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Original Research

Tryptophan and Kynurenine Pathway Metabolites and Psychoneurological Symptoms Among Breast Cancer Survivors

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ABSTRACT

Background: Among breast cancer survivors, pain, fatigue, depression, anxiety, and sleep disturbance are common psychoneurological symptoms that cluster together. Inflammation-induced activation of the tryptophan-kynurenine metabolomic pathway may play an important role in these symptoms.
Aims: This study investigated the relationship between the metabolites involved in the tryptophan-kynurenine pathway and psychoneurological symptoms among breast cancer survivors.
Design: Cross-sectional study.
Setting: Participants were recruited at the oncology clinic at the University of Illinois Hospital & Health Sciences System. Participants/Subjects: 79 breast cancer survivors after major cancer treatment.
Methods: We assessed psychoneurological symptoms with the PROMIS-29 and collected metabolites from fasting blood among breast cancer survivors after major cancer treatment, then analyzed four major metabolites involved in the tryptophankynurenine pathway (tryptophan, kynurenine, kynurenic acid, and quinolinic acid). Latent profile analysis identified subgroups based on the five psychoneurological symptoms. Mann-Whitney U tests and multivariable logistic regression compared targeted metabolites between subgroups.
Results: We identified two distinct symptom subgroups (low, 81%; high, 19%). Compared with participants in the low symptom subgroup, patients in the high symptom subgroup had higher BMI ($p = .024$) and were currently using antidepressants ($p = .008$). Using multivariable analysis, lower tryptophan levels ($p = .019$) and higher kynurenine/tryptophan ratio ($p = .028$) were associated with increased risk of being in the high symptom subgroup after adjusting for BMI and antidepressant status.
Conclusion: The tryptophan-kynurenine pathway and impaired tryptophan availability may contribute to the development of psychoneurological symptoms.

Breast cancer is the most common cancer among women in the United States and it is estimated that 287,850 women will be diagnosed with invasive breast cancer in 2022 (American Cancer American Cancer Society, 2022). Approximately 75% of women with breast cancer have estrogen receptor (ER) positive disease. After surgery, chemotherapy, and radiation therapy, a minimum of 5 years of endocrine therapy is recommended for women with ER-positive early-stage breast cancer (Burstein et al., 2016).

Pain, fatigue, depression, anxiety, and sleep disturbance are the most common and distressing psychoneurological symptoms that occur and cluster together among breast cancer survivors (Doong et al., 2015; Langford et al., 2016). Up to 68% of breast cancer survivors report psychoneurological symptoms during primary cancer treatment (Starkweather et al., 2017), and 22.6% of them report a persistent high severity of fatigue, anxiety, and depression during the first 18 months of adjuvant therapy (Li et al, 2020b).

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Research suggests that previous cancer treatment, pre-treatment symptom burden, advanced disease stage, younger age, higher education level, and lower income are associated with higher levels of psychoneurological symptoms (Gehrman et al., 2016; Langford et al., 2016; Liu et al., 2009). These psychoneurological symptoms can persist for 5 to 10 years after completion of cancer treatment (Bower et al., 2006; Mejdahl et al., 2013) and have a detrimental effect on quality of life (Denieffe et al., 2014; Iwase et al., 2015; Langford et al., 2016), functional status (Langford et al., 2016), and work functioning (Dorland et al., 2016; Dorland et al., 2018).

The co-occurrence of multiple psychoneurological symptoms with the onset of cancer has led researchers to investigate what common mechanisms may underlie these symptoms. Historically, researchers have considered the model of cytokine-induced sickness behavior to be the biological mechanism that results in psychoneurological symptoms (Cleeland et al., 2003). Specifically, researchers have gathered a large amount of evidence supporting a link between increased inflammation, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and the onset of psychoneurological symptoms among cancer survivors (Kim et al., 2012; Kwekkeboom et al., 2018; Starkweather et al., 2017). Recently, inflammation-induced activation of indoleamine 2,3-dioxygenase (IDO) for the tryptophan-kynurenine metabolomic pathway has been suggested as a potential mechanism in pain, depression, fatigue, and cognitive impairment among cancer survivors (Capuron et al., 2003; Kim et al., 2015; Sforzini et al., 2019).

Tryptophan is an essential amino acid, and over 90% of available tryptophan is metabolized by the liver along the kynurenine pathway. Kynurenine is further metabolized to form either the neuroprotective metabolite kynurenic acid or the neurotoxic metabolites 3-hydroxy kynurenine and quinolinic acid (Karu et al., 2016). An imbalance between neuroprotective and neurodegenerative metabolites in the kynurenine pathway has been found among cancer survivors, mostly associated with fatigue and depression (Kurz et al., 2012; Sforzini et al., 2019). Our systematic review showed that decreased tryptophan and increased kynurenine and kynurenine/tryptophan ratio, in parallel with immune activation, are correlated with psychoneurological symptoms among cancer survivors (Li et al., 2020a). Tryptophan is also the precursor of serotonin (5-hydroxytryptamine [5-HT]). Reductions in serotonin play an important role in depression-related symptoms (Cowen & Browning, 2015). Inflammation-induced activation of IDO-1 increases degradation of tryptophan via the kynurenine metabolic pathway, making less tryptophan available for usual physiological functioning. This reaction may play an important role in psychoneurological symptoms among breast cancer survivors and warrants further investigation.

Previous studies have focused on the association between single psychoneurological symptoms and the tryptophan-kynurenine metabolomic pathway among cancer survivors undergoing IFN-α therapy or chemotherapy (Hüfner et al., 2015; Kurz et al., 2012; Lyon et al., 2018; Van Gool et al., 2008). Few of these studies have controlled for confounding factors (i.e., age, body mass index, cancer stage, pharmacologic agents). Given that symptoms of cancer and cancer treatment often linger over time after primary treatments are completed (Joly et al., 2019), it is critical to understand the common mechanisms that underlie co-occurring psychoneurological symptoms after major cancer treatments with the control of possible confounding factors. The purpose of this study was to investigate the relationship between the tryptophan-kynurenine metabolomic pathway and psychoneurological symptoms among breast cancer survivors after major cancer treatments.

Methods

Design

This cross-sectional prospective study was performed between September 2020 and August 2021. The university's institutional review board approved this study (IRB #: 2020-0315).

Sample and Setting

Breast cancer survivors were recruited from the breast oncology clinic at the University of Illinois Hospital & Health Sciences System (UI Health). UI Health has a diverse patient population that is 8% Asian, 48% Black, 24% Hispanic, and 20% non-Hispanic White. Breast cancer survivors were included in the study if they (1) were 18 years of age or older; (2) had completed major cancer treatment more than 3 months prior to study participation (to avoid the influence of surgery, chemotherapy, and radiation therapy on symptoms and metabolites); (3) had self-reported chronic pain, fatigue, depression, or sleep disturbance after cancer treatment; (4) were mentally and physically able to participate; and (5) spoke and read English. Participants were excluded if they (1) had a psychiatric condition that would interfere with study participation (i.e., diagnosis of paranoid schizophrenia or active paranoid delusional thoughts, as determined via a telephone screening assessment) or (2) were pregnant.

Procedures

Participants were identified through a list of breast cancer survivors provided by an oncology clinic. After providing informed consent, each participant completed a self-reported demographic, clinical, and symptom questionnaire. A fasting blood sample (10 cc) was collected between 8:00 and 11:00 a.m. in a red-top Vacutainer tube with no anticoagulant. After collection, we left the blood undisturbed for 30 minutes at room temperature to allow for clotting. This was followed by centrifugation at 2,000 X g for 15 minutes to allow for serum separation. The serum was then aliquoted into clean polypropylene tubes using a Pasteur pipette. Samples were then stored at −80°C until ready for processing.

Targeted metabolomics procedure

Frozen serum samples were processed and analyzed for targeted metabolomics profiling at the Metabolomics Core Facility of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. A standard protocol was used to process the samples. Serum samples were thawed at room temperature for ~30 minutes, then vortexed. Next, 25 μL of each sample was transferred to a 2 mL Eppendorf tube, combined with 150 µL high-performance liquid chromatography (HPLC) grade methanol, vortexed for 2 minutes, and stored at −20°C for 20 minutes. The extraction solution was dried using a SpeedVac. The dried samples were stored at −20°C and were reconstituted in 500 μL of 5 mM ammonium acetate in 40% water/60% acetonitrile, followed by overtaxing for 30 seconds. The samples solution was then centrifuged for 30 minutes at 20,000 g, 4°C, and the supernatant was transferred to a liquid chromatography vial for liquid chromatography-mass spectrometry (LC-MS) analysis.

Targeted metabolomics analysis was carried out by HPLC and high-resolution mass spectrometry and tandem mass spectrometry (HPLC-MS/MS) in both positive and negative ion modes. Extracts were analyzed by LC-MS using an Ultimate 3000 series HPLC (Thermo Fisher Scientific, Courtaboeuf, France) coupled with a Thermo Scientific Q Exactive mass spectrometer in line with an

electrospray source. In positive/negative polarity switching mode, an *m/z* scan range from 60 to 900 was chosen and MS1 data was collected at a resolution of 70,000. The automatic gain control target was set at 1×10^6 and the maximum injection time was 200 ms. The top five precursor ions were subsequently fragmented, in a data-dependent manner, using the higher energy collisional dissociation cell set to 30% normalized collision energy in MS2 at a resolution power of 17,500. Besides matching *m/z*, metabolites were identified by matching retention time with analytical standards and/or with MS2 fragmentation pattern.

Data acquisition and analysis were carried out by Xcalibur 4.1 software and Tracefinder 4.1 software, respectively (both from Thermo Fisher Scientific). Four major metabolites related to the tryptophan-kynurenine pathway (tryptophan, kynurenine, kynurenic acid, and quinolinic acid) were detected using a semi-quantitative LC-MS–based approach in this targeted comprehensive hydrophilic metabolite panel. We then calculated the kynurenine to tryptophan ratio (kynurenine/tryptophan) to estimate the IDO activity.

Measures

Participants self-reported their sociodemographic characteristics (e.g., age, ethnicity, race, education level, occupation, marital status) and clinical characteristics (e.g., weight, height, cancer stage, types of cancer treatments, current antidepressant use) on questionnaires.

Symptom measures

The PROMIS-29 (v1.0) is a 29-item multidimensional generic measure of health that includes seven domains: physical functioning (4 items), anxiety (4 items), depression (4 items), fatigue (4 items), sleep disturbance (4 items), satisfaction with participation in social roles (4 items), and pain interference (4 items), plus an additional single item for pain intensity. Participants rate their responses on a 5-point Likert-type scale. Raw scores for each domain are calculated by summing the item scores while adjusting for missing item responses. Raw scores are transformed using the T-score metric based on the item response theory calibrations, in which scores have a mean of 50 and standard deviation of 10 for the general population in the United States. T-scores were estimated using the scoring tables listed in the PROMIS manuals. A higher PROMIS T-score indicates more severe pain, fatigue, sleep disturbance, depressive symptoms, and anxiety. The severity level for each psychoneurological symptom was determined based on current T-score standards: pain interference (<50 normal; 50-59 mild; 60-69 moderate; ≥70 severe); fatigue (<50 normal; 50-54 mild; 55-74 moderate; ≥75 severe); anxiety/depression (<55 normal; 55-64 mild; 65-74 moderate; ≥75 severe) (Cella et al., 2014); and sleep disturbance (<45 normal; 45-55 mild; 55-60 moderate; ≥60 severe) (Rothrock et al., 2019). The PROMIS-29 is a reliable measure of symptom experiences among cancer patients with good internal consistency and convergent validity (Cronbach's alpha coefficients: 0.86–0.96) (Cessna et al., 2016; Quach et al., 2016). In this study, the PROMIS-29 showed good internal consistency with Cronbach's alpha ranging from 0.87 to 0.98. We used 20 items from the PROMIS-29 for pain interference, fatigue, sleep disturbance, depression, and anxiety in our analysis.

Statistical Analysis

Latent profile analysis (LPA) was used to identify subgroups of breast cancer survivors based on the severity of their pain, fatigue, sleep disturbance, depression, and anxiety. Latent profile analysis was performed using the "tidyLPA" package by R (Rosenberg et al., 2019). To evaluate model fit and determine final number of latent classes, a series of statistical indices were used: (a) the Akaike information criterion (Akaike, 1974); (b) the Bayesian information criterion (Schwarz, 1978); and (c) parametric bootstrapped likelihood ratio test. Consensus on statistical power for detecting classes in LPA is still emerging (Dziak et al., 2014; Tein et al., 2013). Factors such as class separation, number of classes, and indicator quality have been shown to influence power and sample size (Gudicha et al., 2016; Tein et al., 2013). Three previous studies on psychoneurological symptoms among breast cancer survivors have used LPA or LCA to identify well-separated subgroups (2 to 4) with a sample of 353 to 398 (Doong et al., 2015; Illi et al., 2012; Langford et al., 2016). These studies demonstrated that psychoneurological symptoms are highly correlated with latent class subgroups among breast cancer survivors. Adding well-separated classes and high-quality indicators that have strong relationships to the latent class subgroups to an LCA have been shown to improve correct latent class recovery (Wurpts & Geiser, 2014). For simple LCA models with well-separated classes and high-quality indicators, a sample size less than 100 may be sufficient (Nylund-Gibson & Choi, 2018). In this exploratory study, we used high-quality indicators (pain, fatigue, sleep disturbance, depression, and anxiety) with strong theoretical basis from previous studies on psychoneurological symptoms to help mitigate the destabilizing effects of a small sample size.

To identify the differences in demographic and clinical characteristics between subgroups, we used Mann-Whitney U tests for variables with skewed distributions and chi-square and Fischer's exact tests for categorical variables. Effect size was calculated by dividing the absolute (positive) standardized test statistic z by the square root of the number. Multivariable logistic regression was then performed with the psychoneurological symptom cluster subgroup as the dependent variable; this analysis included targeted metabolites and other covariates with a reported $p < .10$ in the univariate analyses. Covariates for the multivariable logistic regression included age, race, education level, body mass index (BMI), cancer stage, and use of antidepressants. A statistical threshold of $p < .05$ was used for determining statistical significance. Statistical analyses were performed in SPSS Statistics version 27 (IBM).

Results

Participant characteristics

Table 1 summarizes demographic and clinical characteristics for the total sample and by symptom subgroup. Of a total of 79 breast cancer survivors, 55 were Black (69.6%) and the average age was 57 years (SD = 9.7). Most participants were non-Hispanic (88.6%), not married (68.4%), and had college as the highest degree completed (43%). Most had stage I breast cancer (88.6%); average BMI was 30.9 (SD = 7.2); and 21.5% of participants were taking an antidepressant. Based on the PROMIS T score cut points for cancer survivors (Cella et al., 2014; Rothrock et al., 2019), participants had mild pain (57.7 ± 9.7), fatigue (53.1 ± 9.5), sleep disturbance (54.3 ± 8.7), anxiety (56.7 ± 9.8), and normal depression (52.4 ± 9.6).

Psychoneurological symptom subgroup membership and its related factors

Two distinct symptom subgroups were identified based on the severity (low versus high) of the psychoneurological symptom cluster (pain, fatigue, sleep disturbance, depression, and anxiety).

Table 1
Demographic and Clinical Characteristics (N = 79)

Characteristic	Total (N = 79)	High symptom subgroup (n = 15)	Low symptom subgroup (n = 64)	*p* value
	Mean ± SD or n (%)			
Age (y)	56.6 ± 9.6	52.8 ± 10.8	57.6 ± 9.3	.510
Race				.126
White	15 (19.0%)	5 (33.3%)	10 (15.6%)	
Black	55 (69.6%)	10 (66.7%)	45 (70.3%)	
Other	9 (11.4%)	0 (0%)	9 (14.1%)	
Married/partnered				.876
Yes	25 (31.6%)	5 (33.0%)	20 (31.1%)	
No	54 (68.4%)	10 (67.0%)	44 (68.9%)	
Ethnicity				.224
Hispanic	9 (11.4%)	3 (20.0%)	6 (9.4%)	
Non-Hispanic	70 (88.6%)	12 (80.0%)	58 (90.6%)	
Highest education				.799
High school	21 (26.6%)	4 (28.6%)	17 (27.0%)	
College	34 (43.0%)	7 (50.0%)	27 (42.9%)	
Graduate	22 (27.8%)	3 (21.4%)	19 (30.2%)	
Body mass index (kg/m^2)	30.9 ± 7.2	35.5 ± 9.3	29.9 ± 6.2	.024[a]
Cancer stage				.346
0	9 (11.4%)	2 (13.3%)	10 (16.1%)	
I	70 (88.6%)	6 (40%)	29 (46.8%)	
II	21 (26.6%)	4 (26.7%)	17 (27.4%)	
III	6 (7.6%)	1 (6.7%)	5 (8.1%)	
IV	3 (3.8%)	2 (13.3%)	1 (1.6%)	
Previous chemotherapy				.567
Yes	53 (67.1%)	11 (73.3%)	42 (65.6%)	
No	26 (32.9%)	4 (26.7%)	22 (34.4%)	
Taking antidepressant				.008[b]
Yes	17 (21.5%)	7 (46.7%)	10 (15.6%)	
No	62 (78.5%)	8 (53.3%)	54 (84.4%)	
PROMIS T-scores				
Pain	57.7 ± 9.7	62.4 ± 8.4	56.6 ± 9.7	0.037[a]
Fatigue	53.1 ± 9.5	63.7 ± 6.1	50.6 ± 8.4	<0.001[b]
Sleep disturbance	54.3 ± 8.7	66.0 ± 3.6	51.6 ± 7.1	<0.001[b]
Depression	52.4 ± 9.6	58.3 ± 8.8	51.0 ± 9.3	0.007[b]
Anxiety	56.7 ± 9.8	64.5 ± 9.5	54.9 ± 9.1	<0.001[b]

p values are from Mann-Whitney U test and Chi-square and Fischer's exact tests.
PROMIS: Patient-Reported Outcomes Measurement Information System.
[a] $p < .05$.
[b] $p < .01$.SD = standard deviation.

Approximately 19% (n=15) of the participating breast cancer survivors were in the high symptom subgroup, reporting high severity of pain, fatigue, sleep disturbance, depression, and anxiety.

Based on the Mann-Whitney U test and chi-square statistics, BMI ($p = .024$) and antidepressant status ($p = .008$) were significantly different between the symptom subgroups. Breast cancer survivors in the high symptom group had a higher BMI and were more likely to be taking antidepressants compared with the low symptom group. There were no significant differences in subgroup membership in relation to any of the demographic characteristics.

Based on the PROMIS T score cut points for cancer survivors (Cella et al., 2014), participants in the high symptom group had significant higher severity of pain interference (moderate versus mild, $p = .037$), fatigue (moderate versus mild, $p < .001$), sleep disturbance (moderate versus mild, $p < .001$), depression (mild versus normal, $p = .007$), and anxiety (mild versus normal, $p < .001$) than participants in the low symptom group.

Subgroup membership and tryptophan-kynurenine metabolism

Using a semiquantitative LC-MS–based approach (Malm et al., 2021), we detected four major metabolites related to the tryptophan-kynurenine metabolomics pathway (tryptophan, kynurenine, kynurenic acid, and quinolinic acid). The kynurenine to tryptophan ratio (kynurenine/tryptophan) is widely used to estimate IDO activity. Table 2 lists the serum levels of these metabolites as measured by LC-MS and expressed in relative units corresponding to chromatographic peak areas across two subgroups. Levels of tryptophan were significantly lower in breast cancer survivors in the high symptom subgroup ($p = .029$, d = .248).

In the multivariable logistic analysis, the only metabolites that remained significant with the control of covariates (BMI, antidepressant status) were tryptophan and kynurenine/tryptophan ratio (see Table 3). Kynurenine ($p = .271$), kynurenic acid ($p = .397$), and quinolinic acid ($p = .401$) were not significant with the control of covariates. Lower tryptophan levels (beta = −0.001, $p = .019$), higher BMI (beta = 0.113, $p = .003$), and currently taking antidepressants (beta = 1.768, $p = .015$) were associated with increased risk of being in the high symptom subgroup in model 1. Higher kynurenine/tryptophan ratios (beta = 0.696, $p = .028$), higher BMI (beta = 0.105, $p = .028$), and currently taking antidepressants (beta = 1.532, $p = .029$) were associated with increased risk of being in the high symptom subgroup in model 2.

Discussion

This study demonstrates a significant association between the psychoneurological symptom cluster among breast cancer survivors and reduced tryptophan availability through the kynurenine pathway. Importantly, this association remained significant after controlling for BMI and antidepressant status. Previous studies have focused on the association between a single psychoneurological symptom and the tryptophan-kynurenine metabolomic pathway

Table 2
Metabolites of the Tryptophan-Kynurenine Pathway by Subgroup

Metabolites	High symptom subgroup	Low symptom subgroup	Effect size	*p* value
Tryptophan	227.50 (72.83)	283.86 (107.63)	0.248	.029[a]
Kynurenine	9.56 (3.20)	10.49 (2.92)	0.070	.539
Kynurenine/tryptophan ratio	0.044 (0.01)	0.037 (0.01)	0.209	.065
Kynurenic acid	0.34 (0.27)	0.28 (0.17)	0.031	.785
Quinolinic acid	0.65 (0.56)	0.55 (0.29)	0.034	.766

Note: *p* values are from Mann-Whitney U test. Tryptophan-kynurenine metabolites: *arbitrary units corresponding to peak area/5* $\times$ 10^4. Effect size was calculated by dividing the absolute (positive) standardized test statistic z by the square root of the number.
[a] $p < .05$.

Table 3
Multivariate Logistic Regression Models for Predictors of Subgroup Membership

Predictors	Beta	*OR*	Z	95% CI	*p* value
Model 1					
Tryptophan	-0.001	0.998	5.462	[0.997, 0.999]	.019[a]
Antidepressant[b]	1.768	5.857	5.755	[1.382, 24.821]	.016[a]
BMI[c]	0.113	1.120	5.239	[1.016, 1.233]	.022[a]
Overall fit: $\chi^2 = 7.889$, $df = 8$, $p = .444$, Nagelkerke $R^2 = .330$					
Model 2					
Kynurenine/ tryptophan ratio	0.696	2.005	4.853	[1.080, 3.723]	.028[a]
Antidepressant[b]	1.523	4.588	4.744	[1.165, 18.073]	.029[a]
BMI[c]	0.105	1.110	4.835	[1.011, 1.219]	.028[a]
Overall fit: $\chi^2 = 8.312$, $df = 8$, $p = .404$, Nagelkerke $R^2 = .310$					

Note: Kynurenine/tryptophan ratio presented values are kynurenine/tryptophan x 100.
[a] $p < .05$.
[b] Current use of antidepressant was reported as Yes or No, with No as the reference group.
[c] BMI was reported in numbers.BMI = body mass index; CI = confidence interval; OR = odds ratio.

among cancer survivors undergoing IFN-α therapy or chemotherapy (Hüfner et al., 2015; Kurz et al., 2012; Lyon et al., 2018; Van Gool et al., 2008). To our knowledge, this is the first study to evaluate the association between the psychoneurological symptom cluster and metabolites involved in the tryptophan-kynurenine pathway among breast cancer survivors who have completed major cancer treatment.

In this study, we identified two subgroups of breast cancer survivors based on the severity of pain, fatigue, sleep disturbance, depression, and anxiety after major cancer treatments. Approximately 19% of breast cancer survivors experienced higher severity of psychoneurological symptoms. This result was consistent with our previous study that 22.6% of postmenopausal women experienced higher severity of fatigue, depression, and anxiety during 18 months of adjuvant therapy (Li et al., 2020b). Recently, Whisenant et al. (2022) also identified two subgroups (77% low, 23% high) of breast cancer survivors based on their symptom burden after major cancer treatment. Some studies have identified 3 subgroups based on the severity of pain, fatigue, sleep disturbance, and depression among breast cancer survivors prior to breast cancer surgery (Doong et al., 2015) and during major cancer treatments (Crane et al., 2020). Heterogeneity of psychoneurological symptoms does exist among breast cancer survivors at different stages of cancer treatment and survivorship.

To explain our current findings, the following mechanisms can be proposed. First, breast cancer survivors usually experience a great amount of stress, both during and after cancer treatment (Alagizy et al., 2020). In response to stress, cortisol levels elevate and therefore enhance tryptophan-2,3-dioxygenase (TDO) activity (Huang et al., 2020). Second, cancer treatments such as chemotherapy and radiation therapy can cause inflammation, which enhances the activity of IDO. Higher levels of pro-inflammatory cytokines are observed in breast cancer survivors prior to cancer treatment (Patel et al., 2015), during chemotherapy (Lyon et al., 2016), and up to 5 years after chemotherapy (Kesler et al., 2013). Together, the rate-limiting enzymes TDO and IDO, stimulated and induced by increased levels of cortisol and inflammatory cytokines, catabolize tryptophan to kynurenine along the kynurenine pathway, ultimately forming immunomodulatory metabolites, such as the neurotoxic metabolites 3-hydroxykynurenine and quinolinic acid, and the neuroprotective metabolite, kynurenic acid. This imbalance of neurodegenerative and neuroprotective effects along the kynurenine pathway can lead to the psychoneurological symptoms observed in people with depression (Ogyu et al., 2018) and Alzheimer's disease (Zwilling et al., 2011).

In this study, we identified a significant weak correlation between tryptophan level, kynurenine/tryptophan ratio, and the psychoneurological symptom cluster subgroups, with a small effect size and correlation coefficient. Consistent with our study, tryptophan depletion and dysregulation of the kynurenine pathway have been reported in psychoneurological symptoms among other populations of cancer survivors. Fosså et al. (2020) found that decreased tryptophan levels and increased kynurenine/tryptophan ratios were observed in fatigued cancer survivors. Hüfner et al. (2015) found that breast cancer survivors with higher anxiety had increased kynurenine/tryptophan ratios and neopterin levels (another marker of inflammation), with small effect sizes. Together, these findings suggest that the tryptophan-kynurenine metabolomic pathway and impaired tryptophan availability have a weak correlation with psychoneurological symptoms.

In our study, between-group differences in the kynurenine/tryptophan ratio became significant after adjusting for antidepressant status and BMI. We note that 21% of the participating breast cancer survivors were taking antidepressant medications. While the mechanisms by which antidepressants affect the kynurenine pathway are not clearly understood, clinical studies have reported that dysfunction in the kynurenine pathway is likely to be normalized by antidepressant treatment (Lyon et al., 2016). The increased levels of 5-HT in individuals taking antidepressants may lead to compensation in the kynurenine pathway to

increase metabolism from tryptophan to kynurenine (Réus et al., 2015). Therefore, it is important to control for antidepressant status when evaluating the relationship between metabolites involved in the tryptophan-kynurenine pathway and psychoneurological symptoms.

A meta-analysis has reported that up to 32.2% of breast cancer survivors experienced depression (Pilevarzadeh et al., 2019). Depression can affect physiological function, adherence to recommended treatment, and quality of life in breast cancer survivors, and is associated with a 24% increase in the risk of cancer recurrence (Wang et al., 2020). It is critical for health care providers to screen for depression among breast cancer survivors, not only at the time of cancer diagnosis but also years after the major cancer treatment.

Limitations

Limitations of the current study include, first, the relatively small sample size. Even though we used high-quality indicators with strong theoretical basis from previous research to help mitigate the destabilizing effects of a small sample size, our small sample size can cause convergence issues, inadequate power to detect latent classes, and improper and unstable solutions (Nylund-Gibson & Choi, 2018). Future studies are thus needed to validate our findings in a larger sample. Second, because this is our first pilot study on this topic, the tryptophan metabolites and tryptophan-kynurenine derivatives were only semi quantified. Based on the results and the signal of the semi quantification, we expect that future studies can quantify the absolute concentrations. In this study, we only conducted targeted metabolomics with specific metabolites. Nontargeted metabolomics can analyze more unknown metabolites comprehensively and systematically. Future studies can conduct both targeted and untargeted metabolomics to have a more comprehensive understanding of the metabolomic mechanisms of psychoneurological symptoms. Third, this is a cross-sectional study; therefore, we were not able to identify causal relationships between psychoneurological symptoms and tryptophan-kynurenine metabolism. Future longitudinal studies will be needed to evaluate the relationships between psychoneurological symptoms and the targeted metabolites using more time points.

Conclusions

The present study demonstrates a cross-sectional association between the psychoneurological symptom cluster among breast cancer survivors and a reduction of tryptophan availability through the kynurenine pathway. Our results raise the possibility that alterations of kynurenine metabolism and impaired tryptophan availability may enable understanding of the biological mechanisms associated with the severity of psychoneurological symptoms among breast cancer survivors. If so, future interventions can be developed to target the tryptophan-kynurenine metabolomic pathway toward better management of psychoneurological symptoms and the psychoneurological symptom cluster.

Clinical Implications

This study provides preliminary evidence to support the development of interventions targeting tryptophan metabolism to manage psychoneurological symptoms. Animal and human studies have found that the tryptophan pathway is highly susceptible to modulation by nutritional and lifestyle-related factors (Gostner et al., 2020). Because of the importance of the cross-talk between the gut and microbiome to tryptophan metabolism, microbiota can be a source of tryptophan and tryptophan-derived metabolites (Laurans et al., 2018). Tryptophan can be found in some foods, such as soybeans, grains, seeds, cashews, walnuts, peanuts, almonds, and salmon (Strasser et al., 2016). A tryptophan-rich diet is a potential protective factor against depression and is positively related to functioning in social cognition (Reuter et al., 2021). Elderly people who consumed cereals containing the higher dose in tryptophan had increased sleep efficiency, actual sleep time, and decreased total nocturnal activity (Bravo et al., 2013). Therefore, nurses and health care providers can encourage breast cancer survivors to consume a diet rich in tryptophan, which may have a positive effect on mood and physical symptoms. In addition to diet, a recent systematic review shows that exercise has significant effects on the kynurenine pathway and psychological outcomes (Lim et al., 2021). Evidence also suggests that acupuncture (Li et al., 2020) and yoga (Gupta et al., 2022) may have positive effects on the tryptophan- kynurenine pathway in managing depression and chronic pain. Nurses and researchers can start to develop dietary, complementary, and integrative health interventions that can regulate the tryptophan-kynurenine metabolomic pathway to manage psychoneurological symptoms among breast cancer survivors.

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