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Long-term course of pain in breast cancer survivors: A four year longitudinal study

Winfried Rief, Ph.D.[1,2], **Wayne A. Bardwell, Ph.D.**[1,3], **Joel E. Dimsdale, M.D.**[1,3], **Loki Natarajan, Ph.D.**[3], **Shirley W. Flatt, M.S.**[3], **John P. Pierce, (Ph.D)**[3,4], and **the Women's Healthy Eating and Living (WHEL) Study Group**

[1] Department of Psychiatry, University of California San Diego, USA

[2] Division of Clinical Psychology, University of Marburg, Germany

[3] Moores UCSD Cancer Center, University of California San Diego, USA

[4] Department of Family and Preventive Medicine, University of California San Diego, USA

Abstract

Background—After successful treatment of early breast cancer, many women still report pain symptoms, and attribute them to the previous illness or its treatment. However, knowledge about the long-term course of pain in breast cancer is limited.

Methods—Baseline assessment included 3,088 women who received a breast cancer diagnosis on average 2 years prior to enrollment, and who completed typical medical treatments. After 4 years, a subsample of 2,160 recurrence-free women (70%) was re-assessed. The major outcome variable was the composite index for general pain symptoms.

Results—Over the 4 year course, a slight but significant increase in pain was reported. If only medical variables were examined, a triple interaction between surgery type, breast cancer stage, and time indicated that pain scores increased in most subgroups, while they decreased in stage II women after mastectomy and stage III women after lumpectomy. Using a regression analytical approach, psychological and other variables added significantly to the prediction of pain persistence. Regression analysis revealed that pain symptoms increased in those women taking tamoxifen at baseline, in those reporting depression at baseline or stressful life events during the first 12 months after enrollment. Exercise at baseline had a beneficial effect on pain recovery.

Conclusions—The persistence or increase of pain symptoms in women surviving breast cancer is associated with some medical factors (surgery type, tamoxifen use), but also with psychological factors. Pain should be a standard outcome variable in the evaluation of cancer treatment programs.

Keywords

breast cancer; pain; depression; physical exercise

Corresponding Author for WHEL Study Group: Dr. John Pierce, Ph.D. Cancer Prevention and Control Program, Rebecca and John Moores UCSD Cancer Center, School of Medicine, University of California, San Diego, La Jolla, CA 92093-0901 (jppierce@ucsd.edu).

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Introduction

Pain can play different roles in cancer development, as well as during cancer treatment and recovery. A new onset of pain symptoms can indicate recurrence of cancer, and may therefore be an ongoing concern of the patient. These cancer-associated pain symptoms can affect different parts of the body [1], and are frequently attributed to cancer or cancer treatments even if this causality remains unclear. For the medical specialist it is hard to decide what has caused the pain symptoms, especially since long-term studies investigating pain in cancer patients are rare and based on low sample size.

In a recently published cross-sectional study, forty-seven percent of women reported pain following breast cancer surgery [2]. Pain symptoms are even more prevalent than fatigue [3]. In fact, fatigue and pain after cancer treatment typically overlap, and both seem to be additionally associated with mental health [4,5]. Pain is a central factor affecting quality of life of patients with breast and gynecological cancer [6], but also other types of cancer [7]. This is especially relevant, because baseline quality of life is a prognostic factor of survival and long-term quality of life [8-10]. Even after successful treatment of early stage Hodgkin's lymphoma, reduced quality of life and associated somatic symptoms remain stable over the years [11]. It is unclear whether the same stability of pain symptoms can be found in breast cancer patients.

The cause of pain in general, but also of pain in cancer patients, frequently remains unclear. Tissue damage is one obvious explanation, although the association between tissue damage and pain symptoms is only marginal [12]. Breast cancer, chemotherapy and radiotherapy are potential sources of the development of neuropathic pain [13]. Pain symptoms can result from medication, e.g., musculoskeletal symptoms caused by aromatase inhibitor medication [14]. So-called cancer breakthrough pain [15] is characterized by intense pain despite adequate analgesic medication, and its cause is often unclear or can be multiply determined. According to the International Association for the Study of Pain (IASP), pain is strongly dependent upon emotional factors and subjective evaluation of bodily experiences [16]. Therefore pain symptoms are prone to psychological and behavioral influences. Anxiety and the expectation of pain can contribute to the development of pain symptoms [17]. Finally, as pain is a ubiquitous phenomenon in the general population [18,19], the report of pain symptoms in cancer patients can sometimes be just a misattribution of symptoms that already existed before the cancer was developed, or that developed post-diagnosis unrelated to cancer.

Due to the relevance of pain in cancer, validated pain measures should be used in clinical trials of cancer pain treatments. Composite measures that combine ratings of different pain areas and pain intensity appear to be both valid and reliable [20]. A multisite assessment of pain is in particular relevant, as the pain can develop on cancer-distant body regions. Therefore the present study will focus on general pain symptoms, not only on cancer site associated pain.

To summarize, knowledge on the long term course of pain symptoms in women with breast cancer is scarce. It is unclear if or how pain symptoms after breast cancer treatment fluctuate over time. Moreover, it is unclear how changes of pain intensity over time are associated with type of medical treatment, breast cancer stage before surgery, and concordant psychological and behavioral factors. To analyze the relevance of these potential sources of pain, the simultaneous analysis of multiple factors in a large sample is needed [13]. Therefore we investigated the long term course of pain in women surviving breast cancer, and analyzed medical and psychological predictors of its course.

Methods

Ethical considerations

The IRBs at all 7 study sites approved the study protocol and consent forms. All participants provided written informed consent.

Subjects

This study is based on the data set of the WHEL study [21] including 3088 women treated for early stage breast cancer from 7 clinical sites in California, Oregon, Arizona, and Texas. For the present purpose, the analyses are based on women with full data at baseline and 4 year follow-up for major variables (2160; 70%). During the 4-year observation period, 362 patients recurred, 50 additional patients died, and 516 of the remaining patients (19.3%) did not answer the questionnaires. Therefore the following analyses are based on these 2160 recurrence-free women. Further details of the sample description are reported in Table 1.

The randomized trial evaluated the use of a special diet. The intervention group (n = 1537) was randomly assigned to receive a telephone counseling program supplemented with cooking classes and newsletters that promoted daily targets of 5 vegetable servings plus 16 oz of vegetable juice; 3 fruit servings; 30 g of fiber; and 15% to 20% of energy intake from fat. The comparison group (n = 1551) was provided with print materials describing the “5-A-Day” dietary guidelines. Because diet was unrelated to pain, all patients were analyzed, regardless of diet assignment. Eligibility criteria included diagnosis of a primary operable invasive breast carcinoma, including women diagnosed with stage I, II, or IIIa breast cancer within the past 4 years. If indicated, cancer surgery, radiation or chemotherapy took place before baseline assessment and inclusion in this study. Concurrent tamoxifen treatment was possible and registered. Further details on clinical outcome of this study can be found elsewhere [21,22].

Measures

In addition to the clinical variables of breast cancer stage and treatment, and basic socio-demographic variables, the following scales were used:

Pain assessment—To assess multisite pain symptoms, we used a composite pain index covering seven pain areas, and items originating from the Symptom Inventory. The Symptom Inventory was especially developed for middle-aged healthy women [23], and its pain items were summed up to a general pain score. Pain symptoms were scored from 0 (did not occur) to 3 (severe) for the past 4 weeks. Patients were asked for the following pain symptoms: general aches or pains, low back pain, neck pain, headaches or migraines, joint pain or stiffness, belly pain or stomach discomfort, pain or burning while urinating. A reliability index (Cronbach's α=.70) confirms the internal consistency of the composite pain index, and this pain index was used for all subsequent analyses.

Quality of life was assessed using the RAND 36-item Health Survey physical health and mental health summary scores [24]. Depression was assessed using a screening version of the Center for Epidemiologic Studies Depression Scale CESD [25] (CESDsf). As some studies indicated a relevance of optimistic attitudes for the course after breast cancer treatment [26], we also included the Life Orientation Scale—Revised to assess optimism [27]. Social support was also postulated to be associated with well-being in cancer patients [28]. Therefore we used the 9 social support items from the Medical Outcome Studies (MOS) [29] to assess social support. Physical activity was assessed by questionnaire [30]; metabolic equivalents of physical activity were then calculated. We also assessed stressful life events using 11 items from the Alameda County Study [31], such as death of partner,

death of a close friend or family member, major problems with money, divorce, major conflict with children or major accidents, job loss, death of a pet. As concurrent life events are thought to influence the persistence of pain symptoms, we assessed life events one year after study enrollment asking for the occurrence of these events during the last 12 months.

Statistics—As a first step to analyze changes during the 4 year course, paired t-tests for dependent variables (e.g., depression, pain) were computed. To analyze the special relevance of medical factors for long term course of pain, we conducted repeated measure ANOVAs with the medical factors as grouping variables, and baseline versus 4 year pain scores as repeated measure. As grouping variables we used stage of cancer, surgery type (mastectomy versus lumpectomy), chemotherapy before study entry, radiation therapy before study entry, and tamoxifen treatment at baseline. Maximally 3 way interactions will be reported, as higher order interactions usually explain only a small amount of variance, and are hard to interpret.

In addition, we also computed a linear regression analysis entering blocks of variables, controlling for baseline pain levels. The dependent variable of the regression analysis was the composite pain score 4 years after baseline. In this second analysis, we entered as the first block socio-demographic variables (age, education status), as well as the baseline pain score. In the second block, we entered medical factors (initial treatment, use of tamoxifen at baseline, stage of breast cancer, and years since diagnosis). In a third block, we entered the following psychosocial variables into the regression analysis: depression, optimism, life events during first 12 months of observation, social support, physical activity. In contrast to the other predictor variables which were taken from baseline assessment, life events were assessed during the first 12 months after enrollment. The retrospective assessment of life events at baseline could be confounded with the cancer diagnosis and first treatment in some women, while the life events during the first 12 months after study enrollment should bemore comparable between women. With this approach, psychological variables are only considered if they add information to the socio-demographic and biomedical variables.

Results

Completer analysis

At 4 year follow-up, we collected data on psychosocial variables for 70% of the women who entered the study. Completers and non-completers differed in terms of pain intensity at baseline, with highest baseline pain scores for those women who died (4.60; SD=3.1), slightly lower scores for women suffering recurrence or dropouts (4.51; SD=3.2), and lower baseline scores for completers with full data at follow-up (4.25; SD=2.9; $F=3.0$; $p<.05$). This confirms the relevance of pain as an index for general health and cancer severity. Comparison of baseline scores revealed that women receiving different medical interventions did not differ significantly in terms of pain, with the exception of lower pain scores for those women who received tamoxifen (4.2, SD = 3.0; no tamoxifen at baseline: pain score 4.6; SD = 3.0; $F = 18.0$; $p < 0.0001$). In general, compared to completers, non-completers are characterized by higher death rates, higher recurrence rates, and all variables that are associated with these poorer outcome variables (see Table 1).

Course of pain syndromes

While depression and quality of life did not change significantly during the observation period, there was a significant increase of pain symptoms, optimism and physical activity (see Table 2). Therefore we examined whether the increase of pain symptoms could be explained by increasing age. For this purpose, we computed a regression equation between

pain symptoms and age based on the baseline data set. The association between pain symptoms and age was not significant (standardized beta = 0.03; t = 1.5; ns).

The relevance of medical factors for pain persistence

The repeated measures ANOVA with pain as repeated measure and medical factors as grouping factors revealed one main effect, namely for tamoxifen use at baseline ($F=7.1$; $p<.009$). Women in the "tamoxifen at baseline" group reported lower pain scores in general. Moreover, a triple interaction was found for type of surgery × stage of breast cancer × time point ($F=3.5$; $p<.04$). The results in terms of estimated scores after controlling for other influencing factors are shown in Table 3. Women with stage 3a breast cancer who received lumpectomy reported lower average pain scores at baseline than most other groups. Pain reductions until follow-up were found after lumpectomy in the cancer stage 3a group, and after mastectomy in the cancer stage 2 group. The most significant increase of pain scores was found for women with stage 2 cancer after lumpectomy, and for stage 1 cancer after mastectomy. No further double or triple interactions were found.

Linear regression analysis with blockwise inclusion of medical and psychological factors

In the first block, we entered baseline pain score, education and age. This prediction model was already significant ($R^2=.38$; $F = 837$; $p < 0.0001$) mainly because of the impact of baseline pain scores. Additionally, education was a small but significant predictor throughout all regression models, with higher education predicting lower pain scores at follow-up. The additional inclusion of medical variables in block 2 improved the prediction model ($R^2=.39$, F change = 2.8; $p<.01$). Notably, use of tamoxifen at baseline had a significant impact on pain 4 years later, as well as years since diagnosis. Other medical factors did not have a significant impact on the regression model (Table 3).

In block 3, additional psychological and behavioral variables were included, which further improved the regression model ($R^2= .40$; F change= 5.6; $p < 0.001$). As expected, in this final regression model baseline pain symptoms played a major role in explaining pain symptoms 4 years later. The only medical variable with a significant impact on pain after 4 years was the use of tamoxifen at baseline, but years since diagnosis before study enrollment also continued to play a role. Baseline depression scores, stressful life events during the first 12 months after enrollment, and low exercise at baseline had an additional significant association with pain symptoms 4 years later. While the standardized beta-scores were in a low range, this was mainly due to the great amount of variance that was already explained by baseline pain scores.

Discussion

In this study, we present 4 year follow-up data of pain symptoms in women who survived breast cancer. In fact, 4 years after initial assessment corresponds to 5-6 years after diagnosis in many patients; therefore this time period includes the typical 5 year observation period for recurrence. Contrary to our expectations, we found a slight increase of pain symptoms during the 4 year observation period. This deterioration of pain scores is mainly predicted by psychological factors (e.g., depression at baseline; life events first 12 months), while medical factors (e.g., surgery type) played a smaller role (see differences in F-change scores). At baseline, pain levels did not differ significantly between the subgroups of patients receiving different medical treatments for breast cancer. We further analyzed the impact of medical baseline factors on long-term course of pain symptoms using a repeated measure ANOVA; this approach is appropriate considering the categorical nature of the medical variables. With this method of statistical analysis, we were able to show that the

original cancer treatment had a small but significant impact on long-term course of pain symptoms, depending on the stage of breast cancer at baseline.

Pain symptoms increased in most subgroups, but women with stage II breast cancer receiving mastectomy reported lower pains scores at follow-up. Also women with stage IIIa breast cancer receiving lumpectomy reported lower pain scores at follow-up, although due to the low subsample size, this result should not be over-interpreted. In contrast to stage II women, most pronounced worsening of pain scores was reported in women after mastectomy for stage I and stage IIIa cancer. If women suffer from stage I breast cancer, lumpectomy predicts lower pain score increases than mastectomy. Notably, these results were controlled for other factors such as chemotherapy or radiation, and were based on estimated scores eliminating the influence of other factors.

In contrast to these results of a general linear model, stepwise regression analysis allows combining categorical and continuous variables as potential predictors of the criteria “pain 4 years later”. In this analysis, we also controlled for baseline pain symptoms. While Tamoxifen use at baseline indicated lower pain scores at baseline, it also predicted a substantial increase of pain scores over time. Therefore this result should be interpreted with caution, because it could be explained by a patient selection bias at first assessment, and could be partially due to the “regression to the mean effect”, indicating that an increase of pain symptoms is the more likely the lower the initial pain scores are. More detailed analyses of subgroups are necessary of women continuing tamoxifen intake for the whole 4 years, or women who stopped intake after the expected 5 years of treatment (which is possible if tamoxifen treatment started more than one year before study enrollment), and women who switched to other medication. However, analyzing these options and considering the other control variables would overstress our approach. Years since diagnosis showed a negative association with pain scores at follow-up. Longer periods since diagnosis seem to indicate more stable health status. The association seen between higher education and lower pain is in line with the fact that socioeconomic status is associated with cancer and cancer treatment [32].

Notably, baseline pain scores are by far the most powerful predictor of pain 4 years later, and explain a significant amount of the variance of the regression model. This not only reflects the chronic nature of pain, but including baseline pain scores also controls for methodological aspects (e.g., response bias of patients). Thus the role of variables entered later in the model could be of relevance, even if the portion of explained variance is low.

Psychological and behavioral variables can also add additional information for the prediction of pain symptoms. Depression was a significant predictor of pain, revealing a comparable impact with tamoxifen use and exercise. It has been frequently shown that depression and pain are closely related, although the two features also have to be distinguished [33]. In patients with breast cancer, other studies confirmed that depression was associated with higher pain levels [34]. Depression diagnosis also predicted elevated cancer mortality in a meta-analysis including 76 prospective studies [35]. Moreover, stressful life events in the first 12 months of the observation period also predicted higher pain levels at follow-up, although this impact is smaller after controlling for baseline scores of pain, depression, and all the other variables. This result is in accordance with other studies showing the relevance of life-events for the course of depression, pain, cancer, and other health issues [36-38].

It has been shown that physical exercise is a behavioral feature that can improve depression, pain, quality of life, and is even discussed as a life-prolongation factor after cancer treatment [39-43]. Therefore it is of interest that exercise levels at baseline also predicted pain levels 4

years later: the more exercise the women did, the less pain symptoms were reported at follow-up. Although the new research on exercise intolerance in cancer has to be considered [44], the general recommendation of establishing and continuing a reasonable exercise level for women with breast cancer is supported by our data. For most patients, exercise seems to have a beneficial effect on well-being or even on reducing risk of recurrence, but without any negative side effects [45].

Although social support and optimism have been discussed [28] as relevant factors in breast cancer, our data did not support their unique role. It has to be kept in mind that these variables were highly related to other variables that have been shown to be relevant in our analysis, such as depression and life events. Therefore discrepant results between studies can occur due to not considering the interrelationship of these variables. Moreover, we did not find any evidence that age influenced our results substantially. This is in line with the study by Kozachik and Deend-Roche [46] who did not find an association of increased risk for pain, fatigue or insomnia symptoms with age. Although other studies reported an age dependency of somatic symptoms in general [19], the increase of age for the 4 years during follow-up does not account for substantial changes of pain symptoms.

Limitations of our study are the inclusion of patients after a varying time since cancer diagnosis. Although we tried to control for this variable statistically, the course of pain in the first months after the diagnosis, but before study enrollment, can differ from what was observed on study. The longer the time since diagnosis, the better the improvement of pain scores during the 4 year observation period, although time since diagnosis did not correlate with pain scores at study entry (data not shown). Moreover, the consideration of multiple potential predictor variables led to sometimes complicated interactions. On the other hand, only a large sample size such as ours allows analysis of these complex interactions. In fact, many of these interactions or predictions can be masked by underlying differences in other variables (to give an example: the role of mastectomy versus breast conserving surgery can only be adequately interpreted if the results are controlled for stage of breast cancer, chemotherapy and radiation). Moreover, predictor analyses reveal correlates, but not causal influences, even in longitudinal studies, as several factors can be confounded (e.g., cancer stage and treatment). Only randomized clinical trials with experimental designs (e.g., comparing the course of pain symptoms after women have been randomized to breast conservation surgery versus mastectomy) would allow a scientifically conclusive interpretation of causality.

To summarize, pain symptoms are a major determinant of quality of life in cancer patients, and should be adequately assessed in clinical trials. New assessment strategies allow the combined assessment of course of multiple pain symptoms in general, and course of medication-induced pain symptoms [47]. Moreover, it is necessary to diagnose and treat comorbid pain conditions in women after breast cancer treatment [48-50]. Also, treatment programs should include an adequate intervention if depressive symptoms are present, and should try to increase physical exercise levels. Just recently, a centralized telephone-based care management has been presented as an economic approach for pain management in cancer [51]. The consideration of underlying psychological features such as fear of recurrence or catastrophizing of somatic symptoms [52] could be a useful addendum to classical cancer treatment. Cancer pain is still a major problem that requires specific treatments [53,54].

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Table 1

General Sample Information

Variable	Full sample	Analyzed sample	F-/X^2-statistics (analyzed vs. missing at follow-up)
Sample size baseline	3088	2160	
Sample size 4 years later	2160 (70%)	2160	
Age	53.2 (9.0)	54.0 (8.7)	10.3**
BMI	27.3 (6.1)	27.0 (5.9)	11.0**
Caucasians	82 %	84 %	6.3*
Education:			
<= High School	11.8 %	11.2 %	
Post-High School	32.4 %	31.8 %	
College degree	27.3 %	28.3 %	
Postgrad Degree	24.5 %	25.8 %	4.2*
Marital Status			
Married	66.8 %	68.4 %	
Divorced	12.3 %	12.2 %	
Single	10.3 %	9.7 %	
Widowed	4.7 %	4.9 %	
Others/unknown	5.9 %	4.8 %	17.1*
Breast Cancer Stage at Baseline			
I	38.6 %	42.5 %	
II	56.4 %	53.7 %	
III a	5.0 %	3.8 %	38.0***
Years since diagnosis	1.95 (1.0)	2.00 (1.0)	1.2 n.s.
Type of breast cancer surgery:			
Lumpectomy	47.7 %	49.8 %	
Mastectomy	52.2 %	50.2 %	14.6**
Radiation	61.5 %	61.9 %	1.7 n.s.
Chemotherapy	69.9 %	66.5 %	29.8***
Use of Tamoxifen Baseline	59.6 %	62.9 %	29.8***
Use of Tamoxifen 4 years later	27.6 %	27.9 %	-
Death confirmed (4 years later)	4.4 %	0 %	-
Depression (log CES-D > .06)	16.8 %	15.4 %	8.6**

Variable	Full sample	Analyzed sample	F-/X^2-statistics (analyzed vs. missing at follow-up)
Number of life events	1.63 (1.4)	1.61 (1.4)	0.1 n.s.
Optimism	17.6 (3.6)	17.7 (3.6)	1.6 n.s.
Exercise (MET minutes per week)	845 (836)	875 (837)	0.4 n.s.

Note: If not otherwise specified, all scores are from baseline assessments. Last column includes comparison of baseline scores for included subjects versus subjects with missing follow-up scores, with t-scores for numeric variables, and chi^2-scores for categorical variables. Significance levels: n.s.=non significant

* p<.05

** p<.01

Table 2

Changes over the 4 year course (Pair-wise comparisons)

	Baseline	4 years later	t score
SF36 Physical Health	76.6 (18.9)	76.6 (20.5)	0.1 (ns)
SF36 Mental Health	77.0 (16.5)	77.3 (17.4)	0.7 (ns)
Depression CES-D	2.7 (2.7)	2.7 (2.8)	0.8 (ns)
Optimism	17.7 (3.6)	17.9 (3.5)	3.0 (p<.004)
Exercise	875 (838)	942 (913)	3.6 (p<.001)
Sum of pain symptoms	4.27 (2.9)	4.54 (3.1)	4.6 (p<.0001)

NOTE: The increase of pain symptoms is also found if the MOS pain score is used (p=0.05).

Table 3

The interaction of surgery type with stage of breast cancer predicts course of pain (repeated measure ANOVA; F=3.5; p<.03)

	Stage I (n=855)	Stage II (n=1080)	Stage IIIa (n=76)
Lumpectomy (n=1003)			
Pain at baseline	4.2 (0.1)	4.5 (0.2)	3.6 (1.2)
Pain 4 years later	4.4 (0.1)	4.9 (0.2)	2.6 (1.3)
Mastectomy (n=1008)			
Pain at baseline	4.3 (0.4)	4.9 (0.3)	4.5 (0.7)
Pain 4 years later	4.8 (0.4)	4.5 (0.4)	5.2 (0.7)

NOTE: Table shows estimated scores after controlling for other variables (radiation; chemotherapy; tamoxifen); means and standard errors

Table 4

Predictors of pain 4 years later (Results of the regression analysis; rearranged according to standardized beta)

	Standardized beta	t-score	Significance
Pain score at baseline	.58	27.2	.000
Tamoxifen use at baseline	.08	3.4	.001
Depression at baseline	.07	2.8	.005
Exercise: Metabolic equivalents at baseline	-.06	-2.9	.004
Life events first 12 months	.05	2.1	.036
Yrs since diagnosis	-.04	-2.1	.04
Education	-.04	2.0	.045