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Social support predicts inflammation, pain, and depressive symptoms: Longitudinal relationships among breast cancer survivors

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Abstract
Objective: Pain and depressive symptoms are commonly experienced by cancer survivors. Lower social support is linked to a variety of negative mental and physical health outcomes among survivors. Immune dysregulation may be one mechanism linking low social support to the development of pain and depressive symptoms over time. Accordingly, the goal of the present study was to examine the relationships among survivors' social support, pain, depressive symptoms, and inflammation.
Methods: Breast cancer survivors (N = 164, stages 0—IIIA) completed two study visits, one before any cancer treatment and the other 6 months after the completion of surgery, radiation, or chemotherapy, whichever came last. Women completed self-report questionnaires assessing social support, pain, and depressive symptoms, and provided a blood sample at both visits.

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Results: Survivors with lower social support prior to treatment experienced higher levels of pain and depressive symptoms over time than their more socially supported counterparts. Furthermore, women with lower pretreatment social support had higher levels of IL-6 over time, and these elevations in IL-6 predicted marginally larger increases in depressive symptoms.
Conclusions: The results of this study suggest that social support at the time of diagnosis predicts the post-treatment development of pain, depressive symptoms, and inflammation. Consequently, early interventions targeting survivors' social networks could improve quality of life during survivorship.
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Although cancer survival rates have increased in recent years, survivors often face additional physical and mental health problems long after treatment has ended (Burgess et al., 2005; Gartner et al., 2009). For example, the prevalence of chronic pain among breast cancer survivors is significantly higher than among adults without a history of cancer (Reyes-Gibby et al., 2006; Peuckmann et al., 2009). In addition, nearly 30% of breast cancer survivors experience chronic pain five years after treatment (Sheridan et al., 2012). A subset of cancer survivors also experience depression and depressive symptoms during longer-term survivorship (van't Spijker et al., 1997; Reyes-Gibby et al., 2006); around 12% of cancer survivors experience major depression and 20—30% have elevated levels of depressive symptoms (Bower, 2008; Mitchell et al., 2013). Pain and depression often accompany serious illness and place people at risk for poor health, reduced quality of life, and premature mortality (Becker et al., 1997; Kroenke et al., 2010; Giese-Davis et al., 2011; Reyes-Gibby et al., 2012). Accordingly, it is important to understand the factors that promote pain and depressive symptoms among cancer survivors.

Low social support has been linked to a variety of negative mental and physical health outcomes among breast cancer survivors and other medical populations (Koopman et al., 1998; Kroenke et al., 2006). For example, survivors with lower social support experienced higher concurrent levels of depressive symptoms than their more socially supported counterparts (Gagliardi et al., 2009; Nausheen et al., 2009). Among breast and ovarian cancer survivors, lower social support at cancer diagnosis predicted the development of depression during the subsequent five years (Hipkins et al., 2004; Burgess et al., 2005). Head and neck cancer patients with lower social support prior to treatment reported greater depressive symptoms six months after treatment ended (de Leeuw et al., 2000). Rheumatoid arthritis patients with lower social support at diagnosis experienced more pain three and five years later than patients with higher social support (Evers et al., 2003). Taken together, previous research suggests cancer survivors with lower social support may be at greater risk for depression and pain than those with higher social support.

1. Understanding potential mechanisms

Immune dysregulation may be one mechanism linking low social support to the development of pain and depression over time (Uchino et al., 2012). Indeed, depressive symptoms, pain, and low social support are all related to heightened concurrent inflammation (Maes et al., 1997; Costanzo et al., 2005; Marsland et al., 2007). For example, lower social support was associated with higher inflammation among ovarian cancer patients, middle aged adults, and older adults (Lutgendorf et al., 2000; Loucks et al., 2006; McDade et al., 2006).

People with major depression often have elevated levels of proinflammatory cytokines, such as interleukin-6 (IL-6; Raison et al., 2006). More depressed breast cancer patients had higher IL-6 than their less depressed counterparts (Soygur et al., 2007). Furthermore, inflammation can produce or increase "sickness behaviors," such as negative mood, fatigue, anhedonia, lethargy, pain sensitivity, and loss of appetite (Dantzer et al., 2008).

Inflammation also enhances pain responses (Watkins and Maier, 2000). IL-6 affects the neural encoding of painful stimuli, and people with higher IL-6 levels may experience more pain in response to injury than people with lower IL-6 levels (Watkins and Maier, 2002; de Jongh et al., 2003). Indeed, higher levels of IL-6 were concurrently associated with greater pain severity in individuals recovering from surgery, as well as people suffering from rheumatoid arthritis (Geiss et al., 1997; Mukai et al., 2000).

2. Current study

Pain and depressive symptoms, two common and health-relevant symptoms among cancer survivors, are linked to inflammation. Social support may be a risk factor for these symptoms. Accordingly, we measured breast cancer survivors' social support, pain, depressive symptoms, and inflammation before treatment began and 6 months after primary treatment completion. We hypothesized that survivors with lower social support prior to treatment would experience higher levels of pain and depressive symptoms over time compared with their more socially supported counterparts. We also explored inflammation as a potential pathway through which social support might affect changes in pain and depressive symptoms. Consequently, we predicted that lower social support prior to treatment would be associated with higher inflammation over time. In turn, survivors with elevated pretreatment inflammation would experience larger increases in pain and depressive symptoms than survivors with lower inflammation. We also investigated whether the links among social support, pain, depressive symptoms, and IL-6 were uni-directional or cyclical, a first step in establishing a causal pathway.

3. Methods

3.1. Setting and participants

Women (N = 164) were recruited from local breast cancer and mammography clinics an average of 3 weeks after their breast cancer diagnosis as part of an ongoing prospective study of fatigue among cancer survivors. Individuals were ineligible if they had HIV/AIDS, any prior history of cancer except basal or squamous cell skin carcinomas, or significant visual, auditory, or cognitive impairments. The women in our sample had stage 0-IIIA breast cancer, were primarily Caucasian (81%), and their average age was 56.13 years (SD = 11.47, range 30—88). Additional demographic characteristics are included in Table 1. The study was approved by the Ohio State University Institutional Review Board, and all participants provided written informed consent before participating.

3.2. Design overview

Participants' first visit (T1) occurred prior to any cancer treatment. The second visit (T2) occurred 6 months after the completion of surgery, radiation, or chemotherapy, whichever came last. Participants completed self-report questionnaires and provided a blood sample during both visits.

3.3. Outcomes and other measures

3.3.1. Questionnaires

The ENRICHD Social Support Instrument (ESSI), a 6-item questionnaire, measures the extent to which people feel supported in their interpersonal relationships (Mitchell et al., 2003). The ESSI includes items such as ''Can you count on anyone to provide you with emotional support (talking over problems or helping you make a difficult decision),'' and ''Is there someone available to you who shows you love and affection?'' The available responses range from ''none of the time'' to ''all of the time.'' The ESSI has good validity and excellent test-retest reliability (Vaglio et al., 2004). In the current sample, the ESSI had excellent internal consistency (T1 α = 89; T2 α = 87).

The Center for Epidemiological Studies Depression (CES-D) Scale is a widely utilized measure of depressive symptoms (Radloff, 1977). The CES-D has good test-retest reliability, as well as good construct and discriminative validity (Basco et al., 1997). The CES-D had excellent internal consistency in the current sample (T1 α = 89; T2 α = 91).

The pain subscale of the RAND-36 1.0 has good psychometric properties and has been extensively utilized within medical populations, including cancer survivors (Hays et al., 1993; VanderZee et al., 1996). The pain subscale consists of two items about pain experienced during the last week. Higher scores reflect less pain; we reverse coded the scale so that higher scores reflected more pain in order to make the

Table 1 Study sample characteristics.

Characteristic	Category	Number (%)
Race	White	132 (80.5)
	Black	21 (12.8)
	Other	11 (6.7)
Education	High school or below	46 (28.0)
	Some college or college graduate	75 (45.7)
	Graduate or professional training	43 (26.2)
Marital status	Single	17 (10.4)
	Married/domestic partner	114 (69.5)
	Separated/divorced/widowed	33 (20.1)
Stage	0	32 (19.5)
	I	75 (45.7)
	II	40 (24.4)
	III	17 (10.4)
Method of diagnosis	Biopsy (excisional, stereotactic core, ultrasound-guided core, unguided core, unspecified)	187 (114.0)
	Fine needle aspiration	2 (1.2)
	MRI	9 (5.5)
	Ultrasound	34 (20.7)
	Mammogram	28 (17.1)
Cancer treatment	Surgery only	54 (32.9)
	Surgery and radiation	45 (27.4)
	Surgery and chemotherapy	25 (15.2)
	Surgery, chemotherapy, and radiation	39 (23.8)
	Unknown	1 (0.6)

Note: N = 164. The reported data reflect information obtained at the first post-treatment visit.

direction of the effects consistent with the depressive symptom measure. The pain subscale demonstrated good to excellent internal consistency in the present sample (T1 α = 83; T2 α = 90).

The Charlson index is a widely utilized comorbidity measure that was originally validated using breast cancer patients (Charlson et al., 1987). The index uses participants' self-reported health information to assign weights to 19 medical conditions based on their ability to influence 1-year mortality. The Charlson has good concurrent validity, predictive validity, test-retest reliability, and inter-rater reliability (de Groot et al., 2003). The Charlson was included to account for potential associations among comorbidities and pain, depressive symptoms, and IL-6.

3.3.2. Inflammation assay

Serum levels of IL-6 were measured using an electrochemiluminescence method with Meso Scale Discovery kits, and read using the Meso Scale Discovery Sector Imager 2400 (see Richter, 2004 for details regarding this assay technique). Each participant's stored samples were assayed for both IL-6 samples simultaneously, thus allowing the same controls across both time points for each person. Sensitivity for the IL-6 assays was 0.3 pg/ml. The intra-assay coefficient of variation (CV) was 1.43% and the inter-assay CV was 4.42%.

3.4. Statistical analyses — primary

3.4.1. Social support predicting pain and depressive symptoms

We performed linear regressions using SPSS 19.0 (IBM, New York) to test the hypothesis that lower pretreatment social support is associated with higher levels of pain and depressive symptoms over time. To test changes over time, we investigated whether T1 social support predicted T2 pain and depressive symptoms, controlling for T1 levels of each outcome. Controlling for T1 created a score reflecting residual change in the outcome from T1 to T2.

3.4.2. Testing a potential mechanism

We conducted a series of linear regressions to test inflammation as a potential mechanism linking social support to the development of pain and depressive symptoms. Specifically, we investigated whether (a) lower social support prior to treatment was associated with increased IL-6 over time and (b) elevated IL-6 predicted increased pain and depressive symptoms. To test changes over time we used the same strategy described above; we predicted each T2 outcome (e.g., IL-6) controlling for T1 levels of the outcome (e.g., IL-6). This strategy provided a strong test of mechanistic pathways because it examined changes in both the mediator and the outcome over time.

3.4.3. Covariates

We selected potential confounds based on their theoretical and empirical relationships to social support, IL-6, depressive symptoms, and pain. All primary analyses adjusted for the following covariates, assessed at T2: body mass index (BMI: kg/m^2), age, education level, comorbidities, cancer stage, and time since treatment (Everson et al., 2002; Salgado et al., 2003; Bozcuk et al., 2004; Arnow et al., 2006; Bjerkeset et al., 2008). The pain analyses also adjusted for pain medication use. Cancer treatment type is largely dictated by the current National Comprehensive Cancer Network (NCCN) guidelines, providing reasonable treatment uniformity within each cancer stage.

3.5. Statistical analyses — ancillary

3.5.1. Additional health-related covariates

In ancillary analyses, we tested whether our effects held after controlling for additional demographic variables, health behaviors, and treatment type. Specifically, we added the following covariates to each model: relationship status (married/domestic partnership versus single), statin use, tamoxifen/aromatase inhibitor use, antidepressant use, and treatment type.

3.5.2. Testing for reverse causality

We also investigated whether the links among social support, pain, depressive symptoms, and IL-6 were uni-directional or cyclical. We tested whether IL-6 levels, depressive symptoms, and pain at T1 predicted change in social support over time. Similarly, we tested whether pain or depressive symptoms at T1 predicted change in IL-6 over time. All analyses used the same analytic process described above.

4. Results

All reported beta coefficients are unstandardized. IL-6 scores were $\log_{10}$ transformed prior to analyses because their distribution was positively skewed. Change in R^2 refers to the proportion of variance in the outcome accounted for by the key predictor. Means and standard deviations for the primary outcomes and covariates can be found in Table 2.

4.1. Primary analyses

4.1.1. Social support predicting pain and depressive symptoms

Survivors with lower social support at T1 experienced higher levels of pain ($b = -.76$, $t(134) = -2.07$, $p = 0.041$, R^2

Table 2 Means and standard deviations of the primary outcomes and covariates.

Characteristic	T1	T2
Social support	29.43 (4.59)	27.96 (5.19)
Pain	19.91 (21.96)	28.1 (26.07)
Depressive symptoms	16.48 (10.99)	11.73 (10.08)
IL-6 ($\log_{10}$)	0.09 (0.27)	0.20 (0.26)
Comorbidities	0.57 (0.96)	0.91 (1.61)
BMI	28.80 (7.32)	28.59 (7.25)
Age	56.13 (11.47)	57.23 (11.40)
Days since treatment	N/A	248.67 (136.59)

Note: $N = 164$. Higher numbers reflect more social support, depressive symptoms, and IL-6. The original pain index was reverse scored so that higher numbers reflect more pain, both in the table and in the analyses. The IL-6 data are log transformed, consistent with the analyses.

change = .02) and depressive symptoms ($b = -.47$, $t(137) = -2.97$, $p = 0.004$, R^2 change = .04) from T1 to T2 than their more socially supported counterparts.

4.1.2. Testing a potential mechanism

Consistent with expectations, women with lower social support at T1 had higher IL-6 levels over time than women who felt more socially supported, $b = -.009$, $t(87) = -2.12$, $p = 0.037$, R^2 change = .02. Contrary to expectations, higher IL-6 levels at T1 did not predict increased pain over time, $b = 4.07$, $t(89) = .51$, $p = 0.609$, R^2 change = .001. However, higher IL-6 levels at T1 marginally predicted increased depressive symptoms over time, $b = 5.28$, $t(98) = 1.72$, $p = 0.089$, R^2 change = .02.

4.2. Ancillary analyses

4.2.1. Additional health-related covariates

The pattern of results remained the same when we added relationships status, statin use, tamoxifin/aromatase inhibitor use, antidepressant use, and treatment type to our analytic models.

4.2.2. Testing for reverse causality

None of the analyses examining reverse causality were significant. Specifically, T1 pain ($p = 0.876$), depressive symptoms ($p = 0.405$), and IL-6 ($p = 0.665$) were unrelated to changes in social support over time. Furthermore, T1 pain ($p = 0.310$) and depressive symptoms ($p = 0.659$) did not predict changes in IL-6 over time.

5. Discussion

Breast cancer survivors with lower social support prior to treatment experienced higher levels of pain and depressive symptoms over time than their more socially connected counterparts. Furthermore, women with lower pretreatment social support had higher levels of IL-6 over time, and these elevations in IL-6 marginally predicted larger increases in depressive symptoms. Contrary to expectations, pretreatment IL-6 levels were unrelated to changes in pain over time, suggesting that other mechanisms played a role in this sample.

Importantly, the links among social support, IL-6, pain, and depressive symptoms held when accounting for a number of potential confounds, including BMI, age, education level, comorbidities, cancer stage, time since treatment, relationships status, statin use, tamoxifin/aromatase inhibitor use, and antidepressant use. Accordingly, social support predicted changes in IL-6, pain, and depressive symptoms independent of survivors' post-treatment BMI, demographics, health, and health behaviors. Depressive symptoms and pain did not predict changes in social support or IL-6 over time. IL-6 was also unrelated to changes in social support, suggesting that the change process is likely uni-directional rather than cyclical.

Previous research has linked low social support to worse overall health and increased distress among breast cancer patients and other medical populations (Ganz et al., 2003). For example, survivors with lower social support experienced more concurrent depressive symptoms than survivors with higher social support (Gagliardi et al., 2009; Nausheen et al., 2009). The current study extends prior work by suggesting that low social support enhances risk for the development of pain, depressive symptoms, and IL-6 over time. Furthermore, elevated IL-6 may be one physiological mechanism linking low social support to the development of depressive symptoms. Research has demonstrated that elevated inflammation induces "sickness behaviors," such as negative mood, fatigue, and anhedonia (Dantzer et al., 2008). Our finding linking IL-6 to changes in depressive symptoms over time, although mechanistically consistent with this framework, was only marginally significant. Given our study design, we were unable to conduct a standard mediation analysis. Therefore, future research will need to investigate IL-6's mechanistic role using standard mediation analysis techniques.

Pain and depressive symptoms affect a significant portion of breast cancer survivors (Bower, 2008; Gartner et al., 2009; Mitchell et al., 2013). Thus, primary care physicians, oncologists, nurses, and mental health practitioners may encounter cancer survivors experiencing these symptoms on a regular basis. The present study demonstrated that social support around the time of diagnosis predicts the post-treatment development of pain, depressive symptoms, and IL-6. Consequently, medical practitioners could benefit from assessing peoples' social support at the time of diagnosis. In addition, early interventions targeting survivors' social networks could improve quality of life during survivorship. Early interventions are particularly important because cancer diagnosis and treatment are often highly distressing (Hegel et al., 2006). Furthermore, intervening at the time of diagnosis may help stop the progression of a negative cascade whereby low social support promotes IL-6 which could enhance risk for depression. Given the health-relevance of depression and inflammation (Schulz et al., 2000; Hansson, 2005), social support interventions at the time of diagnosis may help improve survivors' longer-term health during survivorship.

The participants in the current study were fairly homogeneous in terms of their demographic characteristics, one limitation of this study. Future studies could benefit from investigating the relationships among social support, depressive symptoms, pain, and IL-6 using more diverse samples. Another interesting question is whether social support prior to treatment predicts IL-6, pain, and depressive symptoms years after treatment, during longer-term survivorship.

In conclusion, breast cancer survivors with lower social support prior to treatment experienced higher levels of pain and depressive symptoms over time than their more socially supported counterparts. IL-6 may be one potential pathway through which social support affected depressive symptoms; women with lower social support prior to treatment had higher levels of IL-6 over time, and these elevations in IL-6 marginally predicted larger increases in depressive symptoms. Consequently, early interventions targeting survivors' social networks could improve quality of life during survivorship.

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Conflicts of interest statement

All authors declare that there are no financial conflicts of interest.

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