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Differences in Emotional Awareness Moderate Cytokine-Symptom Associations Among Breast Cancer Survivors

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ABSTRACT

Cancer survivors have elevated levels of proinflammatory cytokines, which could be associated with cancer-related symptoms. Given that proinflammatory cytokines heighten negative affect by directly affecting the brain, we explored these direct associations and whether differences in levels of emotional awareness moderate the associations between proinflammatory cytokines and cancer-related symptoms. This cross-sectional, secondary analysis of baseline data was collected from 162 female breast cancer survivors (aged 36–70 years), who were enrolled 6 ± 4 months after completing cancer treatment. We tested cytokines in serum (IL-1β, IL-6, IL-8, TNF-α, IL-4, IL-10, and TGF-β) and assessed depression, cancer-related fatigue, pain intensity, and pain interference. Emotional awareness was assessed using a performance measure, the Levels of Emotional Awareness Scale. In participants with high but not average or low levels of emotional awareness, positive associations were found for IL-1β, IL-6, and TNF-α with depression and between IL-6 and TNF-α with pain intensity. In addition, IL-6 had a positive association with pain intensity at average levels of emotional awareness. These results suggest that women with high or in some cases average, but not low, emotional awareness reported depression and pain as being positively associated with their cytokine levels. By using emotional awareness as a cognitive resource to promote emotion regulation and distress transformation, interventions may be able to counteract heightened sensitivity to the mood-altering effects of cytokines.

1. Introduction

Approximately 20% to 66% of breast cancer survivors (BCS) experience cancer-related symptoms, such as depression (Pilevarzadeh et al., 2019), cancer-related fatigue (CRF; Abrahams et al., 2016), and pain (Wang et al., 2018), following treatment completion, which may last more than 10 years after diagnosis (Maass et al., 2015). Cancer, its treatment, and cancer-related symptoms—along with intense, persistent, and negative emotions—have been associated with elevated cytokine secretion (Renna et al., 2020). Proinflammatory cytokines are known for inducing sickness behaviors, including depression (McFarland et al., 2022), affective dysregulation, cognitive impairment, insomnia, reduced grooming, and social interaction that conserves resources and energy (Myers, 2008; Patton et al., 2021).

The main cytokines included in studies among BCS and associated with cancer-related symptoms (De Groote et al., 2024; Eyob et al., 2016; McFarland et al., 2022; Patton et al., 2021; Saligan & Kim, 2012) have been proinflammatory interleukin-1 (IL-1), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), anti-inflammatory (downregulate inflammation) interleukin-4 (IL-4), interleukin-10 (IL-10), and tumor growth factor (TGF-β, Dantzer et al., 2008). Although associations between these cytokines and cancer-related symptoms have been widely observed, the studies' results have not always been consistent, and associations with pain have been

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understudied with inconclusive evidence.

A meta-analysis among cancer patients ($n = 5{,}017$) reported that the most studied cytokines, IL-6 and TNF-α, were positively associated with depressive symptoms, whereas IL-1β, IL-4, IL-10, and TGF-β were not (McFarland et al., 2022). A systematic review among advanced cancer patients ($n = 1{,}806$) found that only IL-6 was associated with depression (Patton et al., 2021). Another systematic review found inconsistent associations of IL-6 and TNF-α with CRF among seven cross-sectional studies (Saligan & Kim, 2012). Among cancer patients receiving chemotherapy (in a systematic review of $n = 1{,}312$), cytokines had differential associations with CRF depending on the type of chemotherapy regimen (Eyob et al., 2016). A recent systematic review among cancer survivors with chronic pain ($n = 321$, eight studies, six cancer types) reported moderate evidence for an association between IL-6 and pain intensity and inconclusive evidence for an association with pain interference (De Groote et al., 2024). In that systematic review, no significant results were found between IL-β, TNF-α, and pain intensity and interference. The review concluded that chronic pain associated with cytokines following cancer was still underrecognized and more post-cancer treatment studies were warranted.

Given the suggested effect of proinflammatory cytokines on negative affect and mood (McFarland et al., 2022; Patton et al., 2021), we were interested in exploring whether emotional abilities related to emotion regulation might explain the variability in associations between proinflammatory cytokines and cancer-related symptoms. To our knowledge, only one longitudinal study (involving 136 BCS) has examined the moderating role of acceptance of emotion on the relationship between proinflammatory cytokines and sickness symptoms (e.g., physical, emotional, and functional well-being). That study found no overall association between mean levels of acceptance of emotions and sickness symptoms, and acceptance of emotions did not moderate the association between sickness symptoms and TNF-a. For IL-8, it's mean level was positively correlated with sickness symptoms across multiple time points in the second year after breast cancer treatment when the mean level of acceptance of emotion was high but not low. At individual time points, however, higher IL-8 and TNF-a were associated with higher sickness symptoms only when acceptance of emotion was lower than but not higher than the individual's average (Reed et al., 2016).

To link that finding with the present study, we reasoned that awareness of an emotional state is a prerequisite for accepting emotions. People use *emotional awareness (EA)* to recognize and describe emotional states in themselves and others (Lane & Schwartz, 1987). Therefore, EA may facilitate the acceptance of emotions and have a similar moderating effect on the positive correlation of proinflammatory cytokines and symptoms. A growing body of studies using the Levels of Emotional Awareness Scale (LEAS) suggests that higher EA may facilitate effective emotional regulation, such as reappraisal (Subic-Wrana et al., 2014), increased interoception, and better mental and physical health. Nevertheless, findings across studies have been inconsistent (Lane & Smith, 2021).

To date, the only studies on the association between physiological regulation and EA have involved heart rate variability or cardiac vagal tone and observed a positive association between the two (Spangler et al., 2024; Verkuil et al., 2016). The autonomic nervous system's efferent influence on the heart (which may be assessed through heart rate variability) was also involved in regulating the inflammatory reflex. Negative associations between indices of heart rate variability and proinflammatory cytokines were found in a meta-analysis (Williams et al., 2019). Importantly, cytokines were thought to influence emotional states through vagal afferents and have direct effects on the brain (Dantzer et al., 2008). It has been well-established that proinflammatory cytokines induce a bodily state of sickness, including fatigue (Saligan & Kim, 2012), heightened pain (De Groote et al., 2024; Patton et al., 2021), psychomotor slowing (Dantzer et al., 2008), and depressed mood (McFarland et al., 2022). However, these sickness states may also increase proinflammatory secretion through the creation of negative affect (Renna, 2021).

The three-process model of implicit and explicit emotion (Smith, 2020) might explain the associations between cytokines, affect, EA, physiological regulation, effective emotional regulation strategies, and symptoms. The model specifies that variations in EA result from the interaction of three processes: (1) bodily activation associated with emotion, (2) affective response representation (conceptualization and expression in language), and (3) conscious access, such as attention (Smith, 2020). Conscious access to an emotional experience (the third process) requires the first and second processes. Once an emotional experience becomes conscious, it may enable flexible cognitive, goal-directed, decision-making processes, including effective emotion regulation.

Proinflammatory cytokines may correspond to bodily activation, the physiological basis of a negative affective response (Myers, 2008). In contrast, high EA supports processes of affective representation and conscious access. One study found that high EA is associated with high differentiation between somatic symptoms (e.g., headache, sore throat, and tiredness; Lane et al., 2011). Therefore, participants with high EA may be more sensitive to the bodily activation cytokines induce. The negative affect induced by cytokines may be processed through affective representations and, according to the three-process model, may achieve conscious access to affect and representation. Because conscious access might facilitate effective emotional regulation strategies, symptoms may be regulated by reducing psychological distress (differentiating between somatic symptoms) or other emotional regulation strategies (e.g., reappraisal; Baziliansky & Cohen, 2021; Durosini et al., 2022). Therefore, if EA is associated with cognitive emotional regulation strategies (e.g., reappraisal or increased interoception), it potentially moderates the associations between cytokines and symptoms.

As survival rates for BCS increase and a growing number of survivors experience cancer-related symptoms, identifying factors that moderate the association between proinflammatory cytokines and cancer-related symptoms could improve understanding of the role of emotion-regulation tendencies in developing targeted interventions to reduce symptoms. Based on these considerations, this study aimed to examine the direct associations between proinflammatory cytokines and cancer-related symptoms and the moderating role of EA. The direction of this moderation was unspecified (exploratory) in light of a previous longitudinal study (Reed et al., 2016) of BCS, that found a positive link between proinflammatory cytokines and cancer-related symptoms only when the mean level of emotional acceptance across all time points was high. However, at individual time points when emotional acceptance was higher than the participant's average, no significant association between proinflammatory cytokines and symptoms was found. This suggests higher trait emotional acceptance is associated with greater linkage between cytokines and symptoms. However, the cytokine/symptom association is decoupled at particular points in time when emotional acceptance is elevated. Also, although not observed among BCS, or in relation to proinflammatory cytokines, given the potential benefits of EA in promoting mental and physical health (Lane & Smith, 2021) higher EA might be associated with a weaker relationship between cytokines and symptoms.

2. Methods

2.1. Participants and Procedure

This study was a cross-sectional secondary analysis of baseline data from the randomized controlled trial, "The Role of Emotional Processing in Art Therapy for Breast Cancer Patients" (REPAT). See Czamanski-Cohen et al. (2019) for that study's protocol and Czamanski-Cohen and Weihs (2023) for the intervention protocol. The REPAT was a mechanistic study examining emotional processing and cholinergic anti-inflammatory pathways as mechanisms of the effect of an art therapy intervention on cancer-related symptoms. It was administered at the

Integrative Oncology Medicine unit of the Davidoff Center for Cancer Treatment at Rabin Medical Center, Israel, and in the Israeli community between May 2019 and March 2022. The Helsinki Committee of Beilinson Hospital (0778–17-RMC) and the Faculty of Social Welfare and Health Sciences Ethics Committee at the University of Haifa (234/18) approved the study. Electronic data capture was used to collect and manage the research data (Harris et al., 2019). Participants were informed that they could leave the study at any time without affecting their treatment and received the equivalent of 200 USD in Israeli currency to cover participation expenses.

Inclusion criteria were (a) adult (> 18 years) female BCS with initial diagnosis, first recurrence of breast cancer, or second primary breast cancer; (b) no less than 3 months after completion of chemotherapy or radiation therapy, no less than 1 month after surgery (lumpectomy, mastectomy, or reconstructive surgery), and no more than 18 months after the end of treatment; and (c) could complete the assessments in Hebrew. Exclusion criteria were (a) any history of diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorder or (b) fibromyalgia or chronic fatigue syndrome; (c) responded yes when asked if they had an active suicide plan (if so, they were removed from the study and given phone numbers to contact health care therapy and support); and (d) dementia or other cognitive disorder that would preclude informed consent. For details regarding the rationale for inclusion and exclusion criteria, see Czamanski-Cohen et al.'s (2019).

We recruited 179 Jewish participants for the study. Of these, 17 did not provide blood samples, resulting in a sample size of 162 participants. A priori power analysis using G*Power for multiple regression analysis with 14 (study and background) variables showed that a sample size of 135 participants was sufficient for analysis at a power of 0.80 and $\alpha = 0.05$ (medium effect size; Cohen, 1992).

Any additional or replacement standard medical treatment for cancer was allowed. For blood collection, participants were required to fast and refrain from smoking, exercising, and drinking coffee for at least 12 hours before the blood collection (see Czamanski-Cohen et al., 2019). However, if necessary, a light meal could be eaten 2 hours before the collection. Between 7:00 a.m. and 11:00 a.m., 10cc of blood was collected from each participant into a serum separator tube, kept on ice for a maximum of 4 hours, and then centrifuged for serum separation at 1000xg for 15 min. Serum samples were stored at -80C° until the day of the assay.

2.2. Measures

2.2.1. Demographic and medical information

Sociodemographic data (categorical variables like age, marital status, education, household income, and religiosity), lifestyle habits (e.g., smoking, Mediterranean diet, alcohol consumption), and medical information (e.g., cancer diagnosis, cancer stage, medical treatment, and date of last treatment) were collected through participant self-reports or medical record reviews.

2.2.2. Emotional awareness

To measure EA, we used the 10-item version (Subic-Wrana et al., 2005) of the LEAS, a performance measure of the ability to differentiate and integrate emotions and feelings (Lane et al., 1990). In response to a vignette of a daily life situation, participants wrote about their expected feelings and the other person's feelings using the word *feel* in their answers. Trained raters manually scored the participants' handwritten LEAS responses using a word glossary according to the EA levels. Each vignette received two scores (one for the self and one for the other) between 0 and 4. A total score (0–5) was calculated based on the self and other scores: A score of 5 would be obtained when the participant rated the feeling mentioned in the self and the other as 4 and the ratings reflected different feelings. The summary score for all 10 vignettes was between 0 and 50, with higher scores reflecting greater differentiation and awareness of emotional complexity in self and others. The theory and scale assessed five developmental levels from *implicit or preconscious* EA (Levels 0–2, scores 0–20) to *explicit and conscious* EA (Levels 3–5, scores 30–50; Lane et al., 1990).

Two bilingual experts translated the LEAS from English into Hebrew for this study using the back-translation method and pretested it in a validation study (not yet published). In our study, the Cronbach's alpha of the LEAS total score was 0.80 for internal consistency and 0.90 for interrater reliability.

2.2.3. Depression

We used the Center for Epidemiologic Studies-Depression (CES-D) 10-item measure to assess depression on a four-point frequency scale from 1 (*never*) to 4 (*most of the time*). Participants were asked to recall their previous week and rate how frequently they experienced depression-related symptoms, such as "did not sleep well" and "felt sad and depressed." The Cronbach's alpha for the Hebrew CES-D has been reported as 0.71 (Cwikel & Segal-Engelchin, 2005) and was 0.63 in the present study.

2.2.4. Fatigue

The Fatigue Symptom Inventory (FSI) 13-item scale was developed to measure CRF intensity (four items), perceived interference with quality of life (seven items), and duration (two items (Hann et al., 1998). The FSI in our study was based on a Hebrew translation (Cohen & Fried, 2007). Intensity and interference were rated on an 11-point Likert scale, and duration was rated on 8- and 11-point Likert scales. The duration was measured by the number of days fatigue was present in the past week and the percentage of time it was present each day (α =.95). A total relative mean score was calculated for each fatigue dimension. The correlations between fatigue, duration, intensity, and interference ranged from $r = 0.64$ to $r = 0.75$.

2.2.5. Pain intensity and interference

The Patient-Reported Outcomes Measurement Information System (PROMIS) has been translated from English into Hebrew and validated (Northwestern University, 2023) with the Pain Interference Scale (six items; Amtmann et al., 2010) and the Pain Intensity Scale (three items). Respondents used a five-point Likert scale to rate how often pain interfered with daily tasks in the past 7 days and how intensely the pain affected different aspects of their life (Amtmann et al., 2010; Cella et al., 2007). Each measure's item-level calibration *t* score was calculated based on the raw scores. In our study, Cronbach's alpha for internal consistency was 0.95 for pain interference and 0.87 for intensity.

2.2.6. Cytokines

Concentrations of multiple cytokines (IL-1β, IL-6, IL-8, TNF-α, IL-4, IL-10, and TGF-β) in the participants' serum were quantified using the commercial Luminex® System human cytokine/chemokine kit (R&D Systems, USA), a MAGPIX® reader, and Milliplex Analyst software. A fluorescent microsphere imager, the Luminex System uses color-coded magnetic microspheres as a substrate upon which assays are performed and a magnet device to hold the microspheres in position. Two light-emitting diodes illuminate the particles while closed-circuit cameras capture images of each well based on the color-coded magnetic microsphere signal.

2.3. Statistical analyses

For participants with 20% or fewer missing responses, we performed item mean imputation within each participant's scale (Downey & King, 1998). Results from the cytokines assay with more than a 20% coefficient of variance (CV%) between duplicates of the same serum were deleted from further analysis (Chaturvedi et al., 2011). The intra-assay CV% was calculated by dividing the standard deviation of each duplicate value by the means of the duplicate values and multiplying by 100. The average CV% for each cytokine across all assays was reported as the intra-assay CV%. The Luminex platform kit does not use controls (it uses standard curves); therefore, inter-assay variability could not be determined. The estimated intra-assay CV% for all cytokines ranged from 2.9% to 6.52% and, thus, were within the acceptance criteria (see Table 1). Some cytokines had large ranges, a large portion of low percentages, or no detectable cytokine values (e.g., IL-10 in 103 participants). Therefore, IL-8, IL-10, IL-4, and TGF-β were removed from further analysis. The first author (KH), supervised by the fifth author (MD), conducted the assays at the psychosomatic laboratory of the Emili Sagol Creative Arts Therapies research center.

We used IBM SPSS (Version 25) to test the study hypotheses. Descriptive statistics with means and standard deviations were first calculated for all sociodemographic and medical variables. Pearson correlations were used to assess the direction and strength of associations between cytokines, EA, and cancer-related symptoms. They also examined associations between sociodemographic, and medical variables, with study variables to control for potential confounders in the regression analyses. We conducted stepwise multiple regression analyses controlling for background variables (those associated with the dependent variables) to assess the adjusted variance of each cancer-related symptom explained by cytokines. The stepwise multiple regression analyses accounted for the combined effects and controlled confounding variables.

We used PROCESS for SPSS with 5,000 bootstrap samples to assess the moderating role of EA on the relationship between cytokines and cancer-related symptoms while accounting for covariate background variables (Model 1). We used the 16th, 50th, and 84th percentiles, as Hayes and Rockwood (2017), recommended to guarantee that the probed points were within the observed data range. However, using one standard below/above mean made no difference within the current results. We used the Johnson-Neyman (J-N) technique to examine conditional effects at specific EA levels where cytokines were statistically and significantly (and non-significantly) associated with cancer-related symptoms, including the direction of the association (Hayes & Rockwood, 2017). This technique is particularly useful when relationships between two variables (here, cytokines and cancer-related symptoms) are not constant across all levels of the moderator (here, EA). We applied the Benjamini-Hochberg procedure to account for multiple comparisons. This method is recommended for controlling false discovery rates and balancing between type 1 and type 2 errors (Thissen et al., 2002).

3. Results

3.1. Study sample

The participants ranged in age from 26 years to more than 70 years, 70.4% were married or in a long-term relationship, and 79.6% had more than 14 years of education. Approximately half were employed, and more than 80% had average or above income. Most (78.4%) participants had been diagnosed with Stage 0 to 2 cancer and underwent surgery and radiotherapy. The REPAT baseline assessment used in the present study was conducted 14 months after cancer diagnosis and 6 months after cancer treatment ended. See Table 2 for full details of participants' demographics and medical information.

Table 2
Demographic Characteristics of Participants.

Demographic/characteristic	*n* (%)	*M* (*SD*)
Age (years)		
26–35	4 (2.5)	
36–45	31 (19.1)	
46–70	110 (67.9)	
Older than 70	17 (10.5)	
Education		
High school and below	32 (19.8)	
Certificate and above	129 (79.6)	
Employed	93 (57.4)	
Income		
Below average	21 (13)	
Average	81 (50)	
Above average	58 (35.8)	
Married or in a long-term relationship	114 (70.4)	
Has children	143 (88.3)	
Cancer stage		
0–1	61 (37.7)	
2	66 (40.7)	
3	22 (13.6)	
4	8 (4.9)	
Treatment[a]		
Chemotherapy	96 (59.3)	
Radiotherapy	135 (83.3)	
Surgery	150 (92.6)	
Hormonal (aromatase inhibitors, tamoxifen, letrozole)	125 (77.2)	
Biological	32 (19.8)	
Months from the end of treatment to the baseline		6.05 (4.0)
Months from diagnosis to the baseline		13.45 (5.8)
Body mass index		26.7 (5.2)

Note: [a]Treatment combinations are possible.

3.2. Associations between study variables

The participants' mean levels of cancer-related symptoms (depression, CRF, and pain intensity and interference) were above clinical cutoff points (see Harel et al., 2023, for detailed levels). The mean level of total EA was 28.71 ($SD = 6.66$), between the *implicit* (Levels 0–2) and *explicit* (Levels 3–5) levels. All cytokines were strongly intercorrelated (r = 0.82–.90, $p < 0.01$). Cancer-related symptoms were moderately to strongly intercorrelated (r = 0.24–.80, $p < 0.01$), and EA was not significantly associated with any variable. Several statistically significant but weak correlations (r = 0.16–.23, $p < 0.05$) were found between the cytokines (IL-6, IL-1β, and TNF-α) and the cancer-related symptoms (depression, CRF, and pain interference and intensity). See Table 3 for details.

Table 4 presents Pearson correlations of the background variables (sociodemographic and medical) with the other study variables: dependent and independent (cancer-related symptoms and cytokines) and the moderator (EA). Only *level of income* was significantly associated with the dependent variables depression and CRF ($r = -0.27$, $p < 0.01$). See Table 4 for details.

Stepwise multiple regression analyses were used to assess the associations between cytokines and cancer-related symptoms when adjusting for medical and demographic variables. Only *income level* was included and controlled for in these analyses because no other sociodemographic or medical variable was associated with the dependent

Table 1
Cytokine Range and Intra-Assay Coefficient of Variance (CV).

Parameter	IL-1β	IL-6	IL-8	TNF-α	IL-4	IL-10	TGF-β
N blood samples	156	156	157	161	144	159	156
N zero or under detectable range	89	87	.00	2	65	103	.00
Minimum	.00	.00	.96	.00	.00	.00	6,606
Maximum	7.52	18.73	179.10	122.27	228.20	17.17	228,900
Intra-Assay CV%	4.42	4.68	2.90	4.46	6.52	4.29	3.63

Note. N = number, IL-1β = interleukin-1β, IL-6 = interleukin-6, IL-8 = interleukin-8, TNF-α = tumor necrosis factor-α, IL-4 = interleukin-4, IL-10 = interleukin-10, TGF-β = tumor growth factor, CV − coefficient of variance.

Table 3
Pearson Zero-Order Correlations Between Study Variables, Means, and Standard Deviations.

Variable	1	2	3	4	5	6	7	8
1. IL-1β								
2. IL-6	.85**							
3. TNF-α	.90**	.82**						
4. Depression	.18*	.13	.16*					
5. CRF	.19*	.23**	.14	.50**				
6. Pain interference	.20*	.21*	.15	.27**	.47**			
7. Pain intensity	.16*	.19*	.14	.24**	.38**	.80**		
8. Emotional awareness	.07	.01	.02	.08	.13	−.07	−.09	
M	.55	1.52	12.29	10.90	58.23	57.41	55.74	28.71
SD	1.28	3.01	16.19	5.95	12.60	9.80	12.6	6.66

Note. IL-1β = interleukin-1β, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-α, CRF = cancer-related fatigue.
* $p < 0.05$,
** $p < 0.01$.

Table 4
Pearson Correlations Between Sociodemographic and Medical Variables With Cytokines, Cancer-Related Symptoms, and Emotional Awareness.

Sociodemographic & medical variable	IL-1β	IL-6	TNF-α	Dep	CRF	P.inter	P.inten	EA
Age	.00	−.04	−.01	−.12	−.08	−.08	−.06	−.10
Level of income	−.15	−.16	−.19*	−.27**	−.27**	−.12	−.07	−.10
Level of education	−.12	−.26**	−.17*	−.06	−.15	−.12	−.10	.23**
Married or in a long-term relationship	−.01	−.03	−.00	−.07	−.01	−.02	−.01	−.04
Cancer stage	−.28**	−.19*	−.20*	.03	−.09	−.03	−.07	.10
Cancer treatment								
Chemo	−.05	−.07	−.05	−.07	−.06	.13	.15	.04
Radio	−.02	−.02	.05	−.07	−.09	−.04	−.06	−.11
Surgery	.00	.01	−.00	.08	−.01	−.07	−.07	.08
Hormonal	−.05	−.02	−.04	−.02	.14	−.08	−.05	.11
Biological	.00	−.03	−.00	.04	.01	.08	.08	.03
Months from diagnosis to baseline	−.25**	−.26**	−.23**	−.11	−.04	−.08	−.11	.00
Months from end of treatment to baseline	−.20*	−.15	−.15	−.15	−.10	−.09	−.09	.17*
BMI	−.02	.16	.05	−.04	.06	.08	.06	.07

Note. IL-1β = interleukin-1β, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-α, Dep = depression, CRF = cancer-related fatigue, P.inter = pain interference, P. inten = pain intensity, EA = emotional awareness.
* $p < 0.05$,
** $p < 0.01$.

variables (cancer-related symptoms). See Table 4.

Step 1 showed that depression and CRF were negatively and significantly associated with income level; pain intensity and interference were not. The independent variables (IL-1β, IL-6, TNF-α) were entered in Step 2. Depression and CRF were negatively and significantly associated with income level. The *F* of the R^2 change was 3.57 for depression and 5.27 for CRF. No significant associations were found between depression, CRF, pain intensity, and interference with cytokines. See Table 5 for further details regarding the associations between cytokines and sickness symptoms.

Table 5
Multiple Linear Regression Analyses of the Associations (Standardized Coefficient Betas) Between the Study's Independent Variables and Cancer-Related Symptoms.

Model		Depression	CRF	Pain intensity	Pain interference
Step 1	Income level	−3.19**	−3.83**	−1.40	−.80
	F	10.17**	14.70**	1.95	.65
	R^2	.06	.09	.01	−.00
Step 2	Income level	−2.92**	−3.54**	−1.07	−.46
	IL-1β	1.24	.77	.38	.95
	IL-6	−.76	1.39	1.05	.84
	TNF-α	.00	−1.07	−.38	−.64
	F	3.57**	5.27**	1.62	1.80
	R^2	.07	.10	.02	.02

Note: IL-1β = interleukin-1β, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-α, CRF = cancer-related fatigue, β = beta coefficient, R^2 = adjusted R^2.
*$p < 0.05$, **$p < .01$.
** $p < 0.01$.

3.3. *The moderating role of emotional awareness*

The moderation analyses were adjusted for income level. We first performed the moderation analysis without adjusting for the covariate (income level) and then repeated the moderation analysis accounting for the covariate. Because the effect of interest was not eliminated by accounting for the covariate, these results include the covariate.

Overall, the interactions between EA and cytokines associated with depression were statistically significant for IL-1β (B =.15, SE = 0.07, 95% CI [.01, 0.29]), IL-6 (B = 0.07, SE = 0.03, 95% CI [.02, 0.13]), and TNF-α (B = 0.01, SE = 0.00, 95% CI [.00, 0.02]). These cytokines were positively and significantly associated with depression in participants with high levels of EA.

Specifically, the J-N technique revealed that IL-1β, IL-6, and TNF-α were significantly associated with depression at levels of EA above the 50th percentile, with respective LEAS scores above 32, 31.44, and 32.17. These cytokines were not statistically significantly associated with depression in participants with average or low levels of EA (16th–50th percentiles). Notably, we found a negative association between IL-6 and depression among individuals with levels of EA below 18.24. However, due to the small sample size in this subgroup (5.4% of our total sample) this finding was insufficient for inclusion in our report and not further discussed in this study.

The interactions between EA and IL-1β (2.8%), EA and IL-6 (4.5%), and EA and TNF-α (2.8%) explained the variance in depression. See

Table 6
The Moderated Effects of Specific Levels of Emotional Awareness Scale (LEAS) on the Association Between Inflammation and Depression and the Johnson-Neyman Significant LEAS Regions.

Cytokine	LEAS	B	*SE*	95 % CI		Johnson-Neyman significance region		
				LL	UL	LEAS	% below	% above
IL-1β[a]								
16th pct	24	−.50	.63	−1.74	.74	32.00	76.51	23.50
M	29	.25	.39	−.53	1.03			
84th pct	34	1.00*	.40	.22	1.80			
F	5.32**							
R^2	.13							
IL-6[b]								
16th pct	24	−.23	.21	−.64	.17	18.24	5.40	94.63
M	29	.14	.15	−.16	.43	31.44	72.48	27.52
84th pct	34	.51*	.20	.12	.90			
F	5.02**							
R^2	.12							
TNF-α[c]								
16th pct	24	−.03	.04	−.11	.05	32.17	76.47	23.53
M	29	.02	.03	−.03	.08			
84th pct	34	.08*	.03	.01	.14			
F	4.88**							
R^2	.12							

Note: IL-1β = interleukin-1β, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-α, Pct = percentile. *F* and R^2 refer to the complete model.
[a] $n = 149$;
[b] $n = 149$;
[c] $n = 153$.
[*] $p < 0.05$,
[**] $p < 0.01$.

Table 6 for the associations between cytokines and depression and the J-N technique specifying regions where the moderation effect was significant. See Fig. 1 for a graphic representation of the associations at three levels of EA.

The interaction between EA and cytokines associated with CRF was not statistically significant for IL-1β ($B = 0.33$, $SE = 0.34$, 95% CI [-0.34, 0.99]), IL-6 ($B = 0.13$, $SE = 0.13$, 95% CI [-0.14, 0.39]), or TNF-α ($B = 0.02$, $SE = 0.02$, 95% CI [-0.03, 0.07]), and EA did not moderate the associations between IL- 1β, IL-6, TNF-α, and CRF and therefore was not further probed.

The interaction between EA and cytokines associated with pain interference was not statistically significant for IL-1β ($B = 0.16$, $SE = 0.12$, 95% CI [-0.08, 0.40]), IL-6 ($B = 0.09$, $SE = 0.05$, 95% CI [-0.01, 0.18]), or TNF-α ($B = 0.01$, $SE = 0.01$, 95% CI [-0.01, 0.03]). Therefore, the interaction between the cytokines and pain interference was not further probed or interpreted.

The interaction between EA and cytokines associated with pain intensity was statistically significant for IL-6 ($B = 0.17$, $SE = 0.06$, 95% CI [.05, 0.29]), not statistically significant for IL-1β ($B = 0.29$, $SE = 0.16$, 95% CI [-0.02, 0.59]), and very close to statistical significance ($p = 0.054$) for TNF-α ($B = 0.02$, $SE = 0.01$, 95% CI [-0.00, 0.04]). IL-6 and TNF-α were positively and significantly associated with pain intensity at high levels of EA, as was IL-6 at average levels of EA.

The J-N technique showed that IL-6 and TNF-α were associated with pain intensity at levels of EA above, respectively, 28.87 and 31.61 (above the 50th percentile). Notably, we found a negative association between IL-6 and pain intensity among individuals with levels of EA below 13.59. However, due to the small sample size in this subgroup (2.67% of our total sample) this finding was insufficient for inclusion in our report and not further discussed in this study. The interaction between EA and IL-6 explained 5% of the variance in pain intensity. See Table 7 for the associations between cytokines and pain intensity and the J-N technique specifying regions where the moderation effect was significant. See Fig. 2 for a graphic representation of these associations.

The associations between the cytokines and cancer-related symptoms remained significant after correcting for multiple comparisons using the Benjamini-Hochberg procedure. Details are included in the supplementary material.

4. Discussion

This study is the first to examine whether EA moderates the associations between proinflammatory cytokines and cancer-related symptoms among BCS. The study's main findings reveal that associations between proinflammatory cytokines and cancer-related symptoms vary according to differences in levels of EA. At high levels of EA, IL-1β, IL-6, and TNF-α were positively associated with depression, and IL-6 and TNF- α were positively associated with pain intensity. At mean EA levels, IL-6 was also positively associated with pain intensity. These results suggest that EA plays a role in scaling the direction and magnitude of the relationship between proinflammatory cytokines and cancer-related symptoms.

The bivariate associations between proinflammatory cytokines and cancer-related symptoms were eliminated in the multivariate regression analyses adjusting for medical and demographic variables. When EA was included in these analyses, proinflammatory cytokines were associated with depression and pain only when EA levels were high and average. Previous *meta*-analyses and systematic reviews (e.g., De Groote et al., 2024; McFarland et al., 2022; Patton et al., 2021) reported significant associations of proinflammatory cytokines with depression and pain intensity, but the associations were not always consistent. McFarland et al.'s (2022) systematic review and meta-analysis found positive associations between IL-6, TNF-α, and depression symptoms. Our study extends their findings by incorporating the moderating role of EA and associations found between IL-1β and depression. Similar to previous studies that showed inconsistent results of associations between proinflammatory cytokines and CRF (e.g., Saligan & Kim, 2012), we found inconsistencies. In the Pearson bivariate analyses, IL-1β and IL-6 were significantly associated with CRF, whereas TNF-α was not. However, in the multivariate regression model including medical and demographic variables, these associations were not statistically significant.

Our findings also align with previous findings of positive associations between IL-6 and pain intensity (De Groote et al., 2024) and add new evidence of positive associations between TNF-α and pain intensity at high levels of EA. De Groote et al. (2024) addressed several biases in the studies they reviewed: small samples (1–63 participants), the time of blood collection in most (five) studies was not mentioned, only two

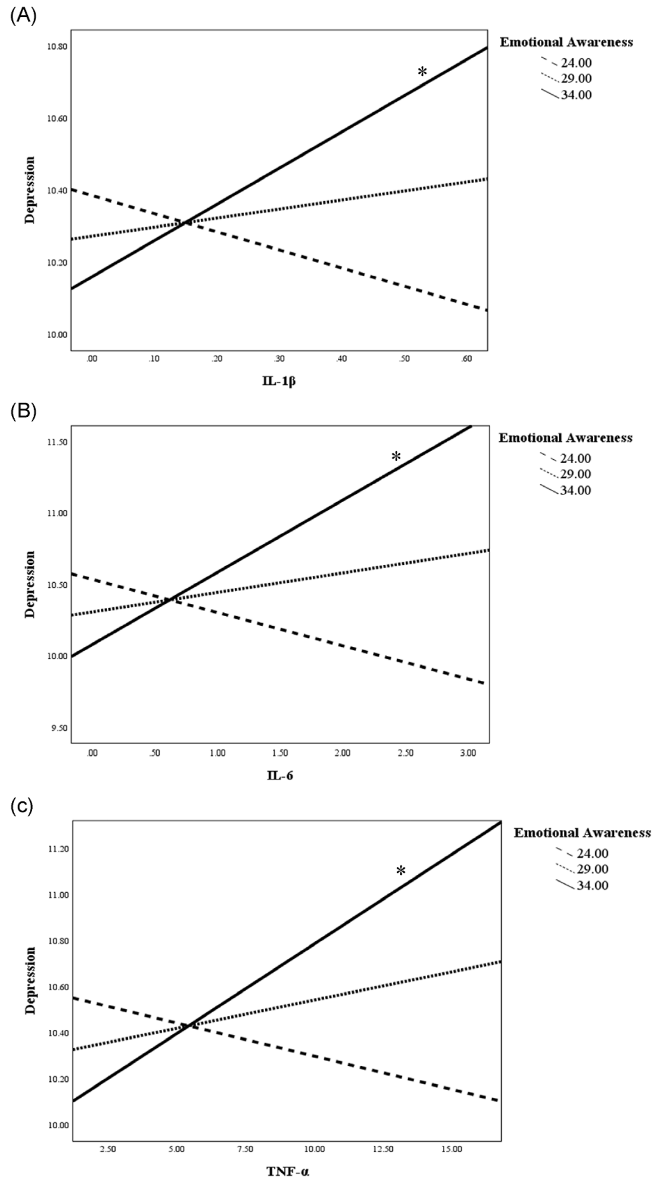

Fig. 1. Relationships Between IL-1β, IL-6, and TNF-α and Depression by Levels of Emotional Awareness. Note. IL-1β = interleukin-1β, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-α. *$p < 0.05$.

studies reported participants were required to fast, and the blood collections did not always coincide with pain ratings. Our study considers all these issues. Our findings also align with previous findings (Reed et al., 2016) of acceptance of emotions as a moderator of the association between proinflammatory cytokines and cancer-related symptoms at high but not low levels of acceptance of emotions. Applying the three-process model of emotions, high emotional awareness provides the level two conceptualization of emotions which enables acceptance of emotions to occur, supporting the validity of our interpretation of these results.

To the best of our knowledge, ours is the first study to examine the effects of EA on the associations between cytokines and cancer-related symptoms. Here, it is important to consider that cytokines have direct effects on affective centers in the brain that mediate negative affect, creating an affective state of perceived threat that parallels the physiological threat to which proinflammatory cytokines respond (Renna et al., 2020). However, we found no direct associations between cytokine levels and cancer-related symptoms.

The core finding in our study is that proinflammatory cytokines are positively associated with depression and pain in patients with higher EA. How can this be understood? Although we observed no direct associations, participants in our study with higher EA levels were likelier to report depressive or pain symptoms if their proinflammatory cytokines were high.

From an evolutionary perspective, depression serves a useful function: It occurs when losses prevent the continued pursuit of goals and induce a state of slowing down and regrouping when a shift in priorities is needed (Nesse, 2023). Could BCS with high EA also have high concentrations of proinflammatory cytokines? Could BCS be more conscious of their existential threat and more alert? Or could it be that participants with higher cytokine levels are more emotionally aware? Considering that no direct association has been found between EA and proinflammatory cytokines, it seems unlikely that cytokines or negative affect would increase EA or vice versa. Notably, in our study's high EA group, low proinflammatory cytokine levels were associated with lower cancer-related symptoms, meaning that not all BCS in the high EA group have high proinflammatory cytokine levels.

As such, the essence of the present set of findings may be that participants with higher levels of EA are more sensitive to the mood- and symptom-altering effects of cytokines. These findings suggest that BCS with higher EA levels may also be more sensitive to interoceptive cues (Lane et al., 2011), possibly induced by proinflammatory cytokines. Given the evidence that higher EA is associated with more differentiated reporting of somatic symptoms in the context of stress (Lane et al., 2011), our findings may support the claim that higher EA is associated with greater sensitivity in perceiving and reporting bodily cues relevant to one's current emotional state. In this context, the three-process model (Smith, 2020) may further elaborate our understanding of the interactions between EA, sensitivity to interoceptive cues, cytokines, symptoms, and conscious awareness.

Following the three-process model, a situational appraisal associated with bodily sensation and the generation of an affective response (the first process) may occur with the detection of cytokines in the high EA group. The cognitive elements of EA, affective response representation (the second process), and conscious access (the third process) include greater sensitivity to the bodily processes that constitute the first process (Kanbara & Fukunaga, 2016; Lane et al., 2011). Therefore, we propose that BCS with high EA are more attuned to their symptoms, which also aligns with their proinflammatory cytokine levels, and they experience heightened sensitivity to the mood-altering effects of cytokines through this attunement.

Given that higher EA is associated with more effective emotion regulation and better mental and physical health (Lane & Smith, 2021), how can we explain the absence of evidence for reduced symptoms? The three-process model (Smith, 2020) explains that the first and second processes must participate for the third process (conscious access) to occur. Conscious access may support flexible use in goal-directed decision-making processes and effective emotion regulation (e.g., decoupling of cytokines and physical symptoms at individual time points when acceptance of emotions is higher; Reed et al., 2016; or reappraisal associated with better mental and physical health; Baziliansky & Cohen, 2021; Durosini et al., 2022).

The present study's results support the interpretation that participants with higher EA report their symptoms according to their proinflammatory cytokine levels. This suggests that although the first, second, and third processes may be activated, physiological regulations may not be sufficient in this group. Possibly, the positive association between proinflammatory cytokines and cancer-related symptoms in participants with high EA is due to a lack of regulatory processes, such as reappraisal, that are not necessarily part of high EA. Research (Hermann et al., 2020; Yang et al., 2020) suggests that reappraisal involves activating brain regions like the ventromedial prefrontal cortex (brain emotion-processing center) and amygdala (brain distress center). If so, the connectivity between these brain regions could be negatively associated with proinflammatory cytokines (Mehta et al., 2018) thus preventing

Table 7
The Moderated Effects of Specific Levels of Emotional Awareness Scale (LEAS) on the Association Between Inflammation and Pain Intensity and the Johnson-Neyman Significant LEAS Regions.

Cytokine	LEAS	B	*SE*	95 % CI		Johnson-Neyman significance regions		
				LL	UL	LEAS	% below	% above
IL-6[a]								
16th pct	24	−.18	.46	−1.08	.72	13.59	2.67	97.33
M	29	.68*	.33	.02	1.33	28.87	48.00	52.00
84th pct	34	1.53**	.44	.67	2.40			
F	4.03**							
R^2	.12							
TNF-α[b]								
16th pct	24	−.03	.09	−.22	.15	31.61	72.73	27.27
M	29	.07	.06	−.05	.20			
84th pct	34	.18*	.08	.03	.33			
F	2.39							
R^2	.06							

Note. IL-6 = interleukin-6, TNF-α = tumor necrosis factor-α. *F* and R^2 refer to the complete model.
[a] $n = 150$;
[b] $n = 154$.
* $p < 0.05$,
** $p < 0.01$.

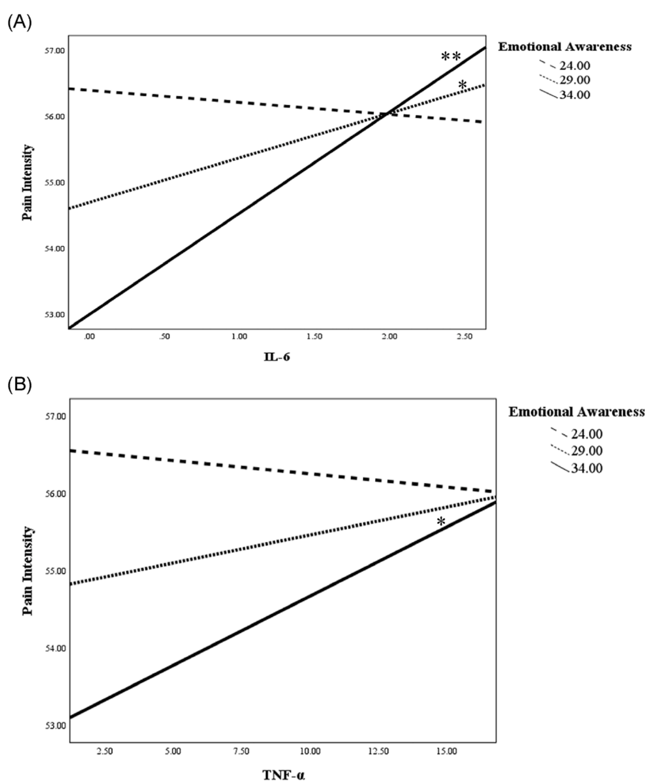

Fig. 2. Relationships Between IL-6 and TNF-α and Pain Intensity by Levels of Emotional Awareness. Note. IL-6 = interleukin-6, TNF-α = tumor necrosis factor-α. *p < 0.05, **p < 0.01.

top-down regulation of brain distress areas by emotion-processing areas. It may also be that physiological regulation through cardiac vagal control or high vagally mediated heart rate variability is lacking, although these have previously been found to be associated with high EA (Spangler et al., 2024; Verkuil et al., 2016) and low proinflammatory cytokines (Williams et al., 2019).

How can we explain the lack of association between proinflammatory cytokines and cancer-related symptoms in BCS with EA levels below the 50th percentile? According to the theory of EA, at lower levels of EA, individuals tend to describe their emotional experience in somatic terms (Lane & Smith, 2021). Lower EA has also been associated with greater pain intensity on a typical day among patients with fibromyalgia (Lumley et al., 2017). No such direct association (between EA and symptoms) was observed in our data when examining the sample as a whole. In this group of BCS with lower EA, undifferentiated emotional distress may be represented as physical pain (a more somatic character), and bodily cues induced by proinflammatory cytokines may not be represented or processed, may be avoided, or may not reach the third process of conscious access (Smith, 2020). In other words, relative to their counterparts with higher EA, low EA subjects are possibly insensitive to the subjective effects of proinflammatory cytokines, and, thus, an association between symptoms and cytokine levels is not observed.

4.1. Translational implications

Our findings may have implications for future studies with BCS and for improving psychotherapy interventions. Observing these associations between proinflammatory cytokines, cancer-related symptoms, and EA in a longitudinal model among BCS would be prudent to observe the EA process across time (Bottaro & Faraci, 2022). A longitudinal model could also examine within-person changes over time, which may present different results (Reed et al., 2016). A longitudinal study could assess EA, proinflammatory cytokines, interoception, levels of perceived existential threat, and differentiation in somatic cues, which may substantiate our interpretation regarding the heightened sensitivity of BCS with high EA to the mood-altering effects of cytokines. Whether participants with high EA possess an interoceptive awareness that can differentiate between somatic symptoms and those induced by cytokines is also an interesting question yet to be explored. It would also be helpful to replicate our study with larger, more diverse samples of BCS, especially among participants with extremely high and low EA.

Future studies would benefit by assessing factors that may moderate physiological regulation in conjunction with proinflammatory cytokines in the presence of high EA. This could be addressed by assessing vagal-mediated heart rate variability (reflecting the autonomic nervous system). If our results are replicated, there may be implications for improving psychotherapy interventions, including those aiming to increase EA (Lane & Smith, 2021) which facilitates coping with reappraisal and/or acceptance of emotion. Clinical trials using EA and expression therapy have demonstrated effective results in reducing pain symptoms among patients with irritable bowel syndrome, fibromyalgia, and somatoform disorders (Lumley et al., 2017; Maroti et al., 2021; Thakur et al., 2017). However, to our knowledge, these interventions have not been examined among BCS.

Breast cancer survivors with low EA may benefit from interventions that aim to increase EA (Neumann et al., 2017). By using EA as a cognitive resource that helps transform undifferentiated emotional distress into conscious emotions, they would then be available for emotional regulation strategies such as reappraisal (Hermann et al., 2020) or acceptance of emotions (Reed et al., 2016). Psychoeducational and psychotherapy modalities that include emotional vocabulary, distinguishing between emotions, sensations, thoughts, and actions, labeling and differentiating emotions, and interoceptive awareness (Chen et al., 2024; Neumann et al., 2017), along with body-based interventions (e.g., dance movement therapy, Majore-Dusele et al., 2021; Payne & Brooks, 2019) are promising venues for supporting high EA. Damasio and Damasio (2006) claimed that perceiving emotions requires mentally representing the body. Such interventions may be able to differentiate unmentalized distress from physical pain, increase physiological regulation, support effective emotional regulation, and decrease cancer-related symptoms.

4.2. Limitations

Our study was limited to Israeli, Jewish, female BCS, which limits generalizability because our findings may not apply to other populations. Additionally, our cross-sectional study design limited our ability to determine causality and directionality. The single time point limited our ability to observe processes such as EA in association with cytokines and symptoms or their changes throughout the process of coping with a cancer diagnosis over time. The overall sample size is small for observational studies but not small for studies examining associations between cytokines and symptoms (De Groote et al., 2024). A study limitation is the lack of quality control measures and inter-assay coefficient of variability calculations, which should be included in future studies to replicate our results. Other immune conditions (e.g., allergies) that were not controlled may have affected our results. It is important to consider all these potential factors when interpreting the results.

4.3. Conclusions

This study has several novel findings regarding the associations between proinflammatory cytokines and cancer-related symptoms. Differences in EA levels were shown to moderate the associations between proinflammatory cytokines and cancer-related symptoms. At high EA levels, proinflammatory cytokines were positively associated with cancer-related symptoms. This suggests EA can be a cognitive resource to promote emotion regulation and transform distress, counteracting a heightened sensitivity to the mood-altering effects of cytokines while coping with breast cancer.

CRediT authorship contribution statement

Keren Harel: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Johanna Czamanski-Cohen:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Miri Cohen:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Richard D. Lane:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Monica Dines:** Writing – review & editing, Supervision, Project administration, Formal analysis, Data curation, Conceptualization. **Opher Caspi:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Karen L. Weihs:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.12.005.

Data availability

Data will be made available on request.

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