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A Cross-Sectional Exploration of Cytokine–Symptom Networks in Breast Cancer Survivors Using Network Analysis

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Abstract

Purpose: The purpose of this study is to (a) visualize the symptom–cytokine networks (perceived stress, fatigue, loneliness, perceived cognitive impairment, daytime sleepiness, sleep quality, and 13 cytokines) and (b) explore centrality metrics of symptom–cytokine networks in breast cancer survivors who completed chemotherapy treatment.

Methods: Cross-sectional analysis of data collected from 66 breast cancer survivors who were on average three years post chemotherapy completion. Perceived stress, fatigue, loneliness, perceived cognitive impairment, daytime sleepiness, and sleep quality were measured with self-report instruments, and a panel of 13 cytokines was measured from serum using multiplex assays. Symptoms and cytokines were simultaneously evaluated with correlations, network analysis, and community analysis.

Results: Network analysis revealed the nodes with the greatest degree and closeness were interleukin-2, granulocyte-macrophage colony-stimulating factor, interleukin-13, and perceived cognitive impairment. Node betweenness was highest for perceived cognitive impairment and interleukin-2. Community analysis revealed two separate communities of nodes within the network (symptoms and the cytokines). Several edges connected the two communities including perceived cognitive impairment, stress, fatigue, depression, interleukin-2, granulocyte-macrophage colony-stimulating factor, interleukin-8, interleukin-13, and interleukin-10. Partial correlation analyses revealed significant negative relationships between interleukin-2 and fatigue, loneliness, stress, and perceived cognitive impairment ($rs = -.27$ to $-.37$, $ps < .05$) and a significant negative relationship between perceived cognitive impairment and granulocyte-macrophage colony-stimulating factor ($r = -.34$, $p < .01$).

Conclusions: Our analyses support that perceived cognitive impairment, stress, loneliness, depressive symptoms, and fatigue co-occur and extend the literature by suggesting that interleukin-2 may contribute to the underlying mechanistic pathway of these co-occurring symptoms. Our findings add to a growing body of literature that is shifting to study symptoms as they co-occur, or cluster, rather than individual symptoms.

Keywords

Breast cancer survivors, cytokines, symptoms, network analysis, community analysis

Background and purpose

Improvements in cancer screening, diagnostics, and treatments have led to a growing cohort of breast cancer survivors (BCS). There are now an estimated 3.1 million women living with a history of breast cancer (BC) in the United States (American Cancer Society, 2017). Unfortunately, cancer survivorship often includes late and long-term physical and psychological effects related to the cancer experience that can negatively affect quality of life (Kenyon et al., 2014).

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BCS frequently report cognitive and psychosomatic symptoms including emotional distress (i.e., anxiety and depressive symptoms) (Maass et al., 2015), fatigue (Bower et al., 2006), perceived cognitive impairments (Runowicz et al., 2016), posttraumatic stress (Arnaboldi et al., 2017), and insomnia (Palesh et al., 2012, 2017). Although these symptoms are independently assessed, they often co-occur and are interrelated (Fagundes et al., 2015; Koutrouli et al., 2016; Nho et al., 2018). Importantly, cancer surveillance models call for the prevention, early intervention, and management of cancer-related side effects (Kenyon et al., 2014).

Assessing and managing multiple independent symptoms within constrained clinical environments is challenging, so we are now trying to understand how certain symptoms co-occur or "cluster" together. Experts have recommended a transformation in symptom science from single symptom research to co-occurring symptoms, especially within the context of chronic diseases such as cancer (Miaskowski et al., 2017). Symptom cluster analysis has been conducted most often in oncology populations. Cluster analysis is typically performed by grouping symptoms by symptom cluster severity (e.g., all high level of symptoms, all now level symptoms) a priori based on the literature (Doong et al., 2015; Kim et al., 2012; Miaskowski et al., 2017).

Our group and others have reported large correlations between loneliness, perceived stress, perceived cognitive impairments, and fatigue (Henneghan, Stuifbergen et al., 2018), suggesting a symptom cluster. Symptom clusters are rarely evaluated empirically via network or community analyses. Network science is well established in fields like computer science and physics and is now being applied to behavioral and health sciences. For example, neuroscientists often use network analyses and graph theory to study brain structure and function (Sporns, 2003). Only recently have a handful of groups started to utilize network analyses to study co-occurring symptoms.

Not only do we need a better understanding of which symptoms cluster in BCS, we also need a better understanding of the mechanistic underpinnings of these symptoms in order to develop targeted interventions to manage and treat symptom clusters. In a 2017 review of oncology symptom cluster research noted that only 10 studies from 1990 to 2015 had evaluated underlying mechanisms of symptom clusters in cancer patients (Miaskowski et al., 2017). Cytokines have been receiving increasing attention as potential biomarkers of unwanted symptoms across chronic disease states including cancer survivorship (Egger & Dixon, 2014). Inflammation has been identified as a key biological mechanism of cognitive and psychological symptoms of BCS including insomnia, fatigue (Bower & Lamkin, 2013; Collado-Hidalgo et al., 2006), cognitive function (Henneghan, Palesh, et al., 2018; S. Kesler et al., 2013), and depressive symptoms (Fagundes et al., 2015). Animal models demonstrate that pro-inflammatory signaling results in behavioral changes including fatigue, depressive symptoms, and cognitive deficits collectively called sickness behavior (Bower et al., 2011; Fagundes et al., 2015). Some studies have linked inflammatory genes and greater symptom burden, and others have linked concentrations of some cytokines with greater symptom burden in oncology populations (Doong et al., 2015; Reyes-Gibby et al., 2012). The statistical methods employed in these studies, namely, hierarchical cluster analysis, latent class structure, and principal component analyses, are limited in answering these specific questions regarding mechanisms of symptom *occurrence* rather than mechanisms of symptom cluster *severity*.

To our knowledge, no studies have evaluated the structure of cognitive and psychosomatic symptoms and biomarkers of inflammation in BCS simultaneously using network analysis. Network analysis is a statistical methodology that can discover and visualize complex relationships among multiple variables and identify potential influencing factors. Network plots are a visual representation of systems and are constructed with "nodes" and "edges" (Freeman, 1979). A *node* is a representation of a variable, and an *edge* represents connections between nodes. Furthermore, metrics of network centrality can highlight the connectedness of each node, aiding in characterizing the nodes of a network and potentially identifying which nodes are "key" or "vital" for explaining the behaviors of a specific network (Freeman, 1979; Lu et al., 2016; Opsahl et al., 2010). Utilizing network analyses to explore the relationships and structure of multiple cognitive and psychosomatic symptoms and inflammatory biomarkers could allow for the identification of potential symptom clusters along with associated biomarkers. The purpose of this study is to (a) visualize the symptom–cytokine networks (perceived stress, fatigue, loneliness, perceived cognitive impairment, daytime sleepiness, sleep quality, and 13 cytokines) and (b) explore centrality metrics of symptom–cytokine networks in BCS who completed chemotherapy treatment up to 10 years prior. The authors hypothesized that symptom–cytokine network analyses would reveal nodes that are most important (i.e., most connected to other nodes) to the network.

Methods and procedures

All study procedures and protocols were approved by the University of Texas at Austin Institutional Review Board (protocol id: 2015-10-0039) and Institutional Biosafety Committee (protocol id: IBC-2017-00269) and are in accordance with the Declaration of Helsinki.

Participants

BCS were recruited through community oncology centers, a local BC navigation center, the local chapter of the Oncology Nursing Society, and the Army of Women (Dr. Susan Love Research Foundation). Participants were included if they had a history of nonmetastatic, noninflammatory BC (stages I–IIIc), completed adjuvant chemotherapy treatments between 6 months and 10 years prior to enrollment, were between the ages 21 and 65 years old, were able to read and write in English, and were of any racial or ethnic group. Participants were excluded if they had a history of inflammatory comorbidities that could influence cytokine concentrations (e.g., rheumatoid arthritis, diabetes mellitus), a precancer history of sleep apnea, insomnia, traumatic brain injury, severe cognitive impairments, neurological or psychiatric disorders (diagnosed by a healthcare provider), or known medical conditions that would interfere with cognition or their ability to complete study surveys or cognitive testing. BCS on endocrine therapy were included. Participants were not screened for study inclusion based on symptom severity. All participants provided written, informed consent.

Data collection procedures

Participants were recruited and enrolled in the study between May 2016 and January 2017. Potential participants were screened via the telephone. Those who were eligible provided verbal consent and were sent written consents and a link for an online survey to complete 24 to 48 h prior to their in person data collection appointment. The online survey included a demographic and treatment questionnaire along with all the self-report measures. In-person appointments were scheduled within 4 h of waking in the morning and included anthropomorphic measures, standardized cognitive testing (cognitive testing data are reported elsewhere; Henneghan, Palesh, et al., 2018), and a nonfasting blood draw.

Blood collection and assay procedures

Ten milliliter of nonfasting blood were collected aseptically by a registered nurse into serum separator tubes (BD, Franklin Lakes, NJ) and allowed to clot at room temperature for 30 min to 2 h. Blood was transported in a cooler that maintained room temperature to the University of Texas at Austin School of Nursing Biobehavioral Laboratory. In the laboratory, the samples were centrifuged at 3330 r/min for 15 min, serum was aliquoted using filtered pipettes into 1 ml polypropylene tubes and stored at −80°C until batch analyses.

Measures

Symptoms. Cognitive function was operationalized as perceived cognitive impairments and measured using the Perceived Cognitive Impairments (PCI) subscale of the functional assessment of cancer therapy (FACT)-cognitive function instrument version 3 (PCI-total) (Wagner et al., 2009). This subscale consists of 20 items measuring how often cognitive impairments occurred in the previous seven days. Lower scores indicate greater perceived cognitive impairments. Loneliness was measured using the University of California Los Angeles (UCLA) Loneliness Scale revised 3.0 (Russell, 1996), total scores could range from 20 to 80. The Perceived Stress Scale (PSS), a 10-item scale, was used to measure perceived stress in the previous seven days (Cohen et al., 1983). Fatigue, anxiety, and depression were measured with a Patient-Reported Outcomes Measurement Information System, "PROMIS" (Cella et al., 2010) scale—Short forms (Cella et al., 2010). These scales ask how frequently symptoms were experienced in the previous seven days. Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), and the Epworth Sleepiness Scale (ESS) was used to measure daytime sleepiness (Enderlin et al., 2011). Higher scores indicated greater symptom severity for all scales except the PCI-total.

Cytokines. Human high sensitivity T cell magnetic, premixed, multiplex assays from EMD Millipore (Darmstadt, Germany) were used to quantify 13 analytes— a mix of pro-inflammatory (tumor necrosis factor alpha (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma (INF-g), interleukin (IL)-2, IL-1b, IL-5, IL-7, and IL-8), anti-inflammatory (IL-10 and IL-13), and both pro/anti-inflammatory (IL-6, IL-2, and IL-4) (Yoshimoto & Yoshimoto, 2014). Standards, controls, and samples were run in duplicate on 96 well plates and analyzed according to the manufacturer's recommendations. The plates were read using a Luminex 200 (Luminex Corporation, Austin, TX) to determine mean fluorescent intensity for each well. Five-parameter logistic regression was used to construct the standard curve, and the R^2 for the standard curves ranged from 0.998 to 1. All the controls were within the manufacturer's specified range and the coefficient of variation between duplicates averaged 6% indicated valid and reliable methods for analyte quantification.

Demographic and clinical variables. A demographic and treatment questionnaire was used to collect demographic information (e.g., age, education, race, ethnicity) and disease and treatment information (e.g., number of treatment modalities, date of chemotherapy completion,

types of cancer treatments, menopausal status, tumor characteristics). Body mass index (BMI) was also measured to use a potential covariate considering BMI is consistently linked to elevated cytokine levels (O'Connor et al., 2009). Height was measured in centimeters to the nearest 0.5 cm, and weight measured on a digital scale (Tanita Model WB-300 Plus, Arlington Heights, IL) to the nearest 100 g, by the same study personnel for all study participants.

Data analyses

Data were analyzed with SPSS 25.0 (IBM SPSS Statistics, 2009) and R (R Foundation). Demographic and clinical variables were analyzed to describe the sample and presented as mean and standard deviation (SD) for continuous variables, and as frequencies and percentages for discreet variables. We created a correlation matrix between all eight symptoms (perceived stress, anxiety, depressive symptoms, fatigue, loneliness, perceived cognitive impairments, daytime sleepiness, and sleep quality) and 13 cytokines (IL-6, TNF-α, GM-CSF, INF-g, IL-2, IL-4, IL-5, IL-7, IL-8, IL-10, IL-12, IL-1b, and IL-13) using Spearman's correlations to account for outliers and skewness in the cytokine measurements (Mukaka, 2012). The variables were all transformed into z scores so that higher numbers represented greater symptoms severity or greater cytokine concentrations prior to analyses. We created a network so that all symptoms and cytokines represented individual "nodes" in the network and "edges" represented significant spearman's rho correlations among all the nodes. Data were then organized in an edge list consisting of three columns where column 1 were the nodes (variables) that were the source of the connection, column 2 were the nodes that were the target of the connection, and column 3 were the weights the edges (based on the absolute value of the spearman rho correlations between the variables). We assumed that each bivariate correlation represented two directional connections since these data were from a cross-sectional study. For example, a correlation between anxiety and depression was entered in the edge list twice (anxiety -> depression, depression -> anxiety).

We used the "igraph" package in R (The R Foundation, www.r-project.org/) (R Core Team, 2018) to visualize the network as a directed graph and estimate network measures of connectedness, or centrality, including "degree" (number of connections of one node to all other nodes), closeness (distance between nodes, higher means that node is "closer" to other nodes), and node betweenness (the number of shortest paths going through a node), "eigen centrality" (similar to "degree," as it is the number of connections a node has with other nodes but also considers the links that extend beyond those nodes) (Freeman, 1979; Opsahl et al., 2010). We also examined the cytokine–symptom network connectivity with "edge density" which is the proportion of possible connections among all the network nodes (Fornito & Bullmore, 2016). The graphical representation of the network was based on the "Fruchterman Reingold" algorithm which positions nodes with more connections closer to each other (Fruchterman & Reingold, 1991). We then examined the structural organization of the nodes using community network analysis. In the "igraph" package, community network analysis is conducted by calculating the community structures from a cluster edge betweenness algorithm of an unweighted graph (Fortunato, 2010). Within networks, edges connecting separate communities have high edge betweenness (the shortest path from one module to the other must travel through them).

Results

Descriptive statistics

A comprehensive description of the sample demographic and treatment variables has been described previously (Henneghan, Palesh, et al., 2018). Briefly, the sample of 66 women were on average 48.44 years old (SD 8.73), white, and non-Hispanic. The majority had a history of stage 2 (62.1%) invasive ductal carcinoma (69.7%) that was hormone receptor positive (84.8%). These women completed chemotherapy treatments on average 35.7 months (SD 27.12) prior to study enrollment (Table 1). Spearman's rho correlations between z score transformed cytokine concentrations and symptoms are displayed in hierarchical clustering format in Figure 1. Moderate positive relationships were found among the cytokines and among the symptoms. Few small negative relationships were found between some cytokines and some symptoms.

Network plots and metrics

A directed network plot of all 20 nodes and 182 edges is displayed in Figure 2. The edge density for the whole network was 48.42%. The nodes with the greatest degree and closeness were IL-2 (degree: 28, closeness: 0.041), GM-CSF (degree: 24, closeness: 0.038), IL-13 (degree: 24, closeness: 0.038), and PCI (degree: 24, closeness: 0.038). Node betweenness was highest for PCI (63.91) and IL-2 (58.76). Eigen centrality scores were overall greater for the cytokine nodes. IL-2 had the highest eigen centrality score (1.00) for the cytokines followed by GM-CSF (0.94), and PCI had the highest eigen centrality score out of the symptom nodes (0.55). Centrality measures for each of the nodes are displayed in Table 2. Figure 2 illustrates that overall the cytokines

Table 1. Descriptive statistics for demographic and treatment variables (N = 66).

Characteristic	n (%)	Mean (SD)	Minimum, maximum
Age		48.44 (8.73)	27, 65
Race			
White	62 (93.4%)		
African American	1 (1.5%)		
Asian	3 (4.5%)		
Ethnicity			
Hispanic	3 (4.5%)		
Non-Hispanic	63 (95.5%)		
Years of education		16.7 (2.16)	12, 22
BC type			
IDC	46 (69.7%)		
DCIS	10 (15.2%)		
ILC	5 (7.6%)		
Multiple (IDC/DCIS/ILC)	5 (7.6%)		
Stage			
1	12 (18.2%)		
2	41 (62.1%)		
3	13 (19.7%)		
ER+/PR+	56 (84.8%)		
HER 2+	26 (39.4%)		
Months since chemotherapy		35.7 (27.12)	6.83, 120.84
Menopausal status			
Pre/perimenopausal	19 (28.8%)		
Menopausal	47 (71.2%)		
Currently on hormonal therapy	44 (66.7%)		

SD: standard deviation; BC: breast cancer; IDC: invasive ductal carcinoma; DCIS: ductal carcinoma in situ; ER: estrogen receptor; HER 2: human epidermal growth factor receptor 2; ILC: invasive lobular carcinoma; PR: progesterone receptor.

in the network are tightly clustered, except for IL-8 and TNF-α (no connections with other cytokines and therefore did not appear on the network plot). Similarly, the symptoms appear tightly connected with greater connectedness between PCI, lonely, stress, depress, and fatigue. Daytime sleepiness, sleep quality, and anxiety do not appear to cluster closely with the other symptoms.

Community analysis

The community analysis (Figure 3) revealed two separate communities of nodes within the network: the symptoms and the cytokines. Several edges connect the symptom community with the cytokine community most notably between the PCI, stress, fatigue, depression, IL-2, GM-CSF, IL-8, IL-13, and IL-10 nodes.

Posthoc

To facilitate interpretation of the symptom–cytokine relationships identified in the network plots, we examined partial correlations between symptoms and cytokines while controlling for variables that could influence cytokine concentrations in this population (age, BMI, hip to waist ratio, cancer stage, and time since chemotherapy completion). Almost all correlations between symptoms and cytokines were negative. IL-2 has significant negative relationships with four of the five identified symptoms (fatigue, loneliness, stress, and PCI) after controlling for the covariates ($ps < .05$). PCI also had a significant negative relationship with GM-CSF ($r = -.34$, $p < .01$). Partial correlations are displayed in Table 3.

Discussion

We conducted an exploratory descriptive network analysis of symptoms and cytokines in a sample of 66 BCS up to 10 years after chemotherapy completion. To our knowledge, we are the first to apply network analysis to the study of symptoms and biomarkers in cancer survivors. Our findings add to a growing body of literature that is shifting to study symptoms as they co-occur, or cluster, rather than individual symptoms (Miaskowski et al., 2017). Our analyses support that perceived cognitive impairment, stress, loneliness, depressive symptoms, and fatigue co-occur and extend the literature by suggesting that IL-2 may contribute to the underlying mechanistic pathway of these co-occurring symptoms. In addition to providing novel insights on symptom–

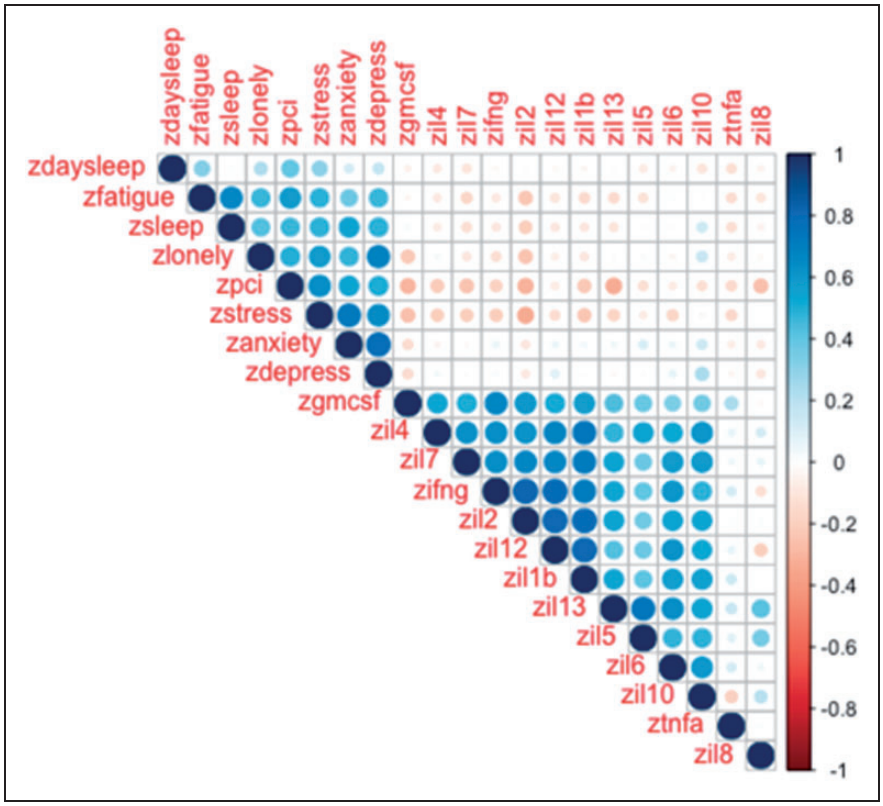

Figure 1. Correlogram of spearman's rho correlation matrix among scores for all symptoms and all cytokines (N = 66). The hierarchical clustering function was used to construct the plot, and therefore variables are within close proximity to variables they have relationships with and far away from those that they have small or no relationships with. Circle size represents the magnitude of the relationship with larger circles representing larger relationships. Blue circles are positive and red circles are negative. zil6: interleukin 6; zgmcsf: Granulocyte-macrophage colony-stimulating factor; zifng: interferon gamma; zil10: interleukin 10; zil12: interleukin 12; zil13: interleukin 13; zil1b: interleukin 1 beta; zil2: interleukin 2; zil4: interleukin 4; zil5: interleukin 5; zil7: interleukin 7; zil8: interleukin 8; zfatigue: PROMIS Fatigue score; zlonely: UCLA-R Loneliness score; zstress: Perceived Stress Scale score; zanxiety: PROMIS Anxiety score; zdepress: PROMIS Depression score; zdaysleep: Epworth Sleepiness Scale score; zpci: Functional Assessment of Cancer Therapy (FACT) Cog PCI subscale score.

cytokine networks, this study provides new knowledge on loneliness and perceived stress in BCS. All participants in our study received chemotherapy as part of their treatments.

While scientific progress has been made toward understanding biological mechanisms of survivors' fatigue (Bower & Lamkin, 2013; Collado-Hidalgo et al., 2006) and depressive symptoms (Fagundes et al., 2015), and insomnia (Palesh et al., 2012, 2017), less is known about the mechanisms of survivors' ongoing loneliness, perceived stress, and perceived cognitive impairments. This is especially important, as BCS experience a unique type of loneliness following the completion of treatment termed "survivor loneliness" that encompasses a sense of loneliness in the face of mortality and ongoing symptom burden (Rosedale, 2009). Cancer survivors also experience one and a half times more stress than the general population (Parelkar et al., 2013). Our findings support preliminary evidence suggesting relationships between loneliness and cognitive dysfunction (Cheung et al., 2012; Jaremka et al., 2014; Mehlsen et al., 2009) and between perceived stress and cognitive dysfunction (Myers et al., 2015; Phillips et al., 2010) in BCS.

Network analyses both visualize the structures of particular networks and provide metrics to evaluate network characteristics. In this sample, we found a tight community of cytokines and tight community of symptoms within the network, per the high edge density, with several connections between the communities. The bridge between symptoms and cytokines appears to between IL-2 and PCI. We evaluated centrality metrics in order to determine which nodes were "key" or "vital" to the network; in other words, which nodes are most important for explaining the behaviors of this specific network. IL-2 had the highest scores across centrality metrics suggesting that it is the most connected (degree and eigen centrality) node in the network that is closest

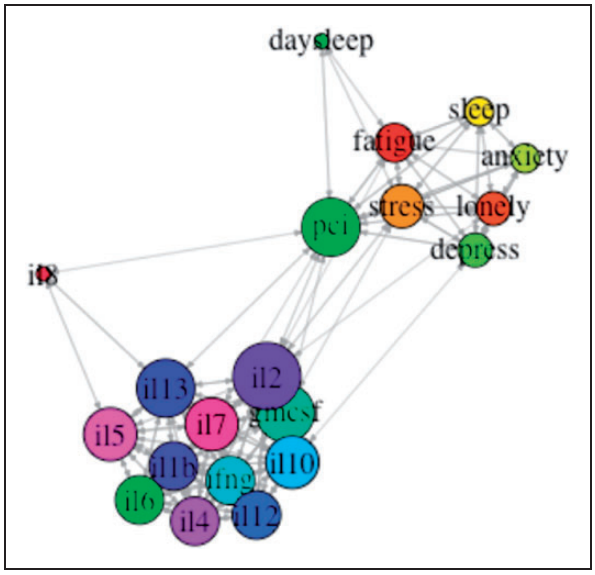

Figure 2. Directed network plot of symptoms and cytokines (N = 66). Node size representing number of degree for each node (degree: number of connections) bigger node is more degree. il6: interleukin 6; gmcsf: granulocyte-macrophage colony-stimulating factor; ifng: interferon gamma; il10: interleukin 10; il12: interleukin 12; il13: interleukin 13; il1b: interleukin 1 beta; il2: interleukin 2; il4: interleukin 4; il5: interleukin 5; il7: interleukin 7; il8: interleukin 8; fatigue: PROMIS Fatigue score; lonely: UCLA-R Loneliness score; stress: Perceived Stress Scale score; anxiety: PROMIS Anxiety score; depress: PROMIS Depression score; daysleep: Epworth Sleepiness Scale score; pci: Functional Assessment of Cancer Therapy (FACT) Cog PCI subscale score. IL-8 and TNF-α were not included because there were no connections with other cytokines.

(closeness) and is part of the majority of "shortest" pathways between other nodes (betweenness) (Freeman, 1979; Opsahl et al., 2010). IL-2 was closely connected to other cytokines and to a symptom cluster consisting of perceived cognitive impairment, stress, loneliness, depressive symptoms, and fatigue. Of the symptom nodes, perceived cognitive impairment demonstrated the highest score on the centrality metrics suggesting it is the most important symptom to consider in the symptom cluster. Based on our analysis, IL-2 and perceived cognitive impairment appear to be the "vital nodes" in the symptom–cytokine network (Lu et al., 2016). These metrics are relative to this sample. Since we did not have a comparison group, there are no concrete interpretations of these values.

After identifying symptom–cytokine pathways though the network analysis, we looked at each of the edges using partial correlations and found some significant negative relationships between IL-2, stress, perceived cognitive impairments, loneliness, and fatigue and suggesting that greater concentrations of IL-2 are associated with lower levels symptoms. Our findings support others who have found significant relationships

Table 2. Centrality metrics for individual symptom and cytokine nodes.

Variable	Degree	Closeness	Node betweenness	Eigen centrality
Range	6–28	0.023–0.041	0.00–63.91	0.11–1.00
Fatigue	16	0.033	9.43	0.28
Lonely	14	0.032	4.02	0.27
Stress	18	0.034	18.93	0.36
Sleep	12	0.026	0.00	0.18
Anxiety	12	0.026	0.00	0.18
Depress	14	0.032	10.28	0.26
Daysleep	6	0.023	0.00	0.11
pci	24	0.038	63.91	0.55
IL-6	22	0.032	0.00	0.87
GM-CSF	24	0.038	20.30	0.95
IFN-g	20	0.032	0.00	0.87
IL-10	22	0.035	17.68	0.89
IL-12	20	0.032	0.00	0.87
IL-13	24	0.038	15.80	0.94
IL-1b	20	0.032	0.00	0.87
IL-2	28	0.041	58.76	1.00
IL-4	20	0.032	0.00	0.87
IL-5	22	0.033	8.00	0.89
IL-7	22	0.037	7.80	0.92
IL-8	8	0.028	1.05	0.23

Note: "Degree" is the number of connections that one node has with other nodes; "closeness" is the distance between nodes, with higher numbers meaning that a node is closer to other nodes; "node betweenness" is the number of shortest paths going through a node; "eigen centrality" is the number of connections a node has with other nodes but also considers the links that extend beyond those nodes. IL-6: interleukin 6, GM-CSF: granulocyte-macrophage colony-stimulating factor, IFN-g: interferon gamma; IL-10: interleukin 10; IL-12: interleukin 12; IL-13: interleukin 13; IL-1b: interleukin 1 beta; IL-2: interleukin 2; IL-4: interleukin 4; IL-5: interleukin 5; IL-7: interleukin 7; IL-8: interleukin 8; fatigue: PROMIS Fatigue score; lonely: UCLA-R Loneliness score; stress: Perceived Stress Scale score; anxiety: PROMIS Anxiety score; depress: PROMIS Depression score; daysleep: Epworth Sleepiness Scale score; pci: Functional Assessment of Cancer Therapy (FACT) Cog PCI subscale score.

between perceived cognitive function and cytokines (Cheung et al., 2015; Ganz et al., 2013; Janelsins et al., 2012) in BCS and extend knowledge on IL-2 specifically. The relationship we found between IL2 and PCI support those from Maydych et al. (2018) who reported better attention was related to higher IL-2 in 60 young adults. Cheung et al. (2015) reported significant relationships between PCI other cytokines (IL-6 and IL1beta), which we did not find. Our findings are inconsistent with reports greater concentrations of Il-2 being reported in persons with mild cognitive impairment (King et al., 2018); however, our sample represents a different clinical population.

Our study findings are congruent with others that have linked psychological stressors to inflammatory markers in BC patients (Han et al., 2016; Wenzel et al., 2012; Witek-Janusek et al., 2007) as well as

survivors (Bower et al., 2007; Carlson et al., 2007; Crosswell et al., 2014; Lengacher et al., 2019) and add new data on the relationship between IL-2 and stress. This finding supports a recent report from another group of a negative relationship between PSS and IL-2 ($r = -.66$) in 228 adults exposed to high stress occupations (Filip et al., 2018) but are contrary to Lynch Kelly et al. (2018) who reported that perceived stress was not associated with inflammatory markers in 24 patients who received stem cell transplant. It is possible that Lynch Kelly et al.'s (2018) study was underpowered due to a small sample and multiple measures which is also true of this study which was not powered to examine relationships between inflammatory markers and stress. However, a power analysis of our correlation matrix with a sample size of 66 revealed that correlations of ±0.34 can be detected at 80% power.

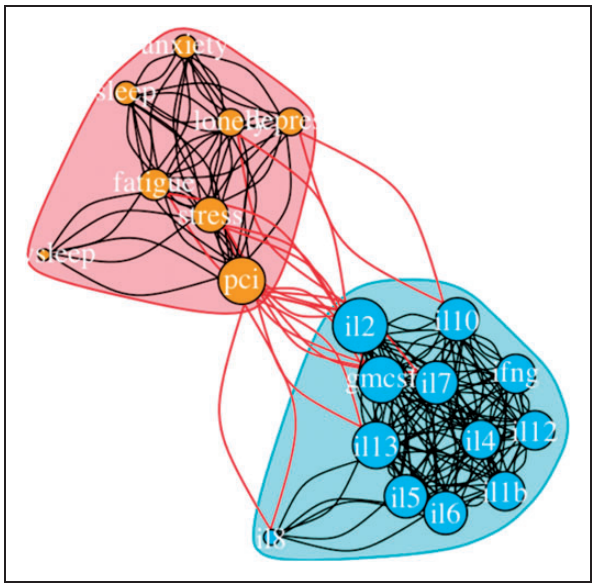

Figure 3. Community analysis of symptoms and cytokines (N = 66). Symptom community in pink and cytokine community in blue. Connections between communities are represented by red curved lines and connections among communities are represented by black curved lines. il6: interleukin 6; gmcsf: granulocyte-macrophage colony-stimulating factor; ifng: interferon gamma; il10: interleukin 10; il12: interleukin 12 p 10; il13: interleukin 13; il1b: interleukin 1 beta; il2: interleukin 2; il4: interleukin 4; il5: interleukin 5; il7: interleukin 7; il8: interleukin 8; fatigue: PROMIS Fatigue score; lonely: UCLA-R Loneliness score; stress: Perceived Stress Scale score; anxiety: PROMIS Anxiety score; depress: PROMIS Depression score; daysleep: Epworth Sleepiness Scale score; pci: Functional Assessment of Cancer Therapy (FACT) Cog PCI subscale score.

Our findings support other reports of relationships between social support, loneliness, and some markers of inflammation (Muscatell et al., 2016; Nausheen et al., 2010; Yang et al., 2014) and are contrary to others that have reported no relationships between inflammatory markers and loneliness in oncology patients and survivors (Jaremka et al., 2013; Marucha et al., 2005). Research in mouse models on social isolation and IL-2 is inconsistent. There are reports of no difference in IL-2 concentrations in mice that are socially isolated compared to those that are not (Krugel et al., 2014) and reports of higher concentrations of IL-2 in mice with liver cancer that were reared in a group compared to reared as individuals (Liu & Wang, 2005). Loneliness is a biopsychosocial stressor that elicits a neuroimmunological stress response than negatively impacts chronic disease, likely through immune mediators including cytokine dysregulation (Theeke et al., 2016), more research is needed to understand the pathways of cytokine dysregulation that may influence, or be a result of, loneliness in cancer patients and survivors. This study adds to a growing body of research linking fatigue and inflammation in BC patients and survivors (Bower et al., 2002, 2006, 2007, 2009, 2011; Bower & Lamkin, 2013), by providing new insights on the role of IL-2. However, our findings are inconsistent with reports in other populations of no differences in IL-2 in persons with chronic fatigue syndrome compared to controls (Brenu et al., 2011), no relationship between IL2 and fatigue in persons with advanced cancer (Paulsen et al., 2017).

Table 3. Partial correlations between symptom and cytokines variables identified in network plot controlling for age, body mass index, hip to waist ratio, cancer stage, and time since chemotherapy completion (N = 66).

	GM-CSF	IL-8	IL-2	IL-13	IL-10	IL-7
Stress	−.21	—	−.37**	—	—	—
Lonely	—	—	−.27*	—	—	—
Fatigue	—	—	−.32*	—	—	—
pci	−.34**	−.08	−.27*	−.10	—	−.21
Depress	—	—	—	—	.25	—

Note: For Perceived Stress Scale, UCLA-R scale, PROMIS Fatigue, FACT-Cog PCI converted to standardized z scores with higher values indicating more symptoms. GM-CSF: granulocyte-macrophage colony-stimulating factor; IL-8: interleukin 8; IL-2: interleukin 2; IL-13: interleukin 13; IL-10: interleukin 10; IL-7: interleukin 7; fatigue: PROMIS Fatigue score; lonely: UCLA-R Loneliness score; depress: PROMIS Depression score; pci: Functional Assessment of Cancer Therapy (FACT) Cog PCI subscale score.
*$p < .05$. **$p < .01$.

The inconsistency in the presence of relationship and the direction of relationships across the studies discussed above between cytokines, including IL-2, and selected symptoms could be explained by in part by the variable roles IL-2 plays in inflammatory responses. It is unclear whether IL-2 is pro or anti-inflammatory. IL-2 has historically been characterized as "pro-inflammatory" in the literature; however, the role of this four a-helical bundle cytokine (Jiang et al., 2016) is not entirely clear despite over 40 years of research. IL-2 is primarily produced by CD4+ T cells, but its' receptors are also expressed by CD4+, CD8+ T cells, and other cell populations (Spolski et al., 2018). The IL-2 receptor is comprised of three subunits (α, β, and γ), and the role of IL-2 largely depends on where and how strongly it binds to other cells in the immune system these different receptors (Jiang et al., 2016). IL-2 has been used therapeutically to treat cancer for several years at high doses; however, it has a toxic profile of side effects and now is being used at lower doses in combination with other immunotherapies and cancer treatments (Jiang et al., 2016). In recent clinical studies, IL-2 has been characterized as "anti-inflammatory" (Boerrigter et al., 2017; Osburn et al., 2013) and researchers have reported IL-2 role in suppressing inflammatory responses (Lan et al., 2008), resulting in a categorization of IL-2 as both anti- and pro-inflammatory (Bessoles et al., 2008). It is clear that IL-2 plays a critical role in the activation, and suppression of the immune system, but the exact roles, behaviors, and mechanisms are still not clear. Our findings indicate that IL-2 may be central to an inflammatory process, or pathway, in BCS and that it is related to symptom severity. Further research is needed in order to better characterize the mechanisms of this association.

The inconsistency in findings on associations among self-reported symptoms and cytokines could also be explained by the nonlinear nature of associations that is common among biological and behavioral variables, another reflection of the variable roles of IL-2. It is possible that previous studies that have largely employed linear statistical tests like correlation, regression, and analysis of variance have not accurately captured the true relationships between these variables. Our group and others have reported nonlinear relationships between biomarkers and behavioral outcomes in cancer survivors (Henneghan, Palesh, et al., 2018; S. R. Kesler et al., 2016). To evaluate the nature of the relationships identified between IL-2 and perceived cognitive impairment, stress, loneliness, and fatigue, scatterplots were created and loess lines fitted to the data (0.5 span for smoothing). These plots did in fact reveal a similar curvilinear pattern between IL-2 and each of the four symptoms suggesting IL-2 is positively associated with the symptom outcomes at certain concentrations and negatively associated with the symptom outcomes at others. These plots can be found in Supplemental Figure 1.

Our study findings need to be considered within the context that all participants received chemotherapy as part of their BC treatment. Certain types of chemotherapy used to treat BC have been reported to have greater toxic effects, including anthracycline-based chemotherapy; 56.1% of our sample had a history of anthracycline chemotherapy treatment (S. R. Kesler & Blayney, 2016), but we did not find significant difference in cytokine concentrations or symptom severity in this group compared to the group without anthracycline chemotherapy history ($ps > .05$). Furthermore, there was high variability in time since chemotherapy in the sample which could impact variability in cytokine concentrations or symptom severity. However, our previous reported findings (Henneghan et al., 2020) indicated no significant correlations between time since chemotherapy, cytokine concentrations, or symptom severity in this sample.

Several study limitations should be noted. First, this is an exploratory descriptive study. Due to the small sample size, cross-sectional design, lack of comparison group, lack of power analysis, and limited statistical testing (no statistical tests for network metrics, only partial correlations tested), these findings could be due to chance. Second, our findings could also reflect a sampling bias as participants were originally recruited for a study examining cognitive functioning after BC, although they were not screened based on cognitive functioning or any other symptom severity criteria. The study needs to be replicated in a larger sample of BCS and matched control group to verify the network organization structure. Third, even though we measured 13 key anti- and pro-inflammatory cytokines, we did not examine all cytokines, so it is possible that cytokines not measured here play important roles in cytokine–symptom networks. Future studies should measure additional cytokine panels to get a more comprehensive cytokine network. Participants completed chemotherapy 6 months to 10 years prior, so it is possible that a range of symptoms occur during this wide time interval and that cytokine levels as treatment-related mechanisms may vary across time.

Conclusion

Despite these limitations, we did attain our study aim which was to describe cytokine–symptom networks using network analytics. This study provides evidence that IL-2 plays a mechanistic role in the co-occurrence of stress, loneliness, perceived cognitive impairment, and fatigue in BCS. Additional prospective research is needed to better understand the quality and strength of the associations among perceived cognitive impairment,

stress, loneliness, and fatigue and cytokines (particularly IL-2) in BCS and how these associations change over time.

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Supplemental Material

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