Published in final edited form as:
Psychooncology. 2014 March ; 23(3): 339–345. doi:10.1002/pon.3422.

Depression, cytokines, and pancreatic cancer

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Abstract

Background—To examine the relationships between cytokines, depression, and pancreatic cancer.

Method—75 individuals were recruited from two New York City hospitals (a cancer center and a psychiatric hospital) and comprised 4 subgroups: patients with adenocarcinoma of the pancreas who did (n=17) and did not (n=26) have a diagnosis of Major Depressive Episode (MDE), and healthy participants with (n=7) and without (n=25) MDE. All individuals completed a battery of self-report measures. Sera was assayed using Meso Scale Discovery techniques to measure the following pro- and anti-inflammatory cytokines: IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12p70, IFN-gamma, TGF-beta, and TNF-alpha; we also calculated the IL-2/IL-4 ratio.

Results—Pancreatic cancer patients had significantly higher levels of IL-6 and IL-10, and significantly lower TGF-beta levels than healthy participants. When the sample was divided into those with and without MDE, the groups only differed with regard to serum IL-6 levels. No significant cancer×depression interaction effect was observed. Severity of depressive symptoms was also significantly correlated with IL-6, r_s=.28, p=.02, while hopelessness was associated with IFN-alpha, r_s=.34, p=.006. Pain, fatigue and sleep disturbance were associated with several of the cytokines assayed including IL-1beta (pain intensity), IL-4 (pain intensity and overall sleep quality), IL-12p70 (pain intensity), TGF-beta (fatigue intensity), but anxiety was not associated with any of the cytokines assayed.

Conclusions—This study demonstrated an association between depression and IL-6, but not with other cytokines. Moreover, IL-6 was not significantly associated with other measures of psychological distress (anxiety, hopelessness) or with symptom distress (pain, fatigue, sleep quality), although some cytokines assayed were associated with specific symptoms. The implications of these findings for the etiology and treatment of depression in pancreatic cancer patients are discussed.

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Keywords

Cytokines; Depression; Pancreatic Cancer; Oncology; IL-6

Fueled by observations of depressive symptoms emerging in patients treated with immune therapies (e.g., alpha interferon), clinicians have suggested that cytokines may have an important role in explaining the high rates of depression often observed among some physically ill populations.[1–5] For example, pancreatic cancer patients have long been known to have high rates of depression,[6–8] perhaps stemming from the connection between depressive symptoms and cytokine production. However, what is less clear from this literature is whether the depression/cytokine relationship reflects a causal association, the effects of treatment (e.g., immune therapies), or merely represents co-occurring phenomena.

In one of the first studies linking cytokines to depression in cancer, Capuron and colleagues analyzed the hypothesized link between depression and markers of immune function in cancer patients receiving immunotherapy with IL-2 and/or alpha interferon.[9] They specifically focused on the role of tryptophan and tyrosine, metabolic precursors to serotonin and norepinephrine respectively. They found that the emergence of depressive symptoms (i.e., diminished appetite, concentration problems, pessimism and suicidal ideation) were significantly associated with the magnitude of tryptophan decreases, suggesting that cytokines may impact mood by reducing the availability of serotonin. Musselman and colleagues specifically examined the relationship between pro-inflammatory cytokines and depression in patients with cancer.[10] They sampled four groups: patients with cancer with and without depression, and physically healthy individuals with and without depression. Despite their small sample size, they observed a significant group difference in plasma IL-6, with depressed cancer patients having the highest concentrations and non-depressed cancer patients having the lowest. This study did not report whether any of the specific group contrasts were significant and they found no significant correlation between depressive symptom severity and IL-6 level. The authors concluded that IL-6 elevations may reflect “an epiphenomenon of the cancer disease process, rather than play a primary causal role in the pathophysiology of major depression.” Lutgendorf et al. examined the relationship between IL-6 and depressive symptoms in a sample of women with ovarian cancer.[11] They found a significant association between IL-6 and “vegetative” symptoms of depression among the subset of patients with “invasive” ovarian cancer, but no significant association with either total depressive symptom severity or severity of “affective” depressive symptoms.

Given the small but compelling literature suggesting a role for pro-inflammatory cytokines in fueling depression among medically ill patients, we sought to address the relationship between depression and cytokine production in a sample of pancreatic cancer patients. We identified pancreatic cancer as a particularly compelling illness subgroup because of both the unusually high rate of depression observed in this population,[6–8] combined with evidence of elevated pro-inflammatory cytokine production compared to other types of cancer.[12–15] Although only a handful of cytokines have been consistently studied with regard to depression and related behavioral problems (e.g., IL-1b, IL-2, IL-4, IL-6, IL-10, TNF-a, and the IL-2/IL-4 ratio), we examined a broad spectrum of cytokines in order to

examine those for which some theoretical rationale existed (i.e., pro- or anti-inflammatory attributes), yet have not been consistently studied (i.e., IL-3, IL-5, IL-12p70, IFN-gamma, TGF-beta).[1–3,10–14]

Materials and Methods

Subjects

Forty-three patients with adenocarcinoma of the pancreas were recruited from the outpatient clinics of Memorial Sloan-Kettering Cancer Center. Prospective patients were identified by clinical staff if they met the following inclusion criteria: fluent in English, diagnosed with stage III or IV disease, on a stable gemcitabine or gemcitabine-based chemotherapeutic regimen, and had no severe cognitive or psychiatric impairment (e.g., dementia, psychosis) that would preclude providing meaningful informed consent or answering questions. In addition, patients were not eligible for participation if they had an active secondary cancer diagnosis, were premenopausal (for women), had taken any antidepressant medications within the preceding two weeks, had used alcohol within the preceding 72 hours, or suffered from any of the following medical conditions: HIV/AIDS; auto-immune diseases such as Multiple Sclerosis, Rheumatoid Arthritis, Polymyalgia Rheumatica, Temporal Arteritis, Chronic Fatigue Syndrome, severe allergies; Congestive Heart Failure; recent stroke; Alzheimer's Disease; active infection; acute pancreatitis, acute pericarditis, acute hepatitis, recent vaccination for viral disease; or any major surgery within the past 6 weeks. Additional exclusion criteria included current or recent treatment with NSAID's, interleukin, interferon, Cox-2 inhibitors, or hormone replacement therapy (for post-menopausal women). These pancreatic cancer patients were subdivided into two groups (depressed/non-depressed) based on the presence (CA-D; $n = 17$) or absence (CA-ND; $n = 26$) of a Major Depressive Episode at the time of study participation (based on SCID interviews, as described below).

Depressed, physically-healthy participants (H-D) were recruited from the outpatient mental health clinics associated with Payne-Whitney Hospital/Weill-Cornell Medical Center ($n = 7$). Prospective participants were identified by treating clinicians if they were currently suffering from a Major Depressive Episode and met the same exclusion criteria as the cancer patient sample, but did not have a cancer diagnosis. Finally, a sample of physically healthy, non-depressed adults (H-ND) was recruited from the staff and visitors of Memorial Sloan-Kettering Cancer Center ($n = 25$). These healthy comparison subjects met the same inclusion and exclusion criteria as the clinical samples (cancer patients and depressed, physically healthy participants) but had no history of cancer or Major Depression. In addition, prospective control subjects were excluded from participation if they had a history of serious medical illness within the year preceding study participation, or had a history of diabetes, cancer (within the preceding five years), renal failure requiring dialysis, chronic pain resulting in disability, or inflammatory bowel disease. All participants provided written informed consent following an explanation of the study nature, risks and benefits. The study procedures were approved by the Institutional Review Boards of Memorial Sloan-Kettering Cancer Center and Weill-Cornell Medical Center.

The total sample (N = 75) included 35 women (46.7%) and 40 men (53.3%) with an average age of 56.8 (s.d. = 11.9, range: 28 to 85). The sample was predominantly Caucasian (n = 63, 85.1%), with 6 African-American (8.1%), 3 Hispanic (4.1%) and 2 (2.7%) participants of mixed or other racial backgrounds. The average years of education completed was 15.5 (s.d. = 2.9, range: 6 to 20). At the time of study participation, most individuals were married (n = 52, 70.3%); 13 (17.6%) were single, 3 (4.2%) were separated and 3 (4.2%) were widowed (data were missing for 4 individuals).

Procedures

Participants were interviewed by a clinical psychologist or psychology doctoral student, using the Depression module from the Structured Clinical Interview for DSM-IV (SCID)[16] to establish a diagnosis of Major Depressive Episode (MDE), as well as with the Hamilton Depression Rating Scale (HDRS)[17] to quantify severity of depressive symptoms. In addition, participants completed a battery of self-report questionnaires including the Beck Anxiety Inventory,[18] the Pittsburgh Sleep Questionnaire,[19] the Brief Pain Inventory[20] and the Brief Fatigue Inventory.[21] Participants were classified as “depressed” if they met DSM-IV criteria for MDE based on the SCID.

Each participant provided 10 cc of sera, which was drawn by a trained phlebotomist between 2 - 5 pm each day (to standardize time across participants). The blood was processed to separate the serum, which was then aliquoted and immediately stored in a −70 degree centigrade freezer. Sera were assayed in a single batch, using Meso Scale Discovery (MSD) multiplex cytokine measurement techniques. Quantification of cytokine levels in sera was performed on the MSD Sector Imager 2400 (Meso Scale Discovery, Inc., Gaithesburg, MD), which allowed up to 10 cytokines to be measured simultaneously with high sensitivity in specially coated 96-well plates. The technology is similar to a sandwich ELISA, in which a spot on the base of each plate was pre-coated with a capture antibody for each cytokine. When samples were incubated in the multi-spot plate, each cytokine binds to its corresponding capture antibody spot. Cytokine levels were subsequently quantified by CCD camera using a cytokine-specific detection antibody labeled with a light-emitting moiety. Patient sera were diluted to 1/1 with 1xPBS before the assay and these diluted sera were analyzed for the following pro- and anti-inflammatory cytokines: IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12p70, IFN-gamma, TGF-beta, and TNF-alpha; the IL-2/IL-4 ratio was also calculated. A 4-parameter logistic fit curve was generated for each analyte using the standards and the concentration of each sera sample calculated. Because cytokine data were not normally distributed, these data were analyzed using a) Spearman correlation coefficients for correlational analyses and b) log transformed values for group comparisons and multivariate analyses. Further, between group analyses were conducted while controlling for demographic variables (e.g., age, gender, body mass index; ANCOVA models), which have been demonstrated to impact levels of circulating cytokines.[22]

Results

A preliminary step in analyzing the associations between cancer, depression and cytokines involved examining potential covariates that have been associated with cytokine levels, in

some of the published research.[22] These included age, gender, body mass index (BMI) and cigarette smoking (coded as a dichotomous variable, but missing for a substantial subset of the participants). There were no significant associations between any of the cytokines measured with gender, BMI, or cigarette smoking status. However, significant Pearson product-moment correlations (based on the log-transformed cytokine values) were observed between age and IL-6 (r= .31, p = .007), IFN-gamma (r = .24, p= .04), and IL-2 (r = .24, p= .04). Given these associations, the statistical analyses described below included age as a covariate (i.e., ANCOVA models).

Cancer patients versus physically healthy adults

A comparison of patients with a pancreatic cancer diagnosis versus the physically healthy sample revealed a number of significant differences including age and severity of depressive symptoms (see Table 1). Among the cytokines assayed, the groups differed in IL-6, IL-10, and TGF-beta (based on log-transformed variables), with cancer patients having significantly higher levels of IL-6 and IL-10 but significantly lower TGF-beta levels. When these immune markers were entered into a stepwise logistic regression model predicting cancer group membership, IL-6 was the only significant predictor, correctly classifying 83% of cases. This finding indicates that IL-6 had the strongest association with pancreatic cancer of any of the cytokines measured, although several cytokines were correlated with one another (described below).

Comparing depressed and non-depressed participants

When the sample was divided into those with and without a Major Depressive Episode (see Table 2), the groups only differed with respect to serum IL-6 and the IL-2/IL-4 ratio, with depressed individuals having significantly higher IL-6 levels than non-depressed participants and a lowerIL-2/IL-4 ratio. Not surprisingly, the groups also differed significantly on each of the psychosocial variables studied (depression, anxiety, hopelessness, overall sleep quality, average pain intensity and fatigue intensity). A stepwise logistic regression model predicting depression group membership from the cytokines measured contained two significant variables: IL-6 and the IL-2/IL-4 ratio, and correctly classified 74% of cases.

The Interaction between Depression and Cancer

A two-way multivariate analysis of covariance (MANCOVA) was conducted to assess the main effects of cancer and depression, as well as their interaction effect, on the cytokines measured. These analyses, which controlled for participant age and used log transformed cytokine levels, revealed an overall significant main effect for cancer status (cancer patients versus physically healthy participants), $F(11,57)=2.90$, p=.004 and depression , $F(11,57)=2.00$, p = .05, but no cancer × depression interaction, $F(11,57)=2.80$, p=.80. There was also no main effect of gender, $F(11,57)=1.02$, p = .44, or age, $F(11,57)=1.47$, p = .17. Examination of the univariate ANCOVA results indicated a significant main effect for cancer on IL-6, $F(1,67)=21.03$, p < .001, IL-10, $F(1,67)=5.61$, p=.02, and TGF-beta, $F(1,67)=7.56$, p=.009. Only one univariate main effect was observed for depression, the IL-2/IL-4 ratio, $F(1,67)=6.20$, p=.02, although IL-6 approached significance, $F(1,67)=3.37$, p=.07. There were no significant effects for the cancer × depression interaction, but age was

a significant predictor in one univariate ANCOVA model predicting IFN-a, F(1,67)=6.07, p=.02.

Associations Between and Within Cytokines and Symptom Distress Variables

Correlational analyses revealed a number of significant correlations between cytokines and psychological and physical symptom distress. Severity of depressive symptoms (based on the HDRS) was significantly correlated with IL-6, r =.27, p=.03, but not with any other cytokines assayed. When depressive symptoms were further divided into somatic/vegetative and cognitive/affective, the correlation with IL-6 was slightly stronger for severity of somatic/vegetative depressive symptoms, r =.29, p=.02, versus cognitive/affective symptoms, r =.24, p=.05. Hopelessness (based on the BHS) was associated with IFN-a, r =.25, p=.03, but was not associated with IL-6 or any other cytokines. Anxiety symptom severity (based on the HARS) was not associated with any of the cytokines assayed. Measures of pain, fatigue and sleep disturbance, on the other hand, were associated with several of the cytokines assayed including IL-1beta, IL-4, IL-12p70 (average pain intensity), TGF-beta (fatigue intensity), and IL-4 (overall sleep quality).

Finally, we analyzed associations between the various cytokines assayed (see Table 4). Not surprisingly, this analysis revealed a number of significant correlations among cytokines. For example, IL-6 was significantly negatively correlated with IL-4 (r = −.25, p = .03) and TGF-beta (r = −.24, p = .04), and significantly positively correlated with IL-10 (r = .43, p < .001), TNF-alpha (r = .30, p = .008) and IFN-gamma (r = .35, p = .002). A number of other significant correlations were observed between the various cytokines assayed (e.g., IL-10 was also significantly associated with several other cytokines), as evident from Table 4.

Discussion

This study adds to the literature demonstrating an association between depression, cancer, and IL-6.[5,10,11,13,22] Unlike previous studies, however, this association was observed in a homogenous sample of pancreatic cancer patients on a consistent chemotherapy regimen (gemcitabine and platinum-based therapy). Moreover, we measured and controlled for multiple potentially confounding variables. As hypothesized, we observed significant associations between IL-6 and depression and pancreatic cancer. However, there was no evidence of a significant interaction effect between depression and cancer, suggesting that IL-6 does not have a synergistic effect on depression in pancreatic cancer patients. In fact, the main effect for depression on IL-6 was no longer significant in an ANCOVA model after the effects of cancer and age were statistically controlled. Similar findings emerged for the IL-2/IL-4 ratio, although the significant main effect remained significant in this model. These modest effects suggest that while IL-6 (and the IL-2/IL-4 ratio) may help differentiate pancreatic cancer patients who develop a depressive disorder from those who do not, these cytokines do not represent the sole, or even primary, cause of depression in this population.

Interestingly, while IL-6 was significantly associated with depression, and somewhat more strongly with the somatic symptoms of depression compared to cognitive/affective symptoms, it was not associated with any other measures of psychological distress (anxiety, hopelessness) or physical symptom burden (pain, fatigue, sleep quality). These findings is

surprising, given that a) many of these symptoms are correlated with depression (and were in this study as well) and b) the concept of a "sickness behavior" syndrome posits an association between IL-6 and several of these variables (pain, fatigue, sleep disturbance).[23–24] Our findings suggest that the relationship between IL-6 and depression may be unique to symptoms of depression, and that other cytokines – some of which are also elevated in the context of pancreatic cancer and other serious illnesses, contribute to the phenomenon of "sickness behavior." Indeed, we observed a number of significant correlations between the cytokines assayed. This finding was also unexpected, given that the correlations between cytokines and distress variables (e.g., depression, pain, sleep, fatigue) were relatively infrequent. This pattern of findings suggests that while cytokines may be broadly affected by pancreatic cancer, the impact of cytokines on physical and psychological functioning may be more specific. For example, fatigue severity was significantly associated (negatively) only with TGF-beta, whereas pain severity was significantly associated with IL-12p70 and sleep quality was significantly associated with IL-4 and the IL-2/IL-4 ratio. Hence, the phenomena of "sickness behavior" may result from the co-occurring effect of illness on multiple cytokines rather than a unique effect of elevated IL-6.

The broad impact of cancer on multiple cytokines was also demonstrated by the significant elevations found in patients with pancreatic cancer. Although IL-6 also had the strongest association with a pancreatic cancer diagnosis, we also observed significant differences between pancreatic cancer patients and healthy controls on IL-10 and TGF-beta. However, in a multivariate model, only IL-6 provided a unique contribution to differentiating pancreatic cancer patients from healthy controls, indicating that IL-6 has the strongest association with pancreatic cancer. Surprisingly, one of the cytokines that we anticipated would play a central role in explaining the high rate of depression in pancreatic cancer, TNF-alpha, was not associated with either a pancreatic cancer diagnosis or any measure of psychological or physical symptom distress. A number of prior studies have suggested a prominent role for TNF-alpha in the etiology of depression among cancer patients.[5,25–26] Our findings, while preliminary, failed to support this hypothesized association.

The findings from this study are bolstered by a number of methodological strengths such as the analysis of multiple different cytokines and well-validated measures of physical and psychological symptom distress, as well as a rigorous assessment of depression, a homogenous sample of pancreatic cancer patients, and the control or measurement of multiple potential covariates that might confound cytokine levels (i.e., through inclusion of covariates and use of numerous exclusion criteria). Nevertheless, our findings are tempered by some methodological limitations. Foremost among these limitations is the modest sample size, with only a handful of physically healthy, depressed patients. Our challenges in recruiting healthy depressed patients no doubt arose from our numerous exclusion criteria (due to potential confounds with cytokine levels), and in particular, with the requirement that participants be free of antidepressant use for a minimum of two weeks prior to study participation. This modest sample size no doubt limited our power to detect possible interaction effects between cancer and depression. Relatedly, while the large number of analyses calculated may see to justify using a correction for Type I error, we have not done so because our primary study focus was on IL-6. To "correct" for the inclusion of additional, exploratory analyses would mask the findings that did emerge. Rather, these data should be

interpreted cautiously given light of the modest effect sizes observed. In addition, while we did not initially intend to analyze the phenomena of "sickness behavior," the absence of any measure of this syndrome that has been developed and validated for use in humans clearly limits our ability to understand this construct.

Despite these limitations, this study helps highlight the complex relationships between cytokines, depression and pancreas cancer. Although our data do not suggest a unique causal role for IL-6 in explaining the high rate of depression observed in pancreas cancer patients, it does suggest that a significant relationship exists between these phenomena. Further research is needed to determine whether these findings have implications for the prevention and/or treatment of depression in this vulnerable population. In addition, better understanding how the various pro- and anti-inflammatory cytokines interact to influence the range of physical and psychological symptoms commonly observed among patients with advanced pancreas cancer may have important implications for understanding the phenomenology of depression and "sickness behavior."

Acknowledgments

The authors acknowledge the contributions of Christopher Gibson, Ph.D., Amy Berg, M.A., and Anna Dickerman, M.D., for assisting in the data collection and literature review. This research was supported by NCI grant number R21 101767 (W. Breitbart, P.I.).

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Table 1

Descriptive statistics for patients with pancreatic cancer (n=37) and healthy participants (n=30)

Variable	Cancer (M / S.D.)	Healthy (M / S.D.)	*p*
Age	60.11 (11.2)	51.1 (11.1)	.002
Education	15.46 (2.6)	15.70 (4.3)	.78
Depression	12.53 (9.3)	6.79 (10.3)	.03
Anxiety	11.60 (11.4)	9.97 (11.3)	.57
Hopelessness	5.17 (5.1)	3.76 (5.1)	.27
Sleep Quality	2.00 (0.9)	2.14 (0.9)	.55
Pain severity	2.29 (2.3)	3.53 (3.3)	.15
Fatigue severity	4.29 (2.6)	2.87 (2.7)	.06
IL-1B	0.17 (0.2)	0.21 (0.2)	.92
IL-2	0.97 (2.6)	0.50 (0.4)	.82
IL-4	0.12 (0.2)	0.16 (0.2)	.54
IL-5	15.74 (82.8)	1.45 (3.2)	.19
IL-6	6.06 (9.4)	2.14 (7.6)	.001
IL-10	160.22 (928.1)	7.27 (21.1)	.02
IL-12p70	21.85 (105.9)	34.84 (113.7)	.23
TNF-a	11.39 (9.4)	9.15 (2.9)	.20
TGF-b	23075.55 (15465.4)	28444.09 (8690.5)	.02
IFN-g	1.49 (2.1)	1.62 (3.7)	.10
IL-2/IL-4	45.61 (214.0)	6.96 (10.2)	.36

Table 2

Descriptive statistics for participants with depression (n=21) versus non-depressed participants (n=46)

Variable	Depressed (M / S.D.)	Not Depressed (M / S.D.)	*p*
Age	57.76 (11.2)	55.33 (12.3)	.45
Education	15.53 (2.7)	15.58 (3.7)	.96
Depression	23.00 (5.9)	3.75 (3.6)	.001
Anxiety	21.50 (13.3)	6.02 (5.5)	.001
Hopelessness	9.43 (5.9)	2.20 (2.2)	.001
Sleep Quality	2.65 (0.9)	1.80 (0.8)	.001
Pain severity	3.81 (3.3)	2.07 (2.1)	.041
Fatigue severity	5.68 (2.4)	2.74 (2.3)	.001
IL-1B	0.15 (0.2)	0.21 (0.2)	.34
IL-2	0.48 (0.4)	0.90 (2.5)	.13
IL-4	0.12 (0.2)	0.13 (0.2)	.70
IL-5	24.02 (111.6)	3.04 (8.7)	.82
IL-6	7.29 (11.4)	3.07 (7.1)	.05
IL-10	265.57 (1254.0)	16.74 (60.3)	.63
IL-12p70	2.80 (3.3)	38.22 (129.0)	.19
TNF-a	9.93 (2.7)	10.93 (9.1)	.83
TGF-b	25668.70 (16093.6)	25274.59 (11807.1)	.51
IFN-g	2.05 (2.8)	1.32 (2.9)	.63
IL-2/IL-4	8.32 (11.9)	38.19 (194.5)	.03

Table 3

Correlations between Cytokines and Psychosocial/Physical Symptom Variables ($N = 75$)

Variable	Depression	Hopelessness	Anxiety	Pain	Fatigue	Sleep
IL-1B	**.26** *	.01	−.12	.25	.11	.08
IL-2	.09	.19	.14	−.13	−.08	−.12
IL-4	.10	.19	.10	.22	−.08	**.29***
IL-5	−07	−.12	.02	−.25	.00	.10
IL-6	**.27***	.13	.14	−.16	.19	−.07
IL-10	.11	.01	.09	−.07	**.**12	−.11
IL-12p70	−.05	−.08	−.04	**.30***	−.11	.15
TNF-a	.06	.10	.07	−.24	−.07	−.10
TGF-b	−.18	−.16	−.06	−.19	**−.23***	−.09
IFN-g	.11	.20	.05	−.18	.00	.10
IL-2/IL-4	.18	−.05	.08	.27	.16	**.26***

Note: Depression: Hamilton Depression Rating Scale Total score, Hopelessness: Beck Hopelessness Scale Total score; Anxiety: Hamilton Anxiety Rating Scale Total score, Pain: Brief Pain Inventory Average Pain Intensity; Fatigue: Brief Fatigue Inventory Average Fatigue Intensity; Sleep: Pittsburgh Sleep Quality Index Total score.

* $p < .05$,

** $p < .01$

Psychooncology. Author manuscript; available in PMC 2015 March 01.

Table 4

Correlations between Cytokines

Variable	IL-1B	IL-2	IL-4	IL-5	IL-6	IL-10	IL-12	TNF-a	TGF-b	IL-2/IL-4
IL-1B	1.0									
IL-2	**.26***	1.0								
IL-4	**.26***	**.35****	1.0							
IL-5	−.01	.15	.01	1.0						
IL-6	−.04	.09	**−.25***	.17	1.0					
IL-10	−.13	.05	−.22	**.55*****	**.43***	1.0				
IL-12p70	**.32****	.09	.21	**.45*****	**−.24***	.19	1.0			
TNF-a	.10	**.24***	−.19	.22	**.30****	**.33*****	.16	1.0		
TGF-b	.12	.10	.20	−.17	**−.24***	**−.36*****	.13	−.05	1.0	
IFN-g	.19	**.42*****	.05	.12	**.35****	.05	−.06	**.32****	−.08	1.0
IL-2/IL-4	−.17	**−.69*****	.21	−.11	**−.24***	−.14	.02	**−.40*****	**−.01**	**−.44*****

* $p < .05$,

** $p < .01$,

*** $p < .001$