

# Evidence of Associations Between Cytokine Gene Polymorphisms and Quality of Life in Patients With Cancer and Their Family Caregivers

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An increasingly recognized patient-reported outcome in oncology is quality of life (QOL) (Trask, Hsu, & McQuellon, 2009). A substantial proportion of the interindividual variability in QOL in patients with cancer (Montazeri, 2008; Singh, Trabulsi, & Gomella, 2010) and their family caregivers (FCs) (Kim & Given, 2008; Kitrungrote & Cohen, 2006) is not explained by demographic characteristics (Bloom, Stewart, Chang, & Banks, 2004; Lam, Ye, & Fielding, 2012), disease severity (Mehnert, Lehmann, Graefen, Huland, & Koch, 2010; Paika et al., 2010; Zenger et al., 2010), or treatment burden (Deshields, Potter, Olsen, Liu, & Dye, 2011; Reeve et al., 2012). Several lines of evidence suggest that genetic factors may account for some of the interindividual differences in QOL (Nes, Roysamb, Tambs, Harris, & Reichborn-Kjennerud, 2006; Romeis et al., 2000, 2005).

Findings from twin studies (Nes et al., 2006; Romeis et al., 2000, 2005) suggested that genetic predisposition influences QOL. In these twin studies, heritability accounted for 11%–35% of the variance in QOL. For example, in one study that measured QOL using the SF-36® (Romeis et al., 2005), additive genetic factors accounted for 17%–33% of the variance in each of the SF-36 subscales. However, the specific genetic variations associated with interindividual differences in QOL remain unknown. Given these initial findings, experts in the fields of QOL and genomics established an international Consortium for Genetics and Quality of Life Research and called for studies to identify the molecular mechanisms that underlie interindividual differences and changes in QOL (Sprangers et al., 2009). Given the potentially large number of genes that could be involved in QOL, the consortium encouraged a focused approach to the investigation of genetic variations in biologic pathways (e.g., candidate gene studies).

Although research on the relationships between genetics and QOL is in its infancy, a substantial amount of evidence suggests that genetic variations in

**Purpose/Objectives:** To identify latent classes of individuals with distinct quality-of-life (QOL) trajectories, to evaluate for differences in demographic characteristics between the latent classes, and to evaluate for variations in pro- and anti-inflammatory cytokine genes between the latent classes.

**Design:** Descriptive, longitudinal study.

**Setting:** Two radiation therapy departments located in a comprehensive cancer center and a community-based oncology program in northern California.

**Sample:** 168 outpatients with prostate, breast, brain, or lung cancer and 85 of their family caregivers (FCs).

**Methods:** Growth mixture modeling (GMM) was employed to identify latent classes of individuals based on QOL scores measured prior to, during, and for four months following completion of radiation therapy. Single nucleotide polymorphisms (SNPs) and haplotypes in 16 candidate cytokine genes were tested between the latent classes. Logistic regression was used to evaluate the relationships among genotypic and phenotypic characteristics and QOL GMM group membership.

**Main Research Variables:** QOL latent class membership and variations in cytokine genes.

**Findings:** Two latent QOL classes were found: higher and lower. Patients and FCs who were younger, identified with an ethnic minority group, had poorer functional status, or had children living at home were more likely to belong to the lower QOL class. After controlling for significant covariates, between-group differences were found in SNPs in *interleukin 1 receptor 2 (IL1R2)* and *nuclear factor kappa beta 2 (NFKB2)*. For *IL1R2*, carrying one or two doses of the rare C allele was associated with decreased odds of belonging to the lower QOL class. For *NFKB2*, carriers with two doses of the rare G allele were more likely to belong to the lower QOL class.

**Conclusions:** Unique genetic markers in cytokine genes may partially explain interindividual variability in QOL.

**Implications for Nursing:** Determination of high-risk characteristics and unique genetic markers would allow for earlier identification of patients with cancer and FCs at higher risk for poorer QOL. Knowledge of these risk factors could assist in the development of more targeted clinical or supportive care interventions for those identified.

**Key Words:** quality of life; cytokines; genetics; growth mixture modeling; family caregivers; radiation therapy

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cytokine-signaling pathways influence the occurrence and severity of common symptoms (e.g., pain, fatigue, sleep disturbance, depression) in patients with cancer (Alfaro et al., 2014; Aouizerat et al., 2009; Dunn, Aouizerat, et al., 2013; Illi et al., 2012; Miaskowski et al., 2010, 2012; Reyes-Gibby et al., 2007, 2008, 2013; Reyes-Gibby, Shete, et al., 2009; Reyes-Gibby, Spitz, et al., 2009) and their FCs who often report multiple comorbid conditions (Aouizerat et al., 2009; Dunn, Aouizerat, et al., 2013; Illi et al., 2012; Miaskowski et al., 2010, 2012). Given that these symptoms are consistently associated with decrements in QOL (Desai, Kim, Fall, & Wang, 2007; Dodd et al., 2011; Dodd, Miaskowski, & Paul, 2001; Esther Kim, Dodd, Aouizerat, Jahan, & Miaskowski, 2009; Fletcher et al., 2008; Granda-Cameron, Viola, Lynch, & Polomano, 2008; Gwede, Small, Munster, Andrykowski, & Jacobsen, 2008) and are a major dimension of QOL instruments, variations in cytokine genes may account for some of the interindividual variability in individual's ratings of overall QOL.

To date, only two articles from the same sample of lung cancer survivors reported on the relationships between cytokine genetic variations and QOL (Rausch et al., 2010, 2012). The findings from those articles suggest that single nucleotide polymorphisms (SNPs) in *interleukin (IL) 10* and *prostaglandin-endoperoxidase synthase 2 (PTSG)* were associated with a number of QOL outcomes evaluated using the SF-36. Although genetic associations were evaluated in individuals who were at various stages of survivorship (i.e., fewer than three years, three to five years, and more than five years since diagnosis), the study's cross-sectional design does not allow for an evaluation of associations between candidate genes and distinct QOL trajectories that persist over time (i.e., subgroups of individuals who report consistently low versus high QOL scores (Dunn, Aouizerat, et al., 2013; Helgeson, Snyder, & Seltman, 2004; Lam et al., 2012). Therefore, additional research is warranted to explore the relationships between QOL and cytokine genes in patients with cancer and their FCs during and following cancer treatment.

From an examination of the QOL literature of patients with cancer and their FCs, a substantial amount of variation seems to exist in how QOL was defined and measured, as well as in sample characteristics, time points for assessment, and attrition across studies. In addition, the methods used to evaluate QOL scores are highly variable. More specifically, in most cross-sectional and longitudinal studies, average QOL scores were reported. By averaging QOL scores for a particular sample, interindividual variability in participants' QOL scores, as well as changes in individuals' QOL scores over time, are not identified.

Given the limitations associated with any evaluation of mean QOL scores, other studies used the statistical approach of growth mixture modeling (GMM) (Muthen

& Muthen, 2000) to identify subgroups of individuals with similar QOL trajectories. To date, only three studies were identified that used latent class analyses to identify subgroups of patients with cancer with distinct QOL trajectories (Dunn, Ng, et al., 2013; Helgeson et al., 2004; Lam et al., 2012). In the first study that evaluated changes in QOL in women who received adjuvant chemotherapy for breast cancer (Helgeson et al., 2004), four distinct latent classes were identified for the physical and mental component summary (PCS and MCS) scores on the SF-36. The largest latent class reported relatively high levels of mental and physical health (43% and 55%, respectively) that increased slightly over time. In contrast, the other three classes with lower PCS and MCS scores were characterized as having trajectories that either remained stable, improved, or deteriorated over time.

In the second study, GMM was used to identify latent classes of patients based on the four QOL domains from the Functional Assessment of Cancer Therapy-General (FACT-G) scale (Lam et al., 2012). Patients with nasopharyngeal cancer were assessed prior to and at four and eight months following radiation therapy (RT). About 55%–85% of these patients were classified as reporting consistently high scores in all four QOL domains. However, 25%–45% of patients were classified as reporting lower QOL scores that either remained stable or fluctuated over time. In a more recent study of patients with colorectal cancer, four distinct QOL trajectories (measured by the Functional Assessment of Cancer Therapy-Colorectal [FACT-C]) were identified using GMM (Dunn, Ng, et al., 2013). Patients were assessed at multiple time points 5–60 months postdiagnosis. Consistent with previous reports (Helgeson et al., 2004; Lam et al., 2012), two of the latent classes reported either consistently high (26%) or moderate QOL (47%) scores. The third class (7%) reported moderate QOL scores at the time of enrollment that decreased over time. The fourth latent class (19%) was characterized as having consistently low QOL scores.

Each of these GMM studies had relatively large samples, considered a variety of predictors in the analyses, and used standard QOL instruments (e.g., SF-36, FACT-G, FACT-C) (Dunn, Ng, et al., 2013; Helgeson et al., 2004; Lam et al., 2012). Of note, a number of demographic, clinical, and psychosocial adjustment characteristics were associated with membership in the lower QOL latent class in all of these studies. For example, in patients with breast cancer, fewer personal and social resources were associated with lower mental health trajectories (Helgeson et al., 2004). In addition, patients who were older and had fewer personal resources had worse physical health trajectories. In patients with nasopharyngeal cancer (Lam et al., 2012), older age, female gender, lower income, lower levels of optimism,

higher pain, less satisfaction with medical information, and less eating enjoyment were associated with membership in the lower QOL latent class. In patients with colorectal cancer (Dunn, Ng, et al., 2013), being younger and female and having less social support, more advanced disease, negative cognitive appraisal, and lower levels of optimism were associated with membership in the lower QOL latent class.

Although these three studies demonstrate that GMM can be used to identify subgroups of patients with cancer with distinct QOL trajectories (Dunn, Ng, et al., 2013; Helgeson et al., 2004; Lam et al., 2012) and one study identified a relationship between cytokine genes and QOL scores (Rausch et al., 2010, 2012), no study has evaluated for associations between subgroups of individuals with distinct QOL trajectories and variations in cytokine candidate genes. Therefore, the purpose of this study was to identify distinct QOL trajectories among patients who underwent RT and their FCs from prior to through four months after the completion of RT. In addition, differences in phenotypic characteristics and polymorphisms in pro- and anti-inflammatory cytokine genes between the latent classes were evaluated.

## Methods

### Participants and Settings

A detailed description of the methods used in this descriptive, longitudinal study that examined multiple symptoms in patients who underwent primary or adjuvant RT and in their FCs is published elsewhere (Aouizerat et al., 2009; Carney et al., 2011; Dhruva et al., 2012, 2013; Dunn, Aouizerat, et al., 2013; Miaskowski et al., 2010, 2011). Patients and their FCs were recruited from two RT departments located in a comprehensive cancer center and a community-based oncology program in northern California. Patients who met the following inclusion criteria were invited to participate in the study: aged older than 18 years; have a Karnofsky Performance Status (KPS) score of 60 or higher; scheduled to receive primary or adjuvant RT for one of four cancer diagnoses (prostate, breast, brain, or lung); able to read, write, and understand English; and able to provide written informed consent. Exclusion criteria included more than one cancer diagnosis, presence of metastatic disease, or a diagnosed sleep disorder. FCs were invited to participate if they were living with the patient; were aged older than 18 years; had a KPS score of 60 or higher; were able to read, write, and understand English; gave written informed consent; and did not have a diagnosed sleep disorder.

### Instruments

The demographic questionnaire obtained information on gender, age, education, employment status,

marital status, ethnicity, and the presence of a number of comorbid conditions. Functional status was evaluated using the KPS score (Karnofsky, Abelmann, Craver, & Burchenal, 1948). Disease and treatment information were abstracted from patients' medical records.

QOL was measured using the **QOL Scale–Patient Version (QOL-PV)** and the **QOL Scale–Family Version (QOL-FV)** (Padilla et al., 1983; Padilla, Ferrell, Grant, & Rhiner, 1990). The QOL-PV is a 41-item instrument that measures four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being) in patients with cancer, in addition to a total QOL score. Each item is rated on a 0–10 numeric rating scale, with higher scores indicating a better QOL. The QOL-PV has established validity and reliability (Ferrell, 1995; Ferrell, Dow, & Grant, 1995; Padilla et al., 1983, 1990). In the current study, the Cronbach alpha for the QOL-PV total score was 0.94.

The QOL-FV is a 37-item instrument that measures the QOL of FCs on four dimensions (i.e., physical, psychological, social, and spiritual well-being). Each item is rated on a 0–10 numeric rating scale with higher scores indicating a better QOL. The QOL-FV has established validity and reliability (Ferrell, 1995; Ferrell, Dow, Leigh, Ly, & Gulasekaram, 1995). In the current study, the Cronbach alpha for the QOL-FV was 0.95. The total QOL score, which is a mean of the 41 and 37 items that ranges from 0–10, was used in subsequent analyses in the current study.

### Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco, and at the second site. Patients were invited to participate in the study about one week prior to the start of RT. A research nurse explained the study protocol to the patient and FC, assessed eligibility, and obtained written informed consent. If the FC was not present, he or she was contacted by telephone to assess participation interest and completed the enrollment procedures at home.

At enrollment, participants (patients and FCs) completed the self-report questionnaires, and blood specimens were obtained for genetic analyses. Participants completed the QOL questionnaire one month after the initiation of RT, at the end of RT, and monthly after the completion of RT for four months (seven assessments over six months). Disease and treatment information were abstracted from patients' medical records.

### Analysis of Clinical Data

Data were analyzed using SPSS<sup>®</sup>, version 21, and Mplus, version 6.11. Descriptive statistics and frequency distributions were generated on the sample characteristics. Independent sample t-tests and chi-square analyses were

conducted to evaluate for differences in phenotypic and genotypic characteristics between the QOL latent classes.

GMM with robust maximum likelihood estimation was employed to identify subgroups of participants (i.e., latent classes) with distinct QOL trajectories (i.e., total QOL scores) during the study's six-month time period (Muthen & Kaplan, 2004). Because 65% of the participants were in patient and FC dyads, models were estimated with dyad status as a clustering variable to account for any dependency between the QOL scores for the patient and FC dyad. The GMM methods are described in detail elsewhere (Dunn, Aouizerat, et al., 2013). First, a single growth curve representing the average change trajectory was estimated in the entire sample. Subsequently, the number of latent classes that best fit the data was determined using established guidelines (Jung & Wickrama, 2008; Nylund, Asparouhov, & Muthen, 2007; Tofighi & Enders, 2008).

Adjustments were not made for missing data, so the sample size for each analysis was dependent on the largest set of available data. Differences among clinical and demographic characteristics and genetic factors between the latent classes were considered statistically significant at  $p < 0.05$ .

## Analysis of Genomic Data

**Gene selection:** Cytokines, their receptors, and select transcription factors are proteins that mediate inflammation. These proteins can be grouped into pro- and anti-inflammatory cytokines. Pro-inflammatory cytokines induce systemic inflammation and include *interferon gamma (IFNG) 1*, *IFNG receptor 1 (IFNGR1)*, *IL1*, *IL1 receptor 1 (IL1R1)*, *IL2*, *IL8*, *IL17A*, *nuclear factor kappa beta (NFKB1)*, *NFKB2*, and *tumor necrosis factor alpha (TNFA)*. Anti-inflammatory cytokines counteract the actions of pro-inflammatory cytokines and include *IL1R2*, *IL4*, *IL10*, and *IL13*. A subset of these candidate genes (i.e., *INFG1*, *IL1B*, *IL6*) possess pro- and anti-inflammatory activities (Seruga, Zhang, Bernstein, & Tannock, 2008).

**Blood collection and genotyping:** Genomic deoxyribonucleic acid (gDNA) was isolated from buffy coats using the PUREGene DNA Isolation System. Of the 287 participants recruited, DNA was successfully recovered from 253 archived buffy coats (i.e., 168 patients and 85 FCs).

Genotyping was performed blinded to latent class membership, and positive and negative controls were included. DNA samples were quantitated by spectrophotometry (Nanodrop Spectrophotometer, ND-1000) and normalized to 50 ng/μl in 10 mM Tris/1 mM ethylenediaminetetraacetic acid. Genotypes were measured using the GoldenGate assay platform and processed using GenomeStudio.

**Single nucleotide polymorphism selection:** Tagging and literature-driven SNPs were identified for analysis. The criteria for selection of tagging SNPs included being

common (i.e., minor allele frequency of 0.05 or greater) and captured unmeasured SNPs with linkage disequilibrium (LD) of greater than 0.85 in public databases. To ensure robust genetic association analyses, quality-control filtering of measured SNPs was performed (i.e., SNPs with call rates of less than 95% or Hardy-Weinberg  $p < 0.001$  were excluded from downstream analysis). A total of 92 SNPs among the 15 candidate genes were retained for genetic association analysis after quality-control filtering was completed (see Table 1). Putative functional roles for SNPs associated with QOL latent class membership were evaluated with PUPASuite 2.0.

**Statistical analyses:** Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg equilibrium was assessed by the chi-square or Fisher's exact test. Measures of LD (i.e.,  $D'$  and  $r^2$ ) were computed from the participants' genotypes with Haploview 4.2. LD-based haplotype block definition was based on  $D'$  confidence interval (Gabriel et al., 2002).

SNPs belonging to the same haploblock were used to infer haplotypes in said haploblock in an attempt to better localize the association signal within a given gene region and to ascertain whether a haplotype improved the magnitude of the estimate of association with latent class membership. Haplotypes were inferred using PHASE, version 2.1.

Ancestry informative markers (AIMs) were used to minimize confounding from population stratification (Halder, Shriver, Thomas, Fernandez, & Frudakis, 2008; Hoggart et al., 2003; Tian, Gregersen, & Seldin, 2008). Population stratification from cryptic relatedness (e.g., race, ethnicity) among participants was evaluated using principal component analysis (Price et al., 2006) with Helix Tree. Principal components were estimated from 106 AIMs. The first three principal components, which were included as a block of three covariates in all logistic regression models, were deemed sufficient to adjust for potential confounding as a result of population stratification from race and ethnicity.

For association tests, additive, dominant, and recessive genetic models were evaluated for each SNP. Barring trivial improvements (i.e., defined as a delta of less than 10%), the model that maximized the significance of the  $p$  value of the bivariate genetic association test was employed for all subsequent logistic regression analyses of each SNP.

Multiple logistic regression, which included significant covariates identified in the bivariate analyses and which force included both genomic estimates of and self-reported race and ethnicity, was employed to estimate the relationship between each SNP/haplotype and QOL latent class membership. To arrive at the most parsimonious model, a backward-stepwise approach was employed. With the exception of genomic estimates of and self-reported race and ethnicity, only

**Table 1. Single Nucleotide Polymorphisms Analyzed for Pro- and Anti-Inflammatory Cytokine Genes and the Growth Mixture Model Analysis for Total Quality-of-Life Score**

Gene	SNP	Position	Chromosome	MAF	Alleles	Chi-Square	p	Model
<i>IFNG1</i>	rs2069728	66834051	12	0.079	G>A	2.965	0.227	A
<i>IFNG1</i>	rs2069727	66834490	12	0.411	A>G	2.271	0.321	A
<i>IFNG1</i>	rs2069718	66836429	12	0.442	C>T	0.095	0.954	A
<i>IFNG1</i>	rs1861493	66837463	12	0.264	A>G	0.346	0.841	A
<i>IFNG1</i>	rs1861494	66837676	12	0.279	T>C	0.069	0.966	A
<i>IFNG1</i>	rs2069709	66839970	12	0.008 <sup>a</sup>	G>T	NA	NA	NA
<i>IFNG1</i>	HapA3	—	12	—	—	0.346	0.841	—
<i>IFNG1</i>	HapA5	—	12	—	—	2.271	0.321	—
<i>IFNGR1</i>	rs9376268	137574444	6	0.246	G>A	4.839	0.089	A
<i>IL1B</i>	rs1071676	106042060	2	0.198	G>C	2.848	0.241	A
<i>IL1B</i>	rs1143643	106042929	2	0.331	G>A	0.004	0.998	A
<i>IL1B</i>	rs1143642	106043180	2	0.095	C>T	1.851	0.396	A
<i>IL1B</i>	rs1143634	106045017	2	0.196	C>T	3.431	0.18	A
<i>IL1B</i>	rs1143633	106045094	2	0.345	G>A	0.069	0.966	A
<i>IL1B</i>	rs1143630	106046282	2	0.103	C>A	0.158	0.924	A
<i>IL1B</i>	rs3917356	106046990	2	0.432	G>A	0.079	0.961	A
<i>IL1B</i>	rs1143629	106048145	2	0.353	T>C	1.084	0.581	A
<i>IL1B</i>	rs1143627	106049014	2	0.39	T>C	0.042	0.979	A
<i>IL1B</i>	rs16944	106049494	2	0.38	G>A	0.264	0.876	A
<i>IL1B</i>	rs1143623	106050452	2	0.248	G>C	0.107	0.948	A
<i>IL1B</i>	rs13032029	106055022	2	0.428	C>T	0.114	0.945	A
<i>IL1B</i>	HapA1	—	—	—	—	0.637	0.727	—
<i>IL1B</i>	HapA3	—	—	—	—	FE	0.737	—
<i>IL1B</i>	HapA4	—	—	—	—	0.005	0.997	—
<i>IL1B</i>	HapA5	—	—	—	—	3.164	0.206	—
<i>IL1B</i>	HapB1	—	—	—	—	1.001	0.606	—
<i>IL1B</i>	HapB7	—	—	—	—	0.065	0.968	—
<i>IL1B</i>	HapB9	—	—	—	—	0.073	0.964	—
<i>IL1B</i>	HapB11	—	—	—	—	0.126	0.939	—
<i>IL1R1</i>	rs949963	96533648	2	0.213	G>A	1.255	0.534	A
<i>IL1R1</i>	rs2228139	96545511	2	0.066	C>G	0.451	0.798	A
<i>IL1R1</i>	rs3917320	96556738	2	0.068	A>C	FE	0.441	A
<i>IL1R1</i>	rs2110726	96558145	2	0.333	C>T	3.36	0.186	A
<i>IL1R1</i>	rs3917332	96560387	2	0.124	A>T	0.374	0.83	A
<i>IL1R2</i>	rs4141134	96370336	2	0.401	T>C	FE	0.003	D
<i>IL1R2</i>	rs11674595	96374804	2	0.233	T>C	0.197	0.906	A
<i>IL1R2</i>	rs7570441	96380807	2	0.393	G>A	3.163	0.206	A
<i>IL1R2</i>	HapA1	—	—	—	—	5.701	0.058	—
<i>IL1R2</i>	HapA2	—	—	—	—	6.231	0.044	—
<i>IL1R2</i>	HapA4	—	—	—	—	9.541	0.008	—
<i>IL2</i>	rs1479923	119096993	4	0.302	C>T	0.591	0.744	A
<i>IL2</i>	rs2069776	119098582	4	0.244	T>C	3.1	0.212	A
<i>IL2</i>	rs2069772	119099739	4	0.238	A>G	0.913	0.634	A
<i>IL2</i>	rs2069777	119103043	4	0.054	C>T	FE	0.672	A
<i>IL2</i>	rs2069763	119104088	4	0.287	T>G	0.825	0.662	A
<i>IL2</i>	HapA1	—	—	—	—	0.491	0.782	—
<i>IL2</i>	HapA2	—	—	—	—	0.764	0.683	—
<i>IL2</i>	HapA3	—	—	—	—	2.679	0.262	—
<i>IL2</i>	HapA5	—	—	—	—	0.591	0.744	—
<i>IL4</i>	rs2243248	127200946	5	0.101	T>G	3.84	0.147	A
<i>IL4</i>	rs2243250 <sup>b</sup>	127201455	5	0.26	C>T	NA	NA	NA
<i>IL4</i>	rs2070874	127202011	5	0.219	C>T	1.042	0.594	A
<i>IL4</i>	rs2227284	127205027	5	0.399	C>A	0.107	0.948	A
<i>IL4</i>	rs2227282	127205481	5	0.401	C>G	0.049	0.976	A
<i>IL4</i>	rs2243263	127205601	5	0.124	C>G	FE	0.541	A

(Continued on the next page)

A—additive; D—dominant; FE—Fisher's exact test; Hap—haplotype; IFNG—interferon gamma; IFNGR—interferon gamma receptor; IL—interleukin; NA—not applicable; NFkB—nuclear factor kappa beta; R—recessive model; TNFA—tumor necrosis factor alpha

<sup>a</sup>Single nucleotide polymorphisms (SNPs) excluded from association analyses because of violation of minor allele frequency (MAF) criterion (MAF < 0.05)

<sup>b</sup>SNPs excluded from association analyses because of violation of Hardy-Weinberg expectations (p < 0.001)

**Table 1. Single Nucleotide Polymorphisms Analyzed for Pro- and Anti-Inflammatory Cytokine Genes and the Growth Mixture Model Analysis for Total Quality-of-Life Score (Continued)**

Gene	SNP	Position	Chromosome	MAF	Alleles	Chi-Square	p	Model
IL4	rs2243266	127206091	5	0.203	G>A	1.561	0.458	A
IL4	rs2243267	127206188	5	0.205	G>C	1.359	0.507	A
IL4	rs2243274	127207134	5	0.262	G>A	0.603	0.74	A
IL4	HapA1	–	–	–	–	0.119	0.942	–
IL4	HapA10	–	–	–	–	1.418	0.492	–
IL6	rs4719714	22643793	7	0.196	A>T	1.152	0.562	A
IL6	rs2069827	22648536	7	0.071	G>T	FE	0.035	D
IL6	rs1800796 <sup>b</sup>	22649326	7	0.095	G>C	NA	NA	NA
IL6	rs1800795	22649725	7	0.355	C>G	FE	0.044	D
IL6	rs2069835	22650951	7	0.066	T>C	FE	0.845	A
IL6	rs2066992 <sup>b</sup>	22651329	7	0.091	G>T	NA	NA	NA
IL6	rs2069840	22651652	7	0.308	C>G	1.113	0.573	A
IL6	rs1554606	22651787	7	0.405	G>T	FE	0.006	D
IL6	rs2069845	22653229	7	0.405	A>G	FE	0.006	D
IL6	rs2069849	22654236	7	0.039 <sup>a</sup>	C>T	NA	NA	NA
IL6	rs2069861	22654734	7	0.083	C>T	FE	0.38	A
IL6	rs35610689	22656903	7	0.242	A>G	1.26	0.533	A
IL6	HapA4	–	–	–	–	1.022	0.6	–
IL6	HapA6	–	–	–	–	4.868	0.088	–
IL8	rs4073	70417508	4	0.498	T>A	2.515	0.284	A
IL8	rs2227306	70418539	4	0.366	C>T	0.747	0.688	A
IL8	rs2227543	70419394	4	0.374	C>T	1.674	0.433	A
IL8	HapA1	–	–	–	–	0.756	0.685	–
IL8	HapA3	–	–	–	–	0.747	0.688	–
IL8	HapA4	–	–	–	–	2.515	0.284	–
IL10	rs3024505	177638230	1	0.138	C>T	0.611	0.737	A
IL10	rs3024498	177639855	1	0.236	A>G	2.217	0.33	A
IL10	rs3024496	177640190	1	0.459	T>C	0.211	0.9	A
IL10	rs1878672	177642039	1	0.452	G>C	0.577	0.749	A
IL10	rs3024492	177642438	1	0.207	T>A	3.25	0.197	A
IL10	rs1518111	177642971	1	0.267	G>A	1.892	0.388	A
IL10	rs1518110	177643187	1	0.267	G>T	1.892	0.388	A
IL10	rs3024491	177643372	1	0.448	G>T	0.339	0.844	A
IL10	HapA5	–	–	–	–	2.139	0.343	–
IL10	HapA6	–	–	–	–	1.805	0.405	–
IL10	HapA8	–	–	–	–	3.206	0.201	–
IL10	HapA9	–	–	–	–	0.623	0.732	–
IL13	rs1881457	127184713	5	0.192	A>C	0.579	0.748	A
IL13	rs1800925	127185113	5	0.227	C>T	1.447	0.485	A
IL13	rs2069743	127185579	5	0.021 <sup>a</sup>	A>G	NA	NA	NA
IL13	rs1295686	127188147	5	0.252	G>A	2.158	0.34	A
IL13	rs20541	127188268	5	0.174	C>T	1.195	0.55	A
IL13	HapA1	–	–	–	–	2.556	0.279	–
IL13	HapA4	–	–	–	–	0.714	0.7	–
IL17A	rs4711998	51881422	6	0.293	G>A	0.615	0.735	A
IL17A	rs8193036	51881562	6	0.255	T>C	0.087	0.957	A
IL17A	rs3819024	51881855	6	0.374	A>G	1.275	0.529	A
IL17A	rs2275913	51882102	6	0.345	G>A	0.62	0.734	A
IL17A	rs3804513	51884266	6	0.027 <sup>a</sup>	A>T	NA	NA	NA
IL17A	rs7747909	51885318	6	0.225	G>A	1.812	0.404	A
NFKB1	rs3774933	103645369	4	0.444	T>C	0.427	0.808	A
NFKB1	rs170731	103667933	4	0.397	A>T	0.727	0.695	A
NFKB1	rs17032779	103685279	4	0.023 <sup>a</sup>	T>C	NA	NA	NA
NFKB1	rs230510	103695201	4	0.366	T>A	1.233	0.54	A
NFKB1	rs230494	103706005	4	0.477	A>G	0.422	0.81	A

(Continued on the next page)

A—additive; D—dominant; FE—Fisher's exact test; Hap—haplotype; IFNG—interferon gamma; IFNGR—interferon gamma receptor; IL—interleukin; NA—not applicable; NFKB—nuclear factor kappa beta; R—recessive model; TNFA—tumor necrosis factor alpha

<sup>a</sup>Single nucleotide polymorphisms (SNPs) excluded from association analyses because of violation of minor allele frequency (MAF) criterion (MAF < 0.05)

<sup>b</sup>SNPs excluded from association analyses because of violation of Hardy-Weinberg expectations (p < 0.001)

**Table 1. Single Nucleotide Polymorphisms Analyzed for Pro- and Anti-Inflammatory Cytokine Genes and the Growth Mixture Model Analysis for Total Quality-of-Life Score (Continued)**

Gene	SNP	Position	Chromosome	MAF	Alleles	Chi-Square	p	Model
NFKB1	rs4648016	103708706	4	0.017 <sup>a</sup>	C>T	NA	NA	NA
NFKB1	rs4648018	103709236	4	0.025 <sup>a</sup>	G>C	NA	NA	NA
NFKB1	rs3774956	103727564	4	0.479	C>T	0.62	0.733	A
NFKB1	rs10489114	103730426	4	0.025 <sup>a</sup>	A>G	NA	NA	NA
NFKB1	rs4648068	103737343	4	0.366	A>G	1.233	0.54	A
NFKB1	rs4648095	103746914	4	0.052	T>C	FE	0.831	A
NFKB1	rs4648110	103752867	4	0.205	T>A	0.861	0.65	A
NFKB1	rs4648135	103755716	4	0.06	A>G	FE	1	A
NFKB1	rs4648141	103755947	4	0.188	G>A	3.332	0.184	A
NFKB1	rs1609798	103756488	4	0.337	C>T	1.015	0.602	A
NFKB1	HapA1	–	–	–	–	1.347	0.51	–
NFKB1	HapA9	–	–	–	–	0.788	0.674	–
NFKB2	rs12772374	104146901	10	0.157	A>G	FE	0.031	R
NFKB2	rs7897947	104147701	10	0.229	T>G	3.08	0.214	A
NFKB2	rs11574849	104149686	10	0.085	G>A	2.39	0.303	A
NFKB2	rs1056890	104152760	10	0.317	C>T	0.046	0.977	A
TNFA	rs2857602	31533378	6	0.36	T>C	4.167	0.125	A
TNFA	rs1800683	31540071	6	0.388	G>A	0.467	0.792	A
TNFA	rs2239704	31540141	6	0.37	G>T	4.152	0.125	A
TNFA	rs2229094	31540556	6	0.256	T>C	1.492	0.474	A
TNFA	rs1041981	31540784	6	0.388	C>A	0.467	0.792	A
TNFA	rs1799964	31542308	6	0.202	T>C	0.249	0.883	A
TNFA	rs1800750	31542963	6	0.019 <sup>a</sup>	G>A	NA	NA	NA
TNFA	rs1800629	31543031	6	0.157	G>A	1.738	0.419	A
TNFA	rs1800610	31543827	6	0.105	C>T	4.026	0.134	A
TNFA	rs3093662	31544189	6	0.072	A>G	0.791	0.673	A
TNFA	HapA1	–	–	–	–	0.282	0.869	–
TNFA	HapA5	–	–	–	–	0.634	0.728	–
TNFA	HapA8	–	–	–	–	5.15	0.076	–

A—additive; D—dominant; FE—Fisher's exact test; Hap—haplotype; IFNG—interferon gamma; IFNGR—interferon gamma receptor; IL—interleukin; NA—not applicable; NFKB—nuclear factor kappa beta; R—recessive model; TNFA—tumor necrosis factor alpha

<sup>a</sup>Single nucleotide polymorphisms (SNPs) excluded from association analyses because of violation of minor allele frequency (MAF) criterion (MAF < 0.05)

<sup>b</sup>SNPs excluded from association analyses because of violation of Hardy-Weinberg expectations ( $p < 0.001$ )

statistically significant variables ( $p < 0.05$ ) were retained in the final multiple variable model. Logistic regression analyses were conducted using STATA, version 9.

As was done in the authors' previous studies (Alfaro et al., 2014; Dunn, Aouizerat, et al., 2013; Illi et al., 2012; McCann et al., 2012; Merriman et al., 2014; Miaskowski et al., 2012)—based on recommendations in the literature (Hattersley & McCarthy, 2005; Rothman, 1990), the implementation of rigorous quality controls for genomic data, the nonindependence of SNPs/haplotypes in LD, and the exploratory nature of the analyses—adjustments were not made for multiple testing. Statistically significant SNPs and haplotypes identified in the bivariate analyses were evaluated further using multiple logistic regression analyses to control for differences in clinical and demographic characteristics, potential population stratification, and genetic associations among other SNPs or haplotypes in the same gene. Only SNPs and haplotypes that remained significant ( $p < 0.05$ ) in the final and most parsimonious model were presented. Therefore, the

statistically significant and independent genetic associations identified are less likely to be a result of chance.

## Results

### Participant Characteristics

The majority of the participants were Caucasian, well educated, and married or partnered. Patients made up about 66% ( $n = 168$ ) of the total sample. The mean age of the total sample was 61.4 years. The average participant had greater than four comorbid conditions and a mean KPS score of 92. Gender was evenly represented within the total sample, with 46% ( $n = 116$ ) male and 54% ( $n = 137$ ) female participants. The majority of the FCs ( $n = 79$ ) were the patients' spouses. About 38% ( $n = 64$ ) of the patients had breast cancer, 49% ( $n = 82$ ) had prostate cancer, 7% ( $n = 12$ ) had brain cancer, and 6% ( $n = 10$ ) had lung cancer. The total sample had a mean QOL score of 6.9 ( $SD = 1.5$ ) at enrollment and 7.2 ( $SD = 1.5$ ) at study completion. At enrollment, no significant

differences were found between patients' ( $\bar{X} = 6.8$ ,  $SD = 1.5$ ) and FCs' ( $\bar{X} = 7.1$ ,  $SD = 1.4$ ) QOL scores ( $p = 0.22$ ).

## Results of Growth Mixture Modeling Analysis

Two distinct latent classes of QOL trajectories were identified using GMM. As shown in Table 2, a two-class model was selected because its Bayesian information criterion was smaller than for the one-class and three-class models and by comparisons of the other fit indices. In addition, each class in the two-class model had a reasonable size and interpretability (Jung & Wickrama, 2008).

The parameter estimates for the two latent classes are listed in Table 3. The largest percentage of participants (62%) was grouped in the higher QOL class. These participants had a mean QOL score at enrollment of 7.8 ( $SD = 0.9$ ), which generally increased slightly over time. The lower QOL class (38%) had a mean QOL score at enrollment of 5.5 ( $SD = 1.3$ ), which increased slightly over time. The estimated QOL over time was about the same as the observed QOL for both groups. The between-group difference in QOL scores at enrollment was statistically significant ( $p < 0.001$ ) and clinically meaningful (Cohen's  $d = 1.04$ ) (Cohen, 1988; Norman, Sloan, & Wyrwich, 2003; Osoba, 1999; Osoba, Rodrigues, Myles, Zee, & Pater, 1998).

## Differences in Demographic Characteristics

As summarized in Table 4, no differences were found between the two latent classes in gender, education, employment status, living arrangements, having an older adult at home, number of comorbid conditions, and weight. In addition, no significant differences were found in the percentage of patients or FCs in either QOL class ( $p = 0.49$ ). Within the higher QOL class, no differences in mean QOL scores were found between patients ( $\bar{X} = 7.7$ ,  $SD = 0.8$ ) and FCs ( $\bar{X} = 7.9$ ,  $SD = 0.9$ ,  $p = 0.4$ ) at enrollment. Within the lower QOL class, no differences were found in mean QOL scores for patients ( $\bar{X} = 5.5$ ,  $SD = 1.3$ ) and FCs ( $\bar{X} = 5.7$ ,  $SD = 1.2$ ,  $p = 0.35$ ) at enrollment.

Participants in the lower QOL class were more likely to be younger ( $p < 0.001$ ), have a lower KPS score ( $p < 0.001$ ), be members of an ethnic minority group ( $p < 0.001$ ), and have children living at home ( $p < 0.001$ ). Compared to Caucasian participants, participants of Asian or Pacific Islander ethnicity or Hispanic, mixed background, or other ethnicity were more likely to be members of the lower QOL class ( $p = 0.02$  and  $p = 0.002$ , respectively). Compared to African American participants, participants

of Asian or Pacific Islander ethnicity or Hispanic, mixed background, or other ethnicity were more likely to be members of the lower QOL class ( $p = 0.004$  and  $p < 0.001$ , respectively). No significant differences in latent class membership were observed between Caucasian compared to African American participants ( $p = 0.16$ ) or Asian or Pacific Islanders compared to Hispanic, mixed background, or other ethnicity participants ( $p = 0.29$ ).

## Candidate Gene Analyses

The genotype frequencies were significantly different between the two latent classes for six SNPs: *IL1R2* rs4141134, *IL6* rs2069827, *IL6* rs1800795, *IL6* rs1554606, *IL6* rs2069845, and *NFKB2* rs12772374. For *IL1R2* rs4141134 ( $p = 0.003$ ), *IL6* rs2069827 ( $p = 0.035$ ), *IL6* rs1800795 ( $p = 0.044$ ), and *IL6* rs2069845 ( $p = 0.006$ ), a dominant model fit the data best. For *IL6* rs1554606 ( $p = 0.006$ ) and *NFKB2* rs12772374 ( $p = 0.031$ ), a recessive model fit the data best. Significant differences were found between the latent classes for two of the haplotypes: *IL1R2* HapA2 ( $p = 0.044$ ) and *IL1R2* HapA4 ( $p = 0.008$ ).

## Multiple Logistic Regression Analyses of Cytokine Genes and Latent Classes

To improve the estimate of the odds ratio of the effects of a SNP/haplotype on QOL class membership, multiple logistic regression was employed that controlled for genotype, genomic estimates of and self-reported race or ethnicity, age, functional status, and having children at home.

Two genetic associations remained significant in the multiple logistic regression models: *IL1R2* rs4141134 and *NFKB2* rs12772374 (see Table 5 and Figure 1). In the model for *IL1R2* rs4141134, carrying one or two doses of the rare C allele (i.e., TT versus TC+CC) was associated with a 64% decrease in the odds of belonging to the lower QOL class. In the model for *NFKB2* rs12772374, being

**Table 2. Fit Indices for the Class Solutions**

GMM	LL	AIC	BIC	Entropy	VLMR <sup>a</sup>
1-Class <sup>b</sup>	-1,701.874	3,431.748	3,481.215	NA	NA
2-Class <sup>c</sup>	-1,638.264	3,320.528	3,398.262	0.663	127.220*
3-Class	-1,623.552	3,305.103	3,407.572	0.671	29.424**

\*  $p < 0.001$ ; \*\*  $p$  value is nonsignificant.

<sup>a</sup> Chi-square statistic for the VLMR. When significant, the VLMR test provides evidence that the K-class model fits the data better than the K-1-class model.

<sup>b</sup> Random intercepts latent growth curve model with linear and quadratic components; chi-square = 94.695,  $df = 28$ ,  $p < 0.00005$ , comparative fit index = 0.963, root mean square error of approximation = 0.097

<sup>c</sup> 2-class model was selected, based on its having the smallest BIC and a significant VLMR. Further, the VLMR is not significant for the 3-class model.

AIC—Akaike information criterion; BIC—Bayesian information criterion; GMM—growth mixture modeling; LL—log likelihood; VLMR—Vuong-Lo-Mendell-Rubin likelihood ratio test



**Table 3. Estimates for QOL Total Score Latent Class<sup>a</sup> Solution With Seven Assessments (N = 253)**

Parameter Estimate <sup>b</sup>	Higher QOL (n = 156)		Lower QOL (n = 97)	
	$\bar{X}$	SE	$\bar{X}$	SE
Intercept	7.819***	0.249	5.79***	0.258
Linear slope	0.198**	0.065	0.0****	0.08
Quadratic slope	-0.019*	0.009	0.009****	0.011
Variance	Variance	SE	Variance	SE
Intercept	0.512***	0.143	1.245***	0.214
Linear slope	0 <sup>c</sup>	–	0.022***	0.006

\* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001; \*\*\*\* p value is nonsignificant.

<sup>a</sup> Trajectory group sizes are for classification of individuals based on their most likely latent class probabilities.

<sup>b</sup> Growth mixture model estimates were obtained with robust maximum likelihood, with dyad as a clustering variable to account for dependency between patients and family caregivers within the same dyad. Quadratic slope variances were fixed at zero to improve estimation.

<sup>c</sup> Fixed at zero  
QOL—quality of life; SE—standard error

homozygous for the rare G allele (i.e., AA+AG versus GG) was associated with a 47.7-fold increase in the odds of belonging to the lower QOL class.

## Discussion

The current study is the first to identify distinct subgroups of patients with cancer and their FCs based on changes in QOL scores and to evaluate for associations between subgroup membership and variations in cytokine genes. Consistent with previous reports (Dunn, Ng, et al., 2013; Helgeson et al., 2004; Lam et al., 2012), the largest latent class (62%) consisted of individuals with a mean enrollment QOL score of 7.8 (SD = 0.9) that increased slightly over time. The remaining 38% of the sample was classified into a lower QOL trajectory, with a mean QOL score at enrollment of 5.5 (SD = 1.3), which increased slightly over time. These initial between-group differences in QOL scores are statistically significant and clinically meaningful (Cohen's d = 1.04) (Cohen, 1988; Norman et al., 2003; Osoba, 1999; Osoba et al., 1998). In contrast to previous studies that identified three to four distinct latent classes depending on the QOL mea-

sure used, only two latent classes were identified in the current study. A number of factors may account for these inconsistent findings, including the measures used to evaluate QOL, the specific dimensions of QOL that were evaluated (e.g., total QOL versus subscale scores), the timing of the QOL assessments in relationship to the patients' disease trajectory (e.g., active treatment versus survivorship), and the size and composition of the samples.

One obvious explanation for the differences in the number of latent classes identified might be the inclusion of FCs in the current analysis. Most QOL studies have examined patients with cancer and FCs separately, based on assumptions that the stressors experienced by patients and FCs differ. However, mounting evidence suggests that demographic, dispositional, and personality characteristics, as well as the occurrence of chronic illnesses, explain substantial variability in the QOL of patients with cancer and their FCs (Awadalla et al., 2007; Chen, Chu, & Chen, 2004; Hagedoorn, Buunk, Kuijer, Wobbles, & Sanderman, 2000; Northouse et al., 2002). This idea is supported by the

**Table 4. Differences in Demographic Characteristics Between the Latent QOL Classes at Enrollment (N = 253)**

Characteristic	Higher QOL (n = 156)		Lower QOL (n = 97)		p
	$\bar{X}$	SD	$\bar{X}$	SD	
Age (years)	65.3	9	55.2	11.8	< 0.001
Education (years)	16	3	15.8	3	0.57
Number of comorbid conditions	4.5	2.6	4.8	2.8	0.41
Weight (pounds)	178.9	36.3	169.3	42.1	0.06
Karnofsky Performance Status score <sup>a</sup>	95.4	7.9	86.3	14	< 0.001
Characteristic	n	%	n	%	p
<b>Gender</b>					0.05
Female	76	49	60	62	–
<b>Ethnicity</b>					< 0.001
Caucasian	122	79	66	68	–
African American	26	17	8	8	–
Asian or Pacific Islander	5	3	11	11	–
Hispanic, mixed ethnicity, or other	2	1	12	12	–
Missing data	1	1	–	–	–
Lives alone	35	22	19	20	0.41
Married or partnered	113	72	61	63	0.2
Has children at home	13	8	23	24	< 0.001
Has older adult at home	2	1	5	5	0.1
Employed	70	45	45	46	0.9
<b>Part of dyad</b>					0.5
Patient	101	65	67	69	–
Family caregiver	55	35	30	31	–

<sup>a</sup> Range = 0–100, where higher score indicates better quality of life

Note. Because of rounding, percentages may not total 100.

**Table 5. Multiple Logistic Regression Analyses for *IL1R2* and *NFKB2* Candidate Gene Markers**

Predictor	OR	SE	95% CI	Z	p
<b><i>IL1R2</i> genotype<sup>a</sup></b>	0.36	0.162	[0.151, 0.87]	-2.27	0.02
Age	0.56	0.067	[0.442, 0.706]	-4.88	< 0.001
Ethnicity	17.84	22.553	[1.497, 212.58]	2.28	0.02
KPS	0.37	0.08	[0.241, 0.564]	-4.61	< 0.001
Children at home	4.19	2.519	[1.291, 13.614]	2.39	0.02
<b><i>NFKB2</i> genotype<sup>b</sup></b>	47.7	68.498	[2.86, 795.777]	2.69	0.01
Age	0.54	0.068	[0.423, 0.692]	-4.89	< 0.001
Ethnicity	15.08	19.2	[1.244, 182.838]	2.13	0.03
KPS	0.34	0.074	[0.225, 0.525]	-4.94	< 0.001
Children at home	5.1	3.071	[1.569, 16.598]	2.71	0.01

<sup>a</sup>Overall model fit: chi-square = 106.86,  $p < 0.0001$ ,  $R^2 = 0.4154$

<sup>b</sup>Overall model fit: chi-square = 110.09,  $p < 0.0001$ ,  $R^2 = 0.4279$

Note. Multiple logistic regression analysis of GMM latent classes for total QOL scores (0 = higher, 1 = lower). For each model, the first three principal components derived from the analysis of ancestry informative markers as well as self-report ethnicity were retained in all models to adjust for potential confounding because of ethnicity (data not shown). Predictors evaluated in each model included genotype, age in five-year increments, self-reported ethnicity, children living at home, and functional status (KPS score in 10-unit increments).

CI—confidence interval; GMM—growth mixture modeling; *IL1R2*—interleukin 1 receptor 2; KPS—Karnofsky Performance Status; *NFKB2*—nuclear factor kappa beta 2; OR—odds ratio; QOL—quality of life; SE—standard error

fact that, in the current study, no differences were found in proportion of patients and FCs in each of the QOL classes. In addition, within each QOL class, no differences were found between patients and FCs in their QOL scores at enrollment. Additional research is warranted to determine the number and types of QOL trajectories in patients with cancer and their FCs during various phases of the patient's cancer experience (e.g., diagnosis, active treatment, survivorship).

To the best of the authors' knowledge, this study is first to evaluate the relationships between variations in cytokine genes and distinct QOL trajectories. Across 15 candidate genes, associations were identified in *IL1R2* and *NFKB2*. *IL1R2* is one of the two receptors for the pro-inflammatory cytokine *IL1*. However, because it lacks a cytoplasmic signaling domain, *IL1R2* is a decoy receptor that blocks *IL1* signal transduction (Colotta et al., 1993). In the current study, individuals who were heterozygous or homozygous for the rare C allele in *IL1R2* rs4141134 were less likely to be classified in the lower QOL class. *IL1R2* rs4141134 is located in the promoter region of the gene and may affect *IL1R2* expression. In a previous study that evaluated for associations between this SNP and osteoarthritis (Nakki et al., 2010), no association was found. Evidence suggests that this SNP is methylated in human brain tissue, so it may play a role in modulating *IL1R2* activity (Kent et al., 2002; Maunakea et al., 2010).

In the authors' previous studies of associations between cytokine gene variations and depressive symptoms in the same sample (Dunn, Aouizerat, et al., 2013)

and sleep disturbance in a sample of patients with breast cancer (Alfaro et al., 2014), associations were found between haplotypes in *IL1R2* and latent class membership. In the first study of the same sample (Dunn, Aouizerat, et al., 2013), each additional dose of the *IL1R2* haplotype A1 (composed of rs4141134-rs11674595-rs7570441) was associated with a two-fold increase in the odds of belonging to the more severe depressive symptoms class. In the study of patients with breast cancer (Alfaro et al., 2014), each additional dose of the *IL1R2* haplotype A2 (composed of rs11674595-rs7570441) was associated with a two-fold increase in the odds of belonging to the worse sleep disturbance class. Although these findings appear somewhat contradictory because previous studies found that more severe symptoms are associated with decrements in QOL (Desai et

al., 2007; Dodd et al., 2001, 2011; Esther Kim et al., 2009; Fletcher et al., 2008; Granda-Cameron et al., 2008; Gwede et al., 2008), two explanations are plausible. First, in the study of patients with breast cancer (Alfaro et al., 2014), the SNPs used to infer *IL1R2* haplotype A2 did not include rs4141134. Although rs4141134 was used to infer *IL1R2* haplotype A1 in the study of depressive symptoms in the same sample (Dunn, Aouizerat, et al., 2013), the different subsets of participants in the QOL, as compared to depressive symptom GMM classes, may have resulted in differing LD associations with unmeasured causal SNPs. Second, although the total QOL score used in the GMM analyses included an assessment of common symptoms, the total score represents a composite measure that includes an evaluation of physical, psychological, social, and spiritual well-being. Additional research is warranted to determine the associations between polymorphisms in *IL1R2* and various dimensions of QOL.

The second association identified in this study was with *NFKB2* rs12772374, which is located in the intron region of the gene and has no known function. *NFKB* plays a role in mounting an effective immune response, in addition to having roles in development, cell proliferation, apoptosis, and in response to tissue damage. The *NFKB* system is also activated in emotionally stressful situations and is linked to cancer and inflammatory diseases (Schmitz, Mattioli, Buss, & Kracht, 2004). In the current study, individuals who were homozygous for the rare G allele were more likely to be classified in the lower QOL class. In the authors' previous studies of associations between

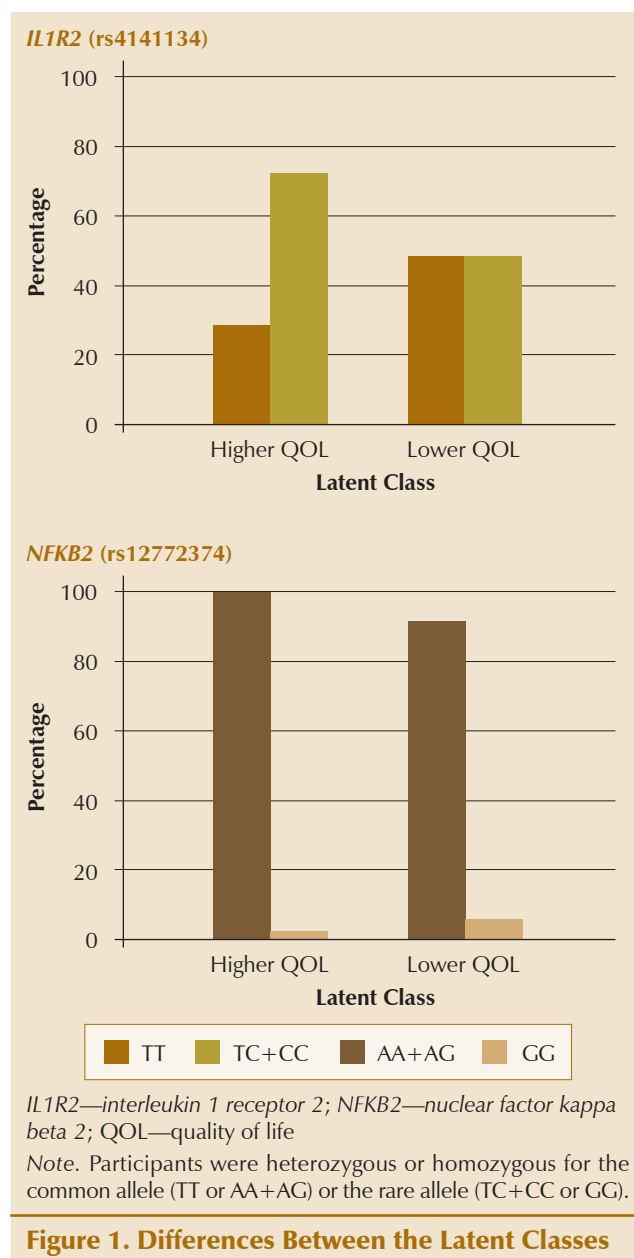
cytokine gene polymorphisms and sleep disturbance, two different SNPs in *NFKB2* that were in modest LD with rs12772374 (i.e., rs1056890 [Alfaro et al., 2014] and rs7897947 [Miaskowski et al., 2012]) were identified. In both of these studies, individuals who were heterozygous or homozygous for the rare allele (i.e., dominant model) were more likely to be classified in the higher sleep disturbance class. These somewhat consistent findings warrant additional investigation.

In the only articles that reported results on associations between cytokine gene and QOL (Rausch et al., 2010, 2012), polymorphisms in *IL10* and *PTSG* were associated with overall QOL scores (i.e., PCS and MCS scores on the eight-item Short-Form Health Survey [SF-8], mental health and social function on the SF-8) in patients with lung cancer. However, the specific directions for these associations are not described. In the current study, no associations were found in the bivariate analyses between *IL10* and QOL latent class membership. These inconsistent findings may be related to differences in the QOL measures used and determination of the QOL phenotype (i.e., cross sectional analysis versus latent class analyses), as well as sample characteristics.

In terms of demographic characteristics, consistent with the previous studies that used GMM to identify distinct QOL subgroups (Dunn, Ng, et al., 2013; Helgeson et al., 2004; Lam et al., 2012), younger participants were more likely to be classified in the lower QOL class. Younger participants may need to balance employment and social responsibilities (e.g., children at home) in addition to the stressors associated with cancer and its treatment, which can have a negative effect on their QOL (Baker, Denniston, Smith, & West, 2005; Costanzo et al., 2007). This hypothesis is supported by this study's and others' (Bloom et al., 2004; Eisemann & Lalos, 1999) finding that participants with children at home are more likely to be classified in the lower QOL class. In contrast, older individuals may experience a "response shift" in their perception of QOL, whereby a person's judgment of health may vary as a result of new information, changes in values and priorities, or changes to what they perceive as QOL following the diagnosis of a serious illness (Schwartz & Sprangers, 1999).

Consistent with previous reports (Lockett et al., 2011; Powe et al., 2007), participants who self-reported their ethnicity as Asian or Pacific Islander or Hispanic, mixed background, or other were more likely to be classified in the lower QOL class. In both regression analyses, the odds of belonging to the lower QOL class were about 15 times higher for these minority groups. However, these findings need to be interpreted with caution because of the relatively small number of individuals in each of these ethnic groups. Consistent with previous reports (Caissie et al., 2012; Lien et al., 2012; Movsas, Scott, &

Watkins-Bruner, 2006), lower functional status scores were associated with membership in the lower QOL class. Although the KPS scores of both classes were relatively high, the between-class difference in KPS scores was clinically meaningful ( $d = 0.41$ ). These findings suggest that subtle differences in functional status are associated with noticeable decrements in QOL for patients and their FCs. The factors that contributed to these differences in functional status warrant additional investigation. One may speculate that the lower KPS scores in the lower QOL class would be associated with a higher number of comorbidities (Deshpande, Sefko, Jeffe, & Schootman, 2011; Ostroff et al., 2011). However, participants in the higher QOL class ( $\bar{X} = 4.5$ ,  $SD = 2.6$ ) and the lower QOL class ( $\bar{X} = 4.8$ ,  $SD = 2.8$ ) reported a similar number of comorbidities.



**Figure 1. Differences Between the Latent Classes**

## Knowledge Translation

Patients and family caregivers (FCs) need to be evaluated for changes in quality of life (QOL) during the course of patients' treatment.

Younger patients and FCs who are members of a racial or ethnic minority group, have children living at home, and have poorer functional status should be assessed for decrements in QOL.

An understanding of genomic markers causing decrements in QOL may contribute to the development of molecular tests that can be used to identify high-risk patients and FCs.

In previous studies, higher education (Knight et al., 2007; Movsas et al., 2006) and being married (Kwan et al., 2010; Movsas et al., 2006) were associated with higher QOL scores and living alone (Dieperink et al., 2012) was associated with lower QOL scores in patients with cancer; these associations were not found in the current study. These inconsistent findings may be the result of differences in the QOL measures used, as well as differences in sample characteristics and timing of the assessments.

## Limitations

Several study limitations need to be acknowledged. This study evaluated QOL among outpatients with cancer and their FCs using QOL-PV and QOL-FV questionnaires (Padilla et al., 1983, 1990). The total QOL score is an aggregate measure of a person's subjective experience related to their physical, psychological, social, and spiritual well-being. Although previous studies did evaluate for differences in latent classes using various QOL subscales (Dunn, Ng, et al., 2013; Helgeson et al., 2004; Lam et al., 2012), future research needs to evaluate for differences in genotypic associations among these latent classes. The sample size for the GMM analysis was adequate (Nylund et al., 2007; Tofighi & Enders, 2008), but larger samples may identify additional latent classes. In terms of the genetic association analyses, studies are warranted in an independent sample(s) to validate the associations described in the current study. Future studies could include additional cytokine genes (e.g., cytokine genes

that encode for cytokines that participate in the same pathway as those identified herein) as well as protein levels of cytokines to evaluate the functional impact of these genetic associations.

## Implications for Nursing Practice and Conclusions

Despite these limitations, findings from the current study provide preliminary evidence for distinct classes of QOL trajectories in patients with cancer and their FCs. Given the increasing importance of QOL as a patient-reported outcome (Trask et al., 2009), clinicians need to assess patients and FCs for changes in QOL throughout and beyond cancer treatment. Clinicians should evaluate patients and FCs who may be at higher risk for decrements in QOL. Given the results of this study, individuals who are younger, identify with an ethnic minority group, have a poorer functional status, and have children living at home may be at greater risk. The candidate gene associations found in the current study suggests a role for inflammation in QOL. Ultimately, an increased understanding of genomic markers associated with decrements in QOL may contribute to the development of molecular tests that can be used to identify high-risk patients and FCs.

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## References

- Alfaro, E., Dhruva, A., Langford, D.J., Koettters, T., Merriman, J.D., West, C., . . . Miaskowski, C. (2014). Associations between cytokine gene variations and self-reported sleep disturbance in women following breast cancer surgery. *European Journal of Oncology Nursing, 18*, 85–93.
- Aouizerat, B.E., Dodd, M., Lee, K., West, C., Paul, S.M., Cooper, B.A., . . . Miaskowski, C. (2009). Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. *Biological Research in Nursing, 11*(1), 27–41.
- Awadalla, A.W., Ohaeri, J.U., Gholoum, A., Khalid, A.O., Hamad, H.M., & Jacob, A. (2007). Factors associated with quality of life of outpatients with breast cancer and gynecologic cancers and their family caregivers: A controlled study. *BMC Cancer, 7*, 102. doi:1471-2407-7-102
- Baker, F., Denniston, M., Smith, T., & West, M.M. (2005). Adult cancer survivors: How are they faring? *Cancer, 104*(11, Suppl.), 2565–2576. doi:10.1002/cncr.21488
- Bloom, J.R., Stewart, S.L., Chang, S., & Banks, P.J. (2004). Then and now: Quality of life of young breast cancer survivors. *Psycho-Oncology, 13*, 147–160. doi:10.1002/pon.794
- Caissie, A., Culleton, S., Nguyen, J., Zhang, L., Zeng, L., Holden, L., . . . Chow, E. (2012). EORTC QLQ-C15-PAL quality of life scores in patients with advanced cancer referred for palliative radiotherapy. *Supportive Care in Cancer, 20*, 841–848.

- Carney, S., Koettters, T., Cho, M., West, C., Paul, S.M., Dunn, L., . . . Miaskowski, C. (2011). Differences in sleep disturbance parameters between oncology outpatients and their family caregivers. *Journal of Clinical Oncology*, *29*, 1001–1006.
- Chen, M.L., Chu, L., & Chen, H.C. (2004). Impact of cancer patients' quality of life on that of spouse caregivers. *Supportive Care in Cancer*, *12*, 469–475. doi:10.1007/s00520-004-0636-z
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.
- Colotta, F., Re, F., Muzio, M., Bertini, R., Polentarutti, N., Sironi, M., . . . Mantovani, A. (1993). Interleukin-1 type II receptor: A decoy target for IL-1 that is regulated by IL-4. *Science*, *261*, 472–475.
- Costanzo, E.S., Lutgendorf, S.K., Mattes, M.L., Trehan, S., Robinson, C.B., Tewfik, F., & Roman, S.L. (2007). Adjusting to life after treatment: Distress and quality of life following treatment for breast cancer. *British Journal of Cancer*, *97*, 1625–1631. doi:10.1038/sj.bjc.6604091
- Desai, M.J., Kim, A., Fall, P.C., & Wang, D. (2007). Optimizing quality of life through palliative care. *Journal of the American Osteopathic Association*, *107*(12, Suppl. 7), ES9–ES14.
- Deshields, T.L., Potter, P., Olsen, S., Liu, J., & Dye, L. (2011). Documenting the symptom experience of cancer patients. *Journal of Supportive Oncology*, *9*, 216–223.
- Deshpande, A. D., Sefko, J. A., Jeffe, D. B., & Schootman, M. (2011). The association between chronic disease burden and quality of life among breast cancer survivors in Missouri. *Breast Cancer Research and Treatment*, *129*, 877–886. doi:10.1007/s10549-011-1525-z
- Dhruva, A., Aouizerat, B.E., Cooper, B., Paul, S.M., Dodd, M., West, C., . . . Miaskowski, C. (2013). Differences in morning and evening fatigue in oncology patients and their family caregivers. *European Journal of Oncology Nursing*, *17*, 841–848. doi:10.1016/j.ejon.2013.06.002
- Dhruva, A., Lee, K., Paul, S.M., West, C., Dunn, L., Dodd, M., . . . Miaskowski, C. (2012). Sleep-wake circadian activity rhythms and fatigue in family caregivers of oncology patients. *Cancer Nursing*, *35*(1), 70–81. doi:10.1097/NCC.0b013e3182194a25
- Dieperink, K.B., Hansen, S., Wagner, L., Johansen, C., Andersen, K.K., & Hansen, O. (2012). Living alone, obesity and smoking: Important factors for quality of life after radiotherapy and androgen deprivation therapy for prostate cancer. *Acta Oncology*, *51*, 722–729. doi:10.3109/0284186X.2012.682627
- Dodd, M.J., Cho, M.H., Cooper, B.A., Petersen, J., Bank, K.A., Lee, K.A., & Miaskowski, C. (2011). Identification of latent classes in patients who are receiving biotherapy based on symptom experience and its effect on functional status and quality of life. *Oncology Nursing Forum*, *38*, 33–42.
- Dodd, M.J., Miaskowski, C., & Paul, S.M. (2001). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum*, *28*, 465–470.
- Dunn, J., Ng, S.K., Breitbart, W., Aitken, J., Youl, P., Baade, P.D., & Chambers, S.K. (2013). Health-related quality of life and life satisfaction in colorectal cancer survivors: Trajectories of adjustment. *Health and Quality of Life Outcomes*, *11*(1), 46.
- Dunn, L.B., Aouizerat, B.E., Langford, D.J., Cooper, B.A., Dhruva, A., Cataldo, J.K., . . . Miaskowski, C. (2013). Cytokine gene variation is associated with depressive symptom trajectories in oncology patients and family caregivers. *European Journal of Oncology Nursing*, *17*, 346–353. doi:10.1016/j.ejon.2012.10.004
- Eisemann, M., & Lalos, A. (1999). Psychosocial determinants of well-being in gynecologic cancer patients. *Cancer Nursing*, *22*, 303–306.
- Esther Kim, J.E., Dodd, M.J., Aouizerat, B.E., Jahan, T., & Miaskowski, C. (2009). A review of the prevalence and impact of multiple symptoms in oncology patients. *Journal of Pain and Symptom Management*, *37*, 715–736.
- Ferrell, B.R. (1995). The impact of pain on quality of life: A decade of research. *Nursing Clinics of North America*, *30*, 609–624.
- Ferrell, B.R., Dow, K.H., & Grant, M. (1995). Measurement of the quality of life in cancer survivors. *Quality of Life Research*, *4*, 523–531.
- Ferrell, B.R., Dow, K.H., Leigh, S., Ly, J., & Gulasekaram, P. (1995). Quality of life in long-term cancer survivors. *Oncology Nursing Forum*, *22*, 915–922.
- Fletcher, B.S., Paul, S.M., Dodd, M.J., Schumacher, K., West, C., Cooper, B., . . . Miaskowski, C.A. (2008). Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. *Journal of Clinical Oncology*, *26*, 599–605.
- Gabriel, S.B., Schaffner, S.F., Nguyen, H., Moore, J.M., Roy, J., Blumenstiel, B., . . . Altshuler, D. (2002). The structure of haplotype blocks in the human genome. *Science*, *296*, 2225–2229. doi:10.1126/science.1069424
- Granda-Cameron, C., Viola, S.R., Lynch, M.P., & Polomano, R.C. (2008). Measuring patient-oriented outcomes in palliative care: Functionality and quality of life. *Clinical Journal of Oncology Nursing*, *12*, 65–77. doi:10.1188/08.CJON.65-77
- Gwede, C.K., Small, B.J., Munster, P.N., Andrykowski, M.A., & Jacobsen, P.B. (2008). Exploring the differential experience of breast cancer treatment-related symptoms: A cluster analytic approach. *Supportive Care in Cancer*, *16*, 925–933. doi:10.1007/s00520-007-0364-2
- Hagedoorn, M., Buunk, B.P., Kuijjer, R.G., Wobbles, T., & Sanderman, R. (2000). Couples dealing with cancer: Role and gender differences regarding psychological distress and quality of life. *Psycho-Oncology*, *9*, 232–242.
- Halder, I., Shriver, M., Thomas, M., Fernandez, J.R., & Frudakis, T. (2008). A panel of ancestry informative markers for estimating individual biogeographical ancestry and admixture from four continents: Utility and applications. *Human Mutation*, *29*, 648–658. doi:10.1002/humu.20695
- Hattersley, A.T., & McCarthy, M.I. (2005). What makes a good genetic association study? *Lancet*, *366*, 1315–1323.
- Helgeson, V.S., Snyder, P., & Seltman, H. (2004). Psychological and physical adjustment to breast cancer over 4 years: Identifying distinct trajectories of change. *Health Psychology*, *23*, 3–15. doi:10.1037/0278-6133.23.1.3
- Hoggart, C.J., Parra, E.J., Shriver, M.D., Bonilla, C., Kittles, R.A., Clayton, D.G., & McKeigue, P.M. (2003). Control of confounding of genetic associations in stratified populations. *American Journal of Human Genetics*, *72*, 1492–1504.
- Illi, J., Miaskowski, C., Cooper, B., Levine, J.D., Dunn, L., West, C., . . . Aouizerat, B.E. (2012). Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. *Cytokine*, *58*, 437–447. doi:10.1016/j.cyto.2012.02.015
- Jung, T., & Wickrama, K.A.S. (2008). An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass*, *2*(1), 302–317.
- Karnofsky, D., Abelmann, W.H., Craver, L.V., & Burchenal, J.H. (1948). The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer*, *1*, 634–656.
- Kent, W.J., Sugnet, C.W., Furey, T.S., Roskin, K.M., Pringle, T.H., Zahler, A.M., & Haussler, D. (2002). The human genome browser at UCSC. *Genome Research*, *12*, 996–1006. doi:10.1101/gr.229102
- Kim, Y., & Given, B.A. (2008). Quality of life of family caregivers of cancer survivors: Across the trajectory of the illness. *Cancer*, *112*(11, Suppl.), 2556–2568. doi:10.1002/cncr.23449
- Kitrungrate, L., & Cohen, M.Z. (2006). Quality of life of family caregivers of patients with cancer: A literature review. *Oncology Nursing Forum*, *33*, 625–632. doi:10.1188/06.ONF.625-632
- Knight, S.J., Latini, D.M., Hart, S.L., Sadetsky, N., Kane, C.J., DuChane, J., & Carroll, P.R. (2007). Education predicts quality of life among men with prostate cancer cared for in the Department of Veterans Affairs: A longitudinal quality of life analysis from CaP-SURE. *Cancer*, *109*, 1769–1776. doi:10.1002/cncr.22597
- Kwan, M.L., Ergas, I.J., Somkin, C.P., Quesenberry, C.P., Jr., Neugut, A.I., Hershman, D.L., . . . Kushi, L.H. (2010). Quality of life among women recently diagnosed with invasive breast cancer: The Pathways Study. *Breast Cancer Research and Treatment*, *123*, 507–524. doi:10.1007/s10549-010-0764-8
- Lam, W.W., Ye, M., & Fielding, R. (2012). Trajectories of quality of life among Chinese patients diagnosed with nasopharyngeal cancer. *PLoS ONE*, *7*(9), e44022. doi:10.1371/journal.pone.0044022

- Lien, K., Zeng, L., Zhang, L., Nguyen, J., Di Giovanni, J., Popovic, M., . . . Chow, E. (2012). Predictive factors for well-being in advanced cancer patients referred for palliative radiotherapy. *Clinical Oncology, 24*, 443–451.
- Luckett, T., Goldstein, D., Butow, P.N., Gebiski, V., Aldridge, L.J., McGrane, J., . . . King, M.T. (2011). Psychological morbidity and quality of life of ethnic minority patients with cancer: A systematic review and meta-analysis. *Lancet Oncology, 12*, 1240–1248. doi:10.1016/S1470-2045(11)70212-1
- Maunakea, A.K., Nagarajan, R.P., Bilenky, M., Ballinger, T.J., D'Souza, C., Fouse, S.D., . . . Costello, J.F. (2010). Conserved role of intragenic DNA methylation in regulating alternative promoters. *Nature, 466*, 253–257. doi:10.1038/nature09165
- McCann, B., Miaskowski, C., Koetters, T., Baggott, C., West, C., Levine, J.D., . . . Aouizerat, B.E. (2012). Associations between pro- and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery. *Journal of Pain, 13*, 425–437.
- Mehnert, A., Lehmann, C., Graefen, M., Huland, H., & Koch, U. (2010). Depression, anxiety, post-traumatic stress disorder and health-related quality of life and its association with social support in ambulatory prostate cancer patients. *European Journal of Cancer Care, 19*, 736–745. doi:10.1111/j.1365-2354.2009.01117.x
- Merriman, J.D., Aouizerat, B.E., Langford, D.J., Cooper, B.A., Baggott, C.R., Cataldo, J.K., . . . Miaskowski, C. (2014). Preliminary evidence of an association between an interleukin 6 promoter polymorphism and self-reported attentional function in oncology patients and their family caregivers. *Biological Research in Nursing, 16*, 152–159.
- Miaskowski, C., Cooper, B.A., Dhruva, A., Dunn, L.B., Langford, D.J., Cataldo, J.K., . . . Aouizerat, B.E. (2012). Evidence of associations between cytokine genes and subjective reports of sleep disturbance in oncology patients and their family caregivers. *PLoS ONE, 7*(7), e40560. doi:10.1371/journal.pone.0040560
- Miaskowski, C., Dodd, M., Lee, K., West, C., Paul, S.M., Cooper, B.A., . . . Aouizerat, B.E. (2010). Preliminary evidence of an association between a functional interleukin-6 polymorphism and fatigue and sleep disturbance in oncology patients and their family caregivers. *Journal of Pain and Symptom Management, 40*, 531–544.
- Miaskowski, C., Lee, K., Dunn, L., Dodd, M., Aouizerat, B.E., West, C., . . . Swift, P. (2011). Sleep-wake circadian activity rhythm parameters and fatigue in oncology patients before the initiation of radiation therapy. *Cancer Nursing, 34*, 255–268. doi:10.1097/NCC.0b013e3181f65d9b
- Montazeri, A. (2008). Health-related quality of life in breast cancer patients: A bibliographic review of the literature from 1974 to 2007. *Journal of Experimental and Clinical Cancer Research, 27*, 32. doi:10.1186/1756-9966-27-32
- Movsas, B., Scott, C., & Watkins-Bruner, D. (2006). Pretreatment factors significantly influence quality of life in cancer patients: A Radiation Therapy Oncology Group (RTOG) analysis. *International Journal of Radiation Oncology, Biology, and Physics, 65*, 830–835.
- Muthen, B., & Muthen, L.K. (2000). Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. *Alcohol Clinical and Experimental Research, 24*, 882–891.
- Muthen, B.O., & Kaplan, D.W. (2004). Latent variable analysis: Growth mixture modeling and related techniques for longitudinal data. In D. Kaplan (Ed.), *The Sage handbook of quantitative methodology for the social sciences* (pp. 345–368). Newbury Park, CA: Sage.
- Nakki, A., Kouhia, S.T., Saarela, J., Harilainen, A., Tallroth, K., Vide-man, T., . . . Kujala, U.M. (2010). Allelic variants of IL1R1 gene associate with severe hand osteoarthritis. *BMC Medical Genetics, 11*, 50.
- Nes, R.B., Roysamb, E., Tams, K., Harris, J.R., & Reichborn-Kjennerud, T. (2006). Subjective well-being: Genetic and environmental contributions to stability and change. *Psychological Medicine, 36*, 1033–1042. doi:10.1017/S0033291706007409
- Norman, G.R., Sloan, J.A., & Wyrwich, K.W. (2003). Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. *Medical Care, 41*, 582–592.
- Northouse, L.L., Mood, D., Kershaw, T., Schafenacker, A., Mellon, S., Walker, J., . . . Decker, V. (2002). Quality of life of women with recurrent breast cancer and their family members. *Journal of Clinical Oncology, 20*, 4050–4064.
- Nylund, K.L., Asparouhov, T., & Muthen, B.O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural Equation Modeling, 14*, 535–569.
- Osoba, D. (1999). Interpreting the meaningfulness of changes in health-related quality of life scores: Lessons from studies in adults. *International Journal of Cancer, 12*(Suppl.), 132–137.
- Osoba, D., Rodrigues, G., Myles, J., Zee, B., & Pater, J. (1998). Interpreting the significance of changes in health-related quality-of-life scores. *Journal of Clinical Oncology, 16*, 139–144.
- Ostroff, J.S., Krebs, P., Coups, E.J., Burkhalter, J.E., Feinstein, M.B., Steingart, R.M., . . . Park, B.J. (2011). Health-related quality of life among early-stage, non-small cell, lung cancer survivors. *Lung Cancer, 71*, 103–108. doi:10.1016/j.lungcan.2010.04.011
- Padilla, G.V., Ferrell, B., Grant, M.M., & Rhiner, M. (1990). Defining the content domain of quality of life for cancer patients with pain. *Cancer Nursing, 13*, 108–115.
- Padilla, G.V., Present, C., Grant, M.M., Metter, G., Lipsett, J., & Heide, F. (1983). Quality of life index for patients with cancer. *Research in Nursing and Health, 6*, 117–126.
- Paika, V., Almyroudi, A., Tomenson, B., Creed, F., Kampletsas, E.O., Sifaka, V., . . . Hyphantis, T. (2010). Personality variables are associated with colorectal cancer patients' quality of life independent of psychological distress and disease severity. *Psycho-Oncology, 19*, 273–282. doi:10.1002/pon.1563
- Powe, B.D., Hamilton, J., Hancock, N., Johnson, N., Finnie, R., Ko, J., . . . Boggan, M., Jr. (2007). Quality of life of African American cancer survivors: A review of the literature. *Cancer, 109*(2, Suppl.), 435–445. doi:10.1002/cncr.22358
- Price, A.L., Patterson, N.J., Plenge, R.M., Weinblatt, M.E., Shadick, N.A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics, 38*, 904–909.
- Rausch, S.M., Clark, M.M., Patten, C., Liu, H., Felten, S., Li, Y., . . . Yang, P. (2010). Relationship between cytokine gene single nucleotide polymorphisms and symptom burden and quality of life in lung cancer survivors. *Cancer, 116*, 4103–4113. doi:10.1002/cncr.25255
- Rausch, S.M., Gonzalez, B.D., Clark, M.M., Patten, C., Felten, S., Liu, H., . . . Yang, P. (2012). SNPs in PTGS2 and LTA predict pain and quality of life in long term lung cancer survivors. *Lung Cancer, 77*, 217–223. doi:10.1016/j.lungcan.2012.02.017
- Reeve, B.B., Stover, A.M., Jensen, R.E., Chen, R.C., Taylor, K.L., Clauser, S.B., . . . Potosky, A.L. (2012). Impact of diagnosis and treatment of clinically localized prostate cancer on health-related quality of life for older Americans: A population-based study. *Cancer, 118*, 5679–5687. doi:10.1002/cncr.27578
- Reyes-Gibby, C.C., El Osta, B., Spitz, M.R., Parsons, H., Kurzrock, R., Wu, X., . . . Bruera, E. (2008). The influence of tumor necrosis factor-alpha -308 G/A and IL-6 -174 G/C on pain and analgesia response in lung cancer patients receiving supportive care. *Cancer Epidemiology, Biomarkers and Prevention, 17*, 3262–3267.
- Reyes-Gibby, C.C., Shete, S., Yennurajalingam, S., Frazier, M., Bruera, E., Kurzrock, R., . . . Spitz, M.R. (2009). Genetic and nongenetic covariates of pain severity in patients with adenocarcinoma of the pancreas: Assessing the influence of cytokine genes. *Journal of Pain and Symptom Management, 38*, 894–902.
- Reyes-Gibby, C.C., Spitz, M., Wu, X., Merriman, K., Etsel, C., Bruera, E., . . . Shete, S. (2007). Cytokine genes and pain severity in lung cancer: Exploring the influence of TNF-alpha-308 G/A IL6-174G/C and IL8-251T/A. *Cancer Epidemiology, Biomarkers and Prevention, 16*, 2745–2751.
- Reyes-Gibby, C.C., Spitz, M.R., Yennurajalingam, S., Swartz, M., Gu, J., Wu, X., . . . Shete, S. (2009). Role of inflammation gene polymorphisms on pain severity in lung cancer patients. *Cancer Epidemiology, Biomarkers and Prevention, 18*, 2636–2642.
- Reyes-Gibby, C.C., Wang, J., Spitz, M., Wu, X., Yennurajalingam, S., &

- Shete, S. (2013). Genetic variations in interleukin-8 and interleukin-10 are associated with pain, depressed mood, and fatigue in lung cancer patients. *Journal of Pain and Symptom Management, 46*, 161–172. doi:10.1016/j.jpainsymman.2012.07.019
- Romeis, J.C., Heath, A.C., Xian, H., Eisen, S.A., Scherrer, J.F., Pedersen, N.L., . . . True, W.R. (2005). Heritability of SF-36 among middle-age, middle-class, male-male twins. *Medical Care, 43*, 1147–1154.
- Romeis, J.C., Scherrer, J.F., Xian, H., Eisen, S.A., Bucholz, K., Heath, A.C., . . . True, W.R. (2000). Heritability of self-reported health. *Health Services Research, 35*(5, Pt. 1), 995–1010.
- Rothman, K.J. (1990). No adjustments are needed for multiple comparisons. *Epidemiology, 1*(1), 43–46.
- Schmitz, M.L., Mattioli, I., Buss, H., & Kracht, M. (2004). NF-kappaB: A multifaceted transcription factor regulated at several levels. *Chembiochem, 5*, 1348–1358. doi:10.1002/cbic.200400144
- Schwartz, C.E., & Sprangers, M.A. (1999). Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. *Social Science and Medicine, 48*, 1531–1548.
- Seruga, B., Zhang, H., Bernstein, L.J., & Tannock, I.F. (2008). Cytokines and their relationship to the symptoms and outcome of cancer. *Nature Reviews. Cancer, 8*, 887–899.
- Singh, J., Trabulsi, E.J., & Gomella, L.G. (2010). The quality-of-life impact of prostate cancer treatments. *Current Urology Reports, 11*, 139–146. doi:10.1007/s11934-010-0103-y
- Sprangers, M.A., Sloan, J.A., Veenhoven, R., Cleeland, C.S., Halyard, M.Y., Abertnethy, A.P., . . . Zwiderman, A.H. (2009). The establishment of the GENEQOL consortium to investigate the genetic disposition of patient-reported quality-of-life outcomes. *Twin Research and Human Genetics, 12*, 301–311. doi:10.1375/twin.12.3.301
- Tian, C., Gregersen, P.K., & Seldin, M.F. (2008). Accounting for ancestry: Population substructure and genome-wide association studies. *Human Molecular Genetics, 17*(R2), R143–R150.
- Tofighi, D., & Enders, C.K. (2008). *Identifying the correct number of classes in growth mixture models*. Charlotte, NC: Information Age.
- Trask, P.C., Hsu, M.A., & McQuellon, R. (2009). Other paradigms: Health-related quality of life as a measure in cancer treatment—Its importance and relevance. *Cancer Journal, 15*, 435–440. doi:10.1097/PPO.0b013e3181b9c5b9
- Zenger, M., Lehmann-Laue, A., Stolzenburg, J.U., Schwalenberg, T., Ried, A., & Hinz, A. (2010). The relationship of quality of life and distress in prostate cancer patients compared to the general population. *Psycho-Social Medicine, 7*, Doc02. doi:10.3205/psm000064