Are Perceived Stress and Cytokine Genotypes Clinically Feasible as Predictors of Psychoneuroimmune Symptoms in Advanced Cancer?

Stephanie Gilbertson-White, PhD, APRN-BC[1]; Ariana Shahnazi, MA[1]; Catherine Cherwin, PhD, RN[1]

Perm J 2019;23:18-120

E-pub: 07/08/2019

https://doi.org/10.7812/TPP/18-120

ABSTRACT

Context: Genetic variability and perceived stress have been identified as likely predictors of psychoneuroimmune (PNI) symptoms in patients with cancer. In the clinical setting, the ability to identify the patients at greatest risk of development of severe PNI symptoms continues to be elusive.

Objective: To evaluate the feasibility of cytokine genes and perceived stress scores as clinical predictors of PNI symptom severity in patients with a new diagnosis of advanced cancer compared with cancer-free controls (CFCs).

Design: Patients with advanced-stage cancer beginning chemotherapy and CFCs completed questionnaires at 6 time points during 24 weeks and provided blood samples for genotyping.

Main Outcome Measures: Associations between single-nucleotide polymorphisms in cytokine genotypes and perceived stress scores with PNI symptom severity were evaluated using bivariate analysis.

Results: Forty-two participants were recruited (21 patients with cancer and 21 CFCs). Patients with cancer and CFCs were demographically similar and had similar allele frequencies for 15 of 16 single-nucleotide polymorphisms. Cancer-affected patients reported higher perceived stress and PNI symptom severity. Associations were found between several single-nucleotide polymorphisms and PNI symptoms, but no clear pattern emerged across time. Perceived stress was associated with PNI symptom severity for memory problems and fatigue at all 6 time points.

Conclusion: Perceived stress performed better than cytokine genotypes as a clinical predictor of PNI symptoms in this small-scale study. Assessing perceived stress is an easy and low-cost approach that can be used to identify patients at high risk of PNI symptom development.

INTRODUCTION

Clinically reliable tools that identify patients at high risk of development of distressing symptoms during cancer treatment are part of the promise of precision health.[1] A growing body of literature suggests a clear relationship between inflammatory cytokines, perceived stress, and psychoneuroimmune (PNI) symptoms in patients with cancer. Genetic variability in inflammatory cytokines and perceived stress have been identified as key factors in PNI symptom development. However, little research has been done evaluating whether cytokine genotypes[2] or perceived stress scores[3] are adequately specific to be used in the clinical setting to predict which patients will develop PNI symptoms.

Given the explosion of research in genetic and genomic relationships among cytokines, stress response, and cancer symptoms,[4-6] we attempted to evaluate 2 promising precision health approaches to identifying patients at increased risk of symptoms worsening in severity. The purpose of this study was to evaluate the feasibility of using cytokine genotypes and perceived stress scores as clinical predictors of PNI symptom severity in patients with a new diagnosis of advanced cancer compared with a sample of matched cancer-free controls. This study is a secondary analysis from a larger, longitudinal study of cancer symptom experiences and inflammation in patients with a new diagnosis of advanced cancer (in preparation). The underlying hypothesis is that biological variability in stress response is a contributor to PNI symptom severity; therefore, patients with advanced cancer and cancer-free control participants were included in this study to control for the role of cancer and cancer treatment. The foci of this analysis are to 1) describe the cytokine genotypes, perceived stress scores, and symptom severity over 6 time points and 2) evaluate the use of cytokine genotypes and perceived stress scores to predict symptom severity. By identifying patients at risk of high symptom burden, clinicians can provide targeted symptom management interventions to the right patients at the right time.

In patients with cancer, PNI symptoms (eg, pain, fatigue, disturbed sleep, memory problems, feeling upset, feeling sad, and lack of appetite) are highly prevalent,[7,8] can be extremely distressing, and are associated with decreases in functional status and quality of life.[9,10] Breakthroughs in cancer symptom science have improved understanding of the factors that contribute to PNI symptom development in patients with advanced cancer. Indeed, a framework demonstrating the link between cytokines and symptom burden (ie, sickness behavior, which is a cluster of symptoms that include pain, fatigue, anxiety, and depression) has been discussed in the literature.[11] However, because of the sheer number of documented cytokines, little is known about specific cytokines that may be linked to high symptom burden. The ability to prospectively identify the patients at greatest risk of development of a high PNI symptom burden continues to elude both researchers and clinicians.

The conceptual model first posited by Cleeland et al[11] provides the guiding framework for this research (Figure 1). The model proposes that cancer and cancer treatments are the result of inflammatory cytokines released in the periphery by immunocytes. Downstream responses to these cytokines include release of glutamate, nitric oxide, prostaglandins, and substance P acting on

Author Affiliations

[1] College of Nursing, University of Iowa, Iowa City

Corresponding Author

Stephanie Gilbertson-White, PhD, APRN-BC
(stephanie-gilbertson-white@uiowa.edu)

Keywords: advanced-stage cancer, cytokine genes, genetics, immune, inflammatory cytokines, palliative care, psychoneuroimmune symptoms, stress

various regions of the brain, which in turn lead to activation of the hypothalamic-pituitary-adrenal axis and the associated sickness behavior symptoms of pain, loss of appetite, fatigue, memory changes, anxiety, and depressed mood.

Growing evidence suggests that variability in genes that code for inflammatory cytokines have been associated with interindividual variability in cancer symptoms.[12-18] For example, the single-nucleotide polymorphism (SNPs) rs1800629 in the tumor necrosis factor α (TNF-α) gene (*TNFA*)[19] and rs4719714 in the interleukin-6 (IL-6) gene[20] were found to be associated with overall ratings and trajectories of sleep disturbance and fatigue for patients with cancer. Similarly, IL-6 (rs2069845), IL-13 (rs1295686), and TNF-α (rs18800610) were found to be related to pain, fatigue, sleep disturbance, and depression in patients with breast cancer.[14]

In addition, the physiologic stress response is 1 source of cytokine release that may contribute to variability in PNI symptom severity in patients with advanced cancer.[21,22] Physiologic stress response refers to the physical arousal and outcomes that result from stressors, which are described as agents that cause psychologically stressful feelings of uncertainty, hardship, or anxiety.[23] In the context of advanced cancer, the physiologic stress response can become chronic as the stressor (eg, a life-threatening diagnosis) does not resolve. Chronic stress has been linked to increased levels of IL-6,[24] C-reactive protein,[25] and pro-inflammatory genes.[26,27] Psychological variables, such as perceived stress scores, have been associated with PNI symptoms and shorter life expectancy in individuals with cancer.[3,5]

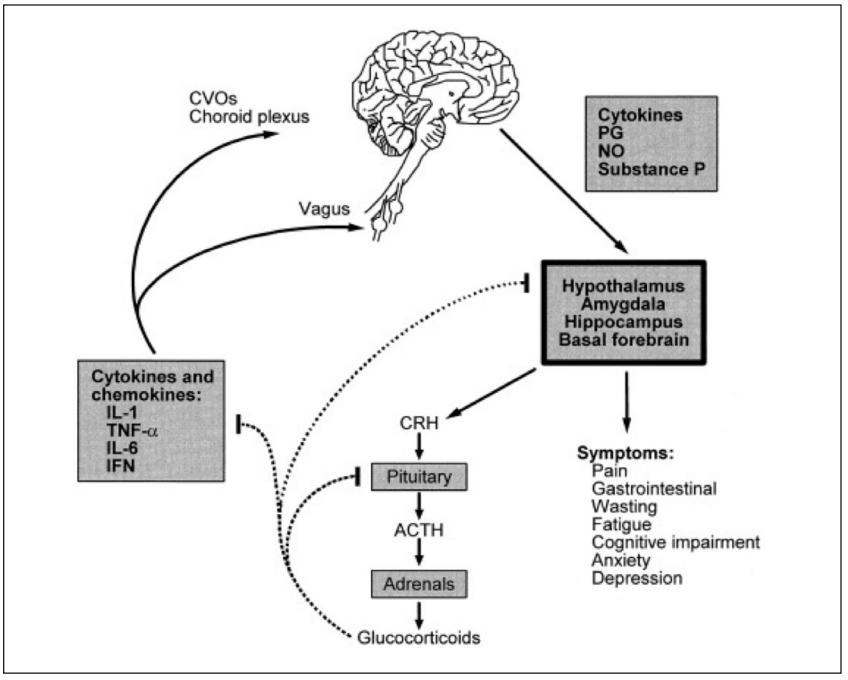

Figure 1. Conceptual model: Biologic/physiologic mechanistic framework for cytokine-induced sickness behavior.[11]
ACTH = corticotropin; CRH = corticotropin-releasing hormone; CVO = circumventricular organ; IL = interleukin; IFN = interferon; NO = nitric oxide; PG = prostaglandin; TNF = tumor necrosis factor.
Reprinted with kind permission from Charles S Cleeland, PhD: Cleeland CS, Bennett GJ, Dantzer R, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer 2003 Jun 1;97(11):2919-25. DOI: https://doi.org/10.1002/cncr.11382.

METHODS

Setting, Sample, and Data Collection

The sample consisted of 21 patients with advanced-stage cancer and 21 cancer-free controls. All procedures described were approved by the University of Iowa institutional review board. Patients with a new diagnosis of advanced cancer were recruited from a large Midwestern comprehensive cancer center. Eligibility criteria for patients with cancer included age 18 years or older; diagnosis of stage IIIB or IV solid tumor with a primary origin of lung, pancreas, or colon-rectum; no prior cancer treatment; and scheduled to receive anticancer therapy (chemotherapy, immunotherapy, or targeted therapy) via intravenous infusion. Exclusion criteria included cancer treatment in the prior 12 months or unknown primary cancer site. Cancer-free controls' eligibility criteria included age 18 years or older and no active cancer or treatment of cancer in the prior 12 months. The cancer-free controls were recruited after data collection of the patients with cancer, allowing us to match the samples on age, sex, and race. Cancer-free controls were excluded if they currently had an active, acute inflammatory health condition (eg, current infection, uncontrolled asthma, autoimmune disorder).

Baseline data collection was scheduled to coincide with the day of the first planned infusion. Questionnaires and blood collection were completed for patients with cancer on the day of their scheduled infusions, beginning with the first infusion. Subsequent data collection occurred every 3 to 4 weeks for up to 6 time points (24 weeks). Blood samples were kept on ice until processing. The ethylenediaminetetraacetic acid (EDTA) tubes were centrifuged for 10 minutes, and the buffy coat layer was extracted by pipette and stored in a -62.2°C (-80°F) freezer.

Appointments for cancer-free controls were scheduled approximately 3 to 4 weeks apart to correspond with time lapses between cancer-affected patients' infusion appointments. Cancer-free control participants' blood was collected following the identical procedure described for patients with cancer.

Measures

Sociodemographics

Participants reported age, sex, and income on a standardized sociodemographic survey.

Perceived Stress

Perceived stress was measured using the Perceived Stress Scale 4. This scale measures levels of perceived stress in a general population.[28] Patients answer 4 items (eg, "In the last month, how often have you felt that you were unable to control the important things in your life?") on the

basis of feelings and thoughts during the last month. Possible responses range from 0 ("never") to 4 ("very often"). Higher scores indicate greater levels of stress. The Perceived Stress Scale 4 has established reliability ($\alpha = 0.78$) and validity in multiple populations.[29]

Psychoneuroimmune Symptom Severity

Severity of PNI symptoms was measured using individual symptom severity items on the core MD Anderson Symptom Inventory. The symptom severity scale consists of 13 core symptoms that are frequently reported across cancer diagnoses.[30] Participants were asked to rate the severity of each symptom in the past 24 hours on a 0-to-10 numeric rating scale, with 0 meaning not present and 10 meaning worst severity possible. The core MD Anderson Symptom Inventory has well-established reliability and validity in cancer populations.[30-33] Severity scores for pain, fatigue, disturbed sleep, memory problems, feeling upset, feeling sad, and lack of appetite were examined for this study. These symptoms were selected from the core MD Anderson Symptom Inventory for this analysis because they map directly onto the PNI symptoms proposed in the sickness behavior model (Figure 1).

Genotypes

A candidate gene approach was used. On the basis of a review of the literature, 16 SNPs that are located in genes that are part of the inflammatory cytokine pathway and associated with functional changes in PNI symptoms were identified. These SNPs were selected using evidence of established functional associations with cancer and/or PNI symptoms available in the National Center for Biotechnology Information SNP database (dbSNP) at the time of the analysis. The center's dbSNP (www.ncbi.nlm.nih.gov/projects/SNP/) is a public-domain archive of documented genetic polymorphisms. All selected SNPs were documented to have more than 10% allele frequency in the dbSNP.

From the buffy coat layer of the ethylenediaminetetraacetic acid tubes, DNA was extracted using a nucleic acid extraction machine (QuickGene 610L, AutoGen, Holliston, MA). DNA quantification was performed using a fluorometer (Qubit 2.0 Fluorometer, Life Technologies Corp, Grand Island, NY), with quantities ranging from 0 to 800 ng/μL; genotyping was attempted on available samples, regardless of quantification outcome. Assays (TaqMan SNP Genotyping Assays, Life Technologies, Carlsbad, CA) were used on a sequence detection system (ABI Prism 7900HT, Applied Biosystems Inc, Foster City, CA) to genotype the SNPs of interest. Results were analyzed with software (SDS 2.4, Applied Biosystems Inc) with a no-call rate of 3% in this sample. Participants were then dichotomized as homogenous wild type or mutant type (ie, 1 or 2 mutant alleles) for each SNP. The total number of mutant types was calculated as the sum score.

Data Analysis

Data from patients with cancer and cancer-free controls were examined as independent samples and as a pooled sample with the rationale that genetic variability and psychological characteristics (eg, perceived stress) exist independent of a diagnosis of cancer. Descriptive statistics of the study variables at all time points were computed. Items with missing responses were excluded from individual analyses, but no participants were excluded from the study because of systematic missingness. *T*-tests were used to compare differences in symptom severity scores on the basis of genotype for all 16 SNPs. Pearson

Table 1. Sample demographics and perceived stress scores

Characteristic	Total sample (N = 42)	Cancer (n = 21)	Cancer-free control (n = 21)	p value
Age, mean (SD), y	59.5 (10.4)	59.9 (9.3)	59.1 (11.6)	NS
Male, no. (%)	22 (52.4)	12 (57.1)	10 (47.6)	NS
White, no. (%)	42 (100)	21 (100)	21 (100)	NS
Income, median, US $	40,000-49,999	40,000-49,999	40,000-49,999	NS
Perceived stress score, mean (SD)	4.9 (3.9)	6.6 (4.3)	3.1 (2.6)	0.025
Total number of gene mutant types, mean (SD)	9.8 (0.9)	9.9 (1.0)	9.6 0.8)	NS

NS = not significant; SD = standard deviation.

Table 2. Allele frequency for single-nucleotide polymorphisms (SNPs) identified in interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, IL-10, and interferon-γ[a]

Cytokine	SNP (rs no.)	Cancer (n = 21)		Cancer-free control (n = 21)		χ^2, p value
		Wild hom	Mutant het/hom	Wild hom	Mutant het/hom	
IL-1 β	rs1143629	9	6	10	8	0.797
	rs1143634	14	7	13	7	0.910
	rs1143643	5	16	7	13	0.431
	rs1143627	5	15	7	13	0.490
IL-6	rs2069832	2	16	4	13	0.330
	rs8192282	4	17	3	18	0.679
	rs1075264	12	9	8	12	0.272
	rs1880243	0	20	0	19	—
	rs1800795	1	18	8	9	**0.004**[b]
TNF-α/*TNFAIP3*	rs1800629	2	18	1	20	0.520
	rs598493	4	14	4	17	0.807
	rs2230926	17	2	18	3	0.720
IL-10	rs1800872	1	19	1	20	0.972
	rs3024505	14	6	12	7	0.651
IFN-γ	rs2069718	8	13	6	15	0.513
	rs2098395	7	13	11	8	0.152

[a] Alleles not detected in all samples.
[b] This value is statistically significant.
het = heterozygous; hom = homozygous; IFN = interferon; rs = reference SNP identification.

correlation scores were calculated to determine bivariate relationships between perceived stress scores and symptom severity scores. The relationship between genotypes, perceived stress, and symptoms was evaluated across time because we expected symptoms to vary over time as a function of changes associated with ongoing activation of the hypothalamic-pituitary-adrenal axis from the cancer and cancer treatments. A significance level of 0.05 was used for statistical tests. SPSS Version 17 (SPSS Inc, Chicago, IL) was used for all analyses.

RESULTS

Sample Description

The total sample consisted of 42 participants. Patients with cancer (n = 21) and cancer-free controls (n = 21) were similar in demographic characteristics. Patients with cancer reported significantly higher perceived stress scores at baseline. Full descriptions of the sample are reported in Table 1.

Cytokine Allele Frequencies

Allele frequencies were similar in both groups, with a difference of 15% or less for 12 of 16 SNPs evaluated (Table 2). There was a lower rate of wild type for IL-6 (rs2069832), wild type for IL-10 (rs1800872), mutant type for IL-10 (rs3024505), and mutant type for interferon (IFN)-γ (rs2098395) in patients with cancer compared with cancer-free controls. Chi-squared analysis revealed no statistical differences in the allele frequencies for all 16 SNPs except 1. For IL-6 rs1800795, the allele frequency for cancer-free controls was evenly distributed, but in patients with cancer, all were mutant type except 1 (p = 0.004). The total number of mutant alleles for the sample was 9.8 (± 0.9) with no difference between patients with cancer and cancer-free controls.

Symptom Severity

PNI symptom severity mean scores were higher for patients with cancer than for cancer-free controls for all symptoms at most but not all time points (Figure 2). Fatigue and disturbed sleep were the most severe symptoms reported by patients with cancer, followed by memory problems, lack of appetite, and pain. Feeling sad and feeling upset were the least severe symptoms. Mean symptom severity scores for cancer-free controls were very low, with slightly elevated fatigue scores at all time points.

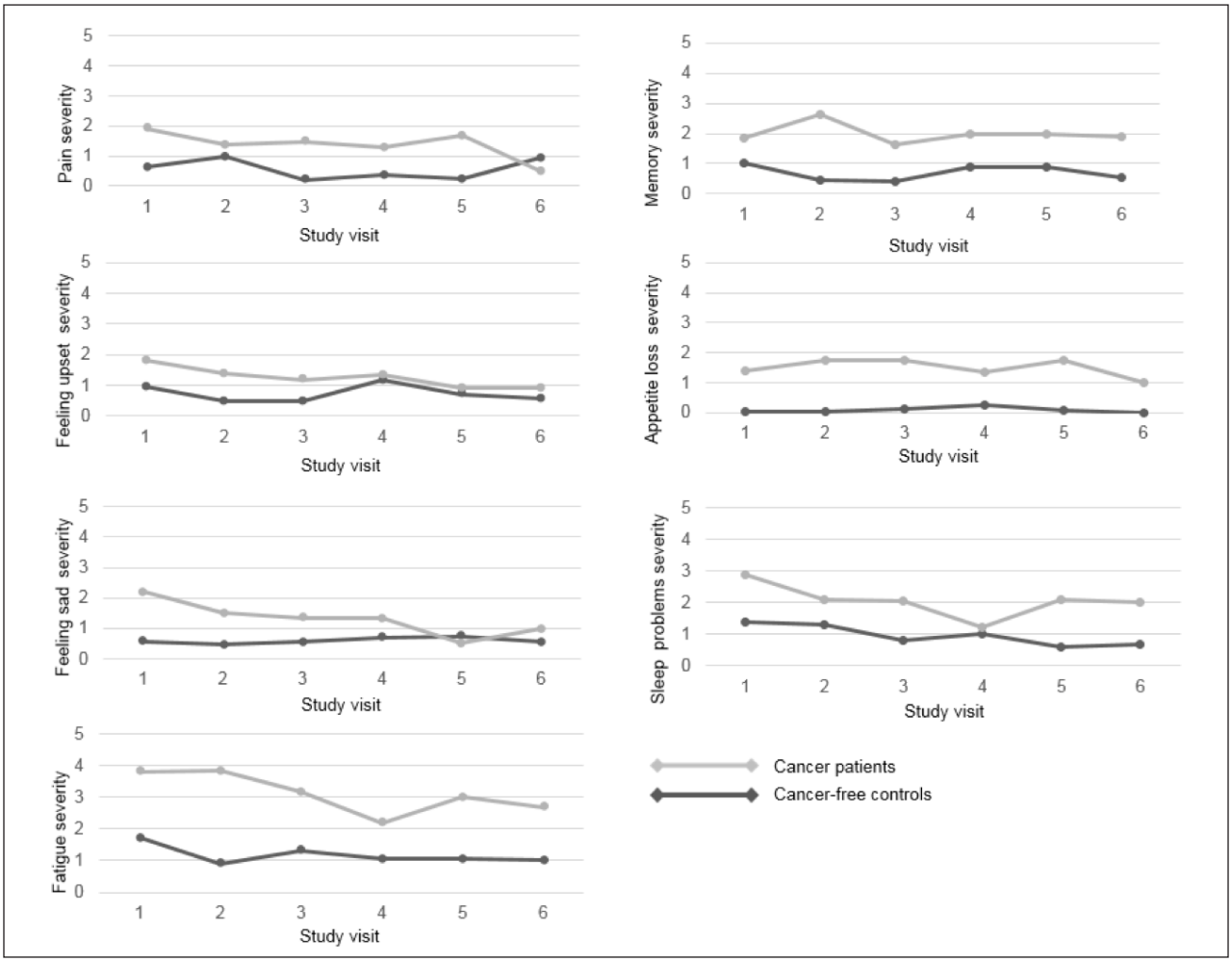

Figure 2. Psychoneuroimmune symptom severity mean scores for cancer patients (n = 21) and cancer-free controls (n = 21) at 6 visits over 24 weeks.[a]

[a] Symptom severity is rated on a 0-to-10 numeric rating scale.

Table 3. Differences in symptom severity between wild-type and mutant-type cytokine genotypes[a]

	IL-1β				IL-6r	IL-6			TNF-α /*TNFAIP3*			IL-10		IFN-γ	
Symptom	rs1143629	rs8192282	rs1143634	rs1143643	rs8192282	rs2069832	rs1075264	rs1800795	rs1800629	rs598493	rs2230926	rs1800872	rs3024505	rs2069718	rs2098395
Pain															
Visit 1								P							
Visit 2						P		P	P						
Visit 3				P											
Visit 4															
Visit 5															
Visit 6														CF	
Upset															
Visit 1										P					
Visit 2															
Visit 3															
Visit 4															
Visit 5															
Visit 6															
Memory															
Visit 1						P									
Visit 2								CF						CF	
Visit 3		P			P	P		P							
Visit 4														CF	
Visit 5															
Visit 6		CF			CF									CF	
Sad															
Visit 1						CF								P, C	
Visit 2			CF												
Visit 3						CF					CF				
Visit 4							P			C					C
Visit 5															
Visit 6															
Sleep															
Visit 1										CF			C		CF
Visit 2	P							P	C	CF					
Visit 3			P												CF
Visit 4														CF	
Visit 5										CF				CF	
Visit 6						P, CF	P								
Appetite															
Visit 1						P		P							
Visit 2						P		P							
Visit 3				P				P							
Visit 4															
Visit 5															
Visit 6				C									C		
Fatigue															
Visit 1										CF		P			
Visit 2								P		CF				CF	
Visit 3				C										CF	
Visit 4										CF				CF	
Visit 5									P	CF				CF	
Visit 6										CF				CF	

[a] Blank cells were not significant. Cells with C, CF, or P were significant with $p < 0.05$.

C = patients with cancer (n = 21); CF = cancer-free controls (n = 21); IFN = interferon; IL = interleukin; P = pooled sample of patients with cancer and cancer-free controls (N = 42); rs = reference single-nucleotide polymorphism identification; TNF = tumor necrosis factor.

Association Between Cytokine Genotype and Symptom Severity

Several cytokines' SNPs were associated with significant differences in symptom severity scores in cancer-free controls, patients with cancer, and a pooled sample of patients with cancer and cancer-free controls. The results were reviewed to identify any significant difference between individual SNPs and PNI symptoms at each time point. Only the SNPs with one or more significant differences were included in Table 3. The results were highly variable across the various SNPs and PNI symptom combinations. Although there were a number of significant differences in symptom severity scores between mutant and wild types in patients with cancer, cancer-free controls, and the pooled sample, no clear patterns emerged among these relationships. No SNPs were found to be significantly related to differences in symptom severity across all time points. Two SNPs had multiple associations at multiple time points. In cancer-free controls, INF-γ rs2069718 was significantly associated with more severe scores for sleep and memory, and *TNFAIP3* rs598493 was associated with more severe scores for sleep and fatigue.

Perceived Stress and Symptom Severity

Higher perceived stress scores were correlated with higher symptom severity for multiple symptoms at multiple visits in the pooled sample (Table 4). The strength of some of these correlations was evident when cancer-free controls and patients with cancer were evaluated separately. Higher perceived stress was associated with high severity of memory problems and fatigue at every visit in the pooled sample.

Table 4. Correlations between perceived stress score and symptom severity score at each time point for pooled, cancer-free controls, and participants with cancer

Visit and sample[a]		Pain	Upset	Memory	Sad	Sleep	Appetite	Fatigue
1	Pooled (n = 42)	*r* = -0.307; p = 0.05	*r* = 0.489; p = 0.001	*r* = 0.433; p = 0.005	*r* = 0.516; p = 0.001	*r* = 0.408; p = 0.009	*r* = 0.257; NS	*r* = 0.577; p < 0.001
	Cancer-free control (n = 21)	*r* = 0.099; NS	*r* = 0.487; p = 0.03	*r* = 0.360; NS	*r* = 0.496; p = 0.03	*r* = 0.128; NS	*r* = 0.265; NS	*r* = 0.210; NS
	Cancer (n = 21)	*r* = 0.257; NS	*r* = 0.413; NS	*r* = 0.392; NS	*r* = 0.447; p = 0.05	*r* = 0.395; NS	*r* = 0.126; NS	*r* = 0.626; p = 0.003
2	Pooled (n = 39)	*r* = 0.207; NS	*r* = 0.407; p = 0.01	*r* = 0.630; p < 0.001	*r* = 0.324; p = 0.04	*r* = 0.085; NS	*r* = 0.348; p = 0.03	*r* = 0.431; p = 0.007
	Cancer-free control (n = 20)	*r* = -0.071; NS	*r* = 0.397; NS	*r* = -0.108; NS	*r* = 0.424; NS	*r* = 0.151; NS	*r* = -0.113; NS	*r* = 0.133; NS
	Cancer (n = 19)	*r* = 0.370; NS	*r* = 356; NS	*r* = 0.707; p = 0.001	*r* = 0.225; NS	*r* = -0.046; NS	*r* = 0.270; NS	*r* = 0.325; NS
3	Pooled (n = 36)	*r* = 0.359; p = 0.03	*r* = 0.422; p = 0.01	*r* = 0.432; p = 0.008	*r* = 0.642; p<= 0.001	*r* = 0.223; NS	*r* = 0.520; p = 0.001	*r* = 0.528; p = 0.001
	Cancer-free control (n = 19)	*r* = 0.326; NS	*r* = 0.455; p = 0.05	*r* = 0.196; NS	*r* = 0.468; p = 0.04	*r* = 0.520; p = 0.02	*r* = 0.525; p = 0.02	*r* = 0.138; NS
	Cancer (n = 17)	*r* = 0.303; NS	*r* = 0.367; NS	*r* = 0.396; p = 0.001	*r* = 0.687; p = 0.002	*r* = -0.115; NS	*r* = 0.466; NS	*r* = 0.607; p = 0.01
4	Pooled (n = 33)	*r* = 0.568; p = 0.001	*r* = 0.330; p = 0.06	*r* = 0.413; p = 0.01	*r* = 0.433; p = 0.01	*r* = 0.248; NS	*r* = 0.533; p = 0.001	*r* = 0.436; p = 0.03
	Cancer-free control (n = 18)	*r* = 0.285; NS	*r* = 0.198; NS	*r* = 0.138; NS	*r* = 0.152; NS	*r* = 0.116; NS	*r* = 0.093; NS	*r* = 0.190; NS
	Cancer (n = 15)	*r* = 0.625; p = 0.01	*r* = 0.579; p = 0.02	*r* = 0.449; NS	*r* = 0.634; p = 0.01	*r* = 0.382; NS	*r* = 0.603; p = 0.01	*r* = 0.444; NS
5	Pooled (n = 30)	*r* = 0.362; p = 0.05	*r* = 0.263; NS	*r* = 0.724; p = 0.003	*r* = 0.188; NS	*r* = 0.265; NS	*r* = 0.379; p = 0.04	*r* = 0.404; p = 0.03
	Cancer-free control (n = 18)	*r* = 0.359; NS	*r* = 0.177; NS	*r* = 0.124; NS	*r* = 0.136; NS	*r* = -0.031; NS	*r* = -0.109; NS	*r* = 0.076; NS
	Cancer (n = 12)	*r* = 0.330; NS	*r* = 0.499; NS	*r* = 0.531; NS	*r* = 0.534; NS	*r* = 0.254; NS	*r* = 0.404; NS	*r* = 0.460; NS
6	Pooled (n = 28)	*r* = -0.021; NS	*r* = 0.255; NS	*r* = 0.375; p = 0.04	*r* = 0.434; p = 0.02	*r* = 0.331; NS	*r* = 0.482; p = 0.011	*r* = 0.383; p = 0.05
	Cancer-free control (n = 18)	*r* = -0.024; NS	*r* = 0.134; NS	*r* = -0.067; NS	*r* = 0.155; NS	*r* = 0.128; NS	Not run[b]	*r* = 0; NS
	Cancer (n = 10)	*r* = 0.164; NS	*r* = 0.531; NS	*r* = 0.490; NS	r = 0.726; p = 0.02	r = 0.289; NS	*r* = 0.520; NS	*r* = 0.488; NS

[a] Total sample size at baseline data collection for each variable.
[b] Not run because of missing data for this timepoint.
NS = not significant.

DISCUSSION

The purpose of this study was to evaluate the feasibility of using cytokine genotypes and perceived stress scores as clinical predictors of PNI symptom severity over time. Cancer and cancer treatments are stressors that can result in PNI symptoms; however, variability in symptom severity is related to personal characteristics and not simply a function of the cancer. Our decision to use both patients with cancer and cancer-free control participants was based on the proposition that the development of PNI symptoms is related to genetic variability and biopsychological stress response. In this sample, in terms of demographic characteristics, patients with cancer and cancer-free controls were very similar, and both groups were also very similar with regard to allele frequencies for all the SNPs evaluated. This permitted comparisons of the 2 groups as well as an analysis as a pooled sample. Not surprisingly, patients with cancer had higher perceived stress scores at visit 1 and generally had higher PNI symptom severity scores across all time points compared with cancer-free controls.

In terms of possible predictors of PNI symptom severity for future research, only 2 SNPs stood out as having some consistency in correlations with symptoms; INF-γ rs2069718 and *TNFAIP3* rs598493 had notable associations with symptom severity in cancer-free controls. Although careful attention was paid to exclude cancer-free controls who may have had an active or acute inflammatory process (eg, asthma, respiratory infection, autoimmune disease), it is plausible that the INF-γ and *TNFAIP3* SNPs were associated with symptom severity in this sample of controls because of some underlying similarity in their comorbidities not measured in this study.

Although this study was not powered to detect symptom severity differences associated with genotypes, it is possible that the best SNPs to predict PNI symptoms were not selected for this analysis despite the best available evidence in the dbSNP. However, the results of this study do provide enough evidence to warrant a closer examination of the association between INF-γ rs2069718 and *TNFAIP3* rs598493 SNPs and higher symptom burden. With 456 cytokine genes, greater than 63,000 SNPs, and 853 SNP-associated diseases,[34] results from this study are valuable in guiding future research.

Research has shown that people with cancer can experience as many as 11 concurrent symptoms,[7] and these symptoms can be very severe and distressing. Finding ways to predict which patients are at higher risk of increased symptom burden would be a meaningful advancement in cancer care.[35] Emerging research has linked certain genetic mutations to symptom severity in people with cancer. However, the human genome is complex, and many genetic mutations remain uninvestigated. In fact, a candidate gene approach, such as the one used in this study, may be too limited because the pleiotropic (and often unexpected) effects of genes continue to be discovered.[36]

An underlying assumption of this research is that variation in cytokine genes will result in variation of the protein products of those genes. Future research is needed that includes measurement of circulating cytokines to further explore this aspect of the genotype to phenotype relationship in PNI symptoms.

One limitation of the study to acknowledge is the small sample size. As such, we evaluated only for bivariate relationships, and any significant levels reported should be evaluated within the context of the limited sample size. Despite the small sample size, this work presents an opportunity to report cytokine mutations in a sample of cancer and cancer-free control populations as well as the clinical feasibility of using cytokine SNPs and perceived stress scores to predict symptom severity.

CONCLUSION

The goals of the study were twofold: To report cytokine genotype mutations that may be responsible for symptom severity in people with cancer and to evaluate the practicality of using cytokine genotypes to predict symptom severity. Although we were unable to establish whether specific SNPs can be used as clinical predictors for symptom development, this work adds to the biobehavioral literature as an initial exploration of the clinical utility of specific genetic mutations as predictors of symptom burden. Several SNPs identified in this study warrant more detailed examination, because they have the potential to be useful clinical predictors of symptom burden. Future research using a multivariate approach, including genotype and perceived stress, would help move the answer to this question forward. In addition, the role of epigenetic changes and gene expression needs further exploration in the context of PNI symptoms and cancer.

Notably, perceived stress wer consistently related to severity scores for multiple PNI symptoms at several times. Assessing perceived stress can be easily done in the clinical setting to identify patients whose symptoms are at risk of worsening. Until the mysteries of the human genome are better understood, brief patient-reported measures such as perceived stress may be the best tools for predicting symptom burden in patients with cancer. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

The author(s) would like to thank the University of Iowa Tissue Procurement Core facility (TPC), which manages the University of Iowa Biobank (UIBB – IRB#201103721), for services provided related to acquisition of study specimens and/or data. The TPC is supported by an award from NIH (NCI award number P30CA086862) and by funding identified by the University of Iowa Carver College of Medicine. In addition, we would like to gratefully acknowledge the participants of the research studies presented in this report.

Kathleen Louden, ELS, of Louden Health Communications performed a primary copy edit.

How to Cite this Article

Gilbertson-White S, Shahnazi A, Cherwin C. Are perceived stress and cytokine genotypes clinically feasible as predictors of psychoneuroimmune symptoms in advanced cancer? Perm J 2019;23:18-120. DOI: https://doi.org/10.1278/TPP/18-120

References

1. Calzone KA, Kirk M, Tonkin E, Badzek L, Benjamin C, Middleton A. The global landscape of nursing and genomics. J Nurs Scholarsh 2018 May;50(3):249-56. DOI: https://doi.org/10.1111/jnu.12380.
2. Gilbertson-White S, Aouizerat BE, Miaskowski C. Methodologic issues in the measurement of cytokines to elucidate the biological basis for cancer symptoms. Biol Res Nurs 2011 Jan;13(1):15-24. DOI: https://doi.org/10.1177/1099800410379497.
3. Gilbertson-White S, Sherwood P, Donovan H, King L. Use of distress screening to identify shorter

life expectancy in patients with advanced cancer newly referred to palliative care. J Palliat Med 2016 Aug;19(8):800-1. DOI: https://doi.org/10.1089/jpm.2016.0142.
4. Steel JL, Terhorst L, Collins KP, et al. Prospective analyses of cytokine mediation of sleep and survival in the context of advanced cancer. Psychosom Med 2018 Jun;80(5):483-91. DOI: https://doi.org/10.1097/PSY.0000000000000579.
5. Kwekkeboom KL, Tostrud L, Costanzo E, et al. The role of inflammation in the pain, fatigue, and sleep disturbance symptom cluster in advanced cancer. J Pain Symptom Manage 2018 May;55(5):1286-95. DOI: https://doi.org/10.1016/j.jpainsymmam.2018.01.008.
6. Chou JL, Chao TY, Chen TC, et al. The relationship between inflammatory biomarkers and symptom distress in lung cancer patients undergoing chemotherapy. Cancer Nurs 2017 Mar/Apr;40(2):E1-8. DOI: https://doi.org/10.1097/NCC.0000000000000369.
7. Deshields TL, Penalba V, Liu J, Avery J. Comparing the symptom experience of cancer patients and non-cancer patients. Support Care Cancer 2017 Apr;25(4):1103-9. DOI: https://doi.org/10.1007/s00520-016-3498-2.
8. Cleeland CS. Cancer-related symptoms. Semin Radiat Oncol 2000 Jul;10(3):175-90. DOI: https://doi.org/10.1053/srao.2000.6590.
9. Cleeland CS. Symptom burden: Multiple symptoms and their impact as patient-reported outcomes. J Natl Cancer Inst Monogr 2007;(37):16-21. DOI: https://doi.org/10.1093/jncimonographs/lgm005.
10. Osoba D, Hsu MA, Copley-Merriman C, et al. Stated preferences of patients with cancer for health-related quality-of-life (HRQOL) domains during treatment. Qual Life Res 2006 Mar;15(2):273-83. DOI: https://doi.org/10.1007/s11136-005-0580-5.
11. Cleeland CS, Bennett GJ, Dantzer R, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer 2003 Jun 1;97(11):2919-25. DOI: https://doi.org/10.1002/cncr.11382.
12. Reyes-Gibby CC, Wu X, Spitz M, et al. Molecular epidemiology, cancer-related symptoms, and cytokines pathway. Lancet Oncol 2008 Aug;9(8):777-85. DOI: https://doi.org/10.1016/S1470-2045(08)70197-9.
13. Wright F, Hammer M, Paul SM, et al. Inflammatory pathway genes associated with inter-individual variability in the trajectories of morning and evening fatigue in patients receiving chemotherapy. Cytokine 2017 Mar;91:187-210. DOI: https://doi.org/10.1016/J.CYTO.2016.12.023.
14. Doong SH, Dhruva A, Dunn LB, et al. Associations between cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression in patients prior to breast cancer surgery. Biol Res Nurs 2015 May;17(3):237-47. DOI: https://doi.org/10.1177/1099800414550394.
15. Kyranou M, Puntillo K, Dunn LB, et al. Predictors of initial levels and trajectories of anxiety in women before and for 6 months after breast cancer surgery. Cancer Nurs 2014 Nov-Dec;37(6):406-17. DOI: https://doi.org/10.1097/NCC0000000000000131.
16. Illi J, Miaskowski C, Cooper B, et al. Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. Cytokine 2012 Jun;58(3):437-47. DOI: https://doi.org/10.1016/j.cyto.2012.02.015.
17. Miaskowski C, Paul SM, Cooper BA, et al. Predictors of the trajectories of self-reported sleep disturbance in men with prostate cancer during and following radiation therapy. Sleep 2011 Feb 1;34(2):171-9. DOI: https://doi.org/10.1093/sleep.34.2.171.
18. Gilbertson-White S, Aouizerat BE, Jahan T, Miaskowski C. A review of the literature on multiple symptoms, their predictors, and associated outcomes in patients with advanced cancer. Palliat Support Care 2011 Mar;9(1):81-102. DOI: https://doi.org/10.1017/S147895151000057X.
19. Aouizerat BE, Dodd M, Lee K, et al. Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. Biol Res Nurs 2009 Jul;11(1):27-41. DOI: https://doi.org/10.1177/1099800409333871.
20. Miaskowski C, Dodd M, Lee K, et al. Preliminary evidence of an association between a functional interleukin-6 polymorphism and fatigue and sleep disturbance in oncology patients and their family caregivers. J Pain Symptom Manage 2010 Oct;40(4):531-44. DOI: https://doi.org/10.1016/j.jpainsymman.2009.12.006.
21. Anisman H, Hayley S, Turrin N, Merali Z. Cytokines as a stressor: Implications for depressive illness. Int J Neuropsychopharmacol 2002 Dec;5(4):357-73. DOI: https://doi.org/10.1017/S1461145702003097.
22. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. Psychosom Med 2003 Jul-Aug;65(4):571-81. DOI: https://doi.org/10.1097/01.PSY.0000074003.35911.41.
23. Lazarus RS. Coping theory and research: Past, present, and future. Psychosom Med 1993 May-Jun;55(3):234-47. DOI: https://doi.org/10.1097/00006842-199305000-00002.
24. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci 2003 Jul 22;100(15):9090-5. DOI: https://doi.org/10.1073/pnas.1531903100.
25. Rohleder N, Marin TJ, Ma R, Miller GE. Biologic cost of caring for a cancer patient: Dysregulation of pro- and anti-inflammatory signaling pathways. J Clin Oncol 2009 Jun 20;27(18):2909-15. DOI: https://doi.org/10.1200/JCO.2008.18.7435.
26. Cole SW, Hawkley LC, Arevalo JM, Sung CY, Rose RM, Cacioppo JT. Social regulation of gene expression in human leukocytes. Genome Biol 2007;8(9):R189. DOI: https://doi.org/10.1186/gb-2007-8-9-r189.
27. Miller GE, Chen E, Sze J, et al. A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased NF-kappaB signaling. Biol Psychiatry 2008 Aug 15;64(4):266-72. DOI: https://doi.org/10.1016/j.biopsych.2008.03.017.
28. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-96. DOI: https://doi.org/10.2307/2136404.
29. Cohen S, Hoberman HM. Positive events and social supports as buffers of life change stress. J Appl Soc Psychol 1983;13(2):99-125. https://doi.org/10.1111/j.1559-1816.1983.tb02325.x.
30. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: The MD Anderson Symptom Inventory. Cancer 2000 Oct 1;89(7):1634-46. DOI: https://doi.org/10.1002/1097-0142(20001001)89:7<1634::AID-CNCR29>3.0.CO;2-V.
31. Armstrong TS, Mendoza T, Gning I, et al. Validation of the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). J Neurooncol 2006 Oct;80(1):27-35. DOI: https://doi.org/10.1007/s11060-006-9135-z.
32. Gning I, Trask PC, Mendoza TR, et al. Development and initial validation of the thyroid cancer module of the M D Anderson Symptom Inventory. Oncology 2009;76(1):59-68. DOI: https://doi.org/10.1159/000178809.
33. Rosenthal DI, Mendoza TR, Fuller CD, et al. Patterns of symptom burden during radiotherapy or concurrent chemoradiotherapy for head and neck cancer: A prospective analysis using the University of Texas MD Anderson Cancer Center Symptom Inventory-Head and Neck Module. Cancer 2014 Jul 1;120(13):1975-84.DOI: https://doi.org/10.1002/cncr.28672.
34. Bhushan S, Perumal NB. Disease associated cytokine SNPs database: An annotation and dissemination model. Cytokine 2012 Jan;57(1):107-12. DOI: https://doi.org/10.1016/j.cyto.2011.10.009.
35. Miaskowski C, Aouizerat BE. Biomarkers: Symptoms, survivorship, and quality of life. Semin Oncol Nurs 2012 May;28(2):129-38. DOI: https://doi.org/10.1016/j.soncn.2012.03.008.
36. Paaby AB, Rockman MV. The many faces of pleiotropy. Trends Genet 2013 Feb;29(2):66-73. DOI: https://doi.org/10.1016/j.tig.2012.10.010.