis reduce metastatic breast carcinoma pain. Psychosom Med 1983;45:333–9.

Stevens PE, Dibble SL, Miaskowski C. Prevalence, characteristics, and impact of postmastectomy pain syndrome: an investigation of women's experiences. Pain 1995;61:61–8.

Tasmuth T, von Smitten K, Hietanen P, Kataja M, Kalso E. Pain and other symptoms after different treatment modalities of breast cancer. Ann Oncol 1995;6:453–9.

Tasmuth T, Estlanderb AM, Kalso E. Effect of present pain and mood on the memory of postoperative pain in women treated surgically for breast cancer. Pain 1996a;68:343–7.

Tasmuth T, von Smitten K, Kalso E. Pain and other symptoms during the first year after radical and conservative surgery for breast cancer. Br J Cancer 1996b;74:2024–31.

Tasmuth T, Kataja M, Blomqvist C, von Smitten K, Kalso E. Treatment-related factors predisposing to chronic pain in patients with breast cancer. Acta Oncol 1997;36:625–30.

Tasmuth T, Blomqvist C, Kalso E. Chronic post-treatment symptoms in patients with breast cancer operated in different surgical units. Eur J Surg Oncol 1999;25:38–43.

Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. Eur J Pain 2002;6:17–24.

Vecht CJ. Arm pain in the patient with breast cancer. J Pain Symptom Manage 1990;5:109–17.

Velanovich V, Szymanski W. Quality of life of breast cancer patients with lymphedema. Am J Surg 1999;177:184–8.

Wallace AM, Wallace MS. Postmastectomy and postthoracotomy pain. Anesth Clin North Am 1997;15:353–70.

Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. Pain 1996;66:195–205.

Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 1998;50: 1837–41.

Watson CPN, Evans RJ. Intractable pain with breast cancer. Can Med Assoc J 1982;126:263–6.

Watson CPN, Evans RJ. The postmastectomy pain syndrome and topical capsaicin: a randomized trial. Pain 1992;51:375–9.

Watson CPN, Evans RJ, Watt VR. The post-mastectomy pain syndrome and the effect of topical capsaicin. Pain 1989;38:177–86.

Watson CPN, Vernich L, Chipman M, Reed K. Nortriptyline versus

amitriptyline in postherpetic neuralgia: a randomized trial. Neurology 1998;51:1166–71.
Wong L. Intercostal neuromas: a treatable cause of postoperative breast surgery pain. Ann Plast Surg 2001;46:481–4.
Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. Nature 1992;355:75–8.
Wyatt GK, Friedman LL. Physical and psychosocial outcomes of midlife and older women following surgery and adjuvant therapy for breast cancer. Oncol Nurs Forum 1998;25:761–8.
Yildirim E, Dalcic T, Berberoglu U. Prognostic significance of young age in breast cancer. J Surg Oncol 2000;74:267–72.