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Pain and Inflammation in Women with Early-Stage Breast Cancer Prior to Induction of Chemotherapy

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Abstract

Context—Pain is a commonly experienced and distressing symptom in women with breast cancer (BCA), and recent evidence suggests that immune activation may be associated with pain and other co-occurring symptoms. However, no studies to date have explored the relationships among perceived pain and biomarkers of inflammation in women with early-stage BCA during the initial course of treatment but before induction of chemotherapy.

Objectives—The purpose of this research study was to examine the relationships among pro- and anti-inflammatory biomarkers and the presence of pain and other symptoms (anxiety, depression, fatigue, and sleep disorder) in women with early-stage BCA during the initial course of treatment.

Methods—This was a secondary analysis of baseline data from two research studies that measured perceived symptoms, including the presence of pain and pain interference, and plasma levels of pro- and anti-inflammatory cytokines and c-reactive protein (CRP) in women with early-stage BCA ($N = 32$) at one month after surgery but prior to receiving chemotherapy.

Results—Women experiencing pain had significantly higher levels of CRP ($p<.01$), interleukin (IL)-13 ($p<0.2$), IL-7 ($p< .02$), more pain interference ($p<.01$), depression ($p<.01$), and sleep disturbance ($p<.01$) compared to women reporting no pain. Similar differences were found when examining pain interference groupings. After accounting for differences in type of surgery (breast biopsy, lumpectomy, mastectomy), the presence of pain demonstrated significant positive partial correlations with CRP (rs=0.46, $p<.01$) and IL-13 (rs =0.36, $p=.04$).

Conclusion—The presence of pain during the initial course of treatment in women with early-stage BCA was associated with significantly higher levels of CRP and IL-13, suggesting a potential role of immune activation in perceived pain. Further research to examine the precise effects of these biological factors in modulating pain are needed. Perceived pain was also associated with multiple co-occurring symptoms, and this finding has important implications for symptom management. Nursing assessment of pain and pain interference during the early course

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of BCA treatment may help to identify women who will benefit the most from multimodal symptom management interventions.

Keywords

breast cancer; cancer pain; pain; pain interference; inflammation; c-reactive protein (CRP); interleukin-7 (IL-7); interleukin-13 (IL-13); symptom management; symptoms

Pain and Inflammation in Women with Breast Cancer

Women in the early course of breast cancer (BCA) treatment commonly report adverse symptoms, and more than 54% experience moderate to severe pain during the treatment trajectory (van den Beuken-van Everdingen et al., 2007). Pain is one of the most frequently reported adverse sequalae of breast cancer surgery (Geller et al., 2004) and the most frequent, intense, and distressful symptom after chemotherapy (Byar, Berger, Bakken, & Cetak, 2006; Rietman et al., 2004). Whether occurring as part of the disease process or as a side-effect of treatment, pain is a significant problem for a majority of women with BCA and has a negative effect on quality of life (Caffo et al., 2003; Miaskowski et al., 2006).

Accumulating evidence suggests that immune activation modulated through the increased release of proinflammatory cytokines is a mechanism involved in the development of distressing symptoms for women with BCA (Lyon, McCain, Walter, & Schubert, 2008; Reyes-Gibby et al., 2008) including the generation of pain and hyperalgesia (Sommer, 2006). Supporting a role of the immune system in symptom manifestation, several recent studies have reported associations among increased levels of interleukin(IL)-1, IL-6, fatigue, pain, and sleep disturbance in BCA survivors (Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006; Starkweather, 2010). However, there have not been any published research studies focused on identifying biological factors associated with perceived pain early in the course of treatment, at a time when potential therapeutics may be employed to prevent the occurrence of persistent symptoms (Reyes-Gibby, Morrow, Buzdar, & Shete, 2009). Thus, our initial step in this program of research was to focus on perceived pain during the early course of treatment, which was defined as one month following BCA surgery (breast biopsy, lumpectomy, or mastectomy) but before receiving chemotherapy. The purpose of this research study was to examine the relationships among pro-and anti-inflammatory biomarkers, perceived pain and other symptoms (anxiety, depression, fatigue, and sleep disorder) in women with early-stage (I-III) BCA at one month after surgical biopsy or tumor excision but prior to receiving chemotherapy.

Perceived Pain in Women with Early-Stage Breast Cancer: A Review of the Literature

More than 200,000 women in the United States will be diagnosed with BCA this year (Jemal, Siegal, Xu, & Ward, 2010), and as part of disease process and/or curative treatment, a majority of these women will experience pain (van den Beuken-van Everdingen et al., 2007). Multiples studies have shown that while women with BCA perceive benefit from their cancer treatment, they report problems with pain, functioning, and global quality of life regardless of the type of surgical procedure or other treatments (Caffo et al., 2003; Montazeri et al., 2008; Schnur et al., 2007). The presence of pain during treatment for breast cancer (BCA) is associated with persistent symptoms in survivorship (Reyes-Gibby, Morrow, Buzdar, & Shete, 2009), which is of particular importance in this patient population, who are typically young and constitute the largest group of cancer survivors in the United States (Mantyh, 2006).

Perceived pain is often reported along with other co-occurring symptoms, including depression, fatigue, and sleep disturbance among women with BCA (Dodd, Miaskowski, & Lee, 2004; Miaskowski et al., 2006), Although it has been proposed that symptom clusters may share a common biological mechanism (Cleeland et al., 2006; Fox & Lyon, 2007; Fox, Lyon, & Farace, 2007), very few studies have evaluated potential relationships among biological factors and BCA symptoms. Prior research incorporating biological factors have been limited to only a few select cytokines (Bower, Ganz, Aziz, & Fahey, 2002; Bower et al., 2009; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006). While these studies have focused on one particular symptom, such as fatigue, no prior research has examined perceived pain and biological factors in women with early-stage BCA.

Biological factors, such as pro- and anti-inflammatory cytokines, are released by immune cells in response to tumor growth, and many of these same factors have been shown to function as pain modulators (Reyes-Gibby et al., 2009). Proinflammatory cytokines, in particular, can directly sensitize peripheral nerves thereby lowering the pain transduction threshold, leading to peripheral sensitization (Sommer, 2006; Watkins, Hutchinson, Milligan, & Maier, 2007). Interleukin (IL)-1 and IL-2 levels have been associated with pain response and variations in pain medication requirements (Bessler et al., 2006; Backonja, Coe, Muller, & Schell, 2008; Finley, Happel, Kaminski, & Rogers, 2008). IL-6 has an important role in neuropathic pain (Lee, Lee, Son, Hwang, & Cho, 2004) while levels of tumor necrosis factor (TNF)-alpha are associated with severity of pain in lung cancer (Reyes-Gibby et al., 2008). In patients with rheumatoid arthritis, pain severity is associated with levels of C-reactive protein (CRP; Kojima et al., 2009). Although these studies suggest critical relationships among inflammatory biomarkers and perceived pain, to date there have not been any studies to examine pain-cytokine relationships in women with early-stage BCA.

With the high prevalence of reported pain in women with BCA and evidence implicating immune activation as a biological mechanism underlying perceived pain, the purpose of this study was to examine the relationships among pro- and anti-inflammatory biomarkers and the presence of perceived pain and other symptoms (depression, fatigue, and sleep disturbance) in women with early-stage BCA at one month after surgery but prior to receiving chemotherapy treatment.

Methods

This is a secondary analysis of baseline data from a research study carried out in two university health systems in the mid-Atlantic region between September 2003–June 2006. Women diagnosed with Stages I–III BCA (N=32) were approached about study participation one month following fine-needle biopsy or breast tumor resection (lumpectomy or mastectomy). This time point was selected because it provided an adequate duration of time after surgery for return of baseline immune parameters. Inclusion criteria were women over the age of 18 years diagnosed with Stages I–III BCA and fluency in English. Exclusion criteria included a past medical history of another form of cancer or immune-related disease (ie. multiple sclerosis, HIV, lupus), recent symptoms of illness (cough, fever), or use of anxiolytics, anti-depressants, or anti-inflammatory medications. All participants verbalized understanding and gave informed consent to the research protocol, which was approved by the university's institutional review board.

Procedures

At the time of consent, participants were asked about demographic variables, including age, ethnicity, and menopausal status. Menopausal status was defined using the following categories: premenopause as having had a menstrual period within 3 months and no

hormone replacement therapy (HRT) use or having had a hysterectomy with at least one ovary intact and no HRT use; perimenopausal status as having amenorrhea for at least 3 but less than 12 months and no current HRT use or having current HRT use for less than one year; postmenopause as having amenorrhea for at least 12 months or bilateral oopherectomy at least 6 months previous (Young, Finn, Austin, & Peterson, 2003). Following the collection of demographic information, participants were asked to complete self-report questionnaires, including the Brief Pain Inventory–Short Form, Hospital Anxiety and Depression Scale, Brief Fatigue Inventory, and General Sleep Disturbance Scale.

After completing the questionnaires, a 10 mL blood sample was collected from each participant using a standard phlebotomy protocol into a serum separator vacutainer without anticoagulant, and the vial was transported on ice directly to the laboratory for processing. Sera were separated by centrifugation, and all specimens were aliquoted immediately, frozen, and stored in a −70 °C freezer until batch processing.

Materials

The instruments used to measure the presence and severity of symptoms are described below:

Brief Pain Inventory–Short Form—The Brief Pain Inventory (BPI)–Short Form is a pain assessment tool that has well-established reliability and validity for adult patients with no cognitive impairment in studies of cancer and its symptoms (Caraceni, 2001). The BPI assesses the severity of pain, location of pain, pain medications, the amount of pain relief in the past 24 hours or the past week, and the impact of pain on daily functions. The estimated time for completion of the BPI is 5 minutes for the short form. In the present study, “worst pain” or the arithmetic mean of the four severity items was used as a measure of pain severity, and the arithmetic mean of the seven interference items was used as a measure of pain interference. In widespread testing, the Cronbach’s alpha reliability has ranged from 0.70 to 0.91 (Caraceni, 2001). The Cronbach’s alpha in this study was 0.89.

Hospital Anxiety and Depression Scale—The Hospital Anxiety and Depression Scale (HADS) is a brief, 14-item, self-report questionnaire developed to detect the presence and severity of both anxiety and depressive symptoms (Snaith, 2003). Because the HADS was developed for use in medically ill patients, it does not rely upon somatic symptoms of depression and anxiety such as pain and weight loss; instead, it focuses on cognitive symptoms of anxiety and depression. Each question is rated on a scaleof 0 – 3, with a possible score of 0 – 21 for depressionor anxiety and a possible total score of 0 – 42. The HADS has well-established reliability and validity for both depression and anxiety in women with breast cancer. In this study, Cronbach’s alpha for the depression subscale was 0.77 and 0.81 for the anxiety subscale.

Brief Fatigue Inventory—The Brief Fatigue Inventory (BFI) is a simple, 9-item scale that taps into a single dimension of fatigue severity and the interference fatigue creates in daily life (Mendoza et al., 1999). The BFI is a clinically validated tool used to assess cancer-related fatigue and its impact on daily functioning. The BFI uses simple numeric rating scales from 0 – 10 that are easily understood. On the BFI, severe fatigue can be defined as a score of 7 or higher. The BFI has demonstrated excellent reliability in clinical trials, with Cronbach’s alpha ranging from 0.82 to 0.97 (Mendoza et al., 1999). The Cronbach’s alpha for the BFI in this study was 0.92.

General Sleep Disturbance Scale—The General Sleep Disturbance Scale (GSDS) is a 21-item tool (Lee et al., 2004). In the present study, participants rated the frequency of sleep

problems over the past week on a 0 – 7 scale (0 = Never; 7 = Every day). The GSDS has well-established reliability and validity and has demonstrated robust psychometric properties, particularly in women (Miaskowski et al., 2006). In the current study, Cronbach's alpha was 0.80.

Measurement of Biological Factors—Plasma concentrations of cytokines were measured with the Bio-Plex Human 17-Plex (Bio-Rad, Hercules, CA). This standardized kit includes coupled beads, detection antibodies, and standards for the detection of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, G-CSF, granulocyte-macrophage colony-stimulating factor, interferon-gamma (IFN-γ), monocyte chemoattractant protein-1, macrophage inflammatory protein-1β, and TNF-α. After incubation, contents of each microplate well were drawn into the Bio-Plex array reader, and precision fluidics align the beads in a single file through a flow cell, where two lasers excite the beads individually. High-speed digital signal processors and Bio-Plex Manager software (Bio-Rad; Hercules, CA) record the fluorescent signals simultaneously for each bead. Levels of CRP were determined using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) (ALPCO Diagnostics, Salem, NH). Sensitivity of all measurements = 10 pg/mL.

Power analysis

This exploratory study sought to examine the relationships among pro-and anti-inflammatory biomarkers and the presence of perceived pain and other symptoms. One approach to assessing the importance of correlations in the midst of multiplicity is to use the *p*-value as a "cutoff value." In these cases, the *p*-value should be interpreted as defining a point at which a set cutoff value (such as 0.05) marks a correlation as "important." Thus, a traditional power assessment would provide an indication of the size of the correlation that could be declared important. For a sample size of 32, a 0.05 two-sided Fisher's *z* test of the null hypothesis with the correlation coefficient $\rho = 0$ will have an 80% power to detect a correlation as small as 0.45. Since correlations of 0.45 are of interest in this initial exploratory study, it was estimated that a sample size of 32 participants would provide sufficient power.

Statistical analysis

Descriptive statistics and correlations of pain and pain interference with symptom and biological factors were computed overall and by type of surgery (biopsy, lumpectomy, or mastectomy). Due to non-normality, Spearman rank rather than Pearson product moment correlations were calculated. Further, because a reasonably large number of individuals experienced no pain (37.5%) or pain interference (48.4%), analyses were also conducted to determine any significant differences between symptom and biological factors by pain and pain interference status. The samples were stratified into pain groups: those experiencing no pain vs. some pain. Separately, they were stratified by pain interference groups: those experiencing no pain interference vs some pain interference. Significant differences in symptom and biological factors were examined between groupings. For non-normally distributed variables, the non-parameteric Wilcoxon rank sum test was used to test for significant differences between those with and without pain and separately for those with and without pain interference. Otherwise independent t-tests were conducted with post-hoc tests applied as necessary to correct for multiple comparisons.

Differences in study variables by type of surgery (biopsy, lumpectomy or mastectomy) were also examined using either non-parametric Kruskal Wallis test or analysis of variance (ANOVA) for normally distributed variables. Effects on study variables were further examined in general linear models by pain groupings (either by those experiencing pain or no pain or by those experiencing pain interference or no pain interference) using type of

surgery as a covariate. Least square means were reported for significant differences in pain or pain interference groupings. Finally, partial Spearman correlations between study variables and continuous measures of pain and pain interference were examined using type of surgery as a covariate. All analyses were conducted in SASv9.2 and assumed an alpha=0.05 level of significance.

Results

Table 1 gives the sample characteristics. This sample of 32 women had a mean age of 47.7 years (*SD* 7.7, Range 27–63), was mainly Caucasian (*n*=20, 62.5%), and was slightly more post-menopausal (*n*=17, 53%) than pre-menopausal (*n*=15, 46.9%). None of the women met criteria for perimenopausal status. The majority of women underwent mastectomy (*n*=21, 65.6%) as opposed to lumpectomy (*n*=7, 21.9%) or breast biopsy (*n*=4, 12.5%).

Overall Spearman correlations revealed significant positive relationships among pain, pain interference, and other symptoms. There were significant positive associations between pain and depression (rs=0.61, $p<.01$) and sleep disturbances (rs=0.50, $p<.01$). Pain interference was significantly and positively related to all the symptoms: anxiety (rs=0.43, $p<.02$), depression (rs =0.71, $p<.01$), fatigue (rs =0.53, $p<.01$), and sleep disturbance (rs =0.68, $p<.01$). Only IL-13 (rs =0.40, $p=.02$) and CRP (rs =0.55, $p<.01$) were significantly and positively correlated with pain, and IL-7 (rs =0.40, $p<.02$) and CRP (rs =0.46, $p<.01$) were significantly and positively correlated with pain interference.

Means, standard deviations and medians for age, each symptom, and biological factors are provided in Table 2. After correcting for multiple comparisons, women experiencing pain had significantly higher levels of IL-7 ($p<.02$), IL-13 ($p<.02$), CRP ($p<.01$), more pain interference ($p<.01$), depression ($p<.01$), and sleep disturbance ($p<.01$). Similar differences were found when examining pain interference groupings. Women experiencing pain interference had significantly higher levels of IL-7 ($p=.01$), IL-13 ($p=.04$), and CRP ($p=.02$), and more pain ($p<.01$), anxiety ($p=.02$), depression ($p<.01$), fatigue ($p=.01$), and sleep disturbance ($p<.01$).

Analyses including type of surgery

Table 3 lists descriptive statistics for study variables by type of initial BCA surgery (breast biopsy, lumpectomy, or mastectomy). In general, those women who received breast biopsy reported worse symptoms, and women who received lumpectomy reported fewer symptoms than those who received mastectomy. There were significant differences in symptoms of pain, pain interference, and depression between these groups (Table 3). Further, women who underwent breast biopsy had higher levels of tumor necrosis factor (TNF)-α (462.38 + 52.15 pg/mL) than those who received lumpectomy (142.57 ± 40.65 pg/mL) or mastectomy (183.14 ± 59.4 pg/mL; $p<.02$).

Partial Spearman correlations were computed for pain and pain interference. These correlations demonstrate relationships of symptoms and biological factors to pain and pain interference after accounting for type of surgery. There was a significant positive partial correlation of pain with pain interference (rs =0.70, $p<.01$), symptoms of depression (rs =0.51, $p<.01$), and sleep disturbance (rs =0.44, $p=.01$). Similarly, there were significant positive partial correlations of pain interference with pain (rs =0.70, $p<.01$), symptoms of depression (rs =0.63, $p<.01$), fatigue (rs =0.43, $p=.02$), and sleep disturbance (rs =0.66, $p<.01$). Only pain demonstrated significant positive partial correlations with IL-13 (rs =0.36, $p<.04$) and CRP (rs =0.46, $p<.01$) after adjustment for type of surgery. There were no significant positive partial correlations of pain interference with any of the biological factors measured.

Discussion

In this sample of women with early-stage BCA at one month following breast biopsy or tumor resection but prior to receiving chemotherapy, 62.5% reported the presence of pain, and 53.1% reported the presence of pain interference. The presence of pain was positively and significantly associated with symptoms of depression and sleep disturbance while pain interference was significantly and positively related to all the symptoms: anxiety, depression, fatigue, and sleep disturbance. These findings suggest that when pain interferes with functioning in women with BCA, a greater number of co-occurring symptoms are likely to be present. Women experiencing pain or pain interference were not only more likely to report co-occurring symptoms, they had more severe symptoms.

These findings have important implications for both practice and research. The high number of women who reported perceived pain and/or pain interference informs clinicians that routine assessment and evaluation of pain, pain severity, and pain interference should be performed, even in the early course of BCA treatment. The findings also suggest that women who report perceived pain/pain interference should be assessed for other co-occurring symptoms as they are more likely to be present, and more severe, than women who do not report pain.

To our knowledge, this is the first study to report an association among perceived pain, pain interference, and increased levels of CRP, IL-13, and IL-7 among women undergoing early management of BCA. While the cross-sectional nature of this study makes it impossible to infer any causal relationships, there is evidence that these biological factors are involved in other painful disorders. For instance, CRP, IL-7 and IL-13 have been implicated in modulating pain sensitivity among patients with rheumatoid arthritis (Horwood, 2008; Kojima et al., 2009), as well as in experimental pain (Angst et al., 2007). Whether increased levels of these biological factors have any direct effect in modulating pain pathways remains unclear although similar patterns of immune response have been demonstrated in animal models of neuropathic pain (Lee, Lee, Son, Hwang, & Cho, 2004; Rittner & Brack, 2007; Zhang, 2007). Further studies are needed to confirm these findings and identify the signaling pathways and functional effects of elevated CRP, IL-7, and IL-13 in women with early-stage BCA. Future research focused on genetic regulation of immune reactivity could provide a more comprehensive view of the relationships between cytokines and symptom manifestation, and indeed, this work is already moving forward in BCA survivors (Collado-Hidalgo, Bower, Ganz, Irwin, & Cole, 2008).

Analyses among the different types of BCA surgery revealed that women who underwent a breast biopsy had more severe symptoms compared to women who received breast tumor resection (lumpectomy or mastectomy). In contrast, women who underwent lumpectomy had significantly less pain, pain interference, depression, fatigue, and sleep disturbance than the breast biopsy or mastectomy groups. These findings suggest that perceived pain and other adverse symptoms are not related to the extent of BCA surgery, which is consistent with previous findings (Caffo et al., 2003; Montazeri et al., 2008). Pre-surgical distress and expectancies of pain and fatigue have been found to predict post-surgical pain and fatigue in women with BCA (Schnur et al., 2007). While the small sample sizes of each surgical subgroup likely affected the ability to detect significant differences among other cytokine levels, these preliminary results provide some support of altered pro- and anti-inflammatory cytokines levels at one month post-surgery. Future research to examine changes in cytokine levels from pre- to post-operative status, along with measurement of psychological distress and symptom expectancies would be informative in clarifying the role of these biological factors in the symptom experience of women with early-stage BCA during the initial course of treatment.

Limitations

Several limitations of this secondary analysis should be discussed, most notably the small sample size and cross-sectional descriptive design that make it impossible to infer any cause-effect relationship between perceived pain and the biological factors measured. In addition, although participants were questioned about recent symptoms of illness or exposure to illness, and other cofactors (ie. menopausal status) that can affect cytokine levels, there may have been additional conditions or events that were not controlled or accounted for during data collection or analysis, such as psychological distress or symptom expectancies. Finally, because of the limited publications on multiple cytokine levels at one month post-BCA surgery there were no data from which comparisons could be made. Although altered levels of cytokines have been associated with adverse symptoms in patients with other types of cancer (Reyes-Gibby et al., 2008) the effects remain unclear and may differ according to individual characteristics, such as genetic factors, cancer type, and treatment modalities (Seruga, Zhang, Bernstein, & Tannock, 2008).

Conclusions

In this secondary analysis, a high percentage of women with early-stage BCA reported perceived pain and/or pain interference at one month post-surgery but before induction of chemotherapy. Women who reported perceived pain and/or pain interference had greater severity of multiple co-occurring symptoms in comparison to women without pain. The findings of this secondary analysis extend previous research by demonstrating alterations in pro- and anti-inflammatory cytokine levels, regardless of the type of surgery (breast biopsy, lumpectomy, mastectomy). This is also the first study to report a positive association among perceived pain, CRP and IL-13 at one month post-surgery in women with early-stage BCA. More research is needed to confirm these findings and determine the functional effects of elevated CRP and IL-13 on pain modulation. The study findings support the need for assessment of perceive pain and pain interference during the initial course of early-stage BCA treatment and suggest that women who do experience perceived pain are more likely to have more severe depression, fatigue, and sleep disturbance than women without pain.

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Table 1

Sample Characteristics

	N	Percent
Menopause		
Pre-menopause	15	46.88%
Post-menopause	17	53.13%
Race		
African American	9	28.13%
Caucasian	20	62.50%
Other	3	9.38%
Surgical type		
Mastectomy	21	65.6%
Lumpectomy	7	21.9%
Breast biopsy	4	12.5%
Perceived Pain		
No pain (0)	12	37.5%
Mild pain (1–2)	3	9.4%
Moderate-Severe pain (3–10)	17	53.1%
Pain Interference		
No	15	46.9%
Yes	17	53.1%

Table 2

Biological Factors and Symptom Measures Overall and by Perceived Pain

	Overall (n=32)		Perceived Pain grouping				Pain interference grouping			
			Without perceived pain (n=12)		With perceived pain (n=20)		Without pain interference (n=15)		With pain interference (n=17)	
	Mean (std dev)	Median	Mean (std dev)	Median	Mean (std dev)	Median	Mean (std dev)	Median	Mean (std dev)	Median
Age	47.66 (7.68)	49.50	45.58 (7.54)	46.00	48.90 (7.68)	50.00	46.60 (7.94)	47.00	48.44 (7.79)	50.00
Symptoms (range)										
Anxiety (0–12)	6.25 (3.93)	6.0	6.00 (4.94)	4.5	6.40 (3.32)	6.5	5.20 (4.25)	3.0	7.63 (3.05)*	7.5
Depression (0–10)	3.26 (3.12)	2.0	1.67 (2.74)	0.0	4.26 (2.98)*	3. 0	1.33 (1.80)	1.0	5.33 (2.94)*	6.0
Fatigue (0–9)	6.8 (1.46)	6.0	5.7 (1.84)	0.0	7.35 (1.97)	6.9	5.14 (1.26)	5.0	8.12 (2.55)*	8.5
Sleep disturbance (0–65)	44.81 (18.71)	44.0	36.58 (12.46)	32.5	50.0 (20.37)*	45.0	33.21 (12.56)	32.5	54.19 (18.28)*	56.0
Pain severity (0–6)	1.72 (1.40)	3.0	0.0	0.0	2.9 (1.65)*	3.0	0.55 (1.86)	0.0	3.29 (1.65)*	3.0
Pain interference (0–5)	1.34 (2.10)	0.14	0.0	0.0	2.17 (2.34)*	1.14	0.0	0.0	2.03 (1.09)*	1.48
Biological Factors										
IL1β (pg/mL)	188.08 (369.18)	65.00	106.04 (80.31)	77.25	237.30 (460.26)	65.00	96.20 (74.29)	64.50	263.34 (509.93)	63.25
IL2 (pg/mL)	321.09 (500.31)	144.50	293.67 (323.11)	214.75	337.55 (589.24)	113.50	267.37 (294.37)	208.50	346.03 (649.49)	99.00
IL4 (pg/mL)	490.39 (113.60)	503.25	456.96 (79.05)	462.00	510.45 (127.70)	518.75	476.00 (80.35)	481.50	502.59 (142.30)	515.00
IL5 (pg/mL)	36.78 (37.85)	26.50	46.88 (59.84)	24.50	30.73 (12.70)	28.00	42.47 (53.90)	23.00	31.81 (13.72)	28.00
IL6 (pg/mL)	289.94 (505.34)	134.00	188.00 (163.41)	134.00	351.10 (625.06)	133.00	177.37 (147.93)	130.00	389.66 (695.33)	129.50
IL7 (pg/mL)	123.80 (124.85)	90.75	85.71 (30.15)	87.25	146.65 (153.10)*	94.25	85.03 (27.30)	86.00	154.56 (168.74)*	93.25
IL8 (pg/mL)	647.31 (989.42)	232.50	758.46 (1244.11)	239.25	580.63 (829.84)	232.50	655.33 (1123.59)	230.00	642.91 (919.03)	232.00
IL10 (pg/mL)	231.98 (378.00)	122.00	148.83 (81.99)	115.25	281.88 (471.43)	122.00	142.57 (73.87)	115.50	306.25 (524.17)	122.50
IL12 (pg/mL)	188.08 (420.86)	88.25	288.21 (669.43)	86.75	128.00 (139.33)	89.25	247.07 (599.51)	84.50	137.59 (154.96)	90.00
IL13 (pg/mL)	56.16 (37.23)	47.50	44.54 (9.95)	40.50	63.13 (45.48)	49.00	45.13 (9.01)	43.50	65.28 (50.54)*	50.00
IL17 (pg/mL)	167.30 (27.14)	166.25	162.42 (35.35)	158.25	170.23 (21.32)	175.50	162.70 (32.11)	160.50	171.13 (22.80)	177.00
GMCSF (pg/mL)	335.25 (375.59)	225.50	251.71 (113.42)	219.00	385.38 (464.40)	225.50	241.17 (107.60)	223.00	400.75 (508.44)	224.75
IFNγ (pg/mL)	110.08 (250.70)	38.00	48.08 (26.79)	37.50	147.28 (313.44)	38.00	45.47 (24.40)	37.00	170.56 (348.22)	38.50
TNFα (pg/mL)	209.17 (194.20)	177.75	164.21 (61.04)	150.00	236.15 (239.44)	183.00	166.80 (55.05)	163.00	255.66 (265.01)	183.75

	Overall (n=32)		Perceived Pain grouping				Pain interference grouping			
			Without perceived pain (n=12)		With perceived pain (n=20)		Without pain interference (n=15)		With pain interference (n=17)	
	Mean (std dev)	Median	Mean (std dev)	Median	Mean (std dev)	Median	Mean (std dev)	Median	Mean (std dev)	Median
CRP (mg/L)	4728.57 (4849.53)	2219.73	2841.29 (4461.45)	1046.50	5860.94 (4821.65)*	3820.5	3421.44 (4838.23)	1391.63	6130.24 (4735.14)*	5123.88

GM-CSF=granulocyte-macrophage colony-stimulating factor, IFN-γ = interferon gamma, TNF-α = tumor necrosis factor alpha Anxiety subscale range from 0–21; Depression subscale range from 0–21; Fatigue scale range from 0–10; Sleep disturbance scale range from 0–147; Pain severity scale range from 0–10; Pain interference scale range from 0–10.

* significant differences for perceived pain groupings: IL-7 p< 0.02, IL-13 p<0.02, CRP p<0.01; depression p<0.01, sleep disturbances p<0.01, pain interference p<0.01.

* significant differences for pain interference groupings: IL-7 p<0.02, IL-13 p<0.04, CRP p<0.03, anxiety p<0.03, depression p< 0.001, fatigue p<0.02, sleep disturbances p<0.001, pain p<0.0003.

Table 3

Biological Factors and Symptom Measurements by Treatment Type

	Lumpectomy			Mastectomy			Breast biopsy			P-values	
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	All 3 treatments	Lump vs mastectomy
Age (rounded)	43.6	8.7	47.0	48.7	7.5	50.0	49.5	5.9	51.5	0.29	0.15
Symptoms											
Anxiety	4.0	2.9	3.0	6.7	3.9	7.0	8.0	4.8	8.0	0.19	0.1
Depression*	1.0	1.8	0.0	3.4	2.9	2.50	6.8	3.0	7.0	0.01*	0.01*
Fatigue	4.3	2.7	0.0	6.8	1.9	3.50	8.7	1.7	8.5	0.10	0.06
Sleep	38.1	10.6	36.0	45.6	21.1	44.5	52.8	16.3	49.0	0.45	0.38
Perceived pain*	0.3	0.8	0.0	2.0	2.2	3.0	3.0	1.3	2.5	0.07	0.03*
Pain interference*	0.0	0.1	0.0	1.6	2.3	0.3	2.6	2.3	2.4	0.04*	0.01*
Biological Factors											
IL1β (pg/mL)	104.6	59.8	95.5	164.3	313.2	59.0	459.1	793.3	67.8	0.51	0.18
IL2 (pg/mL)	353.8	386.1	281.0	301.3	545.4	119.0	367.9	545.0	113.8	0.68	0.21
IL4 (pg/mL)	455.9	80.4	470.0	484.6	116.9	511.0	581.0	124.0	569.8	0.20	0.55
IL5 (pg/mL)	57.8	76.4	32.0	29.4	12.0	27.0	38.9	27.4	25.5	0.86	0.30
IL6 (pg/mL)	212.9	143.9	194.0	282.1	588.8	111.0	466.3	479.8	294.5	0.19	0.16
IL7 (pg/mL)	99.6	36.0	88.5	106.5	77.5	90.0	257.1	302.1	112.5	0.06*	0.82
IL8 (pg/mL)	224.7	64.0	191.0	718.1	1052.7	230.0	1015.4	1444.8	311.5	0.13	0.12
IL10 (pg/mL)	155.4	84.0	122.0	234.1	441.8	115.5	354.8	357.0	211.5	0.32	0.32
IL12 (pg/mL)	127.5	88.2	90.0	198.4	506.6	84.5	240.1	301.1	97.5	0.51	0.44
IL13 (pg/mL)	48.9	15.6	41.0	51.0	17.0	47.0	95.8	97.5	49.0	0.54	0.26
IL17 (pg/mL)	170.4	37.3	160.5	166.7	24.6	175.0	164.9	27.5	155.0	0.94	0.44
GMCSF (pg/mL)	263.1	88.0	241.0	308.8	332.0	197.0	600.1	772.6	236.5	0.62	0.23
IFNγ (pg/mL)	40.8	13.5	36.5	99.5	226.3	38.0	287.0	504.0	37.0	0.50	0.13
TNFα (pg/mL)	142.6	40.7	136.0	183.1	59.4	178.0	462.4	52.2	221.5	0.07*	0.07*
CRP (mg/L)	1798.6	2064.2	1214.4	5026.3	4962.9	2224.3	8292.8	5718.7	8619.2	0.08	0.06

GM-CSF=granulocyte-macrophage colony-stimulating factor; IFN-γ = interferon gamma; TNF-α = tumor necrosis factor alpha