Persistent pain after breast cancer treatment

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Introduction

Breast cancer is the commonest cancer affecting women with a 5-year survival over 80% as a result of earlier diagnosis and improved management. With improved survival rates, increasing attention is focused on the quality of life of these breast cancer survivors.

The major factors that affect survivors’ quality of life are some cancer treatment-related side effects that occur in up to 90% of patients during treatment and can persist for months or years after treatment has ended (1). Chemotherapy, radiation therapy and hormonal therapy can all contribute to the development and persistence of side effects, including: upper extremity restricted lymphedema, cognitive impairment (2-9), fatigue (10-12), sleep difficulty (13), pain (14-16), chemotherapy-induced peripheral neuropathy, cardiotoxicity (17,18), and bone loss (19,20). All these side effects accompanied with breast cancer treatments negatively influence quality of life and daily activities, lead to non-compliance treatments, and ultimately affect prognostic and survival outcomes (21,22). Interventions to alleviate side effects are needed to reduce symptom burden, enhance quality of life and functional capacity, and improve adherence to therapy (1).

One potential debilitating problem that breast cancer survivors may suffer with is persistent pain after breast cancer treatment (PPBCT) that is a common side effect with prevalence as high as 50% (23,24). The International Association for the Study of Pain (IASP) has established 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’ (25).

A multivariate analysis of the presence of chronic pain in breast cancer survivors revealed that only younger age was associated with a significantly increased risk of developing chronic pain at 3 months after surgery (26). Furthermore, more invasive surgery, radiation therapy after surgery, and clinically meaningful acute postoperative pain but not Preoperative emotional status each independently predicted more intense chronic pain at 3 months after surgery (26).

The etiology of PPBCT is probably multifactorial (27). According to a recent systematic review of the prevalence and etiology of neuropathic pain in 13,683 cancer patients identified in 22 eligible studies, either sensory abnormality or diagnostic lesion was confirmed to contribute to the PPBCT in 14 studies (28). Although breast cancer treatment includes different types of surgical interventions (e.g., mastectomy, lumpectomy, sentinel lymph node biopsy, and axillary lymph node dissection), and adjuvant therapies like chemotherapy, radiation and endocrine therapies, only pre-existing nerve damage and radiotherapy appear to be significant risk factors (27). The detailed etiology of PPBCT needs further research efforts.

The mechanisms involved in PPBCT are uncertain and may involve peripheral as well as spinal and supraspinal structures. Event-related potentials (ERPs) of PPBCT patients, cancer treatment without persistent pain patients and healthy volunteers show different characteristics (29). PPBCT is associated with stimulus processing that is both delayed [i.e., increased latency of the ERP positivity between 250-310 ms (P260)], and enhanced (i.e., enhanced P260 amplitude) when compared with breast cancer treatment without persistent pain patients. However, breast cancer treatment without persistent pain is associated with
accelerated stimulus processing (reduced P260 latency) and shows a tendency to be less intense (lower P260 amplitude) that the healthy volunteers. These results suggest that treatment and persistent pain have opposite effects on cortical responsiveness (29).

**Global PPBCT epidemiology**

The global epidemiology of PPBCT is still incomplete probably because of the neglected recognition of PPBCT. It is conceivable that the incidence of PPBCT may be underestimated, since there may be multiple barriers for patients to report their pain to their physicians. Ongoing pain after treatment is an unexpected reality for some women with breast cancer and may induce anxiety about cancer recurrence (30), and some women may not report persistent pain for fearing that they may find out to be cancer recurrence. Barriers to asking questions about pain also include fearing the answer that it is inevitable, and that concerns about pain will be ignored (31). Additionally, multiple other barriers may exist including: fear of bothering their busy physician, fear that their physicians may think less of them (or be annoyed at them), fear that if they complain about their pain - this might distract their physician and take valuable time away during their short interaction that they would rather have focused on discussions about cancer/prognosis.

Peretti-Watel et al. conducted in-depth interviews with French breast cancer survivors 24 months after cancer diagnosis and treatment (32). Fifty percent of participants reported suffering from significant chronic pain. Most of the time, this pain was not captured by the World Health Organization Quality of Life (WHOQOL) questionnaire and was not medically treated. Patients “normalized” their pain in various ways: they considered it either as a necessary step on the road to recovery, as the proof of treatment efficacy, or as a permanent condition one must learn to live with (32). Although there are fragmentary reports on the epidemiology of PPBCT, more efforts should be put on this issue in the future.

**Persistent pain after breast cancer surgery (PPBCS)**

Almost all of the 226,870 women diagnosed with breast cancer in 2012 will undergo surgery (33), which raises the focus on the most commonly studied complications, the persistent pain following breast cancer surgery (PPBCS) (26,34). PPBCS is different from other painful syndromes because it is typically localized to the anterior or lateral region of thorax, axillary and/or medial upper arm, causing burning pain, shooting pain, pressure sensation or numbness (35-37). The incidence of pain syndrome 6 months post-breast cancer surgical treatment was 52.9%. In relation to sensitive alteration, 52.6% patients have shown intercostobrachial pain, 1.3% neuroma and 3.2% have related phantom breast pain. Pain on the shoulder and/or thoracic-scapular area as a consequence of breast cancer surgical treatment was observed in 27.2% patients [relative risk (RR) ¼ 5.23 95% confidence interval (CI): 1.11e24.64] and (RR ¼ 2.01 95% CI: 1.08-3.75). Younger women (<40 years) and those who were submitted to axillary lymphadenectomy (with more than 15 removed lymph nodes) have shown risk of developing pain syndrome after breast cancer surgical treatment (38).

In general, incidences of PPBCS have been estimated as: about 10% for inguinal herniomy (39), 25% to 50% for thoracotomy (40), and about 25% to 60% after breast cancer treatment (41). The severity of PPBCS may vary significantly depending on the surgical procedure performed (41). Gärtner and colleagues conducted a nationwide cross-sectional questionnaire study of 3,754 women aged 18 to 70 years who received surgery and adjuvant therapy (if indicated) for primary breast cancer in Denmark between January 1, 2005, and December 31, 2006 (41). A total of 1543 patients (47%) reported pain in 1 or more areas, of which 201 (13%) reported severe pain (scores of 8-10 on the numeric rating scale of 0-10 scores), 595 (39%) reported moderate pain (scores of 4-7), and 733 (48%) reported light pain (scores of 1-3) (41). Among women reporting severe pain, 77% experienced pain every day, whereas only 36% of women experiencing light pain had pain every day. A total of 278 patients (18%) reported pain in only 1 area, 435 (28%) in 2 areas, 429 (28%) in 3 areas, and 400 (26%) in all 4 areas. The most frequently reported area of pain was the breast area (n=1,331; 86%), followed by axilla (n=975; 63%), arm (n=872; 57%), and side of the body (n=857; 56%) (41). Mastectomy had no significant association on OR for reporting pain compared with BCS, but those women reporting pain after mastectomy had a higher risk of moderate to severe pain compared with light pain OR, 1.37; 95% CI: 1.00-1.87; P=0.048) (41). ALND was associated with an increased risk of pain (OR, 1.77; 95% CI: 1.43-2.19; P=0.001) compared with SLND, and also a risk factor for moderate to severe pain (OR, 1.39; 95% CI: 1.03-1.88; P=0.03) (41).
lymph node surgery continue to experience pain or physical discomfort during the year after treatment (42). Andersen et al. examined PPBCT, sensory disturbances and functional impairment in patients treated with a 2-step axillary lymph node dissection compared to patients with a sentinel lymph node biopsy (SLNB) followed by an immediate axillary lymph node dissection (ALND), and patients with ALND without a prior SLNB (43). Overall prevalence of PPBCT and sensory disturbances was high, with about 55% reporting PPBCT and 77% reporting sensory disturbances in all groups. No differences were found between the groups on prevalence and intensity of PPBCT (P=0.92), sensory disturbances (P=0.32), and functional consequences (P=0.35) (43).

Foley and colleagues (44) 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 (34). 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 revealed during neurologic examination (35,45).

A study specifically evaluating pain after breast reconstruction was conducted in 1996 (46). Women whose reconstruction involving breast implants had a greater prevalence of pain (53%) than patients who had reconstruction without implants (30%), and those women who had reconstruction without implants had a very similar prevalence of pain as patients who had mastectomy without reconstruction. There is some evidence that the incidence of chronic pain following breast cancer surgery, its intensity (47), and associated sensory abnormalities decrease over time. Ivens et al. [1992] found that the likelihood of chronic pain diminished from 31% at 1-2 years to 20% after more than 4 years following breast cancer surgery (48).

Bokhari et al. conducted a prospective, quantitative, longitudinal pilot study before surgery and at 2 days, 10 days, and 3 months postsurgery in efforts to provide a preliminary determination of the prevalence rate of women who suffer from neuropathic pain post breast cancer surgery (PPBCS) and explored potential risk factors associated with its development (49). Twenty-three percent of the patients developed PPBCS. Younger age (younger than 50 years old), more invasive surgery, acute postoperative pain, and less analgesic use during the acute postoperative period were factors associated with the development of PPBCS (before surgery and 2 days, 10 days, and 3 months postsurgery (49).

Sipilä and colleagues conducted a prospective study to develop a screening tool to identify presurgical demographic, psychological and treatment related factors that predict persistence of significant pain in the operated area after 6 months from surgery (50). A six-factor risk index was developed to estimate the risk of developing significant PPBCS. Report of preoperative chronic pain, more than four or more previous operations, preoperative pain in the area to be operated, high body mass index, previous smoking and older age were included in the six-factor model that best predicted significant pain at the follow-up in the 489 women studied (A six-factor risk index was developed to estimate the risk of developing significant pain after breast cancer surgery). Most of the risk factors (e.g., old age, chronic pain conditions, previous smoking and a high number of previous operations) cannot, however, be specifically targeted in efforts to actively modify PPBCS (50).

Miaskowski and colleagues recruited 398 patients prior to breast cancer surgery and followed them for 6 months (51). Using growth mixture modeling, patients were classified into no (31.7%), mild (43.4%), moderate (13.3%), and severe (11.6%) pain groups based on ratings of worst breast pain. Patients in the moderate and severe pain classes reported higher preoperative levels of depression, anxiety, and sleep disturbance than the no pain class. Findings suggest that approximately 25% of women experience significant and persistent levels of breast pain in the first 6 months following breast cancer surgery. Severe breast pain is associated with clinically meaningful decrements in functional status and quality of life (51).

Carriers of the minor allele for a single nucleotide polymorphism (SNP) in interleukin (IL) 1-receptor 1 (IL1R1) (rs2110726) were less likely to report breast pain prior to surgery (P=0.007). Carriers of the minor allele for a SNP in IL13 (rs1295686) were more likely to report breast pain prior to surgery (P=0.019) (52). These findings suggest that breast pain occurs in over a quarter of women who are about to undergo breast cancer surgery likely in part due to difference in inflammatory mechanisms (52).

Edwards and colleagues used quantitative sensory testing to compare psychophysical responses to standardized noxious stimulation in two groups of women who had previously undergone breast cancer surgery: women with (n=37) and without (n=34) persistent postoperative pain (53). Their findings suggested that women with persistent pain...
after breast cancer surgery display enhanced temporal summation of mechanical pain, deficits in endogenous pain inhibition, and more intense painful aftersensations compared with those without long-term pain, suggesting that persistent postoperative pain may be associated with alterations in central nervous system (CNS) pain-modulatory processes (53).

It appears that not only is there a significant degree of persistent pain after breast cancer surgery, but there is also a significant degree of sleep disturbances after breast cancer surgery. Van Onselen et al. published the findings of 390 women who completed self-report measures for a variety of symptoms, 28.2% reported pain in their breast prior to surgery (54). A higher percentage of women in the pain group (i.e., 66.7% versus 53.5%) reported clinically meaningful levels of sleep disturbance (54).

**Classification of PPBCS**

Jung and colleagues distinguished four different types of PPBCS based on the studies of the epidemiology, mechanisms, and treatment for PPBCS (35). Other contributors to the neuropathic pain following breast cancer surgery are damages 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 (Table 1) (35,55).

Estimates for the risk of a painful neuroma following breast cancer surgery also vary widely, ranging from 23% to 49% (35). Neuroma pain may be more common following lumpectomy than mastectomy; Tasmuth et al. (56) [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 (57). However, because a neuroma can reform following excision, relocation to a protected site and attempts to improve regeneration using nerve grafts are the current major neurosurgical treatment options (58,59).

Although there are many etiologies for post-operative pain, the diagnosis of an intercostal neuroma is important as this can be treated surgically. Nguyen and colleagues described three cases of an intercostal neuroma in patients with breast implants (60). A Tinel’s sign can be elicited along the lateral chest wall and a local anesthetic block temporarily alleviates this pain. Surgical management with identification and clipping of the intercostal neuroma and burying it into the underlying muscle significantly decreases post-operative pain for the long term (60).

Kojima and colleagues mailed a questionnaire to 647 specialist members of the Breast Cancer Society in Japan. While PPBCS was recognized by as much as 70.5% of responding physicians, it was treated by as little as 47.7% of the responders (61). In contrast to a prevalent use of non-steroidal anti-inflammatory drugs (NSAIDs), which were proved to be ineffective for PPBCS, were used by 78.4% of the responders, more effective drugs were rarely used; therefore, the treatment was considered ineffective by 69.5% (61). Thus, it appears that a significant number of physicians may not be familiar with optimal therapeutic strategies to address PPBCS.

**Treatment strategies to ameliorate PPBCS**

There are very few randomized, double-blind, placebo controlled trials on PPBCS. In the only randomized controlled trial of topical capsaicin, crossover treatment with capsaicin versus placebo in 25 patients diagnosed with PPBCS 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 (62).

Few drugs have been systematically tested in randomized clinical trials for efficacy specifically for post-mastectomy/lumpectomy pain (PMLP). However, gabapentin, an antiepileptic drug, and venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), appear to be effective in multiple trials involving PMLP. Both drugs attenuated existing chronic pain in women who had previously received breast cancer surgery (63,64). When administered before surgery, gabapentin decreased the time to first post-operative analgesic administration as well as pain scores and adjuvant analgesic use within the first 10 days. However, no effect was observed on long-term chronic pain in the two studies that inquired 3 and 6 months post-surgery (65–67).

Amitriptyline has been examined in a randomized, double-blind, placebo-controlled, crossover trial of neuropathic pain following breast cancer surgery (68). 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.

Tasmuth and colleagues conducted a randomized, double-blind, placebo-controlled, crossover trial and failed to reveal a significant benefit of venlafaxine versus placebo on the primary endpoint (daily pain diary ratings) but did report a greater relief associated with venlafaxine treatment for two secondary endpoints, pain relief and maximum pain (64).

Perioperative treatment with eutectic mixture of local anesthetics (EMLA), mexiletine, or gabapentin appeared to reduce acute post-operative pain, including spontaneous and movement-associated pain, and decreased postoperative analgesic consumption (66,69), however, in the initial study gabapentin and mexiletine did not diminish the incidence or intensity of PPBCS. An eutectic cream mixture of local anesthetics (EMLA) alone may be beneficial as a pre-surgical treatment preventing chronic postoperative pain. When topically administered to the breast and arm area at one day prior to surgery, EMLA decreased analgesic consumption between 2 and 6 days post-surgery and the incidence and intensity of pain 3 months after surgery (69). Similar results were obtained when the same investigators combined EMLA and gabapentin in pre-operative treatment (70).

Grigoras and colleagues conducted a prospective randomized, double-blinded study regarding PPBCT and found that intravenous perioperative lidocaine decreases the incidence and severity of PPBCS (71). Two (11.8%) patients in the lidocaine group and 9 (47.4%) patients in the control group reported PPBCS at 3 months follow-up (P=0.031). McGill Pain Questionnaire revealed greater present pain intensity-visual analog scale (VAS) in the control group (14.6±22.5 vs. 2.6±7.5, P=0.025). Secondary hyperalgesia (pain outside the surgical area) was significantly less in the lidocaine group compared with control group (0.2±0.8 vs. 3.2±4.5 cm, P=0.002) (71).

Dexmedetomidine shows a dose-dependent antiallodynic effect on mechanical and cold stimuli in vincristine-evoked neuropathic rat models (72). Jain and colleagues conducted a prospective double-blind trial to analyze the role of perioperatively administered dexmedetomidine on the occurrence of chronic pain in women who underwent surgery for breast cancer (73).

In total, 84 cases (42 in group D and 42 in group C) were analyzed for acute pain and 69 (34 in group D and 35 in group C) for chronic pain. The consumption of isoflurane/fentanyl intra-operatively and acetaminophen postoperatively was significantly lower in dexmedetomidine group. The verbal numerical scale (VNS) at rest and after movement was significantly lower in dexmedetomidine group at corresponding times (except at 60 min) throughout the assessment period. The brief pain inventory (BPI) and the short-form of the revised McGill Pain Questionnaire (SF-MPQ2) scores were significantly lower in dexmedetomidine group in most of the factors. The quality of life scale (QOLS) score was significantly better in dexmedetomidine group in almost all items (73). They concluded that the perioperative infusion of dexmedetomidine has a pivotal role in attenuating the incidence and severity of chronic pain and improving the quality of life in cases undergoing breast cancer surgery (73).

Paravertebral nerve blocks (PVB) during breast cancer surgery have been reported to decrease acute pain and opioid consumption immediately following surgery in multiple randomized clinical trials (74–76). Andreae and Andreae performed a Cochrane Review which included RCTs comparing local anesthetics or regional anesthesia versus conventional analgesia with a pain outcome at six or 12 months after surgery (77). They pooled two studies on PVB for breast cancer surgery; the pooled data of 89 participants with outcomes at five to six months favored PVB with an OR of 0.37 (95% CI: 0.14 to 0.94). The methodological quality of the included studies was intermediate. They concluded that PVB may reduce the risk
of chronic pain after breast cancer surgery in about one out of every five women treated, although limitations of the study may include performance bias, short comings in allocation concealment attrition, and incomplete outcome data (77).

There are also risk factors for PPBCT, chronic preoperative pain, axillary surgery and psychological robustness significantly predicted acute pain outcomes after surgery for breast cancer. Preoperative identification and targeted intervention of risk subgroups could conceivably enhance the recovery trajectory in cancer survivors (78). Strategies aimed at controlling acute and chronic pain in patients receiving mastectomy and breast reconstruction include: minimally invasive therapies for breast cancer, such as breast conserving therapies of mastectomies and breast reconstruction, sentinel node biopsies, and early treatments of radiation and chemotherapy (79).

**Persistent pain after breast cancer hormonal therapy (PPBCT)**

Previous studies suggested that hormonal disturbance contribute to breast cancer, thus hormonal therapies are recommend. Arthralgias, a common side effect of aromatase inhibitors, can produce painful mobility limitations and impaired daily activities (80,81). Compared with tamoxifen, aromatase inhibitors (AIs) such as anastrozole, letrozole, and exemestane show increased disease-free survival benefits; they have therefore become the standard of care for adjuvant endocrine treatment of postmenopausal women with hormone receptor - positive early breast cancer (82).

Din et al. reviewed the incidence of musculoskeletal symptoms in phase III clinical trials of anastrozole, letrozole, and exemestane (83), and women on those AIs have shown significantly higher rates of arthralgia than with tamoxifen. In a specific study investigating arthralgia in 200 patients on AIs, 47% of patients reported AI-related joint pain, and 44% reported stiffness (84). Typically, patients on AIs experience stiffness, aches, or pain that is frequently symmetric, occurring in the hands, arms, knees, feet, and pelvic and hip bones (85,86). In addition, patients on AIs may develop tenosynovial changes, including fluid in the tendon sheath, increased tendon thickness, trigger finger, and carpal tunnel syndrome (87-89).

Robidoux and colleagues conducted a prospective pilot study investigating the musculoskeletal pain in postmenopausal breast cancer patients receiving aromatase inhibitor therapy (90). Over the 24-week study period, 20 participants (67%) showed no pain symptoms; 5 (17%) experienced low or moderate pain at baseline, which did not increase with AI treatment. During therapy, 5 (17%) showed exacerbation of pain attributable to osteoarthritis of the hand and to finger flexor tenosynovitis. Although all 30 participants had some degree of musculoskeletal conditions before anastrozole therapy started, the pre-existing conditions did not necessarily predispose the women to increased pain during anastrozole treatment (90).

Baseline musculoskeletal assessment showed pre-existing causes for pain in most of the study patients before initiation of the AIs. Exacerbation of existing osteoarthritis pain and tenosynovial symptoms was the primary contributors of pain increase. Musculoskeletal pain assessment at baseline and prompt treatment of pain symptoms may help optimize adherence to AI therapy. The value of routinely assessing inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate was not supported by the pilot study. Gene expression profiles in peripheral blood mononuclear cells may be further explored in larger-scale studies as stratification markers to identify patients at risk of developing arthralgia (90).

**Persistent pain after breast cancer chemotherapy (PPBCC)**

During the advanced stage for breast cancer, metastasis is a big challenge to patients and physicians and are currently be dealt with chemotherapy using drugs including anthracyclines, taxanes, alkylating agents, vinca alkaloids, capecitabine, gemcitabine, and the platinum agents, carboplatin and cisplatin. The taxanes, platinum agents, and vinca alkaloids are most likely to cause PPBCC (35,91).

Thus, women with metastatic breast cancer may have high chance of developing CIPN because of increased exposure to taxanes, antimitabolite chemotherapies, and other standard medications associated with peripheral neuropathy (92). CIPN poses both psychosocial and physical problems that may lead to decrease or halt potentially effective treatments because of dose related toxicity (93,94). Symptoms of CIPN include numbness, tingling, weakness, and pain that can impair function and activities of daily living, as well as balance, leading to falls and injury (93,95).

Andersen and colleagues compared patients treated with cyclophosphamide, epirubicin and fluorouracil (CEF) and cyclophosphamide and epirubicin + docetaxel (CE + T) in relation to PPBCT; sensory disturbances, peripheral sensory disturbances and functional impairment (96). Patients treated with CE + T had a lower risk of sensory
disturbances in the surgical area compared with CEF, OR 0.75 (95% CI: 0.62-0.90), P=0.002. More CE + T patients reported peripheral sensory disturbances in the hands, OR 1.56 (95% CI: 1.27-1.92), P<0.0001, and in the feet, OR 2.0 (95% CI: 1.66-2.42) P<0.0001, compared to CEF. There was no difference in functional impairment (P=0.62). Docetaxel as adjuvant treatment for breast cancer does not increase the risk of PPBCT, sensory disturbances in the surgical area or functional impairment, but increase risk for peripheral sensory disturbances (96).

Golan-Vered and Pud stated that the three major main findings of their descriptive study of breast cancer patients who received paclitaxel (97) were: (I) 2 distinct groups of patients with breast cancer, namely Low Cluster and High Cluster, were identified on the basis of their experiences with 4 highly prevalent symptoms (depression, fatigue, sleep disturbances, pain); (II) 50% of the patients treated with paclitaxel developed CINP; (III) a combination of CINP and clusters revealed a subgroup with no evidence of CINP within the Low Cluster group (35%) and a subgroup with CINP within the High Cluster group (22.5%). These 2 subgroups may be viewed as “double lucky” and “double unlucky”, respectively (97).

Paclitaxel is one of the chemotherapeutic treatments of breast cancer that is associated with a high frequency of peripheral neuropathy in a dose- and exposure-dependent manner. It is characterized first by paresthesias, followed by dysesthesias (91,98). Reyes-Gibby and colleagues conducted a survey of breast cancer patients who had participated in clinical trials of paclitaxel (99). Results showed that 64% experienced CINP during paclitaxel treatment. Follow-up survey data revealed that 27% of those with CINP were subsequently diagnosed with neuropathic pain (NP). Logistic regression analyses showed that those who had experienced CINP were 3 times more likely to develop NP, (95% CI: 1.2-7.2; P<0.001), which persisted in the multivariate logistic model. In addition, NP patients reported twice as many visits to their health care provider (P=0.02) and had taken more prescription (50% vs. 19%; P=0.001) and over-the-counter medications (62.5% versus 45%; P=0.08) for pain than those without NP (99). There are no specific therapies for PPBCC, the treatment of PPBCC is essentially the same as for any treatment of pain after chemotherapy treatments.

**Persistent pain after breast cancer radiation (PPBCR)**

Radiotherapy may cause persistent pain in the breast cancer survivors (100). No specific therapies for PPBCCR are now available, and patients receive the general treatment of pain after radiation treatments.

Hofsø and colleagues conducted a study in which they evaluated the changes in and predictors of occurrence, severity, and distress of six common symptoms (lack of energy, worrying, difficulty sleeping, feeling drowsy, sweats, and pain) during radiation therapy (RT) for breast cancer (23). Their findings suggest that these six symptoms occur at relatively high rates, are of moderate severity, and are associated with moderate levels of distress. An important finding is that some of the symptoms (e.g., feeling drowsy) exhibited complex trajectories of occurrence, severity and distress. In contrast, some symptoms (e.g., pain) persisted (at the same level) over the six months of the study (23).

The risk of developing any late complications after conventionally fractionated megavoltage radiotherapy is estimated to be as low as 1% (101). Although, not entirely clear, it appears that pain in the arm or shoulder due to radiation-induced brachial plexopathy (RBP) may be more likely after hypofractionation in radiotherapy than after conventional treatment employ 2 Gy/day fraction (101-103).

The most common radiation-induced neural insult is RBP. Pierce et al. (104) in their review of 1,624 patients revealed RBP in 1.8% of patients. Other investigators (105-107) have found the incidence of this complication to be less than 1%, whereas Olsen and co-workers (108) in a study of 161 breast cancer patients with a median follow-up period of 50 months, reported that 5% and 9% had a disabling and mild RBP, respectively. Symptoms began from six months to 20 years after radiotherapy (median time 1.5 years) (109). Most patients developed symptoms within three years, but late presentations at 8-20 years later were encountered. Symptoms were progressive in all patients, though the rate did vary. Pain was common and persisted indefinitely in all but one patient. Progressive weakness was universal and resulted in loss of any useful hand function in all but three patients. The time taken to loss of useful hand function ranged from six weeks to five years (median 1.25 years). Three patterns of upper limb weakness were identified, distal limb weakness only (13 patients), global limb weakness that was more marked distally (11 patients), and completely flaccid arm (10 patients). Seventeen patients required long-term morphine to palliate pain. A chemical sympathectomy benefited three of six patients that received the injection (109).

The pathophysiology of radiation-induced neuropathies is incompletely understood. It is currently possible to target
radiation-induced fibrosis and associated factors such as ischemia, oxidative stress and inflammation as well as other pathophysiologic mechanisms suspected of contributing to radiation-induced neuropathies (110,111). A phase III trial evaluating the association of pentoxifylline, tocopherol and clodronate (PENTOCLO, NCT01291433) in radiation-induced neuropathies is now recruiting (110).

**Non-pharmacologic treatment of PPBCT**

Exercise programs that combine aerobic exercise and resistance training as well as various rehabilitation physical medicine techniques among breast cancer patients and survivors may effectively reduce side effects (112-120). A few of these studies are presented. Early stage breast cancer survivors receiving chemotherapy and/or radiation who participated in an aerobic and resistance exercise intervention 2 days a week for 12 weeks reported improvements in CRF, QOL, satisfaction with life, and also improvement in physical function compared to usual care (121,122). Mustian and colleagues (123) have also demonstrated the benefits of performing aerobic and resistance exercise during radiation treatment. A four week individually tailored, home based aerobic and resistance training program resulted in improved CRF, QOL, sleep, aerobic capacity, strength and immune function (123-124).

Women with breast cancer have reported using many of these Complementary and Alternative medicine (CAM) techniques in conjunction with their treatment or after the completion of their treatment. CAM includes natural products, mind body medicine, and manipulative and body-based practices, Mindfulness-based stress reduction (MBSR) [meditation, postures], Mindfulness-based exercise [T’ai Chi Chuan, Yoga], as well as acupuncture.

Jensen et al. performed a pilot study to provide initial support for hypnosis alleviating PPBCT as well as other symptoms (125).

An 8-week water therapy program was effective for improving neck and shoulder/axillary pain, and reducing the presence of trigger points in breast cancer survivors as compared with usual care; however, no significant changes in widespread pressure pain hyperalgesia were found (126).

Wong and colleagues evaluated breast cancer patients with moderate-to-severe PPBCT at 3-6 months after completion of all adjuvant treatments in a pilot study (127). These patients participated in a 12-week comprehensive health improvement program (CHIP) involving exercise training. Intensity was adjusted to reach 65-85% of the patient’s maximal heart rate.

Before the CHIP and at 1 and 6 months after completion of the CHIP, QOL and pain were measured using questionnaires [European Organization for Research and Treatment of Cancer Quality of Life core and breast cancer modules (qol-C30, -BR23) and the McGill Pain Questionnaire short form] completed by the patients. The CHIP team consists of an internist, an oncologist or palliative care physician, a psychologist, a nurse, a physiotherapist, a dietician, and a clinic manager, who together provide the patient with information, treatment, and support. After the CHIP, patients reported significant and clinically important improvements in QOL and symptoms. At 1 and 6 months post-CHIP, patients in the study felt, on average, better in overall QOL than did historical control subjects.

Surgery and radiotherapy are thought to cause acute and chronic breast pain, tenderness, and shoulder impairments in up to 50% of patients who complete breast-conserving therapy (56,128-132). The U.K. START (Standardization of Breast Radiotherapy) trial, which compared hypofractionation with conventional fractionation of adjuvant radiotherapy for breast cancer, assessed the QOL of 2208 patients over 5 years (102). It was observed that 20% and 30% of the patients from both arms of the study experienced breast and arm pain respectively at 5 years of follow-up (102). Randomized controlled studies have shown that, compared with control patients who received no interventions, breast cancer patients directed to exercise more frequently after their diagnosis experienced and clinically important improvements in QOL, and cardiopulmonary functioning (133,134). In 2006, the McGill CHIP, which was originally developed for patients with cardiovascular disease, started to include an exercise rehabilitation program to help cancer survivors recover and reach their full health potential once they had completed their cancer treatments.

**Summary**

Improved breast cancer survival rates appear to have contributed to the revelation of the significant clinical issue of PPBCT. Persistent pain may occur after surgical treatment, hormonal treatment, chemotherapy and/or radiotherapy. Treatment approaches for PPBCT may include pharmacologic, interventional, and nonpharmacologic strategies. Currently therapy for PPBCT remains suboptimal, however, it is hoped that a greater
appreciation of the diagnosis, evaluation, and management of PPBCT may lead to improved overall patient outcomes with better analgesia and less adverse effects.

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References


