Long-Term Follow-Up of Pain and Emotional Characteristics of Women After Surgery for Breast Cancer

Brief Report

Long-Term Follow-Up of Pain and Emotional Characteristics of Women After Surgery for Breast Cancer

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Abstract

Context. Persistent pain after treatment for breast cancer (PPBCT) is a common side effect of breast cancer treatment, with prevalence as high as 50%. It is predominantly a neuropathic condition.

Objectives. The aim of this cross-sectional, questionnaire-based study was to examine the emotional characteristics of patients with PPBCT in long-term breast cancer patients. A secondary objective was to characterize the risk factors and severity of that pain.

Methods. From March 1, 2010 to April 9, 2010, long-term follow-up patients were invited to complete a questionnaire. This recorded their surgical and demographic data and ascertained whether they had PPBCT. If the patient had pain, they completed a range of validated self-report questionnaires and questions about the nature of their pain, including a visual analogue scale.

Results. One hundred eleven patients completed the questionnaire; 33 (29.7%) patients reported chronic pain at a median time of 64 months postoperatively (interquartile range 54.25). Patients with persistent pain were not significantly more anxious ($t_{105} = -0.369$, $P = 0.713$) or depressed ($t_{105} = 0.713$, $P = 0.507$) than patients without pain. Patients with constant pain compared with intermittent pain were significantly more anxious ($t_{25} = -3.460$, $P = 0.002$). Preoperative pain conferred a fivefold increased risk of PPBCT (odds ratio [OR] = 5.17, 95% confidence interval [CI] = 1.79–14.97, $P = 0.002$); chemotherapy conferred a threefold increased risk (OR = 3.004, 95% CI = 1.22–7.40, $P = 0.017$).

Conclusion. We have shown significant numbers of patients suffer from PPBCT. At a median time of 64.5 months, women with pain are not significantly more

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anxious or depressed than women without pain. Preoperative pain and chemotherapy have been highlighted as risk factors. J Pain Symptom Manage 2012;■:■−■. © 2012 U.S. Cancer Pain Relief Committee Published by Elsevier Inc. All rights reserved.

Key Words
Breast neoplasms, neuralgia, postmastectomy pain syndrome, persistent pain after breast cancer treatment

Introduction

Chronic pain may be defined as pain lasting two months or longer after the initial injury.[1] Plastic changes in the nervous system contribute to the development of persistent pain. Neuropathic pain is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[2]

Persistent pain after breast cancer treatment (PPBCT) is a recognized problem after breast cancer surgery. This typically neuropathic condition[3] can be subdivided into several different conditions with largely unknown pathologies. These include tumor-related nociceptive pain, tumor-related neuropathic pain, and treatment-related pain. More specifically, it can be divided into intercostobrachial neuralgia, phantom breast pain, neuroma pain, and "other" pain.[4] It remains controversial whether chemotherapy is a cause of PPBCT. Previous studies have not demonstrated a link between PPBCT and chemotherapy,[5−7] but there is a well-described link between chemotherapy and peripheral neuropathic pain,[8−12] and potential mechanisms have been suggested.[13]

Reports from the U.K. and Denmark consistently estimate the prevalence of PPBCT at ~50%.[5,14,15] This is concerning as 50% of the women who had pain in the Danish study had moderate-to-severe pain.[5] Further research has examined the effects of PPBCT on women after breast cancer surgery. One study showed that women who reported continued pain between seven and 12 years after surgery have a lower quality of life.[15] However, recent work from Denmark suggests that although younger long-term breast cancer survivors (BCSs) report worse health-related quality of life (HRQOL) than the age-matched general population, older BCS report better HRQOL than their age-matched equivalents.[16] This study also showed that being single, having less education, and high body mass index were risk factors for lower HRQOL after breast cancer treatment.[16]

Many risk factors have been suggested, with many possible confounding factors. Despite this, the current literature strongly associates younger age,[3,5,6,15,17] preoperative pain, and severe postoperative pain with increased risk of PPBCT.[6,14,17−19] Higher levels of preoperative anxiety[3,17−20] and the type of breast surgery[5,6,19−21] also are associated with increased risk of PPBCT.

The aim of this cross-sectional, questionnaire-based study was to determine the emotional and painful characteristics of patients with PPBCT. A secondary objective was to assess if known risk factors for PPBCT correlate with risk factors in patients undergoing long-term follow-up after breast cancer treatment.

Methods

A questionnaire (see Appendix available at jpsmjournal.com) was constructed to ascertain the pain and emotional characteristics of women with PPBCT. After ethics committee approval and an initial pilot study, all patients attending the Edinburgh Cancer Center between March 1, 2010 and April 9, 2010 after surgery for breast cancer were invited to complete the questionnaire.

The questionnaire was designed to assess the pain and emotional characteristics of patients with PPBCT. It included questions assessing the broad range of potential risk factors for PPBCT. Patients supplied their demographic, medical, and surgical data. Our primary objective was to investigate the nature of the pain in women and their emotional responses to it. Patients were screened using the question "Do you still experience pain as a result of your treatment?"

If they answered "yes," they completed questions characterizing their pain and the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs[22] (S-LANSS) to ascertain whether their pain was neuropathic. Patients were asked whether they had had preoperative pain (not necessarily breast pain). Patients then filled out the Chronic Pain Acceptance Questionnaire (CPAQ)[20] to assess behavioral measures of pain, specifically "pain willingness" and "activities engagement." At the end of the questionnaire, all patients completed the Hospital Anxiety and Depression Scale[23] (HADS). This determined whether the patients with pain were more anxious or depressed than patients without pain.

Statistical and Analytical Methods

Age, time since surgery, and HADS scores were analyzed using independent sample *t*-tests between patients who reported chronic pain and those who did not. The CPAQ and S-LANSS were analyzed using independent sample *t*-tests between patients with constant pain and those with intermittent pain. Type of surgery, chemotherapy, radiotherapy, hormone therapy, and the presence of preoperative pain were analyzed using a cross-tabulation and χ^2 test. All analyses were performed using SPSS v17.0 (SPSS, Inc., Chicago, IL). Alpha was set at 0.05.

Logistic regression methods were used to assess the impact of procedure, age, time since surgery, preoperative pain, chemotherapy, radiotherapy, and hormone therapy on postoperative pain, as univariate variables and in combination.

Results

Before the analysis, all variables were checked to confirm that they met assumptions for parametric analysis. The baseline characteristics are shown in Table 1. One hundred eleven patients completed the questionnaire at a mean time of 64.5 months postoperatively, of whom 33 (29.7%) reported chronic pain.

Independent sample *t*-tests were performed (Table 2). No difference in time since surgery by development of chronic pain was found ($P = 0.89$). Younger age was not significantly associated with the development of chronic pain, although there was a trend toward significance ($P = 0.07$).

Table 1
Baseline Characteristics of Women Treated for Breast Cancer From 1997 to 2009

Baseline Characteristics ($N = 111$)	Mean (SD)
Age (years)	64.43 (10.95)
Number of operations	1.23 (0.56)
Time since surgery in months, $n = 110$	64.51 (39.42)
Baseline Characteristics ($N = 111$)	***N* (%)**
Patients who had chemotherapy, $n = 100$	43 (43.0)
Patients who had radiotherapy	92 (82.9)
Hormone therapy, $n = 110$	77 (70.0)
Chronic pain as a result of treatment	33 (29.7)

Characterizing PPBCT

If a patient reported PPBCT, they also answered questions characterizing their pain in terms of location, time of onset, duration, and exacerbating factors. Patients were allowed to tick multiple responses for each question. Pain immediately after surgery was reported by 35.7% of patients, 32.1% reported pain starting months postoperatively, and 7.1% reported pain beginning years postoperatively; 17.9% of patients who reported chronic pain said that they had pain before their operation.

Patients were asked whether their pain was intermittent. Of the 30 respondents, seven (23.3%) said pain was constant and 23 (76.7%) said the pain came and went. The questions went on to characterize the duration of the pain. Of the 25 respondents, 29.2% said that their pain lasted for seconds, 16.7% said it lasted for minutes, 20.8% said it lasted for hours, 12.5% said it lasted for weeks, and 20.8% described the duration of their pain as variable.

Exercise exacerbated pain in 32.1% of patients. Exacerbations also were reported in relation to dressing (21.4%), lifting (7.1%), writing (3.6%), using the phone (3.6%), and other factors (21.4%); 42.9% of patients reported that nothing exacerbated their pain.

Twenty-two of 33 (66.6%) patients reporting chronic pain were taking analgesic medications, of which the most popular were paracetamol (acetaminophen), ibuprofen, and cocodamol. Thirteen patients gave details of analgesic efficacy, and, only two said that analgesics relieved their pain. The rest either answered "no" (one), "sometimes" (seven), and "not sure"

Table 2
Comparison of Age, Time Since Surgery, and HADS Scores Between Patients Treated for Breast Cancer From 1997 to 2009 With and Without Chronic Pain[a]

	No Chronic Pain ($N=78$)	Chronic Pain ($N=33$)		*t*-test
Parameters	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	*P*-value
Age (years)	65.68 (10.73)	61.48 (11.08)	4.20 (−0.27, 8.65)	0.065
Time since surgery in months	64.86 (37.36)	63.66 (44.68), $n=32$	1.20 (−15.28, 17.68)	0.89
HADS-A	4.87 (4.20)	5.21 (4.14), $n=29$	−0.34 (−2.14, 1.47)	0.71
HADS-D	2.86 (2.88)	2.45 (2.71), $n=29$	0.41 (−0.81, 1.63)	0.51
S-LANSS ($n=25$)	——	8.36 (6.10)	——	——

HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale-Depression; S-LANSS = Self-Report Leeds Assessment of Neuropathic Symptoms and Signs.
[a]*t*-test.

(three). Slightly surprisingly, only six patients wanted to see a physician about their pain.

Twenty-five of 33 (76%) patients who reported chronic pain completed the S-LANSS. Ten (40%) patients scored 12+, indicating that their pain was likely to be neuropathic; another four respondents scored 11 and were, therefore, borderline. Of the original 111 patients, ~30% had chronic pain and 40% of these patients had neuropathic pain. However, the S-LANSS is only a screening tool and cannot replace specialist clinical judgment. It has been shown to be a conservative measure of neuropathic pain,[22] and, therefore, we can conservatively estimate the prevalence of chronic neuropathic pain in this population at 9% but it is likely to be higher.

The mean visual analogue scale (VAS) score was used to determine the patient's average pain over the last week. Twenty-three patients responded, and the mean score was 3.23 ± 2.61 and, therefore, the mean pain was mild to moderate (VAS < 4). However, five (21.7%) patients were in the moderate range (VAS > 4) and two (8.6%) were in the severe range (VAS > 8). This suggests a very broad spectrum of pain severity.

Emotional/Affective Factors

The HADS scores were analyzed as HADS-Anxiety and HADS-Depression Scores (Table 2). Patients with PPBCT were not significantly more anxious or depressed compared with patients who did not have pain. However, a subset analysis of patients with pain showed that patients who described their pain as constant had significantly greater anxiety ($P=0.002$) compared with patients who reported intermittent pain.

The CPAQ is designed to assess patients' "activities engagement" and "pain willingness;" higher scores indicate greater amounts of pain acceptance and activities engagement. The mean engagement score was 51.27 (of a maximum 66) and the mean pain willingness score was 39.73 (of a possible 54). The CPAQ scores were analyzed by an independent sample *t*-test between those who reported that their pain was constant and those with intermittent pain. Participants with constant pain had significantly lower pain willingness scores ($P=0.037$), indicating greater difficulties with pain acceptance, compared with those with intermittent pain.[20]

Medical and Surgical Risk Factors

No surgical procedure was significantly associated with increased risk of developing PPBCT. Preoperative pain, chemotherapy, and radiotherapy all showed varying degrees of association with the development of chronic pain (Table 3). These variables were then analyzed within a more comprehensive model and a logistical regression analysis was performed.

The logistic regression analysis only allows chemotherapy and preoperative pain into the model. Chemotherapy was shown to increase risk of developing chronic pain by a factor of 3.00 (95% confidence interval [CI] = 1.22−7.40, $P=0.017$). Preoperative pain was shown to confer a fivefold increased risk (95% CI = 1.78−14.9, $P=0.002$) of developing chronic pain.

Discussion

As a group, the patients with PPBCT did not display significantly greater anxiety or depression scores when compared with patients who did not have pain. This may partly explain

Table 3
Comparison of Preoperative Pain, Type of Operation, Radiotherapy, and Chemotherapy Between Patients Treated for Breast Cancer From 1997 to 2009 With and Without Chronic Pain[a]

	No Chronic Pain ($N=78$)	Chronic Pain ($N=33$)		χ^2/Fisher's Exact Test
Parameters	N (%)	N (%)	Mean Difference in % (95% CI), Pain-No Pain	P-value
Preoperative pain	8 (10.3)	12 (36.4)	26.11 (8.37, 43.85)	0.001[b]
Operation	—	—	—	—
Lumpectomy	64 (82.1)	30 (90.9)	8.86 (−4.13, 21.85)	0.24
Re-excision	2 (2.6)	4 (12.1)	9.56 (−2.12, 21.23)	0.06
Mastectomy	14 (17.9)	6 (18.2)	0.23 (−15.44, 15.91)	0.98
SNB	13 (16.7)	5/32 (15.6)	−1.04 (−16.10, 14.01)	0.89
ANC	27 (34.6)	11 (33.3)	−1.28 (−20.52, 17.96)	0.90
ANS	27 (34.6)	14 (42.4)	7.81 (−12.09, 27.70)	0.43
Reconstruction	5 (6.4)	4 (12.1)	5.71 (−6.68, 18.10)	0.31
Implant	1 (1.3)	1 (3.0)	1.74 (−4.61, 8.11)	0.53
Radiotherapy	61 (78.2)	31 (93.9)	15.73 (3.48, 27.99)	0.04[b]
Chemotherapy	24/68 (35.3)	19/32 (59.4)	24.08 (3.62, 44.54)	0.023[b]

SNB = sentinel node biopsy; ANC = axillary node clearance; ANS = axillary node sample.
[a]χ^2/Fisher's exact test.
[b]Denotes significant results.

why only a small number of patients wanted to consult a physician and is supported by recent research.[16]

The severity of pain was at the top of the mild range. This is somewhat reassuring because previous studies have reported higher pain scores and also may partly explain why few women wanted to consult a physician.[5] Patients with constant pain had significantly greater anxiety scores than patients whose pain was intermittent. This group also had lower "pain willingness" scores as measured by the CPAQ. This indicates that there is a subgroup of patients (~6% of the total) who have constant pain and anxiety. This may be the result of the severity of their pain, the neuropathic element, which makes it more difficult to treat, or the fact that it is constant. Further prospective studies with larger numbers may clarify the reciprocal relationships among pain, treatment, and distress.

The estimates for the prevalence of PPBCT are consistently ~50% for women at a mean time of between 24 and 36 months postoperatively.[5,14,15] We have shown in our sample that the percentage of women experiencing chronic pain after surgery for breast cancer was 29.7%, significantly lower than previous estimates. This study has a mean time since surgery of 64.5 months and so takes a longer-term view than previous studies.[5] However, there is a large variation in follow-up time, which makes interpretation of the prevalence of PPBCT at a specific time point difficult. Our patients were treated between 1997 and 2009, and we should remember that treatment for breast cancer has changed a lot in this period; this may make this sample group less representative than modern BCSs.

Similar to other research, the present study did not find a correlation between time since surgery and the risk of development of PPBCT.[14] A previous study suggests that at a mean follow-up time of nine years, there is a chronic pain rate of 17%, down from a rate of 43% at three years postoperatively.[15] The present study loosely supports suggestions from previous research that chronic pain following treatment for breast cancer resolves with time for a proportion of women. However, the large range in follow-up time needs to be borne in mind. It seems that the relationship between length of time since surgery and the development of chronic pain is complex and influenced by several factors. The present study also supports the finding that, for a proportion of women, PPBCT does not resolve even after a considerable length of time.

PPBCT is very variable and it can manifest itself at various times in the course of a patient's treatment. Approximately 40% of the pain is likely to be neuropathic and thus likely to be less responsive to standard analgesics. A substantial number of patients may benefit from access to specialist advice and consultation around the use of antineuropathic agents.

Chemotherapy was shown to significantly increase the risk of developing chronic pain. This finding is supported by the large body of previous literature showing that chemotherapy

is a risk factor for peripheral neuropathic pain.[8–12] These findings, however, are equivocal as there is a body of literature that finds no association between chemotherapy and PPBCT.[5–7] Also, it cannot be ruled out that it is because younger women (who are at greater risk of PPBCT) were more likely to receive chemotherapy. Clearly, further prospective longitudinal research is required. This area also may benefit from systematic review.

Although the exact mechanisms underlying the link between chronic pain and chemotherapy have not been clarified, it is thought that axoplasmic disruption of microtubule transport, distal axonal degeneration, and damage to cell bodies in the dorsal root ganglion may be responsible.[13] The peripheral nervous system may be particularly susceptible because of the lack of an effective neurovascular barrier.[13]

Our study did not demonstrate an association between younger age and increased risk of chronic pain, but there was a trend toward significance. We also did not show an association between different types of operation and increased risk of developing chronic pain; this is similar to some smaller studies[24] but contradicts many others.[5,6,9,21]

Although the questionnaire relied on accurate information from patients (demographic, surgical, and medical data), the items within the questionnaire have all been validated for self-reporting by patients.[20,22,23,25] Epidemiological studies have demonstrated that patients can accurately report such data especially when it involves life-threatening conditions.[26] Also, as a cross-sectional questionnaire study, it is liable to self-selection bias as people can choose whether they wish to complete the questionnaire or not. Finally, our results in relation to preoperative pain do rely on patients retrospectively remembering whether they had pain before their operation. Although we believe patients can accurately recall this, it means that this result needs to be interpreted with caution.

In conclusion, this study shows that, as a whole, long-term BCSs are not significantly more anxious or depressed than long-term survivors without pain. Importantly, however, this study suggests that patients with constant pain are significantly more anxious than patients with intermittent pain. This could mean that there is a subgroup of patients, approximately 6% of the total, with constant PPBCT and anxiety. Patients with constant pain had significantly lower pain willingness scores on the CPAQ. This suggests areas of future research around longitudinal studies of psychological factors in breast cancer treatment and how these influence pathways toward health and recovery. Our study may have been somewhat underpowered to assess risk factors, but these seem to include preoperative pain and chemotherapy. The persistence of PPBCT in BCSs and its prevalence suggests that long-term follow-up patients should be regularly asked about any painful symptoms. More patients could then be referred to pain specialists for treatment.

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Appendix

Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.jpainsymman.2011.10.021.

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