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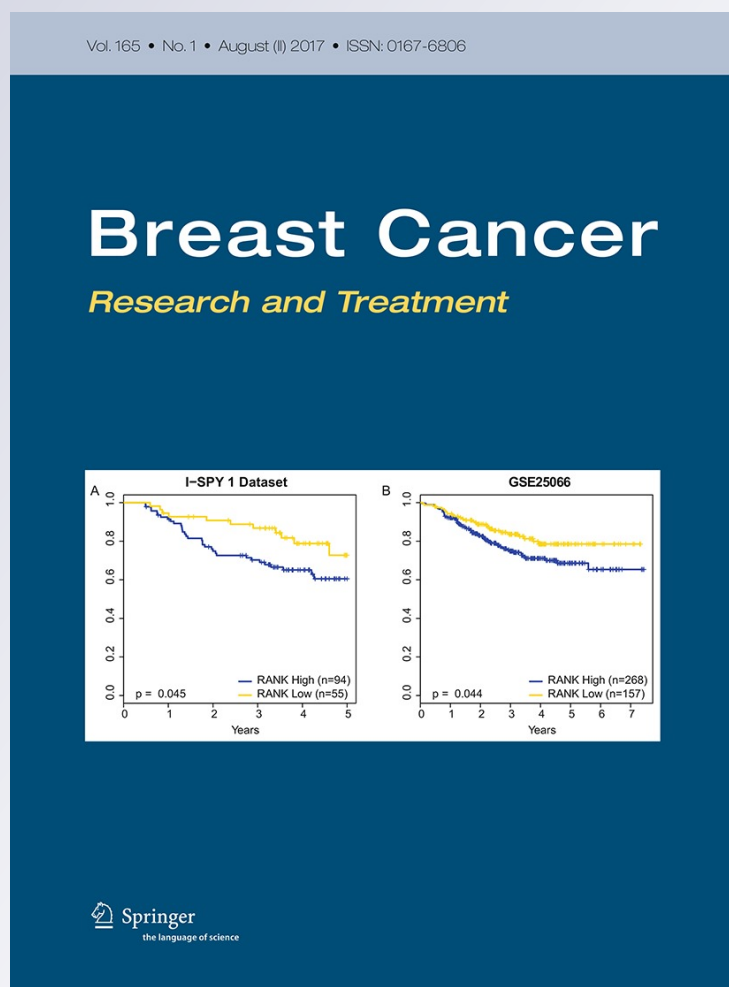
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Social well-being is associated with less pro-inflammatory and pro-metastatic leukocyte gene expression in women after surgery for breast cancer

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Abstract

Purpose Satisfaction with social resources, or “social well-being,” relates to better adaptation and longer survival after breast cancer diagnosis. Biobehavioral mechanisms linking social well-being (SWB) to mental and physical health may involve inflammatory signaling. We tested whether reports of greater SWB were associated with lower levels of pro-inflammatory and pro-metastatic leukocyte gene expression after surgery for non-metastatic breast cancer.

Methods Women ($N = 50$) diagnosed with non-metastatic (0–III) breast cancer were enrolled 2–8 weeks after surgery. SWB was assessed with the social/family well-being subscale of the FACT-B. Leukocyte gene expression for specific pro-inflammatory (cytokines, chemokines, and *COX-2*) and pro-metastatic genes (e.g., *MMP9*) was derived from microarray analysis.

Results Multiple regression analyses controlling for age, stage of disease, days since surgery, education, and body mass index (BMI) found higher levels of SWB related to

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less leukocyte pro-inflammatory and pro-metastatic gene expression ($p < 0.05$). Emotional well-being, physical well-being, and functional well-being did not relate to leukocyte gene expression ($p > 0.05$). Greater SWB remained significantly associated with less leukocyte pro-inflammatory and pro-metastatic gene expression after controlling for depressive symptoms.

Conclusions Results have implications for understanding mechanisms linking social resources to health-relevant biological processes in breast cancer patients undergoing primary treatment.

Clinical Trial Registration Number: NCT01422551

Keywords Breast cancer · Social well-being · Social support · Inflammation · Leukocyte gene expression

Introduction

Breast cancer is the second leading cause of cancer deaths among women [1]. Almost half of these women experience significant adversity during diagnosis and treatment [2]. Smaller social networks and perceptions of inadequate social resources may deleteriously affect both their psychological adaptation [3] and survival [4, 5]. Limited social networks [6], low social support [7], and low social well-being (SWB) [8] are all associated with increased mortality in breast cancer. Additional research is needed to uncover processes that explain negative health outcomes in breast cancer patients reporting deficits in social resources.

Social isolation is associated with alterations in sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis hormones that influence tumor growth and clinical outcomes [9]. One pathway through which these relationships may be mediated is inflammatory signaling by stromal cells such as leukocytes that may interact with cancer cells to promote angiogenesis [10], invasion, extravasation into the circulatory system, and metastasis [11]. Although production of glucocorticoids is often associated with anti-inflammatory effects, chronic social isolation and adversity and accompanying glucocorticoid elevation are associated with upregulated inflammation wherein leukocytes become desensitized to chronically elevated cortisol release, and transcription of genes coding inflammatory cytokines is no longer inhibited [12].

Hughes et al. [13] demonstrated that lower perceived support before treatment for non-metastatic breast cancer predicted more serum interleukin-6 (IL-6), a pro-inflammatory cytokine, at 6-month follow-up. Upregulated leukocyte conserved transcriptional response to adversity (CTRA), which includes upregulation of pro-inflammatory genes, is associated with greater loneliness in older adults

[14], and with low socioeconomic status (SES) in patients awaiting hematopoietic stem cell transplant [15]. High CTRA expression in turn relates to decreased leukemia-free survival [15]. This line of research suggests that chronic social adversity can impair a regulatory mechanism for inflammation, leading to increased levels of inflammation. It follows that a greater sense of SWB may be associated with better inflammatory control, though this has not been studied in the context of cancer generally or in breast cancer specifically.

The present study examined whether SWB related to less leukocyte gene expression for pro-inflammatory and pro-metastatic signaling in women who recently underwent surgery for non-metastatic breast cancer. We hypothesized that women reporting greater SWB would exhibit less expression of leukocyte genes for pro-inflammatory cytokines, chemokines and their receptors, and other pro-inflammatory and tumor-promoting factors. To explore potential pathways connecting SWB to leukocyte gene expression, we repeated the analyses controlling for depression, given prior links between depressive symptoms and inflammatory indicators [16]. Exploratory analyses assessed whether SWB mediated the relationship between depression and leukocyte gene expression. We also explored whether partnered versus non-partnered women would show different SWB by gene expression associations.

Materials and methods

Participants

Women were recruited from cancer treatment centers and surgical oncologist offices in South Florida to participate in a larger parent study testing the effects of stress management in breast cancer. Women were eligible if they were 2–8 weeks post-surgery for non-metastatic (0–III) breast cancer. Phone screens excluded women who reported a prior history of cancer (except minor skin cancers); had already received radiation treatment, immunotherapy, or chemotherapy; were diagnosed with stage IV cancer (metastatic disease); did not speak fluent English; had a severe psychiatric disorder (e.g., psychosis, major depressive disorder), or endorsed suicidality. Data from a subgroup of 78 women who had cryopreserved peripheral blood mononuclear cells (PBMCs) described previously [17] were used in the present analyses.

Procedures

Questionnaires that measured SWB and sociodemographic characteristics are detailed below. A blood sample was collected between 4:00 pm and 6:30 pm, to minimize the

impact of diurnal fluctuations. Vacutainer tubes containing sodium heparin as an anticoagulant (BD catalog # 367874) were used for blood collection. The study was approved by the Institutional Review Board at the University of Miami, and women were compensated \$50.

Measures

Demographics

Participants self-reported age, stage of disease, number of days since surgery, and education on a questionnaire at study entry. Body mass index (BMI) was calculated based on self-reported height and weight. Demographic, medical, and treatment-related information was validated through medical chart reviews.

Well-being

The Functional Assessment of Cancer Therapy-Breast (FACT-B) Version 4 assessed self-reported well-being over the prior 7 days [18]. The social/family well-being subscale measured SWB with items primarily assessing subjective feelings of being close to and generally supported by and satisfied with communication with family and friends. It consists of 7 items with 5 response choices ranging from 1 (not at all) to 5 (very much). Subscales were scored as described by Webster et al. [19]. It was found to be reliable and valid in women diagnosed with breast cancer [18], and the SWB subscale had adequate internal consistency ($\alpha = 0.79$) in this sample. The SWB subscale was associated with less inflammatory cell signaling in women diagnosed with ovarian cancer [20]. The emotional well-being, physical well-being, and functional well-being subscales were administered and were analyzed to assess specificity of the relationship between SWB and leukocyte gene expression. Internal consistency of the emotional well-being ($\alpha = 0.64$), physical well-being ($\alpha = 0.83$), and functional well-being ($\alpha = 0.85$) subscales were adequate.

Depressive symptoms

Interviewers administered the 17-item Hamilton Rating Scale for Depression (HRSD) [21] to assess depressive symptoms. This measure has previously been used in studies of women with breast cancer [22] and reliability was adequate in this sample ($\alpha = 0.80$).

Leukocyte gene expression

We examined leukocyte RNA expression of pro-inflammatory cytokine genes (*IL1A*, *IL1B*, *IL6*, *TNFSF10*,

TNFRSF21, and *PTGS2/COX-2*), genes for pro-inflammatory chemokines and their receptors (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), and genes for other tumor-promoting factors (*MMP9* and *LMNA*) in circulating peripheral blood mononuclear cells (PBMCs). Table 1 describes each gene's function. Genes were selected due to their prior association with psychosocial processes [17], and their central function in inflammation and putative involvement in promoting cancer metastasis [23].

To generate RNA expression units (log₂), RNA was extracted from PBMCs, quality assured for mass and integrity, and assayed by Illumina Human HT-12 v3 Expression BeadChips, with gene abundance estimates derived from low-level fluorescence intensity values, quantile normalized with Illumina Genome Studio software, and log₂-transformed for analysis, as previously described [24, 25]. Composite scores of gene expression for pro-inflammatory cytokines, pro-inflammatory chemokines and their receptors, and tumor-promoting factors were created by averaging the normalized log₂-transformed transcript abundance estimates for genes in each of these three categories based on their known function.

Data analytic approach

Data were analyzed using IBM SPSS Version 22.00. Descriptive statistics characterized participants' demographic, medical, and study variables. Outliers ≥ 3 standard deviations outside the mean were winsorized [26] and variables were then analyzed for normal distribution (skewness < 3.0 , kurtosis < 8.0) [27]. Independent sample *t* tests and χ^2 tests determined whether this subsample differed from the parent study's sample of 240 women on demographic and medical variables. Bivariate correlations were conducted to determine associations between SWB and theoretically related variables, specifically depression.

Primary analyses used multiple regression to test whether SWB was associated with pro-inflammatory and pro-metastatic leukocyte gene expression. Age, stage of disease, days since surgery, education, and BMI were included as covariates based on theoretical associations with inflammation [28]. Analyses were repeated controlling for depression. Secondary analyses used multiple regression to test whether other psychosocial variables, emotional well-being, physical well-being, functional well-being, and depression, might also be related to gene expression using the same covariates.

Exploratory analyses were conducted to determine whether SWB mediated the association between depression and gene expression. To test the generality of the SWB and gene expression associations, moderation analyses examined whether associations between SWB and gene

Table 1 Gene symbols defined by description and function

| Gene symbol | Gene description | Gene function [47, 48]. |
|-----------------------------|---|--|
| Pro-inflammatory cytokines | | |
| <i>IL1A</i> | Interleukin 1 alpha | Encodes cytokine IL-1 α , which is produced by white blood cells (leukocytes) in response to wounds and contributes to inflammation and programmed cell death (apoptosis) |
| <i>IL1B</i> | Interleukin 1 beta | Encodes cytokine IL-1 β , which is produced by leukocytes and contributes to inflammation and programmed cell death (apoptosis) |
| <i>IL6</i> | Interleukin 6 | Encodes cytokine IL-6, which is produced during inflammation and induces further inflammatory transcription |
| <i>TNFSF10</i> | Tumor necrosis factor (ligand) superfamily, member 10 | Encodes a cytokine that induces apoptosis in tumor cells |
| <i>TNFRSF21</i> | Tumor necrosis factor receptor superfamily, member 21 | Encodes a member of the TNF receptor superfamily that induces apoptosis and regulates immune functioning |
| <i>PTGS2/COX-2</i> | Prostaglandin-endoperoxide synthase 2 | Encodes an enzyme involved in synthesis of a prostaglandin (cyclooxygenase-2; COX-2), which acts as a hormone to stimulate inflammation and cell division |
| Pro-inflammatory chemokines | | |
| <i>CCL3</i> | Chemokine (C–C motif) ligand 3 | Encodes a chemokine that signals recruitment of immune cells to sites of inflammation |
| <i>CCL7</i> | Chemokine (C–C motif) ligand 7 | Encodes a chemokine that attracts macrophages during inflammation and metastasis |
| <i>CCL20</i> | Chemokine (C–C motif) ligand 20 | Encodes a chemokine that signals movement of white blood cells involved in inflammation |
| <i>CCL3L1</i> | Chemokine (C–C motif) ligand 3-like 1 | Encodes a pro-inflammatory chemokine that regulates immune functioning |
| <i>CCL4L2</i> | Chemokine (C–C motif) ligand 4-like 2 | Encodes a pro-inflammatory chemokine involved in immune regulation |
| <i>CXCR7</i> | C-X-C chemokine receptor type 7 | Encodes a pro-inflammatory chemokine receptor; regulates migration of tumor cells |
| Pro-metastatic factors | | |
| <i>MMP9</i> | Matrix Metalloproteinase 9 | Encodes proteins that facilitate the breakdown of the extracellular matrix in the context of tissue remodeling and metastasis |
| <i>LMNA</i> | Lamin A/C | Encodes proteins that provide structure near the inner nuclear membrane of a cell. Involved in tissue remodeling |

expression varied as a function of structural sources of social support (partner status). Step 1 consisted of covariates age, days since surgery, stage, education, and BMI. Step 2 consisted of SWB and partner status, and Step 3 contained the interaction of SWB and partner status. The Benjamini–Hochberg procedure [29] was applied to the results of each analysis to correct for multiple comparisons by controlling the false discovery rate to 0.10 [30].

Results

Sample characterization

Sample characteristics are displayed in Table 2. Participants were middle-aged ($M = 49.55$, $SD = 7.51$) with an average of 15.86 years of education ($SD = 2.58$). The majority self-identified as non-Hispanic White (69.2%), and the sample also included Hispanic (20.5%) and African American/Black women (9.0%). Most women were

married or partnered (67.9%). Approximately one-third of participants had children (30.8%), consistent with Florida state population norms at the time of data collection [31]. Average number of children was 2.11 ($SD = 0.85$).

The greatest percentage of women was diagnosed with stage I breast cancer, over half underwent a mastectomy (56.4%) and the remainder a lumpectomy (43.6%). On average, participants were approximately 5 weeks post-surgery at study entry. According to their body mass index (BMI) scores, women were classified as overweight on average ($M = 26.96$ kg/m^2 , $SD = 6.49$).

Average *IL1A*, *IL1B*, *IL6*, and *CCL20* gene expression appeared higher in our sample than in prior studies of breast cancer survivors who had completed treatment [32], which may be because women in the current sample recently had surgery. Levels of social, emotional, physical, and functional well-being were similar to the sample on which the FACT-B was validated [18], and to a contemporary sample of women with non-metastatic breast cancer [33]. Average HRSD score was 6.68 ($SD = 5.52$), which is

Table 2 Demographics, medical characteristics, and key study variables of the participants ($N = 78$)

| Variable | Mean (SD) | Range |
|-------------------------------------|---------------|--------------|
| Sociodemographics | | |
| Age after surgery (years) | 49.55 (7.51) | 32.00–69.00 |
| Years of education | 15.86 (2.58) | 8.00–23.00 |
| Employment | | |
| Employed full time | 64 (82.1%) | – |
| Not employed full time | 14 (17.9%) | – |
| Income (thousands of US dollars) | 76.19 (49.20) | 15.00–300.00 |
| Ethnic identification | | |
| Non-Hispanic white | 54 (69.2%) | – |
| Hispanic/Latino | 16 (20.5%) | – |
| African American/Black | 7 (9.0%) | – |
| Other | 1 (1.3%) | – |
| Marital status | | |
| Married/partnered | 53 (67.9%) | – |
| Separated | 2 (2.6%) | – |
| Divorced | 19 (24.4%) | – |
| Single | 4 (5.1%) | – |
| Children | | |
| Yes | 24 (30.8%) | – |
| No | 54 (69.2%) | – |
| Number of children | 2.11 (0.85) | 1.00–5.00 |
| Medical status | | |
| Cancer stage^a | | |
| Stage 0 | 10 (12.8%) | – |
| Stage I | 37 (47.4%) | – |
| Stage II | 24 (30.8%) | – |
| Stage III | 7 (9.0%) | – |
| Surgery | | |
| Lumpectomy | 34 (43.6%) | – |
| Mastectomy | 44 (56.4%) | – |
| Days since surgery | 38.58 (24.22) | 10.00–133.00 |
| Estrogen receptor status | | |
| Positive | 43 (55.1%) | – |
| Negative | 8 (10.3%) | – |
| Unknown | 27 (34.6%) | – |
| Progesterone receptor status | | |
| Positive | 28 (35.9%) | – |
| Negative | 11 (14.1%) | – |
| Unknown | 39 (50.0%) | – |
| HER2/neu status | | |
| Positive | 11 (14.1%) | – |
| Negative | 31 (39.7%) | – |
| Unknown | 36 (46.2%) | – |
| Medication use | | |
| Anti-depressant | 5 (6.4%) | – |
| Anti-anxiety | 13 (16.7%) | – |
| Sleep | 12 (15.4%) | – |
| Pain | 22 (28.2%) | – |

Table 2 continued

| Variable | Mean (SD) | Range |
|--------------------------------------|--------------|-------------|
| Body mass index (kg/m ²) | 26.96 (6.49) | 18.88–55.81 |
| Gene expression | | |
| Cytokine composite | 10.67 (1.21) | 8.73–13.23 |
| Chemokine composite | 10.87 (1.29) | 7.84–13.04 |
| Pro-metastatic composite | 9.58 (0.86) | 7.52–11.36 |
| <i>IL1A</i> | 9.39 (1.83) | 6.77–12.75 |
| <i>IL1B</i> | 13.05 (1.52) | 8.08–14.55 |
| <i>IL6</i> | 10.36 (2.03) | 7.26–14.95 |
| <i>TNFSF10</i> | 9.54 (1.15) | 6.87–13.17 |
| <i>TNFRSF21</i> | 10.25 (0.90) | 7.75–12.38 |
| <i>CCL3</i> | 12.83 (1.55) | 8.43–15.06 |
| <i>CCL7</i> | 10.22 (1.54) | 6.88–13.61 |
| <i>CCL20</i> | 10.58 (2.02) | 7.40–14.00 |
| <i>CCL3L1</i> | 12.11 (1.60) | 7.78–14.75 |
| <i>CCL4L2</i> | 11.35 (1.51) | 8.60–13.92 |
| <i>CXCR7</i> | 8.09 (0.78) | 7.09–10.61 |
| <i>PTGS2</i> | 11.45 (1.32) | 9.00–13.65 |
| <i>MMP9</i> | 9.20 (1.04) | 7.15–11.53 |
| <i>LMNA</i> | 9.96 (0.84) | 7.89–11.85 |
| Survey data | | |
| Social well-being | 22.56 (4.71) | 8.17–28.00 |
| Emotional well-being | 17.77 (4.12) | 4.00–24.00 |
| Physical well-being | 20.90 (5.21) | 3.00–28.00 |
| Functional well-being | 18.75 (5.73) | 2.00–28.00 |
| Hamilton depression score | 6.68 (5.52) | 0.00–23.00 |

SD standard deviation. Gene expression reported in RNA expression units (log₂)

^a TNM staging system

within the normal range for depressive symptoms. HRSD levels of depressive symptoms in this sample were higher than in several samples of healthy controls [34] and lower than in a sample of cancer patients diagnosed with major depressive disorder [35].

Preliminary analyses

Independent samples two-tailed *t* tests indicated that the subsample of women who provided blood samples for leukocyte gene expression data did not differ significantly from the parent sample on demographic variables and study variables including age, education, annual household income, number of children, days elapsed since breast cancer surgery, BMI, SWB scores, or HRSD scores (all $ps > 0.05$). The parent sample did not differ from the subsample on categorical variables such as employment status, race/ethnicity, marital status, having children, disease stage, surgery type, estrogen receptor status, progesterone receptor status, HER2/neu status, or use of

Table 3 Regression analyses relating leukocyte pro-inflammatory and pro-metastatic gene expression and social well-being in multivariable analyses in models (1–2) controlling for specified covariates

| Model | Independent variable | Dependent variable | β (SE) | <i>t</i> | <i>p</i> | <i>R</i> ² change |
|-------|----------------------|---|----------------|----------|----------|------------------------------|
| 1 | Social well-being | Cytokine composite* [†] | −0.328 (0.040) | −2.127 | 0.039 | 0.089 |
| 2 | Social well-being | Cytokine composite | −0.282 (0.040) | −1.825 | 0.075 | 0.063 |
| 1 | Social well-being | Chemokine composite* [†] | −0.311 (0.040) | −2.032 | 0.048 | 0.080 |
| 2 | Social well-being | Chemokine composite | −0.271 (0.040) | −1.755 | 0.087 | 0.058 |
| 1 | Social well-being | Pro-metastatic composite** [†] | −0.458 (0.026) | −3.081 | 0.004 | 0.173 |
| 2 | Social well-being | Pro-metastatic composite** [†] | −0.394 (0.025) | −2.735 | 0.009 | 0.124 |
| 1 | Social well-being | <i>IL1A</i> * [†] | −0.397 (0.059) | −2.624 | 0.012 | 0.130 |
| 2 | Social well-being | <i>IL1A</i> * | −0.350 (0.059) | −2.317 | 0.025 | 0.098 |
| 1 | Social well-being | <i>IL1B</i> | −0.216 (0.047) | −1.378 | 0.175 | 0.038 |
| 2 | Social well-being | <i>IL1B</i> | −0.178 (0.047) | −1.122 | 0.268 | 0.025 |
| 1 | Social well-being | <i>IL6</i> | −0.242 (0.071) | −1.535 | 0.132 | 0.048 |
| 2 | Social well-being | <i>IL6</i> | −0.197 (0.072) | −1.245 | 0.220 | 0.031 |
| 1 | Social well-being | <i>TNFSF10</i> | −0.117 (0.041) | −0.719 | 0.476 | 0.011 |
| 2 | Social well-being | <i>TNFSF10</i> | −0.107 (0.042) | −0.639 | 0.526 | 0.009 |
| 1 | Social well-being | <i>TNFRSF21</i> [†] | −0.302 (0.026) | −2.006 | 0.051 | 0.075 |
| 2 | Social well-being | <i>TNFRSF21</i> | −0.268 (0.026) | −1.755 | 0.087 | 0.057 |
| 1 | Social well-being | <i>PTGS2/COX-2</i> * [†] | −0.353 (0.042) | −2.313 | 0.026 | 0.103 |
| 2 | Social well-being | <i>PTGS2/COX-2</i> | −0.304 (0.042) | −1.999 | 0.052 | 0.073 |
| 1 | Social well-being | <i>CCL3</i> | −0.251 (0.048) | −1.639 | 0.109 | 0.052 |
| 2 | Social well-being | <i>CCL3</i> | −0.234 (0.049) | −1.487 | 0.145 | 0.043 |
| 1 | Social well-being | <i>CCL7</i> | −0.188 (0.046) | −1.207 | 0.234 | 0.029 |
| 2 | Social well-being | <i>CCL7</i> | −0.149 (0.047) | −0.946 | 0.350 | 0.018 |
| 1 | Social well-being | <i>CCL20</i> * [†] | −0.332 (0.065) | −2.158 | 0.037 | 0.091 |
| 2 | Social well-being | <i>CCL20</i> | −0.286 (0.065) | −1.854 | 0.071 | 0.065 |
| 1 | Social well-being | <i>CCL3L1</i> | −0.245 (0.050) | −1.593 | 0.118 | 0.049 |
| 2 | Social well-being | <i>CCL3L1</i> | −0.218 (0.051) | −1.392 | 0.171 | 0.038 |
| 1 | Social well-being | <i>CCL4L2</i> | −0.273 (0.050) | −1.767 | 0.084 | 0.062 |
| 2 | Social well-being | <i>CCL4L2</i> | −0.234 (0.051) | −1.501 | 0.141 | 0.044 |
| 1 | Social well-being | <i>CXCR7</i> [†] | −0.280 (0.023) | −1.976 | 0.055 | 0.065 |
| 2 | Social well-being | <i>CXCR7</i> | −0.248 (0.024) | −1.724 | 0.092 | 0.049 |
| 1 | Social well-being | <i>MMP9</i> * [†] | −0.353 (0.032) | −2.338 | 0.024 | 0.102 |
| 2 | Social well-being | <i>MMP9</i> | −0.292 (0.032) | −1.982 | 0.054 | 0.068 |
| 1 | Social well-being | <i>LMNA</i> ** [†] | −0.504 (0.024) | −3.531 | 0.001 | 0.210 |
| 2 | Social well-being | <i>LMNA</i> ** [†] | −0.448 (0.024) | −3.203 | 0.003 | 0.160 |

* *p* < 0.05; ** *p* < 0.01

[†] Statistically significant after application of the Benjamini–Hochberg procedure at a false discovery rate of 0.10

^a *SE* standard error. Model 1 analyses controlled for age, stage of disease, days since surgery, education, and BMI. Model 2 analyses controlled for age, stage of disease, days since surgery, education, BMI, and depression. Gene expression reported in RNA expression units (log2)

depression, anxiety, sleep or pain medications (all *ps* > 0.05).

Within the subsample of 78 participants in the present study, data were complete for SWB, leukocyte gene expression, depression, stage, days since surgery, age, and education. BMI data were incomplete for 35.9% of cases; hence, the effective sample size for covariate-adjusted analyses was 50. Women with versus without BMI data did

not differ on the pro-inflammatory gene expression composite.

Primary analyses

We hypothesized that SWB would be significantly related to a downregulation of the expression of pro-inflammatory and pro-metastatic leukocyte genes when controlling for

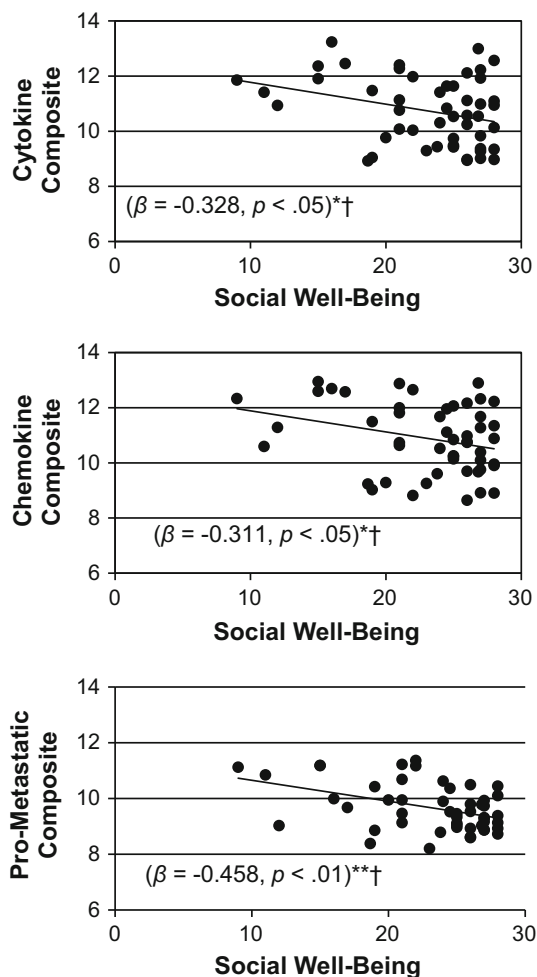


Fig. 1 Scatterplots depicting the association between social well-being and pro-inflammatory and pro-metastatic gene expression composites after breast cancer surgery controlling for age, stage of disease, days since surgery, education, and BMI. Note * $p < .05$; ** $p < .01$. † Remains statistically significant after application of the Benjamini–Hochberg procedure at a false discovery rate of 0.10. Scatterplot depicts data after winsorization. Gene expression reported in RNA expression units (\log_2)

age, stage of disease, days since surgery, education, and BMI. Results of these multiple regression analyses are displayed in Table 3. With covariates entered in Step 1 and SWB in Step 2, greater SWB was related to lower levels of the pro-inflammatory cytokine gene expression composite ($\beta = -0.33$, $p < 0.05$), the chemokine and chemokine receptor gene expression composite ($\beta = -0.31$, $p < 0.05$), and the pro-metastatic leukocyte gene expression composite ($\beta = -0.46$, $p < 0.01$). At the level of individual genes, greater SWB was associated with lower expression of *IL1A* ($\beta = -0.40$, $p < 0.05$), *CCL20* ($\beta = -0.33$, $p < 0.05$), *PTGS2/COX-2* ($\beta = -0.35$, $p < 0.05$), *MMP9* ($\beta = -0.35$, $p < 0.05$), and *LMNA* ($\beta = -0.50$, $p < 0.01$).

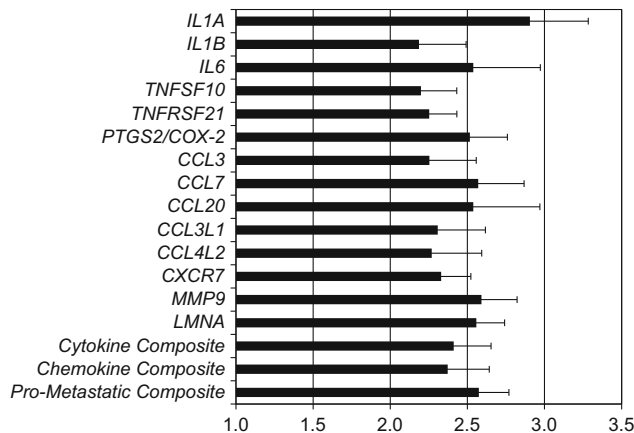


Fig. 2 Fold differences in pro-inflammatory and pro-metastatic gene expression in participants with low ($N = 25$) versus high ($N = 25$) social well-being determined by median split. Note Cytokine composites consisted of *IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2/COX-2*. Chemokine composites consisted of *CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*. Pro-metastatic composite consisted of *MMP9* and *LMNA*

When the Benjamini–Hochberg procedure was applied to these analyses to control for multiple comparisons, SWB remained significantly associated with the pro-inflammatory cytokine, pro-inflammatory chemokine, and pro-metastatic gene expression composites as well as with individual gene expression of *IL1A*, *TNFRSF21*, *CCL20*, *CXCR7*, *PTGS2/COX-2*, *MMP9*, and *LMNA* (see Table 3). Figure 1 depicts the scatterplots of the associations between SWB and gene expression composites, which suggest that the associations were not driven by extreme values. Independent samples *t* tests showed that women scoring at the lowest quintile of SWB did not differ from the highest 80% on gene expression levels (all $ps > 0.05$). This finding suggests that the association between SWB and gene expression likely operates across the continuum of SWB.

For descriptive purposes, Fig. 2 depicts fold differences in pro-inflammatory and pro-metastatic gene expression in participants with low versus high SWB as determined by median split. The low SWB group had 2–2.5 times higher levels of expression for every pro-inflammatory cytokine, chemokine, and pro-metastatic gene and their respective composite scores than their counterparts who reported high SWB, suggesting effects that were meaningful.

Leukocyte gene expression was not associated with the emotional, physical, or functional well-being scales of the FACT (all $ps > .05$).

Exploratory analyses

Additional analyses examined whether depressive symptoms were related to SWB and leukocyte gene expression

Table 4 Regression analyses relating leukocyte pro-inflammatory and pro-metastatic gene expression and depression in multivariable analyses, with and without controlling for social well-being

| Model | Independent variable | Dependent variable | β (SE) | t | p | R^2 change |
|-------|----------------------|--|---------------|-------|-------|--------------|
| 1 | Depression | Cytokine composite | 0.311 (0.035) | 1.909 | 0.063 | 0.073 |
| 2 | Depression | Cytokine composite | 0.255 (0.035) | 1.578 | 0.122 | 0.047 |
| 1 | Depression | Chemokine composite | 0.275 (0.035) | 1.695 | 0.097 | 0.057 |
| 2 | Depression | Chemokine composite | 0.221 (0.035) | 1.371 | 0.178 | 0.036 |
| 1 | Depression | Pro-metastatic composite* [†] | 0.430 (0.023) | 2.710 | 0.010 | 0.140 |
| 2 | Depression | Pro-metastatic composite* | 0.352 (0.022) | 2.336 | 0.024 | 0.090 |
| 1 | Depression | <i>IL1A</i> | 0.324 (0.053) | 1.993 | 0.053 | 0.079 |
| 2 | Depression | <i>IL1A</i> | 0.255 (0.052) | 1.614 | 0.144 | 0.047 |
| 1 | Depression | <i>IL1B</i> | 0.244 (0.041) | 1.500 | 0.141 | 0.045 |
| 2 | Depression | <i>IL1B</i> | 0.209 (0.041) | 1.265 | 0.213 | 0.032 |
| 1 | Depression | <i>IL6</i> | 0.286 (0.062) | 1.748 | 0.088 | 0.062 |
| 2 | Depression | <i>IL6</i> | 0.246 (0.062) | 1.491 | 0.143 | 0.044 |
| 1 | Depression | <i>TNFSF10</i> | 0.076 (0.036) | 0.445 | 0.659 | 0.004 |
| 2 | Depression | <i>TNFSF10</i> | 0.055 (0.037) | 0.312 | 0.756 | 0.002 |
| 1 | Depression | <i>TNFRSF21</i> | 0.240 (0.023) | 1.500 | 0.141 | 0.044 |
| 2 | Depression | <i>TNFRSF21</i> | 0.187 (0.023) | 1.175 | 0.247 | 0.026 |
| 1 | Depression | <i>PTGS2/COX-2</i> * | 0.329 (0.037) | 2.043 | 0.047 | 0.082 |
| 2 | Depression | <i>PTGS2/COX-2</i> | 0.269 (0.036) | 1.695 | 0.097 | 0.053 |
| 1 | Depression | <i>CCL3</i> | 0.141 (0.043) | 0.863 | 0.393 | 0.015 |
| 2 | Depression | <i>CCL3</i> | 0.095 (0.043) | 0.577 | 0.567 | 0.007 |
| 1 | Depression | <i>CCL7</i> | 0.246 (0.040) | 1.525 | 0.135 | 0.046 |
| 2 | Depression | <i>CCL7</i> | 0.216 (0.041) | 1.316 | 0.195 | 0.034 |
| 1 | Depression | <i>CCL20</i> | 0.312 (0.057) | 1.922 | 0.061 | 0.074 |
| 2 | Depression | <i>CCL20</i> | 0.255 (0.057) | 1.588 | 0.120 | 0.048 |
| 1 | Depression | <i>CCL3L1</i> | 0.189 (0.044) | 1.161 | 0.252 | 0.027 |
| 2 | Depression | <i>CCL3L1</i> | 0.146 (0.044) | 0.888 | 0.379 | 0.015 |
| 1 | Depression | <i>CCL4L2</i> | 0.260 (0.044) | 1.598 | 0.117 | 0.051 |
| 2 | Depression | <i>CCL4L2</i> | 0.213 (0.044) | 1.307 | 0.198 | 0.033 |
| 1 | Depression | <i>CXCR7</i> | 0.227 (0.021) | 1.510 | 0.138 | 0.039 |
| 2 | Depression | <i>CXCR7</i> | 0.178 (0.021) | 1.189 | 0.241 | 0.023 |
| 1 | Depression | <i>MMP9</i> * [†] | 0.390 (0.028) | 2.496 | 0.016 | 0.115 |
| 2 | Depression | <i>MMP9</i> * | 0.332 (0.028) | 2.157 | 0.037 | 0.080 |
| 1 | Depression | <i>LMNA</i> * [†] | 0.397 (0.022) | 2.514 | 0.016 | 0.119 |
| 2 | Depression | <i>LMNA</i> * | 0.309 (0.021) | 2.114 | 0.041 | 0.069 |

* $p < 0.05$; ** $p < 0.01$ [†] Statistically significant after application of the Benjamini–Hochberg procedure at a false discovery rate of 0.10^a SE standard error. Model 1 analyses controlled for age, stage of disease, days since surgery, education, and BMI. Model 2 analyses controlled for age, stage of disease, days since surgery, education, BMI, and social well-being. Gene expression reported in RNA expression units (log2)

and whether SWB acted as an intermediary between depression and gene expression. HRSD depression was significantly negatively associated with SWB ($r = -.25$, $p < .05$), yet SWB associations with leukocyte gene expression held after controlling for HRSD, though some associations were attenuated (see Table 3, model 2). Since SWB was associated with depressive symptoms, we initiated mediation analyses to determine whether SWB mediated the effects of depression on gene

expression. Depression was directly related to the pro-metastatic composite (Table 4, model 1). However, when SWB was controlled (Table 4, model 2), the association between depression and pro-metastatic gene expression was attenuated. Examining whether expression of individual genes was directly associated with depression reveals a similar pattern (see Table 4). Here, depression was significantly associated with greater *PTGS2/COX-2*, *MMP9*, and *LMNA* (Table 4, model 1), but this association

was non-significant when controlling for SWB after the Benjamini–Hochberg correction (Table 4, model 2).

The associations between SWB and leukocyte gene expression were not moderated by partner status (all $ps > .05$). This pattern of results suggests that SWB provides a generalizable association with inflammatory signaling that does not vary as a function of structural indicators of social support.

Discussion

Greater SWB was associated with less leukocyte expression of pro-inflammatory and pro-metastatic genes in women who recently underwent surgery for non-metastatic breast cancer and had not yet begun adjuvant therapy. These findings are consistent with the prior literature demonstrating upregulation of pro-inflammatory genes in socially isolated individuals [25]. Results suggest a possible biobehavioral pathway relating SWB to gene transcripts associated with inflammation and pro-metastatic processes that might account for previously reported relations between social resources and survival time [36]. These findings suggest that social processes may influence cancer-promoting biological processes in the critical post-surgical period when any residual cancer cells may be impacted by inflammatory signaling [37, 38].

Interestingly, the associations between leukocyte gene expression and depression also became non-significant when we controlled for SWB. SWB may serve as an intermediary between depression and gene expression. However, given the cross-sectional nature of the study, depression may also serve as an intermediary between SWB and gene expression. We can conclude that SWB and depression overlap in their contribution to individual differences in leukocyte pro-inflammatory and pro-metastatic gene expression during the adverse period of breast cancer treatment.

These findings are consistent with research linking lack of social resources with inflammatory processes. Miller et al. [39] found downregulation of leukocyte genes associated with inflammatory control in children raised in low SES environments. Women with ovarian cancer that reported lower SWB (and emotional support) showed increased levels of tumor promoters [vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), matrix metalloproteases (MMPs) [20, 40], and greater inflammatory gene expression for these tumor promoters [40] than high SWB counterparts. MMPs, derived from monocytes, are involved in wound healing responses and are relevant in promoting changes in the tumor microenvironment (e.g., endothelial–mesenchymal transition [EMT]) that could favor entry of cancer cells into circulation and metastasis

[40]. The present findings suggest that greater SWB may contribute to less leukocyte expression of MMP-associated genes in breast cancer patients.

The association between SWB and less *PTGS2/COX-2* expression suggests that lack of social resources may also relate to cancer progression through prostaglandins. Prostaglandins contribute to vascularization of tumor tissue and encourage tumor progression [41, 42]. Greater COX-2 expression, encoded by the *PTGS2/COX-2* gene, is associated with tumor metastasis, while inhibition of COX-2 is associated with increased tumor cell apoptosis [41]. Greater SWB in women with breast cancer may mitigate leukocyte signaling associated with inflammation, tumor proliferation, and metastasis though the precise mechanisms are unknown.

Alternatively, inflammation may increase social withdrawal, and consequently decrease SWB (and increase depression), as a “sickness behavior” response to illness. In response to infection, circulating pro-inflammatory cytokines may increase cytokine activation in the brain, which signals a reduction in social activity [43] to conserve energy for fighting infection [44]. The current results may be accounted for by leukocyte gene expression encoding pro-inflammatory cytokines that in turn activate social withdrawal and decrease SWB along with increasing depressive symptoms.

Strengths and limitations

This study had several notable strengths. Women with non-metastatic breast cancer participated during the weeks after surgery while anticipating adjuvant treatment, a stressful time when social resources may be particularly important. That associations between SWB and leukocyte gene expression were tested when women had not yet begun adjuvant therapy also reduced the potentially confounding effects of radiation, chemotherapy, and immunotherapy. Several other potential confounders were also controlled, including demographic characteristics, disease stage, point in treatment, and time since surgery. Significant effects persisted above and beyond the effects of age, education, and BMI, which are strongly and consistently associated with inflammation [28]. The statistically significant findings also survived correction for multiple comparisons using the Benjamini–Hochberg procedure, which is a recommended technique when analyzing medical data in the context of directional hypotheses [45].

Present findings are in line with research that sets a precedent for linking “well-being” indices to leukocyte gene expression [24]. Specificity of the relationship between leukocyte gene expression and SWB in women undergoing breast cancer treatment was established through findings that gene expression was not related to

emotional, physical, or functional well-being. Finally, analyzing the impact of SWB on individual genes as well as on gene composite scores offers potential data reduction strategies, while simultaneously highlighting genes that may deserve special attention.

The design was a post hoc secondary analysis of a previously examined cross-sectional dataset; therefore, the direction of the temporal connection between SWB and leukocyte gene expression cannot be determined. The small sample size may have limited ability to detect effects. Excluding participants missing key data (e.g., BMI) from analyses was considered a conservative strategy, though small sample size could have biased the results in the direction of false negatives. SWB was measured with retrospective self-report, and participants may have inaccurately remembered their experiences or underreported dissatisfaction with social resources to appear socially desirable. Although the sample was reasonably ethnically diverse, results may be less applicable to low-income women and women with metastatic disease.

Future directions

Additional longitudinal studies with larger sample sizes are needed to examine the directionality of these relationships between SWB and pro-inflammatory indicators. It will be important to develop more nuanced scales of SWB for use with patients diagnosed with cancer to determine whether specific domains are strongly related to disease promoting factors. Studies of more diverse samples are needed to examine whether these findings hold across different ethnic and racial groups, especially given the culture-specific nature of social resources [46].

Implications

Low SWB may result, in part, from low utilization of available support. Patients may lack assertiveness skills, reducing their ability to request support from others during breast cancer treatment. This possibility provides directions for cognitive-behavioral interventions that could improve SWB by promoting assertiveness, engagement, and communication skills.

Conclusions

This study found robust cross-sectional relationships between SWB and less pro-inflammatory and pro-metastatic leukocyte gene expression in the period after breast cancer surgery, before adjuvant radiation or chemotherapy.

Future longitudinal research should examine mechanisms linking SWB with pro-inflammatory and pro-metastatic leukocyte gene expression and longer-term clinical outcomes. Further research is needed to develop psychosocial interventions that enhance SWB for patients recently diagnosed with breast cancer.

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Compliance with ethical standards

The experiments comply with the current laws of the country in which they were performed.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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