Published in final edited form as:
Cancer. 2010 September 1; 116(17): 4103–4113. doi:10.1002/cncr.25255.

Relationship Between Cytokine Gene Single Nucleotide Polymorphisms and Symptom Burden and Quality of Life in Lung Cancer Survivors

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Abstract

BACKGROUND—Previous research has demonstrated that many lung cancer survivors report difficulties with symptom control and experience a poor quality of life (QOL). Although recent studies have suggested a relationship of single nucleotide polymorphisms (SNPs) in several cytokine genes with cancer susceptibility and prognosis, associations with symptom burden and QOL have not been examined. The current study was conducted to identify SNPs related to symptom burden and QOL outcomes in lung cancer survivors.

METHODS—All participants were enrolled in the Mayo Clinic Lung Cancer Cohort following diagnosis of lung cancer. A total of 1149 Caucasian lung cancer survivors completed questionnaires and had genetic samples available. The main outcome measures were symptom burden as measured by the Lung Cancer Symptom Scale and health-related QOL as measured by the Short-Form General Health Survey.

RESULTS—Twenty-one SNPs in cytokine genes were associated with symptom burden and QOL outcomes. Our results suggested both specificity and consistency of cytokine gene SNPs in predicting outcomes.

CONCLUSIONS—These results provide support for genetic predisposition to QOL and symptom burden and may aid in identification of lung cancer survivors at high risk for symptom management and QOL difficulties.

Keywords

cytokine; single nucleotide polymorphisms; quality of life; lung cancer

Lung cancer is a major public health problem in the United States. The American Cancer Society estimates approximately 213,000 new lung cancer cases annually, and lung cancer is the leading cause of cancer death in the United States for both men and women.[1] Despite considerable clinical research, mortality rates have not declined significantly for this

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CONFLICT OF INTEREST DISCLOSURES

population. In the general population, approximately 25% survive 3 years, and only 15% survive 5 years or beyond.[1] Thus, for many lung cancer patients the goals of treatment often focus on reducing symptom burden and improving quality of life (QOL). Symptom burden and QOL in this population deserve clinical and research attention.

Lung cancer survivors do not experience the same length of life or QOL as their age-matched peers, or other cancer survivors.[2] In fact, lung cancer survivors rate their QOL as lowest among all other cancer survivors.[3] QOL may also be related to health outcomes, as previous studies have suggested that QOL may be the most significant predictor of length of survival in lung cancer patients, even after adjusting for prognostic factors.[4] One of the most provocative findings in cancer research is that QOL is often superior to clinical assessments for predicting a cancer patient's survival.[5]

Recent research findings have suggested that the genetic disposition of cancer patients may impact their QOL.[6] To date, genes that are involved in self-rated health or QOL are not yet identified. Genetic research, however, has been successful in identifying chromosomal regions and genetic variants for related attributes, such as depression,[7–10] cognition,[11] and pain.[12] Translational research focusing on cancer has explored the genetic basis for physical response to treatment and patient survival. But the degree to which genetic structure impacts psychosocial response and QOL in cancer survivors is still unknown.

The primary goal of this study was to identify relationships between single nucleotide polymorphisms (SNPs) in cytokine genes and lung cancer symptoms and QOL. Because lung cancer is 1 of the most prevalent cancers worldwide, because QOL is lowest in lung cancer survivors compared with other cancer groups, and because QOL is an important prognostic indicator, any information related to predicting, intervening, and improving QOL in lung cancer survivors is of potential significance.

Role of Cytokines in QOL

Preliminary evidence suggests that psychosocial, spiritual, and behavioral factors influence immunologically moderated diseases such as cancer. Various psychological states and emotions suppress immune function reliably.[13–15] Social variables have been reliably associated with serum cytokine levels.[16–19] In cancer survivors, serum cytokine levels have been associated with lung cancer symptom burden,[20] fatigue,[17] QOL,[21] cognitive behavioral therapy improvements,[22] stress levels,[23] social activity,[24] relationship satisfaction,[24] coping styles,[20] and optimism.[25] Interventions aimed at improving QOL have begun to show consistent improvement in immune function, traditionally as measured by natural killer cell cytotoxicity, and more recently by changes in serum cytokine levels.[26–28]

Cytokine Gene SNPs

An improved understanding of the genetic factors associated with the severity of cancer-related symptoms and QOL in lung cancer survivors is crucial for the identification of patients at high risk for poor outcome. Human genetic variation can modulate the risk of developing a cancer, the risk of developing symptoms related to cancer and its treatment, and the outcome of cancer.[29] The most common variations in the genome are SNPs.[30]

Studies have suggested that cytokine gene SNPs may cause individual variations in cytokine production, and are closely related to overall immune functioning.[31–33] SNPs in the regulatory regions of cytokine genes affect serum (expression) levels of its respective cytokine[31,34] and represent modifiers for a variety of common diseases, including asthma, autoimmune diseases, periodontal diseases, diabetes, Alzheimer disease, and coronary artery

disease.[35] Although numerous studies are emerging, the role of cytokine gene SNPs in cancer are not currently clearly understood.

In small studies of patients with lung cancer, cytokine gene polymorphisms have been associated with lung cancer survival,[36,37] increased risk of nonsmall cell lung cancer,[38–40] and severity of lung cancer.[41] An important question remains as to whether there is a relationship between cytokine gene SNPs and cancer-related symptoms or QOL. Only 2 published studies have reported associations of cytokine gene polymorphisms with cancer symptoms, which have included pain in lung cancer survivors[42] and fatigue in breast cancer survivors.[43] Serum cytokines have been linked to symptom burden and QOL variables in cancer, and cytokine SNPs have been associated with variations in serum levels; however, there is limited knowledge about the association of cytokine gene polymorphisms with symptoms and QOL in lung cancer survivors. The aim of this study therefore was to evaluate the predictive value of cytokine gene SNPs on symptom burden and QOL in a large sample of Caucasian lung cancer survivors.

MATERIALS AND METHODS

Participants

All participants for this study were enrolled in the Epidemiology and Genetics of Lung Cancer Research Program at Mayo Clinic, Rochester, Minn.[44] Since January 1, 1997, all patients at our institution who were diagnosed with lung cancer have been offered participation in this prospective cohort study. Participation rate has been >90% of eligible lung cancer patients.[44,45] All patients provided written informed consent, and the study has been approved by the Mayo Clinic institutional review board on an annual basis. Upon enrollment, all patients complete baseline health-related surveys and are then mailed similar surveys on an annual basis. The follow-up process started within 6 months after diagnosis and then annually until patients' death.

Information on demographics, previous or concurrent illnesses, tobacco usage and exposure, tumor staging, and cancer therapy were abstracted by study personnel from medical records and entered into a database. Participants self-identified their race on questionnaires. Specifics on ongoing patient recruitment, baseline data retrieval, and patient follow-up are described in a larger study.[44]

Genotyping Methods

All SNP analyses were conducted using the Illumina GoldenGate Genotyping Assay (a flexible, preoptimized assay that uses a discriminatory DNA polymerase and ligase to interrogate up to 1500 SNP loci simultaneously). The specific platform used in this study was a 480-SNP panel. Because of the established relationship between serum cytokines and psychosocial variables, 6 cytokine genes (interleukin [IL]-1B, IL-1RN, IL-6, IL-8, IL-10, and tumor necrosis factor-α [TNF-α]) were chosen to evaluate the relationship between these SNPs and lung cancer symptoms and QOL variables. Genotype data from the HapMap consortium, Seattle SNPs, Perlegen Sciences, and Panel 2 of the National Institute for Environmental Health Sciences[1] were analyzed with ldSelect to bin SNPs with European American minor allele frequency >0.05 at a pairwise linkage disequilibrium threshold of $r^2 \geq 0.8$. The region for each gene included 5 kb upstream and downstream.

Sixty-seven genes were initially selected from multiple pathways after a review of the literature. Tag-SNPs on these genes were selected based on HapMap data (release 22/phase 2 on NCBI B36) by Haploview, version 3, using the Caucasian data available from HapMap. Tag-SNP selection parameters ignored pairwise comparisons of markers >500 kb apart; excluded individuals with >50% missing genotypes; excluded SNPs with Hardy-Weinberg *P*

values of <.001, SNPs with <75% genotype calls, SNPs with >1 Mendelian error, and SNPs with a minor allele frequency <0.001; performed aggressive tagging using a r^2 threshold of 0.8; and included a logarithm of odds threshold for multimarker tests of 3. Table 1 summarizes the 37 SNPs in the 6 cytokine genes that were analyzed, all chosen based on published data that implicated their roles underlying symptom burden and QOL among cancer survivors. It is important to note that all cytokines genes and SNPs were based on existing empirical literature, and this was a hypothesis-driven evaluation.

Genotyping was performed in the Mayo Clinic Genomics Shared Resource following the manufacturer's protocol. The concentration of all DNA samples was verified using Pico Green. For quality control, a CEPH DNA trio (parents and child, Coriell Institute, Camden, NJ), each in duplicate, and 2 sample replicates were included in each 96-well plate. The average sample call rate was 99.5%.

Self-Reported QOL and Lung Cancer Symptom Measurement

Medical Outcomes Study Short-Form General Health Survey—The Medical Outcomes Study Short-Form General Health Survey (SF-8)[46] is a brief version of the SF-36 and contains 8 items yielding 8 separate subscales of health-related QOL: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The SF-36 and the SF-8 have been widely used in cancer health-related QOL studies and have been shown to have high reliability and validity when used in cancer populations.[47–49]

Lung Cancer Symptom Scale—The Lung Cancer Symptom Scale (LCSS)[50,51] is a disease- and site-specific QOL assessment developed to capture the experience of lung cancer, focusing primarily on the physical and functional dimensions of QOL, measuring 6 major symptoms for lung malignancies (appetite, fatigue, cough, dyspnea, hemoptysis, pain), with overall scores for severity of lung cancer symptoms and QOL. Internal consistency and test-retest reliability have been established, as well as content, construct, and criterion validity (including data for both the overall scores and single item scales).[50–52] The scale has been used by the scale authors and other investigators using single items as their own subscales, as well as the total scales.[51–55] Normative data are available for total scores as well as the single item subscales.[52]

RESULTS

Preliminary Analyses

Demographic and disease data—A total of 1319 lung cancer patients in the Mayo Clinic Lung Cancer Epidemiology Project had both self-report and genetic data. Of the patients in the Epidemiology Project, 93.3% were Caucasian. Because of the lack of diversity in our sample, and importantly because of the genetic variance between Caucasians and African Americans in previous studies evaluating cytokine genes,[40,56] cytokine genes in cancer patients,[40] and genetic prediction of symptom burden differences by race in lung cancer patients,[39] we only included the data from Caucasian patients (n = 1149) for these analyses. See Table 2 for demographic and disease variables for the 1149 patients in our analyses.

Mean scores and change across time periods—Results were divided by the time in which the lung cancer survivor last completed questionnaires after receiving their diagnosis. Because of our relatively large sample, we were able to divide our results by <3 years (time 1), 3 to 5 years (time 2), and >5 years (time 3); thus, we were able to capture the full spectrum of possible survivorship. In this epidemiological cohort, the data from the self-

report questionnaires were administered across a 10-year period, and thus, across the years, to minimize patient burden, particular questions were removed from the survey. Thus, as is evident in Table 3, various numbers of patients completed each item on the self-report questionnaires. See Table 3 for a presentation of mean scores on each LCSS and SF-8 item at the different time points.

All items on the LCSS that were negatively valenced with higher scores representing poor outcomes, items were reverse-coded so that on a scale of 0 to 100, 100 represented the best possible outcome (eg, no pain, best QOL), and 0 represented the worst possible outcome. Therefore, higher numbers represent better outcomes on all measures.

The SNPs were coded as categorical variables with 3 levels (0, 1, 2), indicating the number of minor alleles. Any SNP with minor allele frequency <5% was excluded from the analysis; some SNPs had either a lever 1 or level 2 <5%, and these 2 levels were combined. The average QOL domain scores were compared across different levels using a single 2-sample independent samples *t* test or Wilcoxon rank sum test as appropriate for each time period.

The primary analyses were based on conditional logistic regression modeling of SNP level after colinearity diagnostics to ascertain the independence and contribution of the covariates. The covariates considered in the models were age at diagnosis, sex, smoking status, disease stage, and treatment modality. The methods of Belsey[57] were applied to assess the degree of colinearity before modeling processes were initiated. Specifically, Belsey recommends the use of a variance inflation factor statistic and condition index to assess multicollinearity and provides guidelines and thresholds for acceptable levels of collinearity (variance inflation factor <5 and condition index <30).

A multivariate conditional stepwise logistic regression method with the likelihood ratio criterion (inclusion/ exclusion criteria: $P = .15/P > .15$, respectively) was used to investigate the relationship between the SNP and LCSS and SF-8 variables for each time period. This approach was used to develop predictive models adjusting for other potential risk factors identified from the previous analyses such as age at diagnosis, sex, smoking status, disease stage, and treatment modality. Bonferroni correction was used to account for the multiple analyses. We only reported in Tables 4 and 5 the statistically significant findings after Bonferroni correction, which were also clinically significant (by having at least a 10-point difference in mean score on outcomes compared with the other allele frequencies). By using conditional logistic multiple regression modeling, we found significant relationships between 21 different cytokine SNPs and lung cancer symptoms and QOL outcomes.

DISCUSSION

Although recent studies have suggested a relationship between polymorphisms in several cytokine genes with cancer susceptibility and prognosis,[58,59] links with lung cancer symptoms and QOL have not been elucidated. In this study of a large cohort of lung cancer survivors, we found associations between 21 SNPs and symptom severity and QOL, while controlling for important disease and demographic variables.

Pain

Cancer pain affects 17 million people worldwide.[39] Lung cancer is often associated with significant pain, with estimates of 50% to 65% reporting pain.[60] Although cancer pain results from several mechanisms, recent studies have begun to suggest that inflammation caused by tumor-induced mediators such as cytokines may also be a potential mechanism for cancer-related pain.[61] In this study sample, pain symptoms were associated with IL-10 SNPs at times 1 and 2. In numerous animal studies, expression of IL-1, IL-6, and TNF-α is

up-regulated in peripheral nerves, the spinal cord, and in particular regions of the brain after peripheral nerve injury. By contrast, anti-inflammatory cytokines, IL-4 and IL-10, promote analgesia.[62] Reyes-Gibby and colleagues[42] found that variant alleles in IL-8 genes were significantly associated with severe pain in white patients with NSCLC, but found no significant associations with their hypothesized TNF-α or IL-6 genes.

Fatigue

Persistent fatigue has been reported as among the most common and disabling symptoms in cancer survivors,[63–65] yet the mechanisms underlying the occurrence and persistence of this symptom are not known. Proinflammatory cytokines may induce fatigue. A recent review of 20 clinical studies investigating the association between cancer-related fatigue and inflammatory markers among cancer patients showed a significant correlation between cancer-related fatigue and plasma levels of IL-6.[66] In addition, phase 1 studies with recombinant TNF-α, IL-6, and IFN-α in cancer patients report fatigue to be the most common side effect.[67–69]

Collado-Hidalgo et al[43] examined SNPs of cytokine genes in relation to fatigue in 47 breast cancer survivors. They found at least 1 cytosine at IL-1β-511, and homo-zygosity for either variant of the IL-6-174 genotype predicted fatigue. In our sample, IL-1β (at times 1 and 2) and IL-1RN (at time 2) SNPs were associated with fatigue. These results indicated both specificity for IL-1, and consistency across time for IL-1β in symptom manifestation.

Dyspnea

Dyspnea has been among the most frequently reported symptoms in lung cancer survivors.[70,71] In addition, dyspnea is also associated with a greater degree of insomnia, fatigue, and appetite loss, supporting its importance as a clinical indicator of distress. In chronic obstructive pulmonary disease patients, high levels of IL-6 are associated with increased dyspnea.[72] TNF-α, IL-6, IL-8, and IL-10 are also significant modulators of airway inflammation.[73] In our sample, dyspnea was associated with IL-6 SNPs at time 2 and IL-1B SNPs at time 3.

Appetite

In our sample, appetite was associated with an SNP in IL-10 at time 3. Increased levels of IL-1 in the brain have been associated with anorexia in animals.[74] In samples of gastric cancer patients in both the United States and China, previous authors have reported conflicting findings. In a US population,[75] SNPs in the IL1-B gene decreased cachexia, whereas in a Chinese population,[76] SNPs in the same gene increased cachexia.

Coughing

Cough is present in 65% to 75% of lung cancer survivors.[77] However, in our sample, coughing was not associated with any of our cytokine gene SNPs.

Lung Cancer Symptom Severity

The lung cancer symptom severity item from the LCSS (“How bad are your symptoms of lung cancer?”) is a summation item related to total symptomatic distress to allow the individual to rate overall severity of lung cancer symptoms. In a sample of 202 NSCLC patients in Taiwan, Shih and colleagues[39] reported a significant association of SNPs in the TNF-α gene with lung cancer severity and susceptibility. Lung cancer symptom severity in our sample was associated with SNPs in TNF-α and IL1-RN at time 1.

With a variety of cytokine SNPs involved in predicting the severity of lung cancer symptoms, it is very possible that this reflects multiple processes. Therefore, we do not view this finding as a single construct, but perhaps more of a cumulative finding with multiple processes.

QOL

One of the most interesting findings in QOL studies of lung cancer survivors is that initial QOL was found to be the strongest prognostic factor for survival even after correcting for initial performance status, weight loss, stage of disease, number of metastatic sites, and type of treatment.[78,79] QOL has also been closely linked to symptom prevalence and intensity in patients with lung cancer.[4,80,81]

The LCSS overall QOL item in our sample was significantly associated with IL-6 SNPs at times 1 and 2. The SF-8 health-related QOL (HRQOL) revealed numerous significant associations. Several domains of the SF-8 showed consistency, in that several different SNPs of the same cytokine were significant. In addition, several different SNPs showed specificity, in that they were related to specific domains of HRQOL across time, rather than a particular cytokine SNP being related to all HRQOL domains. Il-1RN SNPs were associated with fatigue across both the LCSS and SF-8 measures. In addition, IL-6 SNPs were associated with mental health on the SF-8 and QOL on the LCSS. Interestingly, the same IL-6 SNP at time 1 (rs2069843) was associated with social function on the SF-8, and QOL on the LCSS. In addition, another IL-6 SNP was associated with emotional health on the SF-8. IL-1RN was associated with the lung cancer symptom severity item on the LCSS, and physical function on the SF-8, both overall measures of physical burden.

Conclusions

We found several significant associations between cytokine SNPs and symptom burden and QOL in Caucasian survivors of lung cancer. Our findings are similar to those reported from the serum cytokine literature as elaborated in our discussion. Many of these relationships were significant across time points, also suggesting consistency, and specific cytokine genes were associated with specific symptoms, rather than broad ranges of symptoms, suggesting specificity.

New knowledge gained from these studies could help lung cancer survivors, their healthcare providers, and their caregivers by providing evidence for establishing clinical recommendations to enhance their quantity and quality of life. Lung cancer is a highly lethal disease. Therefore, symptom burden and QOL in this population deserve much clinical and research attention.

Strengths and Limitations

Strengths of this study include the large number of lung cancer survivors in the analyses, the inclusion of both short-and long-term survivors, and genetic data available to analyze these relationships. This study was the first to our knowledge examining the relationship between cytokine gene SNPS and domains of symptom burden and QOL.

Limitations of this study include lack of a control group. Therefore, our conclusions are limited to findings within Caucasian lung cancer survivors only. The general-izability of these results to underserved and minority populations is unknown. Of those completing questionnaires, it is possible that we captured only those with less severe health status. Those in critical health may not have been physically able or psychologically motivated to complete a study questionnaire.

Acknowledgments

This research was funded by NCI grants 5R01CA115857 and 5R01CA084354-08 (to P. Yang, principal investigator).

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Table 1

The Selected SNPs in the 6 Cytokine Genes Analyzed

Gene	No. of SNPs	SNP
IL-10	7	rs1800871
		rs1878672
		rs3021094
		rs3024493
		rs3024498
		rs3024508
		rs3024509
IL-1B	5	rs1143627
		rs1143630
		rs1143633
		rs1143634
		rs2853550
IL-1RN	7	rs3087263
		rs3087266
		rs315952
		rs380092
		rs397211
		rs4252022
		rs4252041
IL-6	9	rs1800795
		rs2066992
		rs2069835
		rs2069840
		rs2069843
		rs2069852
		rs2069857
		rs2069860
		rs2069861
IL-8	2	rs2227306
		rs2227543
TNF-α	7	rs1800629
		rs1800630
		rs3093661
		rs3093662
		rs3093665
		rs3093671
		rs4645843

SNPs indicate single nucleotide polymorphisms; IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 2

Demographic and Disease Variables of Total Sample (N = 1149)

Variable	Value
Age at diagnosis, y	
Mean (SD)	65.2 (9.47)
Median	66.0
Range	35.0–89.0
Sex	
Women	540 (47%)
Men	609 (53%)
Pathologic cell type	
Adenocarcinoma	525 (45.7%)
Squamous	260 (22.6%)
Small cell	146 (12.7%)
Nonsmall cell	60 (5.2%)
Other	157 (13.7%)
Missing	1 (0.01%)
Stage	
Unknown	8 (0.01%)
Limited	91 (8%)
Extensive	53 (4.6%)
IA	285 (25%)
IB	208 (18.2%)
IIA	30 (2.6%)
IIB	80 (7%)
IIIA	129 (11.3%)
IIIB	95 (8.3%)
IV	170 (14.9%)
Treatment modality	
Only surgery	526 (45.77%)
Both surgery and chemotherapy	117 (10.18%)
Both surgery and radiotherapy	40 (3.48%)
Surgery, chemotherapy, and radiotherapy	126 (10.96%)
Only chemotherapy	105 (9.13%)
Both chemotherapy and radiotherapy	204 (17.75%)
Only radiotherapy	10 (0.87%)
No chemotherapy, surgery, or radiotherapy	19 (1.65%)
Cigarette smoking status	
Never	194 (16.9%)
Former	580 (50.5%)
Current	369 (32.1%)
Missing	6 (0.5%)

SD indicates standard deviation.

Table 3

Mean Scores for Each Variable by Length of Survivorship

Years of Survival Group	No. of Observations	Variable	No.	Mean
<3 years	440	LCSS: Appetite	304	66.80
		LCSS: Fatigue	437	48.05
		LCSS: Coughing	440	69.83
		LCSS: Shortness of Breath	439	57.29
		LCSS: Blood in Sputum	306	94.42
		LCSS: Pain	437	76.22
		LCSS: LC Symptoms	299	72.51
		LCSS: Normal Activities	303	59.59
		LCSS: Overall QOL	440	58.32
		SF-8: General Health	133	44.32
		SF-8: Physical Functional	135	38.72
		SF-8: Role Physical	135	38.35
		SF-8: Bodily Pain	134	48.21
		SF-8: Vitality	134	44.56
		SF-8: Social Functional	134	42.70
		SF-8: Mental Health	134	47.27
		SF-8: Role Emotional	134	43.45
		SF-8: Physical Component	131	39.59
		SF-8: Mental Component	131	47.46
3–5 years	354	LCSS: Appetite	144	70.60
		LCSS: Fatigue	351	52.02
		LCSS: Coughing	347	70.85
		LCSS: Shortness of Breath	351	56.67
		LCSS: Blood in Sputum	144	93.73
		LCSS: Pain	349	75.32
		LCSS: LC Symptoms	142	81.03
		LCSS: Normal Activities	144	70.02
		LCSS: Overall QOL	354	67.85
		SF-8: General Health	222	45.01
		SF-8: Physical Functional	222	40.08
		SF-8: Role Physical	221	40.36
		SF-8: Bodily Pain	222	48.91
		SF-8: Vitality	222	47.34
		SF-8: Social Functional	221	44.76
		SF-8: Mental Health	222	48.91
		SF-8: Role Emotional	222	45.75
		SF-8: Physical Component	220	41.26
		SF-8: Mental Component	220	49.97
>5 years	355	LCSS: Appetite	24	77.70

Years of Survival Group	No. of Observations	Variable	No.	Mean
		LCSS: Fatigue	354	51.64
		LCSS: Coughing	353	69.88
		LCSS: Shortness of Breath	353	52.17
		LCSS: Blood in Sputum	25	96.16
		LCSS: Pain	355	70.29
		LCSS: LC Symptoms	25	72.88
		LCSS: Normal Activities	25	64.72
		LCSS: Overall QOL	355	71.45
		SF-8: General Health	344	45.98
		SF-8: Physical Functional	345	40.16
		SF-8: Role Physical	345	40.92
		SF-8: Bodily Pain	345	49.73
		SF-8: Vitality	346	48.09
		SF-8: Social Functional	345	45.29
		SF-8: Mental Health	346	48.94
		SF-8: Role Emotional	345	45.42
		SF-8: Physical Component	340	42.02
		SF-8: Mental Component	340	49.99

LCSS indicates Lung Cancer Symptom Scale; LC, lung cancer; QOL, quality of life; SF-8, Medical Outcomes Study Short-Form General Health Survey.

Table 4

Significant Associations Between SNPs and Lung Cancer Symptoms (LCSS)

Outcome	Period	Cytokine	SNP	OR Estimate
Pain	1	IL-10	rs1800871	0.97–0.99
	2	IL-10	rs1800871	0.94–0.99
Fatigue	1	IL-1B	rs1143633	1.00–1.02
	2	IL-1B	rs2853550	1.01–1.06
	2	IL-1RN	rs397211	0.97–1.00
Appetite	3	IL-10	rs3024498	1.04–1.46
Dyspnea	2	IL-6	rs2069835	0.95–1.00
	3	IL-1B	rs1143633	0.88–0.98
LC symptoms	1	TNF-α	rs1800630	1.00–1.02
	1	IL-1RN	rs397211	0.98–1.00
Hemoptysis	3	IL-10	rs3024498	0.27–0.88
	3	IL-1B	rs1143633	1.09–2.43
QOL	1	IL-6	rs2069843	0.96–1.00
	2	IL-6	rs2069861	1.01–1.05

SNPs indicates single nucleotide polymorphisms; LCSS, Lung Cancer Symptom Scale; Period 1, <3 years; Period 2, 3–5 years; Period 3, >5 years; OR, odds ratio; IL, interleukin; LC, lung cancer; TNF-α, tumor necrosis factor-α; QOL, quality of life.

Table 5

Significant Associations Between SNPs and QOL (SF-8)

SF-8 Variable	Period	Cytokine	SNP	OR Estimate
Bodily Pain	1	IL-1RN	rs315952	0.91–0.99
General Health	2	IL-6	rs1800795	0.86–0.95
	2	IL-1B	rs1143633	0.87–0.99
	2	IL-1RN	rs315952	1.02–1.15
	2	IL-1RN	rs380092	1.00–1.13
	3	IL-10	rs3021094	1.02–1.13
	3	IL-10	rs3024493	1.01–1.11
	3	IL-6	rs2069835	0.89–0.99
	3	IL-1B	rs1143627	0.91–0.98
Mental Health	3	IL-1RN	rs315952	0.94–0.99
	3	IL-1RN	rs380092	0.94–0.99
Physical Function	1	IL-10	rs1800871	0.90–0.98
	1	IL-1B	rs1143634	1.04–1.27
	1	IL-1RN	rs4252041	1.01–1.23
	2	IL-6	rs1800795	0.86–0.95
	2	IL-1B	rs1143633	1.02–1.15
	2	IL-1RN	rs397211	1.00–1.06
	3	TNF-α	rs3093662	0.92–0.99
	3	IL-1B	rs2853550	1.00–1.08
Role Emotion	1	IL-6	rs1800795	0.91–0.99
	1	IL-6	rs2069840	1.01–1.11
Role Physical Function	1	IL-1B	rs1143634	0.83–0.99
	2	IL-1RN	rs315952	0.86–0.95
	2	IL-1RN	rs380092	0.86–0.94
	2	IL-1RN	rs4252041	1.00–1.15
	3	IL-10	rs3021094	0.88–0.97
	3	IL-1B	rs1143627	1.01–1.07
Social Function	1	IL-6	rs2069843	0.68–0.99
	1	IL-1RN	rs380092	0.93–1.00
	3	TNF-α	rs3093661	0.88–0.99
Vitality	2	IL-10	rs1878672	0.91–0.94
	2	IL-10	rs3021094	1.02–1.18
	2	IL1-RN	rs4252041	0.80–0.97
Mental Health Component Summary Score	2	TNF-α	rs1800630	0.91–0.98
Physical Health Component Summary Score	1	IL-10	rs3021094	0.91–0.99
	3	IL-10	rs3024493	0.89–0.96

SNPs indicates single nucleotide polymorphisms; QOL, quality of life; SF-8, Medical Outcomes Study Short-Form General Health Survey; Period 1, <3 years; Period 2, 3–5 years; Period 3, >5 years; OR, odds ratio; IL, interleukin; TNF-α, tumor necrosis factor-α.