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CYTOKINE GENE POLYMORPHISMS ASSOCIATED WITH SYMPTOM CLUSTERS IN ONCOLOGY PATIENTS UNDERGOING RADIATION THERAPY

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Abstract

Context—Most of the reviews on the biological basis for symptom clusters suggest that inflammatory processes are involved in the development and maintenance of the symptom clusters. However, no studies have evaluated for associations between genetic polymorphisms and common symptom clusters (e.g., mood disturbance, sickness behavior).

Objectives—Examine the associations between cytokine gene polymorphisms and the severity of three distinct symptom clusters (i.e., mood-cognitive, sickness-behavior, treatment-related) in a sample of patients with breast and prostate cancer (n=157) at the completion of radiation therapy (RT).

Methods—Symptom severity was assessed using the Memorial Symptom Assessment Scale. Symptom clusters were created using exploratory factor analysis. The associations between cytokine gene polymorphisms and the symptom cluster severity scores were evaluated using regression analyses.

Results—Polymorphisms in C–X-C motif chemokine ligand 8 (*CXCL8*), interleukin (*IL13*), and nuclear factor kappa beta 2 (*NFKB2*) were associated with severity scores for the mood-cognitive symptom cluster. In addition to interferon gamma (*IFNG1*), the same polymorphism in *NFKB2* (i.e., rs1056890) that was associated with the mood-cognitive symptom cluster score was associated with the sickness-behavior symptom cluster. Polymorphisms in interleukin 1 receptor 1 (*IL1R1*), *IL6*, and *NFKB1* were associated with severity factor scores for the treatment-related symptom cluster.

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Conflicts of interest: The authors have no conflicts of interest to declare.

Conclusions—Our findings support the hypotheses that symptoms that cluster together have a common underlying mechanism and that the most common symptom clusters in oncology patients are associated polymorphisms in genes involved in a variety of inflammatory processes.

Keywords

symptom clusters; exploratory factor analysis; cytokine genes; radiation therapy

INTRODUCTION

Given that patients with cancer experience multiple concurrent symptoms,[1] the concept of a symptom cluster was introduced, over 15 years ago, to assist clinicians and researchers to evaluate symptoms in a more systematic fashion.[2,3] As noted in two recent reviews,[4,5] while the science of symptom clusters research is advancing, a number of research gaps warrant careful consideration. Of note, one of the underlying hypotheses in symptom cluster research is that symptoms cluster together because they share a common biological or behavioral mechanism. However, only eight studies have evaluated for potential mechanisms associated with a pre-specified symptom cluster in oncology patients.[6–13]

Of these eight studies, five evaluated the pre-specified symptom cluster of pain, fatigue, and depression[6–10] and three evaluated the pre-specified symptom cluster of fatigue, pain, depression, and sleep disturbance.[11–13] In terms of an evaluation of the mechanisms associated with these pre-specified symptom clusters, the primary ones included: inflammation,[7,8,11–13] immune responses,[6,9] and neuroendocrine responses.[10] In the studies of inflammation, different cytokine gene polymorphisms were associated with the symptom cluster of pain, fatigue, and depression[8] and the symptom cluster of fatigue, pain, depression, and sleep disturbance.[11,12] In the two studies that evaluated for associations with serum levels of inflammatory markers,[7,13] only one study found a positive relationship between serum levels of interleukin (IL) 6 and the symptom cluster of fatigue, pain, depression, and sleep disturbance. In the studies that evaluated for associations between immune markers and the pre-specified symptom cluster of pain, fatigue, and depression, one found a positive association with cytomegalovirus titers[6] and the other found a positive association with eosinophil counts.[9] Finally, in the study that evaluated the relationship between neuroendocrine responses and the pre-specified symptom cluster of pain, fatigue, and depression,[10] higher levels of epinephrine and norepinephrine were associated with more severe symptoms.

While an evaluation of associations between a pre-specified symptom cluster and potential mechanisms is an important aspect of symptom cluster research, an equally important area in this field of inquiry is the identification of symptom clusters “de novo”.[4,5,14,15] The creation of symptom clusters “de novo” involves the administration of a symptom inventory that evaluates symptom occurrence or severity. Using factor analysis or cluster analysis techniques, one or more symptom clusters are derived “de novo”. Once the symptom clusters are identified, investigators name them based on the symptoms contained within each cluster and the characteristics of the oncology patients who were assessed.

Most of the reviews on the biological basis for symptom clusters suggest that inflammatory processes are involved in the development and maintenance of the symptom clusters.[16–19] This hypothesis is based on the fact that two of the most common symptom clusters identified “de novo” are a psychological or mood-related symptom cluster and a sickness behavior symptom cluster. However, no studies that created symptom clusters “de novo” have evaluated for associations between genetic polymorphisms and these clusters. In this paper, we extend our work on the identification of symptom clusters “de novo” and examine the associations between cytokine gene polymorphisms and the severity of three distinct symptom clusters (i.e., mood-cognitive, sickness-behavior, treatment-related) in a sample of patients with breast and prostate cancer at the completion of radiation therapy (RT).[20]

METHODS

Patients and Settings

This study is part of a descriptive, longitudinal study whose primary purpose was to evaluate the trajectories of fatigue, pain, and sleep disturbance in oncology outpatients over the course of RT.[21–26] Patients were included if they: were adults (>18 years of age) who were able to read, write, and understand English; had a Karnofsky Performance Status (KPS) score of ≥60; and were scheduled to receive primary or adjuvant RT. Patients were excluded if they had metastatic disease; had more than one cancer diagnosis; or had a diagnosed sleep disorder. Patients were recruited from RT departments located in a Comprehensive Cancer Center and a community based oncology program. This study was approved by the Human Subjects Committee at the University of California, San Francisco and at the second study site.

Study Procedures

At the time of the simulation visit (i.e., approximately 1 week prior to the start of RT), patients were approached by a research nurse to discuss participation in the study. After obtaining written informed consent, they were asked to complete a number of enrollment questionnaires and symptom inventories. Additional assessments were done over the course of RT and for four months after the completion of RT. For this paper, demographic and clinical data, as well as data from the Memorial Symptom Assessment Scale (MSAS)[27] that was completed at the end of RT were used in these analyses. Patients’ medical records were reviewed for disease and treatment information.

Instruments

The demographic questionnaire provided information on age, gender, marital status, education, ethnicity, and employment status. In addition, patients completed a checklist of co-morbidities and the KPS scale.[28–30] The KPS is widely used to evaluate the functional status of cancer patients and has well established validity and reliability.

The MSAS is a valid and reliable self-report questionnaire designed to measure the multidimensional experience of symptoms.[27] The MSAS contains a list of 32 physical and psychological symptoms that occur as a result of cancer or its treatment. Using the MSAS, patients were asked to indicate whether or not they had experienced each symptom in the

past week. If they had experienced the symptom, they were asked to rate its severity, its frequency of occurrence, and its distress. The patients' responses to the symptom severity items were used to create the symptom clusters. The validity and reliability of the MSAS is well established.[27,31]

Phenotypic Data Analysis

Descriptive statistics—All data analyses were done using SPSS Version 23,[32] MPlus version 7.3,[33] and Stata Release 14.[34] Prior to the symptom cluster analysis, appropriate descriptive statistics were used to generate information on the patients' demographic and clinical characteristics.

Creation of Symptom Clusters—As reported previously,[20] exploratory factor analysis (EFA) was used to determine the number of symptom "factors" (i.e., clusters). If the patient indicated that they did not have the symptom, a severity score of 0 was assigned. If the patient had the symptom, severity was rated using a 4-point Likert scale (i.e., 1=mild, 2=moderate, 3=severe, 4=very severe). In order to have a sufficient amount of data to perform the EFA, the 13 symptoms that were present in ≥20% of the patients were used in the analysis.

The major decisions in factor analysis include how to estimate communality; how to determine the number of factors; and how to determine the method for rotating the factors to obtain the simple structure. For the severity data, polychoric correlations were used to create the matrix of associations among the 13 symptoms. The simple structure was estimated using the method of unweighted least squares with GEOMIN (oblique) rotation. Because of the relatively small sample size (i.e., <200), the unweighted least squares estimator, with a mean and variance adjusted Chi square test, using a full weight matrix (ULSMV) was chosen to improve reliability of the solution (i.e., generalizability) and improve accuracy of the estimates (i.e., reduce bias).[35] Factor loadings were considered meaningful if they exceeded 0.30.[36,37] In this study, symptoms were allowed to load on only one factor. The number of factors was considered sufficient to explain the symptom correlations, if the model's Chi-Square test was not significant, its comparative fit index was ≥0.95, and the root mean square error of approximation (RMSEA) was ≤0.06.[38] For the EFA, two, three, and four factor solutions were inspected.

For each symptom cluster, a factor severity score was calculated as the sum of the severity ratings of all the symptoms within the cluster. These symptom cluster severity scores were used in the regression analyses that evaluated the association between each of the symptom clusters and polymorphisms in cytokine genes.

Genomic Data Analysis

Blood collection and genotyping—As previously described,[39, 40] genomic deoxyribonucleic acid (DNA) was extracted from archived buffy coats using the PUREGene DNA Isolation System (Invitrogen, Carlsbad, CA). DNA samples were quantitated and normalized to a concentration of 50 nanogram (ng)/microliter (μL). Samples were genotyped using the GoldenGate genotyping platform (lllumina, San Diego, CA) and processed

according to the standard protocol using GenomeStudio (lllumina, San Diego, CA). Genotyping was performed blinded to clinical status and positive and negative controls were included.

Single Nucleotide Polymorphism (SNP) Selection—A combination of tagging SNPs and literature driven SNPs were selected for analysis. Tagging SNPs were required to be common (defined as having a minor allele frequency (MAF) of ≥0.05) in public databases. In order to ensure robust genetic association analyses, quality control filtering of SNPs was performed. SNPs with call rates of <95% or Hardy-Weinberg p-values of <.001 were excluded.

As shown in Supplementary Table 1, a total of 92 SNPs among the 15 candidate genes (i.e., interferon gamma (*IFNG*): 5 SNPs, IFNG receptor 1 (*IFNGR1*): 1 SNP; *IL1B*: 12 SNPs; IL1 receptor 1 (*IL1R1*): 5 SNPs; *IL1R2*: 3 SNPs; *IL2*: 5 SNPs; *IL4*: 8 SNPs; *IL6*: 9 SNPs; C-X-C motif chemokine ligand 8 (*CXCL8*, formerly *IL8*): 3 SNPs; *IL10*: 8 SNPs; *IL13*: 4 SNPs; *IL17A*: 5 SNPs; nuclear factor kappa beta 1 (*NFKB1*): 11 SNPs; *NFKB2*: 4 SNPs; tumor necrosis factor super family (*TNF SF*): 9 SNPs), that passed all quality control filters, were included in the genetic association analyses. All genes were identified according to the approved symbol stored in the Human Genome Organization (HUGO) Gene Nomenclature Committee (HGNC) database (http://www.genenames.org). Localization of SNPs and regional annotations were identified using the University of California Santa Cruz (UCSC) Human Genome Browser for the human reference assembly GRCh38/hg38 (http://genome.ucsc.edu/cgi-bin/hgTracks?db=hg38). Potential regulatory involvement of SNPs was investigated using SNPinfo (https://snpinfor.niehs.nih.gov).[41]

Statistical Analyses—Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg equilibrium was assessed by the Chi-square test. Measures of linkage disequilibrium (i.e., D' and r2) were computed from the patients' genotypes with Haploview 4.2. Linkage disequilibrium (LD)-based haplotype block definition was based on D' confidence interval.[42]

For SNPs that were members of the same haplotype, haplotype analyses were conducted in order to localize the association signal within each gene and to determine if haplotypes improved the strength of the association with the phenotype. Haplotypes were constructed using the program PHASE version 2.1.[43] Only haplotypes that were inferred with probability estimates of >0.85, across five iterations, were retained for downstream analyses. Haplotypes were evaluated assuming a dosage model (i.e., analogous to the additive model).

Ancestry informative markers (AIMS) were used to minimize confounding due to population stratification.[44–46] Homogeneity in ancestry among patients was verified by principal component analysis,[47] using Helix Tree (Golden Helix, Bozeman, MT). One hundred and six AIMs were included in the analysis. The first three PCs were selected to adjust for potential confounding due to population substructure (i.e., ancestry) by including these three covariates in all regression models.

For association tests, three genetic models were assessed for each SNP: additive, dominant, and recessive. Barring trivial improvements (i.e., delta <10%), the genetic model that best fit the data, by maximizing the significance of the p-value, was selected for each SNP.

Because the symptom cluster scores were not normally distributed and displayed a common over-dispersed Poisson distribution (as a weighted count) for the mood-cognitive symptom cluster and the sickness-behavior symptom cluster, negative binomial regression analysis that controlled for significant covariates, as well as genomic estimates of and self-reported race/ethnicity, was used to evaluate the relationship between genotype and symptom cluster severity score. For the treatment-related symptom cluster, which had a more symmetrical distribution, linear regression analysis that controlled for significant covariates, as well as genomic estimates of and self-reported race/ethnicity, was used to evaluate the relationship between genotype and symptom cluster severity score. A backwards stepwise approach was used to create a parsimonious model. The demographic (i.e., age, gender, education, marital status, living arrangements, marital status) and clinical characteristics (i.e., body mass index (BMI), KPS score, number of comorbid conditions) that were evaluated as potential covariates were chosen because they were associated with the symptoms in our previous studies with this sample. Except for genomic estimates of and self-reported race/ethnicity, only predictors with a p-value of <.05 were retained in the final model. Genetic model fit and both unadjusted and covariate-adjusted odds ratios were estimated using Stata version 14.[48]

As was done in all of our previous candidate gene studies,[11,49–52] based on recommendations in the literature,[53,54] the implementation of rigorous quality controls for genomic data, the non-independence of SNPs/haplotypes in LD, and the exploratory nature of the analyses, adjustments were not made for multiple testing. Significant SNPs were evaluated using regression analyses that controlled for differences in phenotypic characteristics, potential confounding due to population stratification, and variation in other SNPs/haplotypes within the same gene. Only those SNPs that remained significant were included in the final presentation of the results. Therefore, the significant independent associations reported are unlikely to be due solely to chance. Associations are reported for all SNPs passing quality control criteria in Supplemental Table 1 to allow for subsequent comparisons and meta-analyses.

RESULTS

Demographic and Clinical Characteristics

As shown in Table 1, 51.0% of the 157 patients in this study were male and 55.6% were married, with a mean age of 61.2 (±11.3) years. The majority of the patients were White (72.4%) and well educated (16.1 ± 3.0 years of education). Fifty-one percent of the patients had prostate cancer. The mean BMI for the sample was 27.5 (±5.5) kilograms/metered^2 (kg/m^2), mean KPS score was 92.5 (±9.8), and the mean number of comorbid conditions was 4.9 (±2.6).

Symptom Clusters and Mean Severity Scores

The thirteen symptoms that occurred in ≥20% of the patients and were used in the EFA were: lack of energy (59.4%), pain (51.8%), difficulty sleeping (47.1%), feeling drowsy (44.4%), sweats (39.9%), problems with urination (37.1%), difficulty concentrating (35.9%), feeling irritable (34.0%), itching (31.9%), worrying (29.7%), feeling sad (26.9%) cough (22.3%), and changes in skin (20.0%). As shown in Table 2, twelve symptoms were included in the EFA (i.e., cough did not load). A three factor solution indicated a good fit between the data and the model ($\chi^2 = 24.6$, $p = 0.22$, comparative fit index (CFI) = 0.99, RMSEA = 0.04). The five symptoms in Factor 1 (i.e., difficult concentrating, feeling sad, worrying, itching, feeling irritable) were named the “mood-cognitive symptom cluster”. The five symptoms in Factor 2 (i.e., pain, lack of energy, feeling drowsy, difficulty sleeping, sweats) were named the “sickness behavior symptom cluster”. The two symptoms in Factor 3 (i.e., problems with urination, changes in skin) were named the “treatment-related symptom cluster”.[20]

Association Between Mood-Cognitive Symptom Cluster Score and Cytokine Genes

As shown in Table 3, of the nine patient characteristics that were evaluated (i.e., age, gender, education, marital status, living arrangements, employment status, BMI, KPS score, number of chronic conditions), only age, education, and number of chronic conditions was retained in the final negative binomial regression analyses for the mood-cognitive symptom cluster. After controlling for these patient characteristics, self-report and genomic estimates of race and ethnicity, and other polymorphisms in the same gene, the only genetic associations that remained significant were for *CXCL8* HapA4, *IL13* rs20541, and *NFKB2* rs1056890.

In the negative binomial regression analysis for *CXCL8* HapA4 (that is composed of alleles at rs4073, rs2227306, and rs2227543; A-C-C), for each additional dose of the *CXCL8* HapA4, the mood-cognitive symptom cluster score decreased by 39.0% (p=.009). In the regression analysis for *IL13* rs20541, as the dose of the rare allele increased (i.e., CC versus CT versus TT), the mood-cognitive symptom factor score decreased by 47% (p=.014). In the regression analysis for *NFKB2* rs1056890, having two doses of the rare allele (i.e., CC+CT versus TT) was associated with a 2.30-fold higher mood-cognitive symptom factor score (p=.014).

Association Between Sickness-Behavior Symptom Cluster Score and Cytokine Genes

As shown in Table 4, of the nine patient characteristics that were evaluated (i.e., age, gender, education, marital status, living arrangements, employment status, BMI, KPS score, number of chronic conditions), only age was retained in the final negative binomial regression analyses for the sickness-behavior symptom cluster. After controlling for age, self-report and genomic estimates of race and ethnicity, and other polymorphisms in the same gene, the only genetic associations that remained significant were for *IFNG1* rs1861493 and *NFKB2* rs1056890.

In the negative binomial regression analysis for *IFNG1* rs1861493, having two doses of the rare allele (i.e., AA+AG versus GG) was associated with an 80% decrease in the sickness-behavior symptom factor score (p=.009). In the regression analysis for *NFKB2* rs1056890,

having two doses of the rare allele (i.e., CC+CT versus TT) was associated with a 1.96 fold higher sickness-behavior symptom factor score (p=.012).

Association Between Treatment-related Symptom Cluster Score and Cytokine Genes

As shown in Table 5, of the nine patient characteristics that were evaluated (i.e., age, gender, education, marital status, living arrangements, employment status, BMI, KPS score, number of chronic conditions), only gender was retained in the final linear regression analyses for the treatment-related symptom cluster. After controlling for gender, self-report and genomic estimates of race and ethnicity, and other polymorphisms in the same gene, the only genetic associations that remained significant were for *IL1R1* rs2228139 and *IL1R1* rs3917320, *IL6* rs2069840, and *NFKB1* HapA9.

In the linear regression analysis for *IL1R1*, compared to patients who had zero or one dose of the rare allele in rs2228139, patients who had two doses of the rare allele (i.e., AA+AG versus GG) were more likely to report a higher treatment-related symptom factor score (p=.021). This SNP uniquely explained 3.0% of the variance in the symptom factor score. In the same regression model, for each additional dose of the rare allele in *IL1R1* rs3917320 (i.e., AA versus AC versus CC), patients were more likely to report a lower treatment-related symptom factor score (p=.035). This SNP explained 2.1% of the variance in the symptom factor score. In the linear regression analysis for *IL6* rs2069840, for each additional dose of the rare allele (i.e., CC versus CG versus GG), patients were more likely to report a higher treatment-related symptom factor score (p=.005). This SNP explained 3.9% of the variance in the symptom factor score. In the linear regression analysis for *NFKB1* HapA9 (that is composed of alleles at rs3774933, rs170731, rs230510, rs230494, and rs3774956; G-T-T-G-T), for each additional dose of the *NFKB1* HapA9, patients were more likely to report a lower treatment-related symptom factor score (p=.002). This haplotype explained 4.7% of the variance in the symptom factor score.

DISCUSSION

This study is the first to evaluate for associations between symptom cluster factor scores and cytokine gene polymorphisms. The clinical implications of the specific symptom clusters were discussed in our previous publication.[20] This discussion will focus on the genomic findings. Except for *NFKB2* rs1056890, for the three symptom clusters evaluated, polymorphisms in different genes were associated with variability in the severity scores of each of the symptom clusters. These findings provide support for the hypothesis that one of the reasons that symptoms cluster together is because they share common biological mechanisms. In addition, these findings suggest, as previously hypothesized, that the most common symptoms experienced by oncology patients share some common biological mechanisms associated with inflammation.[55–57]

Mood-Cognitive Symptom Cluster

Polymorphisms in *CXCL8*, *IL13*, and *NFKB2* were associated with severity scores for the mood-cognitive symptom cluster. The *CXCL8* gene, formerly called *IL8*, encodes a chemokine that is one of the major mediators of inflammatory responses. In addition, recent

evidence suggests that *CXCL8* and other chemokines are associated with a variety of neurobiological processes and contribute to the pathophysiology of mood disorders, cognitive impairment, and schizophrenia.[58,59] Each additional dose of the *CXCL8* haplotype composed of three SNPs (i.e. rs4073, rs2227306, rs2227543) was associated with a significant decrease in the mood-cognitive symptom cluster score. CXCL8 rs2227543 is an intron variant with no predicted function in SNPinfo. However, both *CXCL8* rs2227306 (located in an intron) and *CXCL8* rs4073 (located upstream of the transcript start site of the gene), were found in gene regions with histone modifications that are characteristic of regulatory elements.[60] While the effects of this haplotype on protein levels are unknown, higher serum levels of CXCL8 were associated with higher levels of depressive symptoms in some studies[61–63] and a higher symptom burden and increased anxiety in patients with irritable bowel syndrome-associated diarrhea.[64] It is interesting to note that difficulty concentrating was included in the mood-cognitive symptom cluster. While serum levels of CXCL8 were not associated with mild cognitive impairment,[65–67] recent findings suggest that cerebrospinal fluid levels of CXCL8 are elevated in patients with both mild cognitive impairment and Alzheimer's disease.[68] Given the associations between cognitive impairment and depression in oncology patients undergoing cancer treatment,[69,70] future studies need to examine the relationships between CXCL8 and these two symptoms.

IL13 is an immunoregulatory cytokine that is produced by activated Th2 cells. This cytokine downregulates macrophage activity with associated decreases in the production of pro-inflammatory cytokines and chemokines.[71] *IL13* rs20541 is a common coding SNP in exon 4, which causes a nonsynonymous substitution of the amino acid arginine by glutamine.[72] However, in SNPinfo, the effect of this polymorphism was predicted to be benign. Most of the research on this SNP is on its associations with asthma and allergic rhinitis.[73,74] In the current study, as the dose of the rare allele increased, the mood-cognitive symptom cluster score decreased. While no studies have evaluated for associations between mood disorders and serum levels of IL13, given the role of inflammation in these conditions,[75,76] as well as our finding of an association between another SNP in IL13 (i.e., rs1295686) and the symptom cluster of pain, fatigue, sleep disturbance, and depression,[12] additional investigations are warranted in oncology and psychiatric patients.

NFKB2 is a gene that encodes a subunit of the transcription factor complex NFkB. This pleiotropic transcription factor is present on almost all types of cells and is activated by a large number of stimuli involved in inflammation, immunity, cellular differentiation, cell growth, tumorigenesis, and apoptosis.[77] In the current study, patients who were homozygous for the rare T allele in NFKB2 rs1056890 were more likely to report a higher mood-cognitive symptom cluster factor score. This SNP is located in the 3' untranslated region (UTR) of the gene which suggests that it may regulate NF-kB signaling through overexpression of NF-kB2.[78,79] Based on SNPinfo, this polymorphism is predicted to interfere with protein translation by affecting microRNA binding site activity. Of note, our previous work found similar deleterious associations with this SNP. In a study of oncology patients who underwent RT and their family caregivers,[39] participants who were homozygous for the rare T allele in *NFKB2* rs1056890 were more likely to be classified into the lower energy group. In a different sample of breast cancer patients,[80] women who were homozygous for the rare T allele in this SNP were 3.06 times more likely to be diagnosed

with lymphedema. In addition, in a study of patients being treated for multiple myeloma, individuals who were heterozygous or homozygous for the rare T allele had an overall poorer survival rate.[79] Given the fact that a mood-related symptom cluster is one of the most common clusters identified in oncology patients[81–92] and our findings provide support for the involvement of inflammatory processes in this symptom cluster, additional research is warranted to confirm these findings in patients undergoing different types of cancer treatment (e.g., CTX) and in patients with other chronic conditions.

Sickness-behavior Symptom Cluster

In addition to IFNG1 rs1861493, the same polymorphism in *NFKB2* (i.e., rs1056890) that was associated with the mood-cognitive symptom cluster score was associated with the sickness-behavior symptom cluster. For the *NFKB2* polymorphism, the association was in the same direction in that patients who were homozygous for the rare T allele had a 1.96 fold higher sickness-behavior symptom cluster factor score. One potential explanation for the same polymorphism in *NFKB2* being associated with both symptom cluster factor scores is that in many studies of sickness behavior, mood-related symptoms are described as part of this condition.[56,93] In the current study, while two of the symptoms in the mood-cognitive symptom cluster (i.e., difficulty concentrating (0.34), feeling sad (0.32)) had factor loadings that were above 0.30, symptoms were not allowed to load on more than one factor. Future studies with larger samples need to evaluate for associations between this polymorphism and a sickness-behavior symptom cluster that includes mood-related symptoms.

In terms of the specific symptoms within the sickness-behavior symptom cluster, no studies were found on an association between *NFKB2* and fatigue. However, as noted above, in another study by our research team, participants who were homozygous for the rare T allele in *NFKB2* rs1056890 were more likely to be classified into the lower energy group.[39] While no studies were found on the associations between *NFKB2* and pain, feeling drowsy or sweats, polymorphisms in *NFKB2* and sleep disturbance were evaluated in adults living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)[94,95] and oncology patients.[50,96] In the studies of adults with HIV/AIDS,[94,95] no associations were found with this gene. In our previous studies, patients who were heterozygous or homozygous for the rare allele in the two polymorphisms in *NFKB2* (i.e., rs7897947 (TG +GG),[50] and rs1056890 (CT+TT)[96]) were less likely to be classified in the higher sleep disturbance group. These inconsistent findings may be related to the different sleep phenotypes that were evaluated (i.e., symptom cluster factor score versus a self-report measure of sleep disturbance[97]).

IFNG1 codes for a cytokine protein that is secreted by cells of both the innate and adaptive immune systems. When this protein binds to the IFNG receptor, it triggers a cellular response to viral and microbial infections. Mutations in this gene are associated with increased susceptibility to bacterial, viral, and parasitic infections.[98] *IFNG1* rs1861493 is located in an intron and has no predicted function in SNPinfo. No studies were found that described associations between this polymorphism and any of the symptoms in our sickness-behavior symptom cluster. However, in one study that evaluated an association between *IFNG1* rs1861493 and symptom severity scores associated with Q fever in two different

samples,[99] the results are inconsistent. In one sample the rare G allele was associated with a higher symptom burden. However, in the second sample, no association was found between this polymorphism and patients' symptom severity scores. Given this gene's role in infectious processes, additional studies are warranted on its role in the etiology of the symptoms associated with sickness behavior.

Treatment-related Symptom Cluster

Polymorphisms in *IL1R1*, *IL6*, and *NFKB1* were associated with severity factor scores for the treatment-related symptom cluster. *IL1R1* encodes for the cytokine receptor for IL-1 alpha, IL-1 beta, and the IL-1 receptor antagonist. The protein product of this gene is involved in many cytokine-induced immune and inflammatory responses.[98] Both SNPs (i.e., *IL1R1* rs2228139 and *IL1R1* rs3917320) identified as significant in the univariate analyses remained significant in the multivariate analyses. Using SNPinfo, *IL1R1* rs2228139 is a non-synonymous SNP whose functional effects are predicted to be benign. *IL1R1* rs3917320 is a synonymous SNP that is predicted to change the splicing pattern or efficiency of the gene by disrupting a splice site. While no studies have evaluated for associations between these two polymorphisms and the two symptoms in the treatment-related symptom cluster, both the urinary problems in patients with prostate cancer[100] and the skin changes in patients with breast cancer[101,102] are the result of inflammatory responses in the bladder and skin as a result of ionizing radiation.

IL6 is a gene that encodes for an inflammatory cytokine that is produced at sites of acute and chronic inflammation.[98] *IL6* rs2069840 is an intronic SNP that is predicted by SNPinfo to be involved in transcriptional regulation by affecting transcription factor binding site (TFBS) activity. No associations were reported for the IL6 gene and RT-induced cystitis or dermatitis. However, consistent with our finding that the rare C allele in *IL6* rs2069840 was associated with a lower treatment-related symptom factor score, the minor allele was associated with protection against type 2 reaction leprosy[103] and the limited form of cutaneous systemic sclerosis.[104]

NFκ-B is pleotropic transcription factor that is present in most cells. It is produced in response to numerous biological processes including inflammation, immunity, cell growth and differentiation, tumorigenesis, and apoptosis.[98] All of the SNPs in *NFKB1* HapA9 (i.e., rs3774933, rs170731, rs230510, rs230494, and rs3774956) are intronic with no known function predicted by SNPinfo. While no studies have evaluated for associations between cystitis and *NFKB1*, preliminary evidence suggests that polymorphisms in this gene may be associated with atopic dermatitis.[105]

Limitations

Several limitations warrant consideration. Given the relatively small sample size, the findings from this study warrant replication. In addition, the symptoms within each of the symptom clusters may be specific to patients with breast and prostate cancer at the completion of RT. Future studies that identify similar symptom clusters in different groups of oncology patients need to determine if the same genes are associated with these symptom cluster factor scores. While vigorous quality control procedures were used and adjustments

were made for potential confounding due to various demographic and clinical characteristics, some of the relationships identified may be associated with a Type 1 error. Therefore, the genetic associations found in this study warrant replication in independent samples.

Conclusions

This study is the first to describe associations between three different symptom clusters and genes involved in inflammatory processes. Our findings support the hypotheses that symptoms that cluster together have a common underlying mechanism and that the most common symptom clusters in oncology patients are associated polymorphisms in genes involved in a variety of inflammatory processes. Future studies need to determine if the severity factor scores for these symptom clusters correlate with changes in gene expression associated with the identified polymorphisms and with increases or decreases in serum levels of the respective cytokines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Esther Kim JE, Dodd MJ, Aouizerat BE, Jahan T, Miaskowski C. A review of the prevalence and impact of multiple symptoms in oncology patients. J Pain Symptom Manage. 2009; 37:715–736. [PubMed: 19019626]
2. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. Oncol Nurs Forum. 2001; 28:465–470. [PubMed: 11338755]
3. Given B, Given C, Azzouz F, Stommel M. Physical functioning of elderly cancer patients prior to diagnosis and following initial treatment. Nurs Res. 2001; 50:222–232. [PubMed: 11480531]
4. Miaskowski C. Future directions in symptom cluster research. Semin Oncol Nurs. 2016; 32:405–415. [PubMed: 27776833]
5. Miaskowski C, Barsevick A, Berger A, et al. Advancing symptom science through symptom cluster research: Expert panel proceedings and recommendations. J Natl Can Inst. 2016
6. Jaremka LM, Fagundes CP, Glaser R, et al. Loneliness predicts pain, depression, and fatigue: understanding the role of immune dysregulation. Psychoneuroendocrinology. 2013; 38:1310–1317. [PubMed: 23273678]
7. Laird BJ, Scott AC, Colvin LA, et al. Pain, depression, and fatigue as a symptom cluster in advanced cancer. J Pain Symptom Manage. 2011; 42:1–11. [PubMed: 21402467]
8. Reyes-Gibby CC, Swartz MD, Yu X, et al. Symptom clusters of pain, depressed mood, and fatigue in lung cancer: assessing the role of cytokine genes. Support Care Cancer. 2013; 21:3117–3125. [PubMed: 23852407]
9. Steel JL, Kim KH, Dew MA, et al. Cancer-related symptom clusters, eosinophils, and survival in hepatobiliary cancer: an exploratory study. J Pain Symptom Manage. 2010; 39:859–871. [PubMed: 20471546]

10. Thornton LM, Andersen BL, Blakely WP. The pain, depression, and fatigue symptom cluster in advanced breast cancer: covariation with the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Health Psychol. 2010; 29:333–337. [PubMed: 20496988]
11. 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; 58:437–447. [PubMed: 22450224]
12. 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; 17:237–247. [PubMed: 25304131]
13. Starkweather AR, Lyon DE, Elswick RK Jr, et al. Symptom cluster research in women with breast cancer: A comparison of three subgrouping techniques. Adv Breast Cancer Res. 2013; 2:107–113. [PubMed: 24498579]
14. Miaskowski C, Aouizerat BE, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. J Natl Cancer Inst. 2007; 37:39–46.
15. Barsevick A. Defining the symptom cluster: How far have we come? Semin Oncol Nurs. 2016; 32:334–350. [PubMed: 27776831]
16. Miaskowski C, Aouizerat BE. Is there a biological basis for the clustering of symptoms? Semin Oncol Nurs. 2007; 23:99–105. [PubMed: 17512436]
17. Barsevick AM. The elusive concept of the symptom cluster. Oncol Nurs Forum. 2007; 34:971–980. [PubMed: 17878126]
18. Lee BN, Dantzer R, Langley KE, et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. Neuroimmunomodulation. 2004; 11:279–292. [PubMed: 15316238]
19. Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. J Natl Cancer Inst Monogr. 2004; 32:17–21.
20. Kim E, Jahan T, Aouizerat BE, et al. Changes in symptom clusters in patients undergoing radiation therapy. Support Care Cancer. 2009; 17:1383–1391. [PubMed: 19242732]
21. Miaskowski C, Paul SM, Cooper BA, et al. Trajectories of fatigue in men with prostate cancer before, during, and after radiation therapy. J Pain Symptom Manage. 2008; 35:632–643. [PubMed: 18358683]
22. Buffum D, Koetters T, Cho M, et al. The effects of pain, gender, and age on sleep/wake and circadian rhythm parameters in oncology patients at the initiation of radiation therapy. J Pain. 2011; 12:390–400. [PubMed: 21146465]
23. Garrett K, Dhruva A, Koetters T, et al. Differences in sleep disturbance and fatigue between patients with breast and prostate cancer at the initiation of radiation therapy. J Pain Symptom Manage. 2011; 42:239–250. [PubMed: 21454042]
24. Carney S, Koetters T, Cho M, et al. Differences in sleep disturbance parameters between oncology outpatients and their family caregivers. J Clin Oncol. 2011; 29:1001–1006. [PubMed: 21282549]
25. Dhruva A, Dodd M, Paul SM, et al. Trajectories of fatigue in patients with breast cancer before, during, and after radiation therapy. Cancer Nurs. 2010; 33:201–212. [PubMed: 20357659]
26. 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; 40:531–544. [PubMed: 20570482]
27. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer. 1994; 30A:1326–1336. [PubMed: 7999421]
28. Karnofsky D, Abelmann WH, Craver LV, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma. Cancer. 1948; 1:634–656.
29. Schnadig ID, Fromme EK, Loprinzi CL, et al. Patient-physician disagreement regarding performance status is associated with worse survivorship in patients with advanced cancer. Cancer. 2008; 113:2205–2214. [PubMed: 18780322]
30. Ando M, Ando Y, Hasegawa Y, et al. Prognostic value of performance status assessed by patients themselves, nurses, and oncologists in advanced non-small cell lung cancer. Br J Cancer. 2001; 85:1634–1639. [PubMed: 11742480]

31. Chang VT, Hwang SS, Thaler HT, Kasimis BS, Portenoy RK. Memorial symptom assessment scale. Expert Rev Pharmacoecon Outcomes Res. 2004; 4:171–178. [PubMed: 19807521]
32. SPSS. IBM SPSS for Windows (Version 23). Armonk, NY: SPSS, Inc.; 2015.
33. Muthen, LK., Muthen, BO. Mplus User's Guide (7th ed.). 7. Los Angeles, CA: Muthen & Muthen; 1998–2015.
34. StataCorp.. Stata Statistical Software: Release 14, College Station. Texas: Stata Corporation; 2015.
35. Muthen B, Kaplan D. A Comparison of some methodologies for the factor-analysis of non-normal Likert variables. British Journal of Mathematical & Statistical Psychology. 1985; 38:171–189.
36. Brown, TA. Confirmatory Factor Analysis for Applied Research. New York, NY: Guilford Press; 2006.
37. Pett, MA., Lackey, NR., Sullivan, JJ. Making Sense of Factor Analysis: The Use of Factor Analyis for Instrument Development in Health Care Research. Thousand Oaks, CA: Sage Publications, Inc.; 2003.
38. Raykov, T., Marcoulides, GA. A First Courese in Structural Equation Modeling. 2. Mahwah, NJ: Lawrence Erlbaum; 2006.
39. Aouizerat BE, Dhruva A, Paul SM, et al. Phenotypic and molecular evidence suggests that decrements in morning and evening energy are distinct but related symptoms. J Pain Symptom Manage. 2015; 50:599–614. e3. [PubMed: 26031709]
40. Dhruva A, Aouizerat BE, Cooper B, et al. Cytokine gene associations with self-report ratings of morning and evening fatigue in oncology patients and their family caregivers. Biol Res Nurs. 2015; 17:175–184. [PubMed: 24872120]
41. Xu Z, Taylor JA. SNPinfo: integrating GWAS and candidate gene information into functional SNP selection for genetic association studies. Nucleic Acids Res. 2009; 37:W600–605. [PubMed: 19417063]
42. Gabriel SB, Schaffner SF, Nguyen H, et al. The structure of haplotype blocks in the human genome. Science. 2002; 296:2225–2229. [PubMed: 12029063]
43. Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data. Am J Hum Genet. 2001; 68:978–989. [PubMed: 11254454]
44. Halder I, Shriver M, Thomas M, Fernandez JR, Frudakis T. A panel of ancestry informative markers for estimating individual biogeographical ancestry and admixture from four continents: utility and applications. Hum Mutat. 2008; 29:648–658. [PubMed: 18286470]
45. Hoggart CJ, Parra EJ, Shriver MD, et al. Control of confounding of genetic associations in stratified populations. Am J Hum Genet. 2003; 72:1492–1504. [PubMed: 12817591]
46. Tian C, Gregersen PK, Seldin MF. Accounting for ancestry: population substructure and genome-wide association studies. Hum Mol Genet. 2008; 17:R143–150. [PubMed: 18852203]
47. Price AL, Patterson NJ, Plenge RM, et al. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006; 38:904–909. [PubMed: 16862161]
48. StataCorp. Stata Statistical Software: Release 13, College Station. TX: StataCorp LP; 2013.
49. McCann B, Miaskowski C, Koetters T, et al. Associations between pro- and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery. J Pain. 2012; 13:425–437. [PubMed: 22515947]
50. Miaskowski C, Cooper BA, Dhruva A, et al. Evidence of associations between cytokine genes and subjective reports of sleep disturbance in oncology patients and their family caregivers. PLoS One. 2012; 7:e40560. [PubMed: 22844404]
51. Merriman JD, Aouizerat BE, Langford DJ, et al. Preliminary evidence of an association between an interleukin 6 promoter polymorphism and self-reported attentional function in oncology patients and their family caregivers. Biol Res Nurs. 2014; 16:152–159. [PubMed: 23482714]
52. Dunn LB, Aouizerat BE, Langford DJ, et al. Cytokine gene variation is associated with depressive symptom trajectories in oncology patients and family caregivers. Eur J Oncol Nurs. 2013; 17:346–353. [PubMed: 23187335]
53. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990; 1:43–46. [PubMed: 2081237]

54. Hattersley AT, McCarthy MI. What makes a good genetic association study? Lancet. 2005; 366:1315–1323. [PubMed: 16214603]
55. Tizard I. Sickness behavior, its mechanisms and significance. Anim Health Res Rev. 2008; 9:87–99. [PubMed: 18423072]
56. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun. 2007; 21:153–160. [PubMed: 17088043]
57. 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; 97:2919–2925. [PubMed: 12767108]
58. Stuart MJ, Baune BT. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. Neurosci Biobehav Rev. 2014; 42:93–115. [PubMed: 24513303]
59. Stuart MJ, Singhal G, Baune BT. Systematic review of the neurobiological relevance of chemokines to psychiatric disorders. Front Cell Neurosci. 2015; 9:357. [PubMed: 26441528]
60. Ernst J, Kheradpour P, Mikkelsen TS, et al. Mapping and analysis of chromatin state dynamics in nine human cell types. Nature. 2011; 473:43–49. [PubMed: 21441907]
61. Baune BT, Smith E, Reppermund S, et al. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective Sydney Memory and Aging Study. Psychoneuroendocrinology. 2012; 37:1521–1530. [PubMed: 22406002]
62. Kim JM, Stewart R, Kim SW, et al. Physical health and incident late-life depression: modification by cytokine genes. Neurobiol Aging. 2013; 34:356, e1–9.
63. Simon NM, McNamara K, Chow CW, et al. A detailed examination of cytokine abnormalities in Major Depressive Disorder. Eur Neuropsychopharmacol. 2008; 18:230–233. [PubMed: 17681762]
64. Zhen Y, Chu C, Zhou S, Qi M, Shu R. Imbalance of tumor necrosis factor-alpha, interleukin-8 and interleukin-10 production evokes barrier dysfunction, severe abdominal symptoms and psychological disorders in patients with irritable bowel syndrome-associated diarrhea. Mol Med Rep. 2015; 12:5239–5245. [PubMed: 26180016]
65. Magaki S, Mueller C, Dickson C, Kirsch W. Increased production of inflammatory cytokines in mild cognitive impairment. Exp Gerontol. 2007; 42:233–240. [PubMed: 17085001]
66. Marksteiner J, Kemmler G, Weiss EM, et al. Five out of 16 plasma signaling proteins are enhanced in plasma of patients with mild cognitive impairment and Alzheimer's disease. Neurobiol Aging. 2011; 32:539–540. [PubMed: 19395124]
67. Trollor JN, Smith E, Baune BT, et al. Systemic inflammation is associated with MCI and its subtypes: the Sydney Memory and Aging Study. Dement Geriatr Cogn Disord. 2010; 30:569–578. [PubMed: 21252552]
68. Galimberti D, Schoonenboom N, Scheltens P, et al. Intrathecal chemokine synthesis in mild cognitive impairment and Alzheimer disease. Arch Neurol. 2006; 63:538–543. [PubMed: 16606766]
69. Deckx L, van Abbema DL, van den Akker M, et al. A cohort study on the evolution of psychosocial problems in older patients with breast or colorectal cancer: comparison with younger cancer patients and older primary care patients without cancer. BMC Geriatr. 2015; 15:79. [PubMed: 26156892]
70. Von Ah D, Tallman EF. Perceived cognitive function in breast cancer survivors: evaluating relationships with objective cognitive performance and other symptoms using the functional assessment of cancer therapy-cognitive function instrument. J Pain Symptom Manage. 2015; 49:697–706. [PubMed: 25240787]
71. Wynn TA. IL-13 effector functions. Annu Rev Immunol. 2003; 21:425–456. [PubMed: 12615888]
72. Vladich FD, Brazille SM, Stern D, et al. IL-13 R130Q, a common variant associated with allergy and asthma, enhances effector mechanisms essential for human allergic inflammation. J Clin Invest. 2005; 115:747–754. [PubMed: 15711639]
73. Resende EP, Todo-Bom A, Loureiro C, et al. Asthma and rhinitis have different genetic profiles for IL13, IL17A and GSTP1 polymorphisms. Rev Port Pneumol (2006). 2017; 23:10–16. [PubMed: 27561723]

74. Ying XJ, Zhao SW, Wang GL, et al. Association of interleukin-13 SNP rs20541 with allergic rhinitis risk: a meta-analysis. Gene. 2013; 521:222–226. [PubMed: 23545317]
75. Pollmacher T, Haack M, Schuld A, Reichenberg A, Yirmiya R. Low levels of circulating inflammatory cytokines--do they affect human brain functions? Brain Behav Immun. 2002; 16:525–532. [PubMed: 12401466]
76. Kiecolt-Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. J Psychosom Res. 2002; 53:873–876. [PubMed: 12377296]
77. Liptay S, Schmid RM, Nabel EG, Nabel GJ. Transcriptional regulation of NF-kappa B2: evidence for kappa B-mediated positive and negative autoregulation. Mol Cell Biol. 1994; 14:7695–7703. [PubMed: 7969113]
78. Keats JJ, Fonseca R, Chesi M, et al. Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. Cancer Cell. 2007; 12:131–144. [PubMed: 17692805]
79. Du J, Huo J, Shi J, et al. Polymorphisms of nuclear factor-kappaB family genes are associated with development of multiple myeloma and treatment outcome in patients receiving bortezomib-based regimens. Haematologica. 2011; 96:729–737. [PubMed: 21228035]
80. Leung G, Baggott C, West C, et al. Cytokine candidate genes predict the development of secondary lymphedema following breast cancer surgery. Lymphat Res Biol. 2014; 12:10–22. [PubMed: 24502445]
81. Chen ML, Tseng HC. Symptom clusters in cancer patients. Support Care Cancer. 2006; 14:825–830. [PubMed: 16491377]
82. Kim HJ, Barsevick AM, Tulman L, McDermott PA. Treatment-related symptom clusters in breast cancer: a secondary analysis. J Pain Symptom Manage. 2008; 36:468–479. [PubMed: 18718735]
83. Chen ML, Lin CC. Cancer symptom clusters: a validation study. J Pain Symptom Manage. 2007; 34:590–599. [PubMed: 17629670]
84. Molassiotis A, Wengstrom Y, Kearney N. Symptom cluster patterns during the first year after diagnosis with cancer. J Pain Symptom Manage. 2010; 39:847–858. [PubMed: 20226621]
85. Yamagishi A, Morita T, Miyashita M, Kimura F. Symptom prevalence and longitudinal follow-up in cancer outpatients receiving chemotherapy. J Pain Symptom Manage. 2009; 37:823–830. [PubMed: 18804946]
86. Thomas BC, Waller A, Malhi RL, et al. A longitudinal analysis of symptom clusters in cancer patients and their sociodemographic predictors. J Pain Symptom Manage. 2014; 47:566–578. [PubMed: 24035068]
87. Suwisith N, Hanucharurnkul S, Dodd M, et al. Symptom clusters and functional status of women with breast cancer. Thai Journal of Nursing Research. 2008; 12:153–165.
88. Wang D, Fu J. Symptom clusters and quality of life in China patients with lung cancer undergoing chemotherapy. Afr Health Sci. 2014; 14:49–55. [PubMed: 26060457]
89. Phligbua W, Pongthavornkamol K, Knobf TM, et al. Symptom clusters and quality of life in women with breast cancer receiving adjuvant chemotherapy. Pacific Rim International Journal of Nursing Research. 2013; 17:249–266.
90. Yates P, Miaskowski C, Cataldo JK, et al. Differences in composition of symptom clusters between older and younger oncology patients. J Pain Symptom Manage. 2015; 49:1025–1034. [PubMed: 25582681]
91. Huang J, Gu L, Zhang L, et al. Symptom clusters in ovarian cancer patients with chemotherapy after surgery: A longitudinal survey. Cancer Nurs. 2016; 39:106–116. [PubMed: 25837811]
92. Hwang KH, Cho OH, Yoo YS. Symptom clusters of ovarian cancer patients undergoing chemotherapy, and their emotional status and quality of life. Eur J Oncol Nurs. 2016; 21:215–222. [PubMed: 26645947]
93. Dantzer R. Cytokine, sickness behavior, and depression. Neurol Clin. 2006; 24:441–460. [PubMed: 16877117]
94. Gay CL, Zak RS, Lerdal A, et al. Cytokine polymorphisms and plasma levels are associated with sleep onset insomnia in adults living with HIV/AIDS. Brain Behav Immun. 2015; 47:58–65. [PubMed: 25535857]

95. Lee KA, Gay C, Pullinger CR, et al. Cytokine polymorphisms are associated with poor sleep maintenance in adults living with human immunodeficiency virus/acquired immunodeficiency syndrome. Sleep. 2014; 37:453–463. [PubMed: 24587567]

96. Alfaro E, Dhruva A, Langford DJ, et al. Associations between cytokine gene variations and self-reported sleep disturbance in women following breast cancer surgery. Eur J Oncol Nurs. 2014; 18:85–93. [PubMed: 24012192]

97. Lee KA. Self-reported sleep disturbances in employed women. Sleep. 1992; 15:493–498. [PubMed: 1475563]

98. Safran M, Dalah I, Alexander J, et al. GeneCards Version 3: the human gene integrator. Database (Oxford). 2010; 2010:baq020. [PubMed: 20689021]

99. Wielders CC, Hackert VH, Schimmer B, et al. Single nucleotide polymorphisms in immune response genes in acute Q fever cases with differences in self-reported symptoms. Eur J Clin Microbiol Infect Dis. 2015; 34:943–950. [PubMed: 25577174]

100. Budaus L, Bolla M, Bossi A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol. 2012; 61:112–127. [PubMed: 22001105]

101. Bray FN, Simmons BJ, Wolfson AH, Nouri K. Acute and chronic cutaneous reactions to ionizing radiation therapy. Dermatol Ther. 2016; 6:185–206.

102. Hegedus F, Mathew LM, Schwartz RA. Radiation dermatitis: an overview. Int J Dermatol. 2016

103. Sousa AL, Fava VM, Sampaio LH, et al. Genetic and immunological evidence implicates interleukin 6 as a susceptibility gene for leprosy type 2 reaction. J Infect Dis. 2012; 205:1417–1424. [PubMed: 22459738]

104. Cenit MC, Simeon CP, Vonk MC, et al. Influence of the IL6 gene in susceptibility to systemic sclerosis. J Rheumatol. 2012; 39:2294–2302. [PubMed: 23027890]

105. Hoffjan S, Parwez Q, Petrasch-Parwez E, et al. Association screen for atopic dermatitis candidate gene regions using microsatellite markers in pooled DNA samples. Int J Immunogenet. 2006; 33:401–409. [PubMed: 17117949]

Table 1

Demographic and Clinical Characteristics of the Patients (n=157)

Characteristic	**Mean (SD)**
Age (years)	61.2 (11.3)
Education (years)	16.1 (3.0)
Body mass index (kg/m^2)	27.5 (5.5)
Number of comorbid conditions	4.9 (2.6)
Karnofsky Performance status score	92.5 (9.8)
	% (n)
Gender	
Female	49.0 (77)
Male	51.0 (80)
Ethnicity	
White	72.4 (105)
Non-white	27.6 (40)
Married/partnered	
Yes	55.6 (80)
No	44.4 (64)
Lives alone	
Yes	31.8 (50)
No	68.2 (107)
Employment status	
Employed	44.1 (67)
Not employed	55.9 (85)
Diagnosis	
Breast cancer	49.0 (77)
Prostate cancer	51.0 (80)

Abbreviations: kg = kilograms, m^2 = meter squared, SD = standard deviation

Table 2

Symptom Clusters and Symptom Cluster Severity Scores

Mood-Cognitive Symptom Cluster	Sickness-Behavior Symptom Cluster	Treatment-related Symptom Cluster
Difficulty concentrating	Pain	Problems with urination
Feeling sad	Lack of energy	Changes in skin
Worrying	Feeling drowsy	
Itching	Difficulty sleeping	
Feeling irritable	Sweats	
Mean (SD) Symptom Cluster Severity Score[a] (range)		
2.4 (2.9) 0 to 11	3.7 (3.3) 0 to 13	3.7 (1.4) 1 to 7

[a]Memorial Symptom Assessment Scale Severity Scores 0 = not at all, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

Abbreviation: SD = standard deviation

Table 3

Negative Binomial Regression Analyses for the Association between Polymorphisms in *CXCL8*, *IL13*, and *NFKB2* Genes and Mood-Cognitive Symptom Cluster Score

Predictors	IRR	SE	95% CI	z	p-value
CXCL8 HapA4	0.61	.12	0.417, 0.881	−2.63	.009
Age	0.95	.01	0.933, 0.975	−4.18	<.001
Education	1.10	.05	1.012, 1.192	2.25	.024
Number of chronic conditions	1.11	.05	1.019, 1.211	2.39	.017
Overall model fit: χ^2 = 29.68, p = .0002					
IL13 rs20541	0.53	.14	0.318, 0.877	−2.46	.014
Age	0.94	.01	0.923, 0.967	−4.71	<.001
Education	1.10	.05	1.014, 1.200	2.29	.022
Number of chronic conditions	1.11	.05	1.015, 1.210	2.30	.021
Overall model fit: χ^2 = 28.98, p = .0003					
NFKB2 rs1056890	2.30	.77	1.187, 4.448	2.47	.014
Age	0.95	.01	0.928, 0.970	−4.58	<.001
Education	1.09	.04	1.005, 1.180	2.07	.038
Number of chronic conditions	1.12	.05	1.029, 1.222	2.61	.009
Overall model fit: χ^2 = 29.12, p = .0003					

The first three principle components identified from the analysis of ancestry informative markers as well as self-reported race/ethnicity were retained in the model to adjust for potential confounding due to race or ethnicity (data not shown). Predictors evaluated in each of the models included: genotype (*CXCL8* HapA4 that is composed of alleles at rs4073, rs2227306, and rs2227543; *IL13* rs20521 (CC versus CT versus TT); or *NFKB2* rs1056890 (CC+CT versus TT)), age (in years), education (in years), and number of comorbid conditions.

Abbreviations: CI =confidence interval, CXCL8 = C-X-C motif chemokine ligand 8, IL = interleukin, IRR = Incidence Rate Ratio, NFKB = nuclear factor kappa beta 2, SE = standard error

Table 4

Negative Binomial Regression Analyses for the Association between Polymorphisms in *IFNG1* and *NFKB2* Genes and Sickness-Behavior Symptom Cluster Score

Predictors	IRR	SE	95% CI	z	p-value
IFNG1 rs1861493	0.20	.12	0.062, 0.666	−2.63	.009
Age	0.98	.01	0.961, 0.994	−2.69	.007
Overall model fit: χ^2 = 20.29, p = .0025					
NFKB2 rs1056890	1.96	.52	1.163, 3.309	2.53	.012
Age	0.97	.01	0.956, 0.989	−3.26	.001
Overall model fit: χ^2 = 19.19, p = .0039					

The first three principle components identified from the analysis of ancestry informative markers as well as self-reported race/ethnicity were retained in the model to adjust for potential confounding due to race or ethnicity (data not shown). Predictors evaluated in each model included: genotype (*IFNG1* rs1861493 (AA+AG versus GG) or *NFKB2* rs1056890 (CC+CT versus TT)) and age (in years).

Abbreviations: CI =confidence interval, IFNG1 = interferon gamma, IL = interleukin, IRR – Incidence Rate Ratio, NFKB = nuclear factor kappa beta, SE = standard error

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Table 5

Linear Regression Analyses for the Association between Polymorphisms in *IL1R1*, *IL6*, and *NFKB1* Genes and Treatment-related Symptom Cluster Score

Predictors	Coef	SE	95% CI	t	p-value
IL1R1 rs2228139	2.40	1.03	0.362, 4.438	2.34	.021
IL1R1 rs3917320	−0.61	0.28	−1.167, −0.044	−2.14	.035
Gender	−2.12	0.28	−2.537, −1.703	−10.09	<.001
Overall model fit: Adjusted R^2 = 0.52, p <.001					
IL6 rs2069840	0.47	0.17	0.145, 0.801	2.87	.005
Gender	−2.19	0.21	−2.607, −1.773	−10.44	<.001
Overall model fit: Adjusted R^2 = 0.52, p <.001					
NFKB1 HapA9	−0.50	0.16	−0.818, −0.188	−3.17	.002
Gender	−2.13	0.21	−2.564, −1.724	−10.31	<.001
Overall model fit: Adjusted R^2 = 0.56, p <.001					

The first three principle components identified from the analysis of ancestry informative markers as well as self-reported race/ethnicity were retained in the model to adjust for potential confounding due to race or ethnicity (data not shown). Predictors evaluated in each model included: genotype (*IL1R1* rs2228139 (CC+CG versus GG) and *IL1R1* rs3917320 (AA versus AC versus CC); *IL6* rs2069840 (CC versus CG versus GG); or *NFKB1* HapA9 that is composed of alleles at rs3774933, rs170731, rs230510, rs230494, and rs3774956) and gender.

Abbreviations: CI =confidence interval, coef = coefficient, IL1 = interleukin, IL1R = interleukin 1 receptor, NFKB = nuclear factor kappa beta, SE = standard error