Title

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Journal

Journal of pain and symptom management, 55(2)

ISSN

0885-3924

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Publication Date

2018-02-01

DOI

10.1016/j.jpainsymman.2017.09.020

Peer reviewed

HHS Public Access

Author manuscript

J Pain Symptom Manage. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

J Pain Symptom Manage. 2018 February ; 55(2): 334–350.e3. doi:10.1016/j.jpainsymman.2017.09.020.

CYTOKINE GENE POLYMORPHISMS ASSOCIATED WITH VARIOUS DOMAINS OF QUALITY OF LIFE IN WOMEN WITH BREAST CANCER

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Abstract

Context—Little is known about the phenotypic and molecular characteristics associated with various domains of quality of life (QOL) in women following breast cancer surgery.

Objectives—In a sample of women with breast cancer (n= 398), purposes were: to identify latent classes with distinct trajectories of QOL from prior to through six months following surgery and to evaluate for differences in demographic and clinical characteristics, as well as for polymorphisms in cytokine genes, between these latent classes.

Methods—Latent class analyses were done to identify subgroups of patients with distinct QOL outcomes. Candidate gene analyses were done to identify cytokine gene polymorphisms associated with various domains of QOL (i.e., physical, psychological, spiritual, social).

Results—One latent class was identified for the psychological and spiritual domains. Two latent classes were identified for the social domain and overall QOL scores. Three latent classes were identified for the physical domain. For the physical and social domains, as well as for the overall QOL scores, distinct phenotypic characteristics (i.e., younger age, poorer functional status, higher body mass index, and receipt of adjuvant chemotherapy) and a number of cytokine gene polymorphisms (*CXCL8*, *NFKB2*, *TNFSF*, *IL1B*, *IL13*, and *NFKB1*) were associated with membership in the lower QOL classes.

Conclusions—Findings suggest that women experience distinctly different physical well-being, social well-being, and total QOL outcomes during and following breast cancer surgery. The

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genetic associations identified suggest that cytokine dysregulation influences QOL outcomes. However, specific QOL domains may be impacted by different cytokines.

Keywords

quality of life; cytokine genes; breast cancer; polymorphism; growth mixture modeling

INTRODUCTION

While a number of reviews noted that some women report poorer quality of life (QOL) following breast cancer surgery, findings across studies are inconsistent.[1–3] A number of explanations exist for these inconsistent findings. First, while researchers accept that a comprehensive evaluation of QOL should include the assessment of multiple domains,[4] the QOL instruments used across studies are extremely variable.[5] Second, the timing of the QOL assessments were not consistent which makes it difficult to determine the impact of specific treatments on breast cancer patients' QOL. Third, most longitudinal studies of QOL in breast cancer patients reported mean scores which do not allow for an evaluation of inter-individual variability in the various domains of QOL.

Despite the fact that numerous studies have evaluated QOL in patients with breast cancer,[1–3] little information is available on phenotypic characteristics that predict QOL outcomes in the first six months following breast cancer surgery. In the only two studies identified,[6,7] poorer overall QOL scores for up to two years following breast cancer surgery were associated with a number of demographic (e.g., not having a partner at the time of surgery[6]); psychological (e.g., higher levels of mood disturbance,[7] anxiety and depression,[6] poorer body image[7]); and clinical (e.g., higher number of comorbid conditions,[6] receipt of adjuvant chemotherapy (CTX),[6] higher number of positive lymph nodes[6,7]) characteristics.

Only one study was found that evaluated for phenotypic characteristics associated with specific domains of QOL.[8] In this study, that evaluated patients prior to and at three and twelve months after breast cancer surgery, older age was associated with improved social and psychological well-being but with poorer physical well-being. In addition, higher education was associated with higher psychological well-being. Given that QOL is such an important patient-reported outcome,[9] additional research is needed to determine which phenotypic characteristics are associated with poorer outcomes across multiple domains of QOL.

Recent evidence suggests that 11% to 35% of QOL is heritable.[10] As noted in one review,[11] polymorphisms in inflammatory, dopaminergic, serotonergic, neurotrophin signalling, and neuroactive ligand-receptor interaction pathways were associated with changes in QOL. While some pathways were associated with specific QOL domains (e.g., dopaminergic pathway genes and emotional functioning), others (e.g., inflammation) were linked to changes in multiple domains of QOL. While the exact mechanisms by which polymorphisms in inflammatory genes contribute to inter-individual variability in QOL are unknown, inflammation may influence the severity of symptoms experienced by cancer patients, which in turn impacts functional status and QOL.[12]

While no studies evaluated for associations between QOL and genetic variants in breast cancer patients, five studies have reported on associations between a number of polymorphisms in inflammatory pathways (i.e., cytokines) and QOL in cancer patients.[13–17] In a study of lung cancer survivors,[14] variations in a number of cytokine genes were associated with changes in physical functioning (i.e., *interleukin* (*IL) 1B*, *IL10*, *IL1 receptor antagonist (IL1RN)*), mental health (*IL1RN*), emotional role functioning (*IL6*), and social functioning (*IL6*, *IL1RN*, *tumor necrosis factor super family* (*TNFSF*)). In a separate study of the same cohort,[15] three single nucleotide polymorphisms (SNPs) (rs3858300, rs10741191, and rs10741191) in the *O-6-methylguanine-deoxyribonucleic acid* (DNA) *methyltransferase (MGMT)* gene were associated with a 34%, 36%, and 30% increased risk of lower QOL scores, respectively. In separate analyses of the same cohort,[13] carrying one or two doses of the rare "G" alleles for *prostaglandin-endoperoxide synthase 2* (*PTGS2)* rs5277 and rs5275 were associated with lower social function and mental health scores, respectively.

In our previous studies,[16,17] subgroups of oncology patients and their family caregivers (FCs) with distinct QOL trajectories were identified. In terms of social well-being,[17] individuals who were heterozygous or homozygous for the rare "G" allele for nuclear factor kappa beta 2 (*NFKB2)* rs7897947 had a 54% decrease in the odds of belonging in the lower social well-being class. In terms of overall QOL,[16] individuals who were heterozygous or homozygous for the rare "C" allele for *IL1R2* rs4141134 had a 64% decrease in the odds of belonging to the Lower total QOL class. In contrast, individuals who were homozygous for the rare "G" allele for *NFKB2* rs12772374 were 47.7 times more likely to belong to the lower total QOL class. All five studies provide preliminary evidence of associations between genetic polymorphisms and QOL outcomes.[13–17] However, additional studies of oncology patients are needed to confirm these associations Therefore, the purposes of this study, in a sample of women with breast cancer (n= 398), were: to identify latent classes with distinct trajectories of QOL from prior to through six months following surgery and to evaluate for differences in demographic and clinical characteristics, as well as for polymorphisms in cytokine genes, between these latent classes.

MATERIALS AND METHODS

Patients and Settings

This analysis is part of a larger, longitudinal study whose methods are described in detail elsewhere.[18–21] Women were eligible to participate if they: were ≥18 years; were scheduled to undergo unilateral breast cancer surgery; were able to read, write, and understand English; and gave written informed consent. Patients were excluded if they were having bilateral breast cancer surgery or had distant metastasis at the time of diagnosis.

Instruments

Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale[22] and the Self-Administered Comorbidity Questionnaire (SCQ).[23] QOL was evaluated using the Quality of Life-Scale-Patient Version (QOL-PV).[24,25] The QOL-PV consists of 41 items that measure four domains of QOL in cancer patients (i.e., physical well-being,

psychological well-being, social well-being, spiritual well-being). Items are rated on a 0 to 10 numeric rating scale. Patients were asked to rate each item based on their life "at this time". Mean subscale and total scores were calculated. Higher scores indicate better QOL. The QOL-PV has well established validity and reliability.[24,25] Cronbach's alphas for the QOL-PV physical well-being, psychological well-being, social well-being, and spiritual well-being, as well as the total QOL score, were: .80, .86, .80, .63, and .86, respectively.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. During the preoperative visit, a clinician explained the study; determined the patient's willingness to participate; and introduced her to the research nurse. The research nurse met with the woman, determined eligibility, and obtained written informed consent prior to surgery. After obtaining consent, patients completed the enrollment questionnaires an average of 4 days prior to surgery. Patients completed the QOL-PV at enrollment and monthly for 6 months (i.e., 7 assessments). Medical records were reviewed for disease and treatment information.

Genomic analyses

Gene selection—The pro-inflammatory genes evaluated in this study were: *chemokine* (C-C-C motif) *ligand 8* (*CXCL8*, previous gene symbol *IL8)*, *interferon gamma* (*IFNG*), *IFNGR1*, *IL1R1*, *IL2*, *IL17A*, and members of the *TNF* family (i.e., lymphotoxin alpha (*LTA*), *TNF*). The anti-inflammatory genes were: *IL1R2*, *IL4*, *IL10*, and *IL13*. In addition, *IFNG1*, *IL1B*, and *IL6* possess pro- and anti-inflammatory functions and *NFKB1* and *NFKB2* that regulate transcription of cytokine genes were evaluated.[26] All genes were named using the Human Genome Organization (HUGO) Gene Nomenclature Committee (HGNC) database (http://www.genenames.org).

Blood collection and genotyping—Of the 398 patients who completed the enrollment assessment, 310 provided a blood sample from which DNA was isolated from peripheral blood mononuclear cells (PBMCs). Genomic DNA was extracted from PBMCs using the PUREGene DNA Isolation System (Invitrogen, Carlsbad, CA), quantitated using Nanodrop Spectrophotometer (ND-1000), and normalized to a concentration of 50 nanograms/microliter (ng/L). Samples were genotyped using a custom array on the Golden Gate genotyping platform (Illumina, San Diego, CA) and processed according to the standard protocol using GenomeStudio (Illumina, San Diego, CA).

SNP selection—SNPs were required to be common (i.e., a minor allele frequency ≥0.05) in public databases. SNPs with call rates of <95% or Hardy-Weinberg p-values of <.001 were excluded. As shown in Supplementary Table 1, 81 SNPs from a total of 104 SNPs among 15 candidate genes passed all of the quality control filters and were included in the genetic association analyses. Potential regulatory involvement of the significant SNPs identified in this analysis were investigated using SNPinfo (FuncPred, http://www.niehs.nih.gov/snpinfo).[27]

Statistical Analyses for the Phenotypic Data

Data were analyzed using SPSS version 23[28] and STATA Version 13.[29] Descriptive statistics and frequency distributions were generated for sample characteristics. Parametric and non parametric tests were used to evaluate for differences in demographic and clinical characteristics among the latent classes. A p-value of <0.05 was considered statistically significant.

Unconditional growth mixture modelling (GMM) with robust maximum likelihood estimation was carried out to identify latent classes with distinct QOL trajectories using Mplus Version 5.21. These methods are described in detail elsewhere.[21] In brief, a single growth curve that represented the "average" change trajectory was estimated for the entire sample. Then, the number of latent growth classes that best fit the data was identified using guidelines recommended in the literature.[30–32]

Statistical Analyses for the Genetic Data

Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg equilibrium was assessed by Chi-square or Fisher Exact tests. Measures of linkage disequilibrium ((LD), i.e., D' and r^2) were computed from the patients' genotypes with Haploview 4.2. The LD-based haplotype block definition was based on D' confidence interval.[33] Haplotypes were constructed using the program PHASE version 2.1.[34] Only inferred haplotypes that occurred with a frequency of >15% were included in the association analyses.

Ancestry informative markers (AIMs) were used to minimize confounding due to population stratification.[35–37] Homogeneity in ancestry among patients was verified by principal component analysis,[38] using HelixTree (GoldenHelix, Bozeman, MT). The first three PCs were selected to adjust for potential confounding due to population substructure (i.e., race/ethnicity) by including them in all of the logistic regression models. One hundred and six AIMs were included in the analysis.

For association tests, three genetic models were assessed for each SNP: additive, dominant, and recessive. The genetic model that best fit the data (i.e., most significant p-value) was selected for each SNP. Logistic regression analyses, that controlled for significant covariates, as well as genomic estimates of and self-reported race/ethnicity, were used to evaluate the associations between genotype and QOL class membership. Only those genetic associations identified as significant from the bivariate analyses were evaluated in the multivariate analyses. A backwards stepwise approach was used to create a parsimonious model. Except for genomic estimates of and self-reported race/ethnicity, only predictors with a p-value of <.05 were retained in the final model. Genetic model fit and both unadjusted and covariate-adjusted odds ratios were estimated using STATA version 13.[29]

As was done in our previous studies,[18,20,39–52] based on the recommendations in the literature,[53,54] as well as the implementation of rigorous quality controls for genomic data, the non-independence of SNPs/haplotypes in LD, and the exploratory nature of the analyses, adjustments were not made for multiple testing. In addition, significant SNPs identified in the bivariate analyses were evaluated further using logistic regression analyses that

controlled for differences in phenotypic characteristics, potential confounding due to population stratification, and variations in other SNPs/haplotypes within the same gene. Only those SNPs that remained significant were included in the final presentation of the results. Therefore, the significant independent associations reported are unlikely to be due solely to chance. Unadjusted (bivariate) associations are reported for all of the SNPs that passed quality control criteria in Supplementary Table 1, to allow for subsequent comparisons and meta-analyses.

RESULTS

GMM Analyses

The fit indices used for GMM class selection are listed in Table 1. The parameter estimates for the identified classes are listed in Table 2. For physical well-being, three classes were identified (Figure 1A). For psychological well-being, a one-class solution was selected because a model with a larger number of classes was not supported (data not shown; Figure 1B). The mean psychological well-being score at enrollment was 5.76 (±1.82). This score increased slightly over time. For social well-being, two classes were identified (Figure 1C). For spiritual well-being, a one-class solution was selected because a model with a larger number of classes was not supported (data not shown; 1D). The mean spiritual well-being score at enrollment was 5.72 (±1.84). These scores remained relatively stable over time. For the total QOL scores, two classes were identified (Figure 1E).

Physical well-being

For physical well-being, the largest group of patients was named the Higher physical well-being class (n=207, 52.4%). These patients had a mean score prior to surgery of 8.931 (±0.729) and their scores remained relatively stable overtime. The second largest group was named the Lower physical well-being class (n=112, 28.4%) who had a mean enrollment score of 6.220 (±1.588) that remained relatively stable overtime. The third group was named the Changing physical well-being class (n=76, 19.2%). These patients had a mean enrollment score of 8.070 (±1.172). Their mean scores decreased to 5.767 (±1.266) at three months and then increased to 7.382 (±1.126) at six months following surgery.

Compared to the Higher class, patients in the Changing and Lower physical well-being classes were younger; were more likely to have had an axillary lymph node dissection (ALND) and to have received adjuvant CTX; and were less likely to have gone through menopause (Table 3). Compared to the Higher and Changing classes, patients in the Lower physical well-being class had a lower KPS score. Compared to the Higher class, patients in the Lower physical well-being class had a higher SCQ score; a higher body mass index (BMI); and were less likely to be White; and were less likely to have received adjuvant radiation therapy (RT). Compared to the Changing class, patients in the lower physical well-being class were more likely to have a lower income, have a higher stage of disease at the time of diagnosis, and had received neoadjuvant CTX, and less likely to have received adjuvant CTX. Compared to the Higher class, patients in the Changing class were less likely to have received RT in the six months following surgery.

Social well-being

For social well-being, one group of patients was named the Higher social well-being class (n=212, 53.8%), they had a mean enrollment score of 8.099 (±1.196) and their mean scores were relatively stable overtime. The second subgroup was named the Lower social well-being class (n=182, 46.2%). They had a mean enrollment score of 5.604 (±1.905) and their scores decreased slightly overtime.

Compared to the Higher social well-being class, patients in the Lower class were younger; less likely to be White; had a lower KPS score; and were less likely to have gone through menopause. In addition, patients in the Lower social well-being class had a higher stage of disease at diagnosis, more likely to have received neoadjuvant CTX, more likely to have had an ALND, less likely to have received adjuvant RT, and more likely to have received adjuvant CTX.

Total QOL

For total QOL, one class was named the Higher total QOL class (n=169, 42.7%). These patients had a mean enrollment score of 7.054 (±1.074) and their scores increased slightly over time. A second group was named the Lower total QOL class (n=227, 57.3%). These patients had a mean enrollment score of 5.983 (±1.318) and their scores decreased slightly overtime.

Compared to the Higher total QOL class, patients in the Lower class were significantly younger, had a lower KPS score, and were less likely to have gone through menopause. In addition, patients in the Lower class had a higher stage of disease at diagnosis, were more likely to have had an ALND, were less likely to have received adjuvant CTX, and were more likely to have received adjuvant RT.

Candidate Gene Analyses

Candidate gene analyses are summarized in Supplementary Table 1.

Physical well-being

In the ordinal logistic regression analyses for physical well-being, after controlling for age, KPS score, BMI, receipt of CTX during the six months after surgery (i.e., adjuvant CTX), as well as self-reported and genomic estimates of race/ethnicity, and other significant variants in the same gene, only the models fit for *CXCL8* rs4073, *NFKB2* rs11574849, and *TNFSF* rs1800683 remained significant. Pairwise comparisons revealed that the relationship between subgroup membership and the *CXCL8* genotype was due to differences in genotype frequencies between the Higher versus Changing physical well-being class (p = .002, Table 4, Figure 2A). Patients who were homozygous for the rare “A” allele had an 80% decrease in the odds of belonging to the Changing physical well-being class.

For *NFKB2* rs11574849, pairwise comparisons revealed that the relationship between subgroup membership and genotype was due to differences in genotype frequencies between the Changing versus the Lower physical well-being classes (p = .016, Table 4, Figure 2B).

Patients who were heterozygous or homozygous for the rare “A” allele had a 76% decrease in the odds of belonging to the Lower physical well-being class.

For *TNFSF* rs1800683, pairwise comparisons revealed that the relationship between subgroup membership and genotype was due to differences in the genotype frequencies between the Changing versus the Lower physical well-being classes (p = .013, Table 4, Figure 2C). Patients who were heterozygous or homozygous for the rare “A” allele had a 2.73 increased odds of belonging to the Lower physical well-being class.

Social well-being

In the regression analyses, after controlling for age, KPS score, receipt of adjuvant CTX, as well as self-reports and genomic estimates of race/ethnicity and other significant covariates in the same gene, the model fit for *IL1B* rs1143623 remained significant. Patients who were heterozygous or homozygous for the rare “C” allele had a 1.94 increased odds of belonging to the Lower social well-being class (p = .018, Table 5, Figure 3A).

Total QOL

In the regression analyses for total QOL, after controlling for age, KPS score, receipt of adjuvant CTX, as well as self-reports and genomic estimates of race/ethnicity and other significant variations in the same gene, the models fit for *IL13* rs1881457 and *NFKB1* rs4648068 remained significant. Patients who were heterozygous or homozygous for the rare “C” allele for *IL13* rs1881457 had a 1.78 increased odds of belonging to the Lower total QOL class (p = .033, Table 6, Figure 3B). Patients who were homozygous for the rare “G” allele for *NFKB1* rs4648068 had a 3.12 increased odds of belonging to the Lower total QOL class (p = .005, Table 6, Figure 3C).

DISCUSSION

This study is the first to use GMM to identify subgroups of women who reported distinct trajectories for physical well-being, social well-being, and overall QOL prior to and for six months following breast cancer surgery. In addition, this study is the first to evaluate for demographic and clinical characteristics, as well as for variations in cytokine genes, that were associated with poorer outcomes across these QOL domains. In terms of physical well-being, three classes (i.e., Higher, Changing and Lower) were identified. For social well-being and overall QOL, two classes (i.e., Higher and Lower) were identified. Only one class was identified for the psychological well-being and spiritual well-being. In the only study that used GMM to evaluate for distinct QOL trajectories in breast cancer patients who were followed for four years following surgery,[55] four latent classes were identified for both the Physical and Mental component summary scores (i.e., PCS and MCS, respectively) of the SF-36. One consistent finding across both studies was the identification of a group of women with consistently higher physical well-being scores that included approximately 50% of both samples.

While the samples in our study and the previous study[55] were relatively similar, the inconsistent findings related to psychological well-being may be partially explained by differences in the follow-up period. In addition, we used a disease-specific measure of QOL

while the previous study used a generic measure of QOL. Replication of these findings, using both generic and disease-specific measures, is warranted to explore this hypothesis.

Of note, we previously reported four subgroups of patients with different depressive symptom trajectories[21] and two subgroups of patients with different anxiety symptom trajectories[56] in the same cohort of patients. The reason that we did not identify subgroups of patients with distinct trajectories of psychological well-being may be because this subscale of the QOL-PV evaluates other dimensions of psychological well-being (e.g., sense of control, fear of recurrence) that may be of equal concern to all women immediately following breast cancer surgery.

No studies have used the QOL-PV to evaluate QOL in breast cancer patients prior to and following surgery. Most of the previous QOL-PV studies evaluated long-term survivors of breast cancer (i.e., at least five years post treatment).[57–60] Across all of the subscale and total QOL scores in our study, our scores for the various latent classes were in the range of these previous reports. These findings suggest that across the trajectory of treatment for breast cancer and well into survivorship, a considerable amount of inter-individual variability exists across the various QOL domains. The use of latent class analyses in future studies may help to identify higher risk groups.

In our previous studies that used GMM to evaluate various domains and overall QOL of patients undergoing radiation therapy and their FCs,[16,17] we identified two latent classes (i.e., Higher and Lower) for physical well-being, psychological well-being, social well-being, and total QOL scores. The mean scores at enrollment and the trajectories for the Higher physical well-being class, social well-being, and total QOL classes were similar across our two studies. For example, the mean enrollment score (8.919) and trajectory of the Higher physical well-being class in the previous study[17] was similar to that of the current study. In addition, for both studies, only one class was identified for the spiritual well-being domain and the trajectory remained relatively stable overtime. These consistent findings suggest that inter-individual variability in various domains of QOL may be related to factors other than the diagnosis of cancer and the effects of treatment.

Demographic and Clinical Characteristics Associated with Latent Class Memberships

Younger age, poorer functional status, and receipt of adjuvant CTX were the three phenotypic characteristics that remained significant in all the multivariable models. Consistent with previous reports,[61,62] younger women were more likely to be in the worse QOL classes. Perhaps younger cancer patients have more responsibilities[63] and/or experience a higher symptom burden during treatment.[64] However, in two studies of women following breast cancer surgery with a similar age profile,[8,55] older age was associated with Lower physical well-being scores. This inconsistent finding may be related to differences in comorbidities that can affect physical well-being.

Consistent with previous studies,[65,66] lower functional status was associated with membership in the Lower physical and social well-being as well as overall QOL classes. In our study, the mean KPS score for the patients in the lower physical well-being class indicates that they reported ‘some’ signs or symptoms of disease that required effort to carry

on normal activity. In addition, the difference in KPS scores between the two physical well-being classes represents not only a statistically significant but a clinically meaningful difference in this score (i.e., Cohen's d = 0.95).[67] While the differences in KPS scores between the social well-being and total QOL classes were statistically significant, they were not clinically meaningful. These inconsistent findings may be explained by the fact that the overall KPS score for the entire sample was high (i.e., 93.223 (±10.296)). An alternative explanation may be that even small decrements in functional status can have a differential impact on various domains, as well as overall QOL.[68]

Consistent with previous reports,[6,8,69–71] receipt of adjuvant CTX was associated with membership in the lower QOL classes. The higher symptom burden associated with CTX may result in poorer physical and social well-being as well as overall QOL. For example, increased pain during intercourse from vaginal dryness as a side effect of CTX[71] may lead to decreased satisfaction with sex life and decreased support from partners contributing to poorer social well-being.[72]

BMI remained significant in only one of the ordinal logistic regression analyses, namely for physical well-being. Consistent with previous reports,[73,74] compared to the Higher class, patients in the Changing physical well-being class had a higher BMI. While the mean BMIs for both classes are in the 'overweight' category,[75] this finding suggests that even small decreases in BMI may improve the physical well-being of women following breast cancer surgery.

Polymorphims Associated with Latent Class Memberships

This study is the first to evaluate for associations between polymorphisms in cytokine genes and QOL outcomes in women following breast cancer surgery. Of note, across the three QOL outcomes, the genetic associations were completely different. For physical well-being, three genes (i.e., *CXCL8, NFKB2*, *TNFSF*) were associated with membership in lower QOL classes. For *CXCL8* rs4073, patients who were homozygous for the rare "A" allele had a decreased risk of being in the Changing physical well-being class compared to the Higher physical well-being class. According to SNPinfo, this SNP is located in the promoter region of the gene and may alter gene expression by changing transcriptional factor binding sites (TFBS) for transcriptional factors involved in the transcription of DNA into ribonucleic acid (RNA). CXCL8 belongs to a family of chemokines that are responsible for the elimination of pathogens through recruitment and activation of leukocytes during inflammation.[76] Carrying the rare "A" allele for *CXCL8* rs4073 is associated with a variety of conditions including cancer susceptibility,[77–79] infection,[80] and chronic inflammation.[81–83] Consistent with our findings, in a previous study,[84] patients who were homozygous for the rare "A" allele in *CXCL8* rs4073 had a lower risk of CTX toxicities. Perhaps carriers of the rare "A" allele experience fewer symptoms or adverse effects from treatment that contribute to decrements in physical well-being.

For *NFKB2* rs11574849, patients who were homozygous for the rare "A" allele had a decreased risk of being in the Lower physical well-being class than in the Changing class. *NFKB2* encodes for one-half of the NFKB protein, which is a central transcriptional modulator of inflammation.[85] *NFKB2* rs11574849 is located in the intron region of the gene

and has no known function. While no studies were identified that evaluated this SNP, it may be that this SNP is in LD with other functional variants of the same gene.

For *TNFSF* rs1800683, patients who were heterozygous or homozygous for the rare "A" allele had an increased risk of being in the Lower physical well-being class compared to the Changing physical well-being class. *TNFSF* rs1800683 is located in the coding region of the *lymphotoxin-alpha* (*LTA*) gene and is part of the promoter region of *TNFSF*. According to SNPinfo, this SNP may affect *TNFSF* expression by altering TFBS or disrupting messenger RNA (mRNA) splicing and affect LTA protein function. TNFSF and LTA are involved in a broad range of biologic functions including immune responses.[86] Consistent with the findings from this study, the rare "A" allele for *TNFSF* rs1800683 was associated with higher fatigue[87] and wake after sleep onset in adults living with HIV/AIDS,88 and less evening energy in oncology patients and their family caregivers.[43]

Only one SNP was associated with social well-being class membership. For *IL1B* rs1143623, patients who were heterozygous or homozygous for the rare "C" allele had an increased risk of being in the Lower social well-being class. According to SNPinfo, *IL1B* rs1143623 is located in the promoter region of the gene and may alter gene expression by changing TFBS. IL1B is involved in a number of cellular activities including cell proliferation, differentiation, and apoptosis, as well as being an important mediator of acute and chronic inflammatory responses.[89] The rare "C" allele in this SNP was associated with: gout,[90] reduced drug efficacy in type 2 diabetes patients,[91] cancer,[92,93] higher triglycerides and cholesterol,[94] and rheumatoid arthritis.[95] The relationship between this SNP and social well-being requires further exploration. However, the variety in the conditions associated with this SNP highlights the potential widespread involvement of this SNP in cellular activities.

Two SNPs were associated with overall QOL class membership. For *IL13* rs1881457, patients who were heterozygous or homozygous for the rare "C" allele had an increased risk of being in the Lower total QOL class. According to SNPinfo, *IL13* rs1881457 is located in the promoter region of the gene and may alter gene expression by affecting TFBS. Critical to immune responses to allergens, IL13 induces antibody synthesis.[96] In a study of patients with non-small cell lung cancer undergoing CTX,[97] decreased survival and greater disease recurrence were reported in carriers of the rare "C" allele for *IL13* rs1881457. Our finding is partially supported by a review of the literature[98] that highlights the association between poorer QOL scores and poorer survival in cancer patients.

For NFKB1 rs4648068, patients who were homozygous for the rare "G" allele had an increased risk of being in the Lower total QOL class. *NFKB1* rs4648068 is located in the intron region of *NFKB1* and has no known function. In a limited number of studies, rs4648068 was associated with increased risk of ovarian[99] and gastric[100–102] cancer. This study is the first to identify an association between *NFKB1* rs4648068 and outcomes other than cancer risk.

It should be noted that this study's findings and conclusions are preliminary and require replication. The generalizability of our findings is limited to breast cancer patients. Indeed,

none of the cytokine gene associations identified in our previous study of QOL outcomes in oncology patients and their FCs were significant in the current study.[16,17] Reasons for these differences may be related to: differences in participant characteristics such as the inclusion of FCs in the sample and/or differences in the impact or timing of different cancer treatments on QOL outcomes. Lastly, although our sample size was sufficient, larger samples may identify additional latent classes, as well as other phenotypic and genotypic associations.

Conclusions

Findings from this study confirm that women experience distinctly different physical well-being, social well-being, and total QOL outcomes during and following breast cancer surgery. Factors such as younger age, poorer functional status, higher BMI, and receipt of adjuvant CTX may place women at greater risk for poorer QOL. While most of these factors were reported previously, they should be used by clinicians to identify high risk patients prior to surgery. This type of risk profiling may allow for more tailored interventions to support these patients. Furthermore, understanding unique genomic markers would allow for earlier identification of cancer patients at higher risk for poorer QOL outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by grants from the National Cancer Institute (NCI, CA107091 and CA118658). Dr. Christine Miaskowski is an American Cancer Society Clinical Research Professor and is supported by a K05 award from the NCI (CA168960). Dr. Alexander was supported by a Research Career Development Award from the Oncology Nursing Foundation. This project was supported by NIH/NCRR UCSF-CTSI Grant Number UL1 RR024131. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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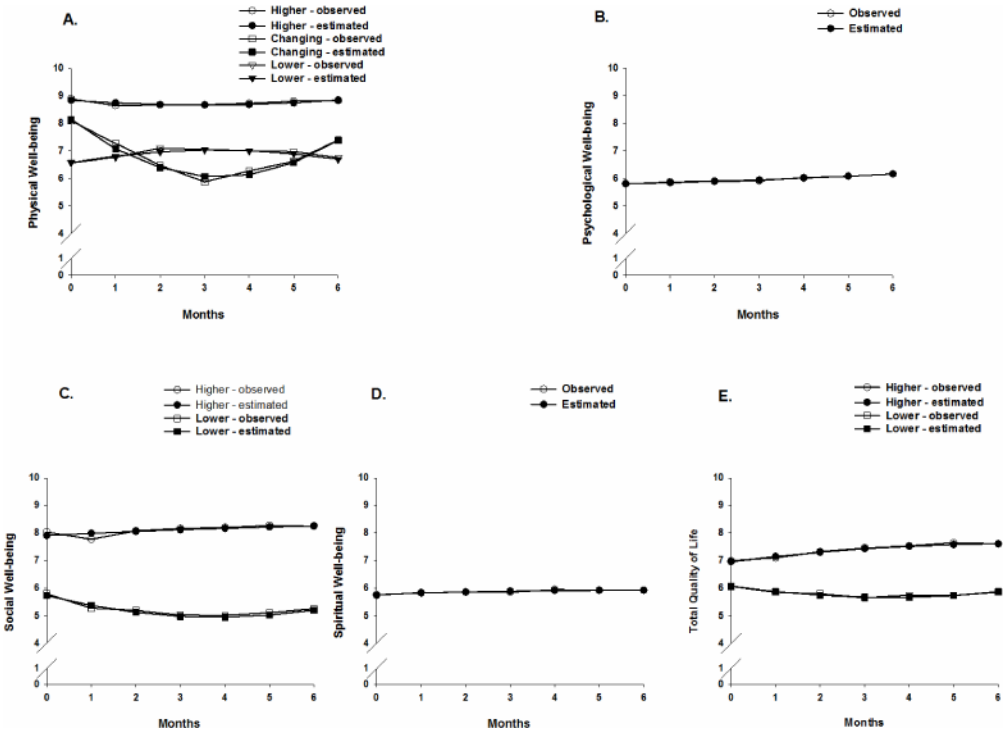

Figure 1.

Observed and estimated physical well-being (Figure 1A), psychological well-being (Figure 1B), social well-being (Figure 1C), spiritual well-being (Figure 1D), and total quality of life (QOL) (Figure 1E) trajectories for patients in each of the latent classes.

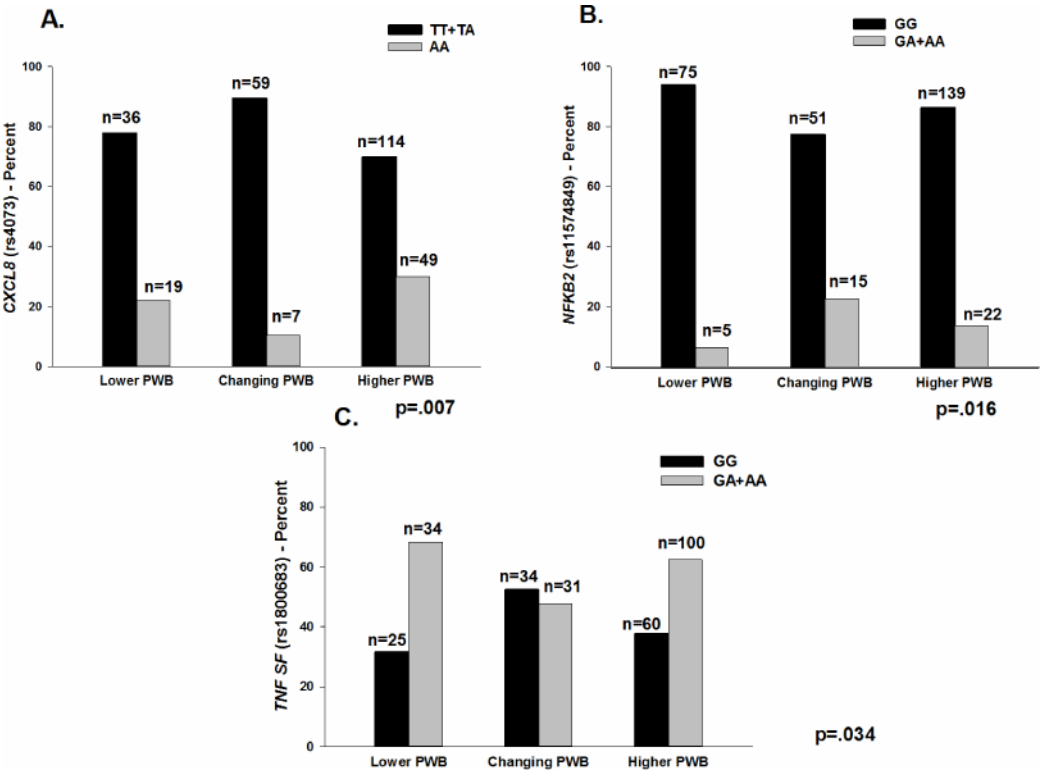

Figure 2.

Figure 2A - Differences among the physical well-being (PWB) latent classes in the percentages of patients who were homozygous or heterozygous for the common allele TT +TA) or homozygous for the rare allele (AA) for rs4073 in chemokine (C-C-C motif) ligand 8 (*CXCL8*). Values are plotted as unadjusted proportions with corresponding p-value.

Figure 2B - Differences among the PWB latent classes in the percentages of patients who were homozygous for the common allele (GG) or heterozygous or homozygous for the rare allele (GA+AA) for rs11574849 in nuclear factor kappa beta 2 (*NFKB2*). Values are plotted as unadjusted proportions with corresponding p-value.

Figure 2C - Differences among the PWB latent classes in the percentages of patients who were homozygous for the common allele (GG) or heterozygous or homozygous for the rare allele (GA+AA) for rs1800683 in tumor necrosis factor super family (*TNFSF*). Values are plotted as unadjusted proportions with corresponding p-value.

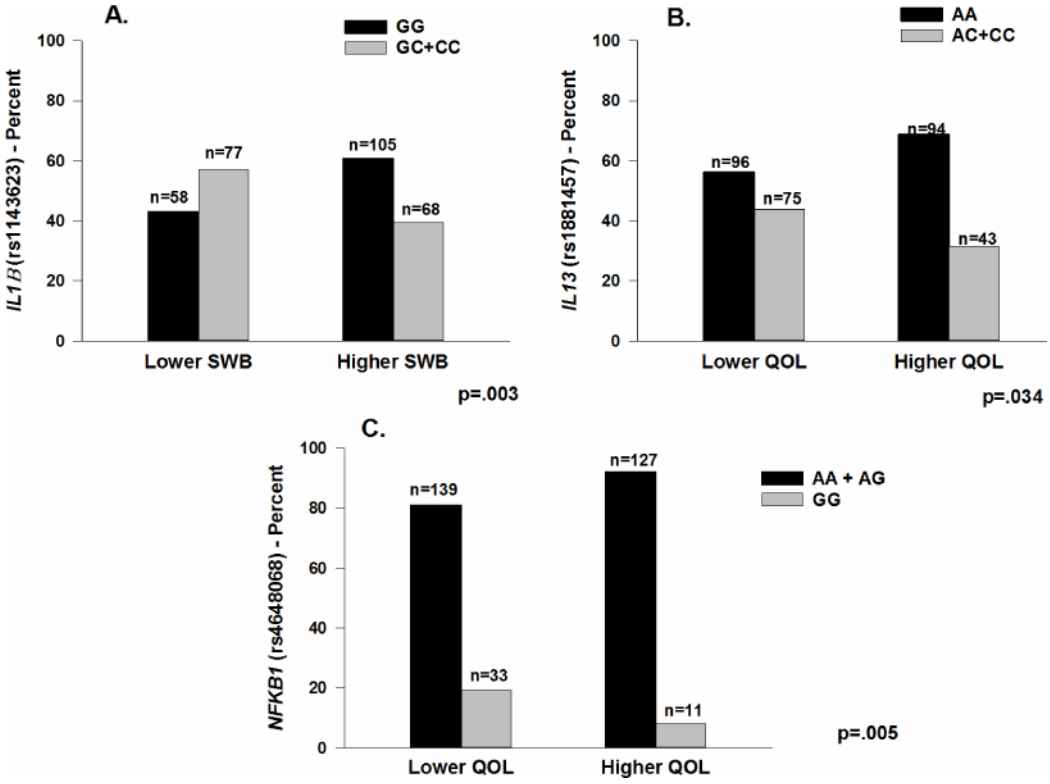

Figure 3.

Figure 3A - Differences between the social well-being (SWB) latent classes in the percentages of patients who were homozygous for the common allele (GG) or heterozygous or homozygous for the rare allele (GC+CC) for rs1143623 in interleukin 1 beta (*IL1B*). Values are plotted as unadjusted proportions with corresponding p-value.

Figure 3B - Differences between the total quality of life (QOL) latent classes in the percentages of patients who were homozygous for the common allele (AA) or heterozygous or homozygous for the rare allele (AC+CC) for rs1881457 in interleukin 13 (*IL13*). Values are plotted as unadjusted proportions with corresponding p-value.

Figure 3C - Differences between the total quality of life (QOL) classes in the percentages of patients who were homozygous or heterozygous for the common allele (AA+AG) or homozygous for the rare allele (GG) for rs4648068 in nuclear factor kappa beta 1 (*NFKB1*). Values are plotted as unadjusted proportions with corresponding p-value.

Table 1

Fit Indices for Physical and Social Well-being Subscales and Total QOL GMM solutions for Breast Cancer Patients over Seven Assessments

GMM	LL	AIC	BIC	Entropy	VLMR[c]
Physical Well-being					
1-Class[a]	−3930.642	7887.284	7939.010	n/a	n/a
2-Class	−3879.130	7796.259	7871.858	0.546	103.025*
3-Class[b]	−3824.433	7698.867	7798.339	0.660	109.393n.s.
4-Class	−3796.173	7654.346	7777.691	0.742	n/a
Social Well-being					
1-Class[d]	−3889.108	7804.216	7855.908	n/a	n/a
2-Class[e]	−3827.538	7691.076	7762.650	0.661	212.643***
3-Class	−3810.305	7666.611	7758.067	0.689	34.465n.s.
Total QOL					
1-Class[f]	−2885.220	5796.440	5848.198	n/a	n/a
2-Class[g]	−2855.037	5748.074	5823.721	0.508	60.366**
3-Class	−2838.897	5727.794	5827.329	0.482	32.280n.s.

*p < .05,

**p < .01,

***p < .001, n.s. = p > .05

[a]Random intercepts and random linear slopes latent growth curve model with linear and quadratic components; Chi^2 = 74.754, 22 df, p < 0.0001, CFI = 0.955, RMSEA = 0.078

[b]The 3-class model was selected, based on its having a smaller BIC than the 2-class model. Further, although the BIC for the 4-class model was smaller, the latent variable covariance matrices for two classes were not positive definite, and one class had only 10 cases (2.7% of the sample), indicating that the estimation for the 4-class model was unreliable.

[c]This value is the Chi^2 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.

[d]Random intercepts and random linear slopes latent growth curve model with linear and quadratic components; Chi^2 = 90.006, 22 df, p < 0.0001, CFI = 0.964, RMSEA = 0.089.

[e]2-class model was selected, because the BIC was smaller than the 1-class solution and the VLMR was significant. Further, although the BIC is smaller for the 3-class solution, one class in the 3-class solution contained only 26 observations (6.6% of the sample) – too small a class size to be reliable.

[f]Random intercepts and random linear slopes latent growth curve model with linear and quadratic components; Chi^2 = 78.244, 22 df, p < 0.0001, CFI = 0.975, RMSEA = 0.084.

[g] 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

Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criterion; CFI = comparative fit index; GMM = growth mixture model; LL = log likelihood; QOL = quality of life; RMSEA = root mean square error of approximation; VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test

Table 2

GMM Parameter Estimates for the Latent Class[a] Solutions for the Physical well-being, Social well-being, and Total QOL Scores

Parameter Estimates[b]	Physical Well-being			Social Well-being		Total QOL	
	Higher QOL n = 207 (52.4%)	Changing QOL n = 76 (19.2%)	Lower QOL n = 112 (28.4%)	Higher QOL n = 212 (53.8%)	Lower QOL n = 182 (46.2%)	Higher QOL n = 169 (42.7%)	Lower QOL n = 227 (57.3%)
	Mean (SE)			Mean (SE)		Mean (SE)	
Intercept	8.833***(0.184)	8.138***(0.251)	6.567***(0.283)	7.908***(0.173)	5.727***(0.170)	6.963***(0.131)	6.073***(0.110)
Linear slope	−0.116**(0.041)	−1.251***(0.197)	0.287*(0.116)	0.085$^{n.s.}$ (0.048)	−0.415***(0.091)	0.202***(0.039)	−0.231***(0.061)
Quadratic slope	0.019**(0.006)	0.187***(0.032)	-0.044*(0.019)	-0.004$^{n.s.}$ (0.007)	0.055***(0.012)	-0.016**(0.005)	0.032***(0.009)
Variances	Variance (SE)			Variance (SE)		Variance (SE)	
Intercept	0.389$^{n.s.}$ (0.303)	0.566$^{n.s.}$ (0.311)	2.193***(0.339)	0.798***(0.157)	2.710***(0.317)	0.953***(0.126)	1.261***(0.143)
Linear Slope	0.000$^{n.s.}$ (0.005)	0.028**(0.010)	0.093***(0.017)	0[c]	0.054***(0.010)	0.002$^{n.s}$ (0.003)	0.017***(0.003)

*p < .05,

**p < .01,

***p < .001

[a]Trajectory group sizes are for classification of individuals based on their most likely latent class probabilities.

[b]Growth mixture model estimates were obtained with robust maximum likelihood. Quadratic slope variances were fixed at zero to improve estimation.

[c]Fixed at zero.

Abbreviations: GMM = Growth mixture model; n.s. = not significant; QOL = quality of life; SE = standard error

J Pain Symptom Manage. Author manuscript; available in PMC 2019 February 01.

Table 3

Differences in Demographic and Clinical Characteristics Between the Physical Well-being, Social Well-being and Total Quality of Life (QOL) Classes

Characteristic	Physical Well-being				Social Well-being			Total QOL		
	Higher QOL (0) n=207 (52.4%) Mean (SD)	Changing QOL(1) n=76 (19.2%) Mean (SD)	Lower QOL (2) n=112 (28.4%) Mean (SD)	Statistics	Higher QOL n=212 (53.8%) Mean (SD)	Lower QOL n=182 (46.2%) Mean (SD)	Statistics	Higher QOL n=169 (42.7%) Mean (SD)	Lower QOL n=227 (57.3%) Mean (SD)	Statistics
Age (years)	58.3(11.3)	52.8(11.8)	50.3(9.9)	F = 20.73 p<.001 1 &2<0	59.6(11.2)	49.5 (9.4)	t = 9.75 p<001	57.9(11.5)	52.8(11.2)	t = 4.41, p<001
Education (years)	15.8(2.7)	15.7(2.7)	15.5(2.6)	F = 0.44 *p* = .646	15.6(2.7)	15.8(2.7)	t = −0.54 p = .587	15.6(2.6)	15.8(2.7)	t = −0.64, p = .521
Karnofsky Performance Status score	96.3(6.9)	95.3 (7.7)	86.2(13.4)	F = 44.64 p<.001 2<0&1	95.7(8.6)	90.4(11.3)	t = 5.05 p<001	95.0 (9.0)	91.9(11.0)	t = 3.05, p = .002
Self-administered Comorbidity Questionnaire score	3.8 (2.5)	4.4 (2.9)	5.0 (3.2)	F = 6.02 p=.003 2>0	4.3 (2.8)	4.3 (2.9)	t = −0.02 p = .982	4.1 (2.7)	4.3(2.9)	t = −0.68, p = .497
Body mass index (kg/rn^)	25.9(5.1)	27.1 (6.0)	28.2 (7.6)	F = 5.14 *p* = .006 2>0	26.6 (6.2)	27.0(6.1)	t = −0.55 p = .586	26.2(6.1)	27.2(6.1)	t = −1.66 p = .097
	n (%)	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Ethnicity				X^2=19.76 p=.003 0>2			X^2 = 13.92 p = .003 0>1			X^2 = 4.77 p = .190
White	153(74.3)	45 (59.2)	57(51.4)		154(73.0)	101 (55.8)		117(69.6)	138(61.1)	
Black	14 (6.8)	8(10.5)	18(16.2)		14 (6.6)	26 (14.4)		18(10.7)	22 (9.7)	
Asian/Pacific Islander	18(8.7)	11 (14.5)	20(18.0)		20 (9.5)	28(15.5)		16(9.5)	34(15.0)	
Hispanic/Mixed ethnic background/Other	21 (10.2)	12(15.8)	16(14.4)		23(10.9)	26 (14.4)		17(10.1)	32(14.2)	
Income										
<$30,000 *	24(13.5)	15(23.1)	30 (35.3)	KW, p = .008 2>1	29(16.3)	39 (26.2)	U, p = .132	20(14.5)	49 (25.8)	U, p = .164
$30,000–99,999	80 (44.9)	25 (38.5)	29(34.1)		78 (43.8)	56 (37.6)		64 (46.4)	70 (36.8)	
>$100,000	74(41.6)	25 (38.5)	26 (30.6)		71 (39.9)	54 (36.2)		54(39.1)	71 (37.4)	

Characteristic	Physical Well-being				Social Well-being			Total QOL		
	Higher QOL (0) n=207 (52.4%) Mean (SD)	Changing QOL(1) n=76 (19.2%) Mean (SD)	Lower QOL (2) n=112 (28.4%) Mean (SD)	Statistics	Higher QOL n=212 (53.8%) Mean (SD)	Lower QOL n=182 (46.2%) Mean (SD)	Statistics	Higher QOL n=169 (42.7%) Mean (SD)	Lower QOL n=227 (57.3%) Mean (SD)	Statistics
Married/partnered (% yes)	77 (37.4)	37 (49.3)	49(44.1)	X^2 = 3.65 p=.161	86 (40.8)	77 (42.8)	FE p = .758	70(41.4)	94 (42.0)	FE p = .918
Work for pay (% yes)	107(51.9)	36 (48.0)	46(41.4)	X^2 = 3.19 p = .203	107(50.5)	82 (45.8)	FE p = .363	86 (50.9)	103(46.0)	FE p = .360
Lives alone (% yes)	47 (22.9)	20 (27.0)	25 (22.5)	X^2=0.61 p = .739	52 (24.8)	39(21.8)	FE p = .548	42 (25.0)	51 (22.9)	FE p = .633
Gone through menopause (% yes)	147(72.1)	41 (55.4)	59 (55.7)	X^2= 11.35 p=.003 1 & 2 < 0	153(73.9)	93 (52.8)	FE p<001	117(70.5)	131 (59.8)	FE p = .032
Stage of disease										
0*	44 (21.3)	9 (11.8)	20 (17.9)		45 (21.2)	28 (15.4)		39 (23.1)	34 (15.0)	
I	87 (42.0)	27 (35.5)	37 (33.0)	KW, p = .027 2 < 1	95 (44.8)	56 (30.8)	U, p < .001 0 > 1	76 (45.0)	75 (33.0)	U, p = .001 0 > 1
IIA and IIB	61 (29.5)	33 (43.4)	45 (40.2)		61 (28.8)	77 (42.3)		46 (27.2)	94 (41.4)	
IIIA, IIIB, IIIC, and IV	15 (7.2)	7 (9.2)	10 (8.9)		11 (5.2)	21 (11.5)		8 (4.7)	24 (10.6)	
Surgical treatment Breast conservation Mastectomy	170 (82.1) 37 (17.9)	62 (81.6) 14 (18.4)	85 (75.9) 27 (24.1)	χ^2 = 1.89 p = .389	175 (82.5) 37 (17.5)	141 (77.5) 41 (22.5)	FE p = .254	136 (80.5) 33 (19.5)	181 (79.7) 46 (20.3)	FE p = .899
Sentinel node biopsy (% yes)	175 (84.5)	63 (82.9)	89 (79.5)	χ^2 = 1.32 p = .518	173 (81.6)	153 (84.1)	FE p = .593	136 (80.5)	192 (84.6)	FE p = .285
ALND (% yes)	61 (29.6)	35 (46.1)	50 (44.6)	χ^2 = 10.30 p = .006 1 & 2 > 0	56 (26.5)	90 (49.5)	FE p < .001	52 (31.0)	95 (41.9)	FE p = .028
Breast reconstruction at the time of surgery (% yes)	41 (19.9)	14 (18.4)	31 (27.7)	χ^2 = 3.21 p = .201	39 (18.5)	47 (25.8)	FE p = .087	35 (20.8)	51 (22.5)	FE p = .713
Neoadjuvant CTX (% yes)	28 (13.6)	7 (9.2)	44 (39.3)	χ^2 = 36.78 p < .001 1 < 2	24 (11.4)	55 (30.2)	FE p < .001	28 (16.7)	51 (22.5)	FE p = .164

Characteristic	Physical Well-being				Social Well-being			Total QOL		
	Higher QOL (0) n=207 (52.4%) Mean (SD)	Changing QOL(1) n=76 (19.2%) Mean (SD)	Lower QOL (2) n=112 (28.4%) Mean (SD)	Statistics	Higher QOL n=212 (53.8%) Mean (SD)	Lower QOL n=182 (46.2%) Mean (SD)	Statistics	Higher QOL n=169 (42.7%) Mean (SD)	Lower QOL n=227 (57.3%) Mean (SD)	Statistics
RT during the first 6 months (% yes)	131 (63.3)	35 (46.1)	58 (51.8)	$\chi^2 = 8.27$ $p = .016$ 1 < 0	136 (64.2)	88 (48.4)	FE $p = .002$	107 (63.3)	117 (51.5)	FE $p = .024$
CTX during the first 6 months (% yes)	44 (21.3)	46 (60.5)	43 (38.4)	$\chi^2 = 39.95$ $p < .001$ 1 & 2 > 0 1 > 2	48 (22.6)	84 (46.2)	FE $p < .001$	30 (17.8)	103 (45.4)	FE $p < .001$

* = reference group

Abbreviations: ALND = axillary lymph node dissection, CTX = chemotherapy, FE = Fisher Exact test, kg = kilograms, KW = Kruskal-Wallis test, m^2 = meter squared, RT = radiation therapy, SD = standard deviation, U = Mann Whitney U test

Table 4

Ordinal Logistic Regression Analyses for CXCL8, NFKB2, and TNFSF Genotypes Comparing the Latent Classes for Physical Well-being

GMM Class Comparison	Predictor	RR Ratio	Standard Error	95% CI	z	p-value
Higher versus Changing Physical Well-being classes	*CXCL8* rs4073	0.20	0.102	0.056, 0.682	−3.13	.002
	Age	0.95	0.016	0.911, 0.990	−2.98	.003
	KPS score	0.97	0.022	0.915, 1.021	−1.48	.139
	BMI	1.08	0.034	1.001, 1.623	2.41	.016
	Adjuvant CTX	3.74	1.304	1.623, 8.615	3.78	<.001
	Overall model fit: χ^2 = 140.20, p <.0001 pseudo R^2 = 0.2334					
Changing versus Lower Physical Well-being classes	*NFKB2* rs11574849	0.24	0.141	0.058, 0.985	−2.42	.016
	Age	0.96	0.020	0.910, 1.003	−2.24	.025
	KPS score	0.93	0.020	0.888, 0.985	−3.10	.002
	BMI	1.04	0.033	0.962, 1.119	1.17	.244
	Adjuvant CTX	0.54	0.212	0.211, 1.380	−1.57	.116
	Overall model fit: χ^2 = 137.30, p <.0001 pseudo R^2 = 0.2306					
Changing versus Lower Physical Well-being classes	*TNFSF* rs1800683	2.73	1.107	1.034, 7.205	2.48	.013
	Age	0.96	0.020	0.913, 1.008	-2.00	.046
	KPS score	0.92	0.021	0.870, 0.970	−3.75	<.001
	BMI	1.03	0.033	0.956, 1.114	0.98	.329
	Adjuvant CTX	0.64	0.252	0.248, 1.640	−1.14	.255
	Overall model fit: χ^2 = 139.52, p <.0001 pseudo R^2 = 0.2359					

Note: For each model, the first three principal components identified from the analysis of ancestry informative markers as well as self-reported race/ethnicity (i.e., White, Black, Asian/Pacific Islander, Hispanic/mixed ethnic background/other) were retained in all models to adjust for potential confounding due to race or ethnicity (data not shown). Predictors evaluated in each model included genotype (*CXCL8* rs4073: TT+TA versus AA; *NFKB2* rs11574849: GG versus GA+AA; *TNFSF* rs1800683: GG versus GA+AA), age, KPS score, BMI, and whether the patient received CTX during the first 6 months following surgery (i.e., adjuvant CTX).

Abbreviations: BMI = body mass index; CTX = chemotherapy; CI = confidence interval; GMM = growth mixture model; *CXCL8 = chemokine ligand* 8; KPS = Karnofsky Performance Status; *NFKB2 = nuclear factor kappa beta 2*; RR = Relative Risk; *TNFSF = tumor necrosis factor superfamily*.

Table 5

Multiple Logistic Regression Analyses for IL1B Genotype Comparing the Latent Classes for Social Well-being

	Predictor	Odds Ratio	Standard Error	95% CI	z	p-value
Higher versus Lower Social Well-being	*IL1B* rs1143623	1.94	0.540	1.122, 3.346	2.37	.018
	Age	0.42	0.062	0.310, 0.557	−5.88	<.001
	KPS score	0.59	0.091	0.437, 0.801	−3.39	.001
	Adjuvant CTX	2.21	0.647	1.247, 3.925	2.71	.007
	Overall model fit: $\chi^2 = 95.56$, pseudo p <.0001 $R^2 = 0.2325$					

Note: For each model, the first three principal components identified from the analysis of ancestry informative markers as well as self-reported race/ethnicity (i.e., White, Black, Asian/Pacific Islander, Hispanic/mixed ethnic background/other) were retained in all models to adjust for potential confounding due to race or ethnicity (data not shown). Predictors evaluated in each model included genotype (*IL1B* rs1143623: GG versus GC+CC), age (in 10-year increments), KPS score (in 10-point increments), and whether the patient received CTX during the first 6 months following surgery (i.e., adjuvant CTX).

Abbreviations: CTX = chemotherapy; CI =confidence interval; GMM = growth mixture model; *IL1B = interleukin 1 beta*; KPS = Karnofsky Performance Status.

J Pain Symptom Manage. Author manuscript; available in PMC 2019 February 01.

Table 6

Multiple Logistic Regression Analyses for IL13 and NFKB1 Genotypes Comparing the Latent Classes for Total Quality of Life

	Predictor	Odds Ratio	Standard Error	95% CI	z	p-value
Higher versus Lower Total QOL	*IL13* rs1881457	1.78	0.481	1.047, 3.021	2.13	.033
	Age	0.78	0.093	0.615, 0.984	-2.10	.036
	KPS score	0.62	0.095	0.455, 0.834	-3.14	.002
	Adjuvant CTX	4.27	1.254	2.402, 7.593	4.95	<.001
	Overall model fit: χ^2 = 60.39, p <.0001 R^2 = 0.1468					
Higher versus Lower Total QOL	*NFKB1* rs4648068	3.12	1.249	1.420, 6.836	2.84	.005
	Age	0.77	0.930	0.608, 0.975	-2.17	.030
	KPS score	0.64	0.094	0.479, 0.853	-3.04	.002
	Adjuvant CTX	4.33	1.267	2.439, 7.684	5.00	<.001
	Overall model fit: χ^2 = 60.47, p <.0001 pseudo R^2 = 0.1460					

Note: For each model, the first three principal components identified from the analysis of ancestry informative markers as well as self-reported race/ethnicity (i.e., White, Black, Asian/Pacific Islander, Hispanic/mixed ethnic background/other) were retained in all models to adjust for potential confounding due to race or ethnicity (data not shown). Predictors evaluated in each model included genotype (*IL13* rs1881457: AA versus AC+CC; *NFKB1* rs4648068: AA+AG versus GG), age (in 10-year increments), KPS score (in 10-point increments), and whether the patient received chemotherapy during the first 6 months following surgery (i.e., adjuvant CTX).

Abbreviations: CI =confidence interval; CTX = chemotherapy; GMM = growth mixture model; *IL13* = interleukin 13; KPS = Karnofsky Performance Status; *NFKB1* = nuclear factor kappa beta 1.